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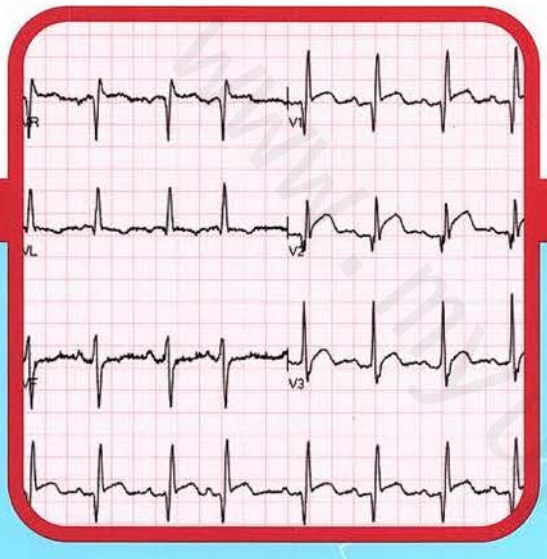

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Welcome to the Cardiovascular Medicine Section of MKSAP 17!

In these pages, you will find updated information on risk assessment in cardiovascular disease, diagnostic testing, coronary artery disease, heart failure, arrhythmias, pericardial and myocardial disease, valvular heart disease, and other clinical challenges. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of cardiovascular medicine.

The publication of the 17th edition of Medical Knowledge Self-Assessment Program (MKSAP) represents nearly a half-century of serving as the gold-standard resource for internal medicine education. It also marks its evolution into an innovative learning system to better meet the changing educational needs and learning styles of all internists.

The core content of MKSAP has been developed as in previous editions—newly generated, essential information in 11 topic areas of internal medicine created by dozens of leading generalists and subspecialists and guided by certification and recertification requirements, emerging knowledge in the field, and user feedback. MKSAP 17 also contains 1200 all-new, psychometrically validated, and peer-reviewed multiple-choice questions (MCQs) for self-assessment and study, including 120 in Cardiovascular Medicine. MKSAP 17 continues to include *High Value Care* (HVC) recommendations, based on the concept of balancing clinical benefit with costs and harms, with links to MCQs that illustrate these principles. In addition, HVC Key Points are highlighted in the text. Also highlighted, with blue text, are *Hospitalist*-focused content and MCQs that directly address the learning needs of internists who work in the hospital setting.

MKSAP 17 Digital provides access to additional tools allowing you to customize your learning experience, including regular text updates with practice-changing, new information and 200 new self-assessment questions; a board-style pretest to help direct your learning; and enhanced custom-quiz options. And, with MKSAP Complete, learners can access 1200 electronic flashcards for quick review of important concepts or review the updated and enhanced version of Virtual Dx, an image-based self-assessment tool.

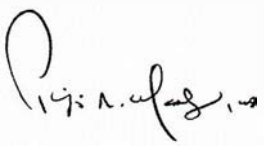
As before, MKSAP 17 is optimized for use on your mobile devices, with iOS- and Android-based apps allowing you to sync your work between your apps and online account and submit for CME credits and MOC points online.

Please visit us at the MKSAP Resource Site (mksap.acponline.org) to find out how we can help you study, earn CME credit and MOC points, and stay up to date.

Whether you prefer to use the traditional print version or take advantage of the features available through the digital version, we hope you enjoy MKSAP 17 and that it meets and exceeds your personal learning needs.

On behalf of the many internists who have offered their time and expertise to create the content for MKSAP 17 and the editorial staff who work to bring this material to you in the best possible way, we are honored that you have chosen to use MKSAP 17 and appreciate any feedback about the program you may have. Please feel free to send us any comments to mksap_editors@acponline.org.

Sincerely,



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Expert reviewer for legal case of infective endocarditis

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MKSAP Resource Site (mksap.acponline.org)

The MKSAP Resource Site (mksap.acponline.org) is a continually updated site that provides links to MKSAP 17 online answer sheets for print subscribers; the latest details on Continuing Medical Education (CME) and Maintenance of Certification (MOC) in the United States, Canada, and Australia; errata; and other new information.

ABIM Maintenance of Certification

Check the MKSAP Resource Site (mksap.acponline.org) for the latest information on how MKSAP tests can be used to apply to the American Board of Internal Medicine for Maintenance of Certification (MOC) points.

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Fellows of the Royal College may earn three credits per hour for participating in MKSAP 17 under Section 3. MKSAP 17 also meets multiple CanMEDS Roles, including that of Medical Expert, Communicator, Collaborator, Manager, Health Advocate, Scholar, and Professional. For information on how to apply MKSAP 17 Continuing Medical Education (CME) credits to the Royal College MOC Program, visit the MKSAP Resource Site at mksap.acponline.org.

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Up to 21 *AMA PRA Category 1 Credits*™ are available from July 31, 2015, to July 31, 2018, for the MKSAP 17 Cardiovascular Medicine section.

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Learning Objectives

The learning objectives of MKSAP 17 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence
- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internists and primary care physicians
- Subspecialists who need to remain up-to-date in internal medicine and in areas outside of their own subspecialty area
- Residents preparing for the certification examination in internal medicine
- Physicians preparing for maintenance of certification in internal medicine (recertification)

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Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon (HVC).

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Errata

Errata for MKSAP 17 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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Cardiovascular Medicine High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 17 in several important ways. MKSAP 17 now includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Cardiovascular Medicine section of MKSAP 17.

- Current guidelines do not support the use of high-sensitivity C-reactive protein (hsCRP) evaluation in the general population, but hsCRP testing may be used in intermediate-risk patients in whom choice of therapy may be affected by reclassification of risk.
- There is currently no role for the routine measurement of Lp(a) lipoprotein levels, homocysteine levels, or evaluation of lipid particle size as these tests are expensive and no studies to date have shown that treatment targeted to these levels affects outcomes.
- The evaluation of subclinical disease with coronary artery calcium scoring may be appropriate to further risk stratify intermediate-risk patients but is not a component of routine risk assessment.
- Aspirin should not routinely be given to patients with diabetes mellitus who are at low cardiovascular risk (men younger than 50 years and women younger than 60 years without other major risk factors such as hypertension or tobacco use) (see Item 88).
- Stress testing is most efficacious in patients with an intermediate pretest probability of coronary artery disease (10%-90%), because it is these patients who, by the result of their stress test, can be reclassified into higher or lower risk categories.
- Exercise electrocardiographic testing is recommended as the initial test of choice in patients who are able to exercise with a normal baseline electrocardiogram and an intermediate pretest probability of coronary artery disease based on age, sex, and symptoms (see Item 87).
- Measurement of coronary artery calcium should be limited to a select group of asymptomatic patients with an intermediate Framingham risk score (10%-20%) in whom results will influence treatment strategy because of its associated cost and radiation exposure.
- Routine yearly imaging evaluation of structural heart disease in asymptomatic patients is usually not indicated.
- Patients with grade 1 or 2 midsystolic murmurs who are asymptomatic with no associated findings and those with continuous murmurs suggestive of a venous hum or mammary souffle do not warrant echocardiographic evaluation.
- For stable angina pectoris, percutaneous coronary intervention is reserved for patients with refractory symptoms while on optimal medical therapy, those who are unable to tolerate optimal medical therapy owing to side effects, or those with high-risk features on noninvasive imaging.
- Clinical practice guidelines do not recommend the routine use of ECG monitoring, stress testing, or anatomic testing (coronary CT angiography or invasive angiography) in asymptomatic patients after percutaneous coronary intervention or coronary artery bypass graft surgery.
- Routine stress testing is not currently recommended for asymptomatic patients following an acute coronary syndrome who are not entering a cardiac rehabilitation program.
- Evaluation of unusual causes of heart failure should not be performed routinely but should be performed when there are suggestions of specific diseases by history or physical examination findings (see Item 116).
- In patients with chronic heart failure who are clinically stable, annual or more frequent follow-up echocardiography rarely provides therapeutic or diagnostic benefit and is not recommended.
- Patients hospitalized for heart failure who are scheduled for a follow-up appointment within 1 week after discharge

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have a reduced risk of future heart failure hospitalization (see Item 34).

- Patients with asymptomatic, mild aortic stenosis or regurgitation require echocardiography every 3 to 5 years.
- Asymptomatic patients with moderate aortic regurgitation should be evaluated clinically on a yearly basis and have echocardiography performed every 1 to 2 years, but they do not require medical or surgical intervention (see Item 59).
- Patients with asymptomatic, severe aortic stenosis with preserved left ventricular function may be managed with close clinical follow-up and echocardiography every 6 to 12 months and should not undergo valve replacement (see Item 20).
- Patients with an asymptomatic bicuspid aortic valve should undergo surveillance transthoracic echocardiography yearly if the aortic root or ascending aortic diameter is greater than 4 cm (see Item 97).
- Infective endocarditis prophylaxis should be limited to those with a prosthetic cardiac valve; a history of infective endocarditis; unrepaired cyanotic congenital heart disease or repaired congenital heart defect with prosthesis or shunt (≤6 months post-procedure) or residual defect; or valvulopathy following cardiac transplantation.
- Antibiotic prophylaxis to prevent bacterial endocarditis is not recommended for nondental procedures, including transesophageal echocardiography and genitourinary or gastrointestinal procedures, in the absence of active infection (see Item 25).
- There is no indication for patent foramen ovale closure or for antiplatelet therapy in asymptomatic patients, and randomized trials do not support patent foramen ovale closure to reduce risk of recurrent stroke or migraine.
- A small atrial septal defect (pulmonary–to–systemic blood flow ratio [Qp:Qs] <1.5:1) with no associated symptoms or right heart enlargement can be followed clinically.
- A small membranous ventricular septal defect without left heart enlargement, pulmonary hypertension, recurrent endocarditis, or valve regurgitation can be observed clinically (see Item 45).
- Screening of asymptomatic patients for abnormalities of the thoracic aorta should be reserved for patients with underlying vascular pathology (such as Marfan or Ehlers-Danlos syndrome), a bicuspid aortic valve, or a family history of aortic disease.
- Invasive imaging of the aorta by angiography is rarely necessary for the diagnosis of acute disease; it should be reserved for patients in whom a percutaneous intervention is planned.
- Diuretics, particularly in high doses, will exacerbate the propensity towards dynamic left ventricular outflow tract obstruction and, therefore, should be avoided in patients with hypertrophic cardiomyopathy (see Item 5).
- When an atrial septal aneurysm is identified incidentally, no further evaluation, medical treatment, or intervention is needed (see Item 10).
- Influenza vaccine should be administered to patients with established cardiovascular disease to reduce the risk of future cardiovascular events (see Item 13).
- Accelerated idioventricular rhythm is a common complication following coronary reperfusion and does not require intervention when it occurs within 24 hours of reperfusion (see Item 42).
- Routine screening for coronary artery disease in asymptomatic patients with diabetes mellitus does not reduce mortality (see Item 65).
- Supervised exercise therapy can effectively treat claudication, with increases in pain-free walking time and maximal walking time, and is recommended as part of the initial treatment regimen for intermittent claudication (see Item 84).
- Asymptomatic first-degree atrioventricular block with bifascicular block does not require pacemaker implantation (see Item 109).
- Patients with acute pericarditis who do not have high-risk features (fever, leukocytosis, acute trauma, abnormal cardiac biomarkers, immunocompromise, oral anticoagulant use, large pericardial effusions, or evidence of cardiac tamponade) can be managed medically on an outpatient basis with close clinical follow-up (see Item 114).

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Cardiovascular Medicine

Epidemiology and Risk Factors

Overview

In the United States, the mortality rate from cardiovascular disease (CVD), including heart disease, stroke, peripheral vascular disease, hypertension, and heart failure has steadily declined over the past decade—33% from 1999 to 2009, likely as a result of better prevention and acute care efforts. Nonetheless, CVD is the leading killer of both men and women, and although mortality of CVD is decreasing, CVD prevalence is increasing. By 2030, according to the American Heart Association's Heart Disease and Stroke Statistics, more than 40% of the U.S. population is projected to have some form of CVD. More than one in three American adults currently have some form of CVD, and the prevalence increases from more than 10% in those aged 20 to 39 years to more than 70% in those aged 60 to 79 years. Based on data from the Framingham Heart Study, two out of three men and one out of two women will develop CVD in their lifetime. Despite the decreasing mortality, hospitalizations for cardiovascular-related diseases have steadily continued to rise. There were nearly 6 million hospital discharges for cardiovascular-related diseases in 2009, with an estimated cost of $312.6 billion.

The prevalence of heart failure continues to rise, with a predicted prevalence in the United States of 25% by 2030. It is estimated that 5.1 million Americans older than 20 years have a diagnosis of heart failure. Currently, the incidence is 1/100 annually in those older than 65 years. Most of these patients have a history of hypertension. Both systolic dysfunction and diastolic dysfunction are associated with the development of symptomatic heart failure, and the prevalence of heart failure with preserved ejection fraction (diastolic dysfunction) is increasing. Mortality in heart failure is quite high—nearly 50% mortality at 5 years.

Cardiovascular Disease in Women

Since 1984, the number of deaths from CVD has been greater for women than men and highest among black women. More than 400,000 women died of CVD in 2009, 51% of all CVD deaths. Women have a higher mortality rate after myocardial infarction: 26% in women versus 19% in men older than 45 years. The death rate for women with heart failure is higher than among men, although women are often older. Incidence of and mortality from stroke is highest among women, with the highest among black women.

Women have a higher prevalence of risk factors for CVD, including elevated cholesterol levels, diabetes mellitus, hypertension, and inactivity. Only tobacco use is higher among men.

More women present with angina than men, but women often have other symptoms in addition to chest pain. Women have "atypical" symptoms more frequently than men, including nausea, shortness of breath, and unusual fatigue. More than two thirds of women who die suddenly from coronary heart disease either did not recognize the symptoms or had no previous symptoms. Women undergo fewer revascularization procedures than men, with 25% of coronary artery bypass surgeries and nearly 33% of percutaneous coronary interventions occurring in women.

Ethnicity and Cardiovascular Disease

The prevalence of CVD and risk factors in the United States vary by ethnicity. American Indians and Alaska Natives have the highest rate of heart disease (12.7%), followed by whites (11.1%), blacks or African Americans (10.7%), Hispanics or Latinos (8.6%), and Asians (7.4%). Peripheral arterial disease affects nearly 8.5% of Americans older than 40 years, and prevalence is highest among older persons, non-Hispanic blacks, and women. The population most affected by heart failure is African Americans, at a rate of 4.6/1000 person-years, followed by Hispanic, white, and Chinese Americans.

Cardiovascular risk factors also vary among ethnicities. Blacks have the highest rate of hypertension, at 33.4% (higher in black women), followed by American Indians or Alaska Natives (25.8%), whites (23.3%), Hispanics or Latinos (22.2%), and Asians (18.7%). Blacks have the highest prevalence of two or more cardiovascular risk factors (48.7%). The prevalence of risk factors is increased with decreasing levels of education and income. Obesity and lack of physical activity are highest among Hispanic/Latino adults and non-Hispanic blacks.

Environmental influences on cardiovascular risk factors are changing the prevalence of CVD in certain populations. In countries with previously low rates of CVD, rates of disease are increasing with the adoption of Western eating habits and increasing tobacco use. With declining rates of infant mortality and death from infectious diseases, the influence of urbanization and change in traditional lifestyles are resulting in increasing rates of CVD.

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Genetics in Cardiovascular Disease

Family history of premature (male <45 years; female <55 years) coronary artery disease (CAD) significantly increases risk of CVD. Having a parent with premature CAD doubles risk of myocardial infarction in men and increases risk in women by 70%. CAD in a sibling increases risk by 50%. Genetic predisposition as well as shared environment may contribute to increased risk in family members. Although prediction models based on the genetics of CVD are not yet available, research continues at a rapid pace.

Lifestyle Risk Factors

As much as 90% of the risk for myocardial infarction has been attributed to modifiable risk factors, with elevated cholesterol levels, smoking, and psychosocial stressors accounting for a significant portion of the attributable risk. The attributable risk for myocardial infarction is highest for cholesterol levels, followed by current smoking, psychosocial stressors, diabetes, hypertension, abdominal obesity, no alcohol intake, inadequate exercise, and irregular consumption of fruits and vegetables.

Elevated cholesterol levels increase the risk of CVD, and multiple studies have shown that reductions in cholesterol levels, particularly LDL cholesterol, reduce risk. Nearly 14% of adults older than 20 years have total cholesterol levels greater than 240 mg/dL (6.21 mmol/L); approximately 6% of adults are estimated to have undiagnosed hypercholesterolemia. Elevated LDL cholesterol and low HDL cholesterol levels are independent risk factors for CVD. For every 1% decrease in LDL cholesterol level, there is a corresponding 1% decrease in risk for coronary artery disease. The risk reduction is even greater with changes in HDL cholesterol, with a risk reduction of 2% to 3% for every 1% increase in HDL cholesterol level. However, randomized clinical trials evaluating pharmacologic therapies that raise HDL cholesterol levels in patients with well-treated LDL cholesterol levels have not shown reduction in clinical endpoints. Long-standing guidelines (Adult Treatment Panel III [ATP III]) have provided treatment goals for LDL and non-HDL cholesterol levels based on cardiovascular risk factors and Framingham risk score. In 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) published revised guidelines that treat lipid blood levels according to cardiovascular risk, rather than LDL cholesterol targets (see MKSAP 17 General Internal Medicine, Dyslipidemia).

The use of tobacco has declined over the past few decades, but despite this decline, in 2011, more than 21.3% of men, 16.7% of women, and 18% of high school students were smokers. The rates were highest among American Indian/Alaska Natives and non-Hispanic black males and lowest among Hispanic females. Tobacco use increases the risk of CVD, including coronary heart disease, stroke, and peripheral vascular disease, for which smoking is a major risk factor, and increases CVD mortality by 2 to 3 times. The risk of coronary artery disease is increased by 25% in women who smoke. Smoking increases the risk of stroke by 2 to 4 times. Secondhand smoke is also a risk factor for CVD, increasing the risk by 25% to 30%. Smoking cessation substantially reduces cardiovascular risk within 2 years, and this risk returns to the level of a nonsmoker within 5 years. Efforts to assess smoking status and provide assistance with cessation should be made at every encounter (see MKSAP 17 General Internal Medicine, Routine Care of the Healthy Patient).

Nearly one in three adults in the United States older than 20 years has hypertension, and the rates are equal among men and women. Nearly 30% of adults older than 20 years have prehypertension (systolic blood pressure 120-139 mm Hg; diastolic blood pressure 80-89 mm Hg). The rates increase with age, with a prevalence greater than 70% in persons older than 65 years. Treatment of hypertension reduces risk for cardiovascular events, including stroke, and reduces end-organ damage such as heart failure and kidney disease. Although the prevalence of blood pressure control (that is, blood pressure within recommended ranges) has improved in the United States from less than 30% two decades ago (1988-1994), it still is only 50% (2007-2008).

Sedentary lifestyle, poor diet, and obesity contribute to increased cardiovascular risk and increased risk for diabetes. Nearly one third of all U.S. adults report no leisure time activity, and less than 30% of high school students engaged in 60 minutes of daily physical activity; this rate was lowest among girls. Between 1971 and 2004, total energy consumption increased by 22% in women and 10% in men. Average fruit and vegetable consumption was 2.4 to 4 servings daily (recommended, >5 daily) and was lowest among blacks. The increased caloric intake coupled with decreased physical activity has led to an increased incidence of obesity. More than two thirds of the American population older than 20 years are overweight (BMI 25-29.9) with more than one third obese (BMI>30). In children and adolescents between the ages of 2 and 19 years, nearly 33% are obese or overweight and 17% of these children are obese.

Psychosocial stressors are an important contributor to cardiovascular risk. These include depression, anger, and anxiety, and are associated with worse outcomes. Depression has been associated with higher risk for cardiovascular events, and psychosocial stressors also affect the course of treatment and adherence to healthy lifestyles after an event. Awareness of these factors and appropriate therapies may improve outcomes in these individuals.

Impaired glucose control is a significant component of the metabolic syndrome, which is characterized by elevated glucose, central obesity, low HDL cholesterol, elevated triglycerides, and high blood pressure. More than 34% of adults older than 20 years meet the criteria for metabolic syndrome (three of the five components). The presence of metabolic syndrome is associated with an increased risk of CVD. This risk increases with an increased number of components and also appears to be higher among women. The National Diabetes Prevention Program found that in persons at high risk for diabetes, improved food choices and at least 150 minutes of exercise weekly led to 5% to 7% weight loss and reduced the risk of

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developing diabetes by 58%, but no interventions have shown a reduction in CVD events to date.

KEY POINT

- Elevated cholesterol levels, smoking, and psychosocial stressors are the greatest modifiable risk factors for cardiovascular disease.

Specific Risk Groups

Diabetes Mellitus

The presence of diabetes mellitus is associated with increased cardiovascular risk, particularly among women. Persons with diabetes have a 2 to 4 times increased risk of CVD, with more than two thirds of those with diabetes eventually dying of heart disease. The risk of stroke is increased 1.8- to 6-fold in persons with diabetes. The presence of diabetes in those older than 65 years is nearly 27%. In those aged 12-19 years, the prevalence of diabetes and prediabetes is increasing, from 9% to 23% from 1999-2007. Diabetes is often undiagnosed, and is frequently diagnosed at the time of an acute event such as myocardial infarction. Appropriate treatment of cardiovascular risk factors in persons with diabetes is associated with reduced cardiovascular risk. The most recent cholesterol guidelines recommend moderate- or high-intensity statin therapy in patients aged 40 to 75 years with diabetes. Patients with diabetes aged 40 to 75 years with a 10-year atherosclerotic cardiovascular disease (ASCVD) risk greater than or equal to 7.5% should receive high-intensity statin therapy because of their increased risk. In patients with diabetes in this age group with a 10-year risk below 7.5%, moderate-intensity statin therapy is recommended.

Chronic Kidney Disease

Chronic kidney disease (CKD) is associated with higher cardiovascular mortality, and more patients with kidney disease will die of CVD than will go on to have end-stage kidney disease requiring dialysis. Chronic kidney disease shares many of the same risk factors for CVD such as hypertension, diabetes, and smoking. The exact etiology of the high death rate in patients with CKD is uncertain and may be related to a higher incidence of fatal arrhythmias, lack of adequate therapies at the time of an acute cardiovascular event, or multi-organ changes related to kidney failure.

Systemic Inflammatory Conditions

Patients with systemic inflammatory conditions, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis, have an increased risk of CVD. Most deaths in persons with SLE and nearly 40% of deaths in those with rheumatoid arthritis are cardiovascular and, in particular, heart failure related. The risk of CVD increases with the duration of the underlying inflammatory condition. The risk of CVD increases from two times that of the general population to three times after 10 years' duration of rheumatoid arthritis. The increased atherosclerotic burden is likely a result of both the inflammatory process of the systemic disease, including a prothrombotic state, as well as the presence of traditional cardiovascular risk factors.

Calculating Cardiovascular Risk

Cardiovascular risk scores should be utilized to stratify patients for appropriate prevention targets. Traditionally, the Framingham risk score has been used to estimate the 10-year risk of a major cardiovascular event (myocardial infarction or coronary death). An online Framingham risk calculator is available at http://cvdrisk.nhlbi.nih.gov/calculator.asp. Using this method, a 10-year risk of ASCVD of less than 10% is considered low risk, 10% to 20% is classified as intermediate risk, and above 20% is designated as high risk. Age is the component that drives most of the risk, with increasing age reflected in increased risk. The Framingham risk score underestimates risk in women and minority populations. In an effort to account for the underestimation in women, the Reynolds risk score was developed, which is a sex-specific score for both men and women that includes family history and high-sensitivity C-reactive protein (hsCRP) levels (www.reynoldsriskscore.org).

The Pooled Cohort Equations are a new risk assessment instrument developed from multiple community-based cohorts (including the Framingham study) that includes a broader range of variables than the Framingham score when evaluating 10-year ASCVD risk. Its use as a primary risk assessment tool was recommended in the 2013 ACC/AHA Guideline on Assessment of Cardiovascular Risk. The ACC/AHA CV risk calculator includes age, sex, race, total and HDL cholesterol levels, systolic blood pressure, blood pressure–lowering medication use, diabetes status, and smoking status. Using this method, a 10-year risk of ASCVD of below 5% is considered low risk, 5% to below 7.5% is classified as intermediate risk, and 7.5% or above is designated as high risk. The new risk calculator can be accessed at http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp.

KEY POINT

- Cardiovascular risk scores should be utilized to stratify patients for appropriate prevention targets; risk assessment tools include the Framingham risk score, the Reynolds risk score, and the American College of Cardiology/American Heart Association's cardiovascular risk calculator based on the Pooled Cohort Equations.

Emerging Risk Factors

Because atherosclerotic disease is thought to be in part an inflammatory process, hsCRP measurement has been investigated for enhancing risk prediction. Current guidelines do not support the use of hsCRP evaluation in the general population. However, hsCRP testing may be used in intermediate-risk patients (Framingham 10-year risk score of 10%-20%) in whom

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choice of therapy may be affected by reclassification of risk. Elevated hsCRP levels should be rechecked within 2 weeks, and other potential causes of infection or inflammation should be ruled out. Although statin therapy has been shown to lower hsCRP levels, therapy targeting hsCRP alone is not appropriate as patients should be treated according to cardiovascular risk.

Although elevated levels of Lp(a) lipoprotein and homocysteine have been associated with elevated cardiovascular risk, these tests should not be routinely performed. Interventions to reduce homocysteine levels with folic acid supplementation have not been shown to reduce cardiovascular events. Although epidemiologic evidence supports the association between elevated levels of Lp(a) lipoprotein and cardiovascular events, to date no trials have shown that treatment to lower Lp(a) lipoprotein levels lowers risk. There is currently no role for the evaluation of lipid particle size and number. No studies to date have shown that treatment targeted to particle size and number affects outcomes.

The evaluation of subclinical disease with coronary artery calcium (CAC) scoring may be appropriate to further risk stratify intermediate-risk patients but is not a component of routine risk assessment. Evidence of calcification of coronary vessels is indicative of atherosclerotic disease, but the absence of calcification does not rule out the presence of soft plaque.

KEY POINTS

HVC
- Current guidelines do not support the use of high-sensitivity C-reactive protein (hsCRP) evaluation in the general population, but hsCRP testing may be used in intermediate-risk patients in whom choice of therapy may be affected by reclassification of risk.

HVC
- There is currently no role for the routine measurement of Lp(a) lipoprotein levels or homocysteine levels or evaluation of lipid particle size as these tests are expensive and no studies to date have shown that treatment targeted to these levels affects outcomes.

HVC
- The evaluation of subclinical disease with coronary artery calcium scoring may be appropriate to further risk stratify intermediate-risk patients but is not a component of routine risk assessment.

Aspirin for Primary Prevention

Aspirin is a powerful agent for both primary and secondary prevention of coronary artery disease. Aspirin for secondary prevention is discussed under Coronary Artery Disease. For primary prevention of myocardial infarction, data suggest that there is greater benefit in men, particularly those older than 45 years. For women, benefit outweighs risk of aspirin therapy after the age of 65 years. Between the ages of 55 and 65 years, the risk of stroke is reduced in women on aspirin therapy. Guidance for using aspirin for primary prevention of myocardial infarction and stroke is provided in **Table 1** and **Table 2**.

It is important to balance the benefits of aspirin therapy with the risks of gastrointestinal (GI) bleeding. The risk of serious bleeding is greatly increased in patients with a history of GI ulcers and who use NSAIDs, and these factors should be considered when assessing the benefits and harms of using aspirin in the individual patient.

Aspirin should not be routinely given to patients with diabetes who are at low risk for CVD (men <50 years and women <60 years with no major additional CVD risk factors; 10-year CVD risk <5%). It is reasonable to give low-dose aspirin to adults with diabetes and no previous history of vascular disease who are at increased CVD risk (10-year Framingham risk >10%) and without increased risk for bleeding.

KEY POINTS

- In men ages 45 to 79 years, aspirin for primary prevention of myocardial infarction is recommended if the benefit of treatment outweighs the risk of gastrointestinal bleeding.
- In women ages 55 to 79 years, aspirin for primary prevention of stroke is recommended if the benefit of treatment outweighs the risk of gastrointestinal bleeding.
- Aspirin should not be routinely given to patients with diabetes who are at low risk; that is, men younger than 50 years and women younger than 60 years with no major additional cardiovascular risk factors. HVC

TABLE 1. Use of Aspirin for Primary Prevention of Cardiovascular Disease

Patient Category	Recommendation
Men age 45-79 years	Aspirin recommended when potential benefit of reduction in MI outweighs risk of GI bleeding
Women age 55-79 years	Aspirin recommended when potential benefit of reduction in ischemic stroke outweighs risk of GI bleeding
Men/women age >80 years	Insufficient evidence for primary prevention
Men age <45 years, women age <55 years	Aspirin not recommended for prevention of MI in men or stroke in women

GI = gastrointestinal; MI = myocardial infarction.

Adapted with permission from U.S. Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009 Mar 17;150(6):396-404. [PMID: 19293072]

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TABLE 2. Risk Level at Which CHD Events Prevented Exceed GI Harms in Patients Taking Daily Aspirin for Primary Prevention

Men		Women	
10-Year CHD Risk[a]		10-Year Stroke Risk[b]	
Age 45-59 years	≥4%	Age 55-59 years	≥3%
Age 60-69 years	≥9%	Age 60-69 years	≥8%
Age 70-79 years	≥12%	Age 70-79 years	≥11%

CHD = coronary heart disease; GI = gastrointestinal.

[a]Risk factors for CHD include age, diabetes mellitus, total cholesterol level, HDL cholesterol level, blood pressure, and smoking. CHD risk estimation tool: http://cvdrisk.nhlbi.nih.gov/calculator.asp. (Note: This is the Framingham risk score.)

[b]Risk factors for ischemic stroke include age, high blood pressure, diabetes mellitus, smoking, history of cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy.

NOTE: This table applies to adults who are not taking NSAIDs and who do not have upper GI pain or a history of GI ulcers.

Adapted with permission from U.S. Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009 Mar 17;150(6):396-404. [PMID: 19293072]

Diagnostic Testing in Cardiology

Clinical History and Physical Examination

The initial step in evaluating for heart disease is a thorough history and physical examination. Specifically, a careful exploration of changes in functional status, associated symptoms, and the timing and nature of symptoms will help focus the assessment and guide selection of appropriate testing, if indicated.

Cardiovascular testing provides both diagnostic and prognostic information and its use should be guided by symptoms, the level of risk for heart disease, and whether outcomes may be altered by interventions based on testing results.

Diagnostic Testing for Atherosclerotic Coronary Disease

Cardiac Stress Testing

Patients are referred for stress testing to establish the diagnosis of coronary artery disease (CAD) most often because of new onset of or a change in symptoms. The utility of stress testing should be interpreted in the context of the pretest likelihood of disease. Those with low probability of disease, such as younger patients, have a higher incidence of false-positive tests and may undergo unnecessary testing without changing patient outcomes. Those with a high probability of disease should proceed directly to an invasive diagnostic strategy, such as cardiac catheterization, because the risk of a false-negative result and missed diagnosis is too high. Furthermore, a negative test in a high-risk patient would not significantly change the post-test probability of CAD, and therefore would not change management. Stress testing is most clinically appropriate in patients with an intermediate risk of CAD. It is these patients who, by the result of their stress test, can be reclassified into higher or lower risk categories. Stress testing also has important prognostic value for predicting the risk of myocardial infarction and death in selected patients. For example, in patients with a previous history of CAD and worsening cardiac symptoms, stress testing is helpful to assess for possible recurrent or progressive disease. However, although the leading cause of death in patients with diabetes mellitus is cardiovascular disease, routine stress testing in asymptomatic patients with diabetes has not been shown to reduce mortality.

The modalities able to detect cardiac ischemia are highly dependent on the degree of impairment of coronary blood flow. The earliest changes with mild stenosis are perfusion changes detectable only with highly sensitive modalities, such as nuclear or cardiac magnetic resonance (CMR) imaging. With progressive coronary occlusion, diastolic dysfunction followed by systolic dysfunction may be seen by imaging studies such as echocardiography. Only when there is significant coronary stenosis will electrocardiographic (ECG) changes be seen and symptoms occur.

The many different types of tests to diagnose CAD can be broadly categorized as assessing either functional or anatomic evidence of ischemia. Functional studies evaluate for obstructive CAD from evidence of ECG changes, myocardial perfusion abnormalities, or wall motion abnormalities, usually under stress conditions. Anatomic studies assess percentage stenosis of the coronary vessels at rest, which can be visualized by single-photon emission CT (SPECT), PET/CT scan, or CMR imaging study. These imaging modalities may also be used to quantify infarction size and assess myocardial viability. More specific signs of ischemia such as reduced regional contractility can be assessed by echocardiography or MRI.

Testing modalities for suspected CAD are summarized in Table 3. In intermediate-risk patients who are able to exercise and have a normal baseline ECG, the initial type of stress testing should be exercise stress testing. The additional prognostic information available with exercise, including functional

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TABLE 3. Diagnostic Testing for Coronary Artery Disease

Diagnostic Test	Utility	Advantages	Limitations
Exercise Stress Testing			
Exercise ECG	Initial diagnostic test in most patients with suspected CAD	Data acquired on exercise capacity, blood pressure and heart rate response, and provoked symptoms	Not useful when baseline ECG is abnormal (LVH, LBBB, paced rhythm, WPW syndrome, >1 mm ST-segment depression)
Stress echocardiography	Recommended when baseline ECG is abnormal or when information on a particular area of myocardium at risk is needed	Exercise data acquired along with imaging for wall motion abnormalities to indicate ischemia Allows evaluation of valve function and pulmonary pressures Relatively portable and less costly than nuclear protocols Entire study is completed in <1 h	Image quality is suboptimal in some patients but can be improved with microbubble transpulmonary contrast Image interpretation is difficult when baseline wall motion abnormalities are present Diagnostic accuracy decreases with single-vessel disease or delayed stress image acquisition
Nuclear SPECT perfusion	Recommended when baseline ECG is abnormal or when information on a particular area of myocardium at risk is needed With LBBB, conduction delay in the septum may cause false-positive abnormality; this can be improved with the use of vasodilator stress	Gating (image acquisition coordinated with the cardiac cycle), use of higher energy agents such as technetium, and techniques used to correct for attenuation provide improved specificity Late reperfusion imaging allows evaluation of myocardial viability if thallium is used	Attenuation artifacts can be caused by breast tissue or diaphragm interference Radiation exposure
Pharmacologic Stress Testing			
Dobutamine echocardiography	Recommended in patients who cannot exercise Recommended when information on an area of myocardium at risk is needed	Because the patient is supine, images are acquired continuously, allowing the test to be stopped as soon as ischemia is evident	Dobutamine contraindications are severe baseline hypertension, unstable angina, and arrhythmias β-Blockers must be withheld before the test
Vasodilator nuclear perfusion (adenosine, dipyridamole, regadenoson)	Recommended in patients who cannot exercise May minimize septal abnormalities frequently seen with nuclear perfusion scanning in patients with LBBB	Vasodilator stress testing may minimize effect of β-blockade on perfusion defect size Can image sooner after myocardial infarction with vasodilator stress	Contraindications are bronchospastic airway disease, theophylline use, sick sinus syndrome, and high-degree AV block Caffeine must be withheld 24 hours before the test Adenosine or dipyridamole may cause chest pain, dyspnea, or flushing Radiation exposure
Dobutamine nuclear perfusion	Recommended in patients who cannot exercise and have contraindications to vasodilators Recommended when information on an area of myocardium at risk is needed	Has comparable sensitivity and specificity to exercise or vasodilator perfusion imaging for diagnosis of myocardial ischemia	Dobutamine contraindications are severe baseline hypertension, unstable angina, and arrhythmias β-Blockers should be withheld before the test Radiation exposure
PET/CT	Provides best perfusion images in larger patients Provides data on myocardial perfusion, function, and viability	Study duration is shorter and radiation dose is lower than conventional nuclear perfusion imaging Absolute myocardial blood flow can be measured Can be combined with CAC scoring	Not widely available More expensive than other imaging modalities Used with pharmacologic stress only (no exercise protocol) Radiation exposure

(Continued on the next page)

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TABLE 3. Diagnostic Testing for Coronary Artery Disease *(Continued)*

Diagnostic Test	Utility	Advantages	Limitations
Other Tests			
Coronary angiography	Provides anatomic diagnosis of the presence and severity of CAD	Percutaneous revascularization can be performed following diagnostic study	Invasive Risks of vascular access and radiocontrast exposure (kidney dysfunction, allergy, bleeding) Radiation exposure
CAC testing	CAC testing is reasonable in asymptomatic patients at intermediate risk for CAD	CAC scores are predictive of cardiovascular risk in selected patients	Does not provide data on coronary luminal narrowing Radiation exposure
Coronary CT angiography	Identifies anomalous coronary arteries Useful for selected patients with intermediate risk for CAD	Coronary artery vessel lumen and atherosclerotic lesions can be visualized in detail	Requires high-resolution (64-slice) CT instruments Does not provide detailed images of distal vessel anatomy Catheterization will be needed if intervention is planned Ability to quantify lesion severity can be limited by significant calcification Radiation and radiocontrast exposure
CMR imaging	Gadolinium-enhanced images identify viable and infarcted myocardium Identifies anomalous coronary arteries	Accurate test for myocardial viability	Some patients experience claustrophobia May be contraindicated in patients with pacemaker, ICD, or other implanted device Gadolinium is contraindicated in kidney failure Sinus rhythm and a slower heart rate are needed for improved image quality Limited availability and expertise

AV = atrioventricular; CAC = coronary artery calcium; CAD = coronary artery disease; CMR = cardiac magnetic resonance; ECG = electrocardiography; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; SPECT = single-photon emission CT; WPW = Wolff-Parkinson-White.

CONT.

capacity and heart rate and blood pressure response, can be utilized in prediction models such as the Duke treadmill score, which factors development of symptoms, degree of ST-segment depression, and exercise duration to provide incremental prognostic information for 5-year mortality risk. Heart rate recovery is another powerful predictor; patients with a heart rate drop of less than 12/min in the first minute after cessation of exercise have a higher mortality rate.

Ischemia is identified on the basis of the development of 1 mm or greater of horizontal or downsloping ST depression with exercise (**Figure 1**), but the coronary territory involved cannot be localized based on the ECG changes alone. Ideally, patients should exercise for 6 to 12 minutes to provide adequate time for development of maximal metabolic demand. Although achieving 85% of the age-predicted maximal heart rate (PMHR) is considered adequate for diagnosis of ischemia, as heart rate and blood pressure are the major determinants of myocardial oxygen demand, patients should continue to exercise until limited by symptoms. Achieving a rate pressure product (heart rate × systolic blood pressure) of at least 25,000 is also considered an adequate workload, as this measure reflects left ventricular myocardial performance. A standard Bruce protocol increases the speed and grade of the treadmill every 3 minutes, and patients who have poor functional capacity and cannot achieve at least the first stage of the Bruce protocol (5 metabolic equivalents [METs]) have significantly higher all-cause mortality. Stress tests should be terminated when the patient has exerted maximal effort and achieved at least 85% PMHR, the patient requests to stop or experiences significant anginal or other physical symptoms, or when other adverse markers develop, such as exertional hypotension, significant hypertension, ST-segment elevation or significant ST-segment depression, or ventricular or supraventricular arrhythmias.

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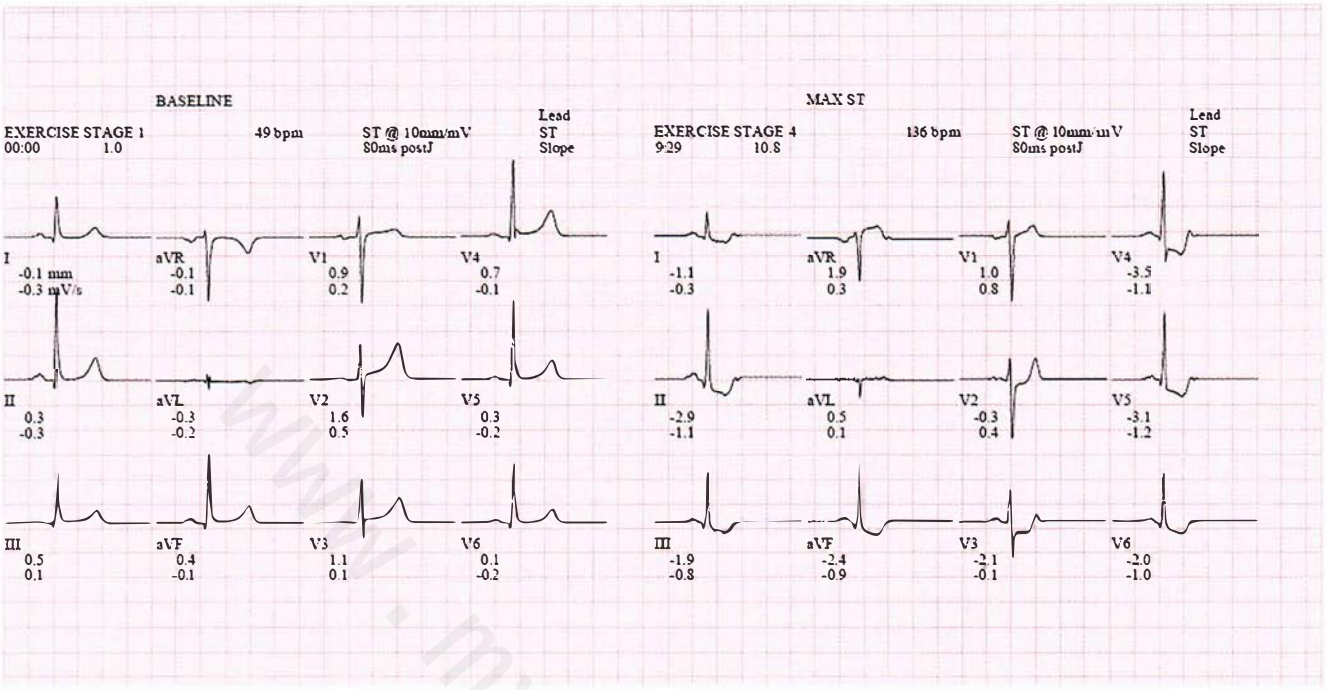

FIGURE 1. Electrocardiogram recorded during exercise stress testing. The presence of 2-mm downsloping ST-segment depressions in leads I, II, III, and aVF, and leads V_3 through V_6 indicates ischemia.

CONT.

The decision about whether to keep a patient on cardiac medications during stress testing should be individualized based on the clinical question being addressed. If the stress test is being performed to establish the diagnosis of CAD, medications such as β-blockers and nitrates should be withheld for at least 24 hours before the test. If the stress test is being performed to evaluate symptoms or to define prognosis in a patient with known disease, the patient should remain on current therapy to determine if ischemia is present on the current regimen.

There are several indications for stress testing with additional imaging with either echocardiography, CMR imaging, or perfusion imaging with SPECT or PET/CT. These include inability to exercise, baseline ECG abnormalities, and conditions in which exercise is contraindicated. Patients with abnormal baseline ECGs that interfere with the interpretation of the exercise ECG (for example, left bundle branch block [LBBB], left ventricular hypertrophy with ST-segment abnormalities, or a paced rhythm) should undergo stress imaging to identify obstructive CAD. In addition, stress testing with imaging may be helpful to elucidate a diagnosis in patients with indeterminate results on treadmill testing. Patients with right bundle branch block (RBBB), bifascicular block, or who are on digoxin can undergo exercise stress testing, but ST segments may be more difficult to interpret or may produce false-positive results. Patients with severe aortic stenosis, abdominal aortic aneurysm, severe hypertension, or uncontrolled arrhythmias should not exercise; rather, these patients should undergo pharmacologic stress testing with vasodilators. Patients who are unable to exercise should undergo pharmacologic stress testing with imaging. In addition, in patients with LBBB undergoing nuclear stress testing, a pharmacologic stressor should be used even if the patient is able to exercise because of the potential for a false-positive test owing to a septal perfusion abnormality that may occur with exercise. The choice of imaging modality should be based on local expertise and patient characteristics.

In stress testing with adjunctive imaging, baseline images are obtained and compared with images obtained after either exercise or pharmacologic stress (**Table 4**). Exercise invokes ischemia as the epicardial vessels become unable to maintain adequate flow related to myocardial oxygen demand via autoregulation, and ischemia develops distal to the obstruction. Dobutamine, like exercise, increases myocardial oxygen demand and elicits ischemia because of insufficient perfusion to the affected myocardium. Vasodilators, such as regadenoson or adenosine, produce hyperemia and a flow disparity between myocardium supplied by the stenotic vessel (in which the distal vasculature is already maximally dilated) as compared with the myocardium supplied by unobstructed vessels. In addition to identifying the presence of disease, perfusion imaging can define the location and extent of reduced perfusion and provide additional prognostic information compared with ECG stress testing alone. These imaging modalities may also be used to quantify infarction and assess myocardial viability. The additional information and impact on patient care obtained with imaging must be balanced with the additional costs, time, and exposure to radiation or contrast agents incurred.

Exercise stress echocardiography is performed with either supine ergometry or treadmill testing. Supine ergometry allows for continuous imaging during exercise, whereas with treadmill testing, images need to be obtained immediately after exercise, and any delay can reduce the accuracy of the information obtained. New regional wall motion abnormalities seen on

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TABLE 4. Interpretation of Stress Testing with Imaging

Stress SPECT		
At Rest	**After Stressor**	**Interpretation**
Normal	Normal	Normal, no ischemia
Normal	Perfusion defect	Normal function at rest, ischemia after stress
Perfusion defect	Perfusion defect	Infarct
Normal	LV dilation	Small or no distinct zone of ischemia, possible balanced ischemia or multivessel CAD
Stress Echocardiography		
At Rest	**After Stressor**	**Interpretation**
Normal	Normal	Normal, no ischemia
Normal	Wall motion abnormality	Normal function at rest, ischemia with stress
Abnormal	Abnormal	Infarct
Normal	LV dilation	Small or no distinct zone of ischemia, possible balanced ischemia or multivessel CAD

CAD = coronary artery disease; LV = left ventricle; SPECT = single-photon emission CT.

CONT.

the echocardiogram following exercise indicate areas of ischemia (see Table 4). Wall motion abnormalities at rest that do not change with exercise usually indicate infarction. Improvement in regional wall motion with low-dose exercise or dobutamine that worsens at higher levels suggests viable but hibernating myocardium. As with perfusion imaging, the extent of wall motion abnormalities provides prognostic information regarding risk of future cardiovascular events.

The sensitivity of stress echocardiography is reduced with single-vessel disease and is dependent on timely imaging. In addition, interpretation can be more subjective than with other modalities, particularly with baseline wall motion abnormalities or systolic dysfunction. A major advantage of stress echocardiography is the ability to obtain additional information, such as changes in pulmonary pressures or changes in valvular function with exercise. At minimum, stress echocardiography allows assessment of wall motion at rest and at peak or immediately following imaging to assess for obstructive CAD. If the examination is performed to assess dyspnea on exertion or valvular function with exercise, these should be specifically requested in order to be sure that adequate echocardiographic information is obtained. Routine transthoracic echocardiography (TTE) evaluates left and right ventricular size, thickness, and function; valvular morphology and function; diastolic function; and the pericardium. These are not necessarily routinely performed in a stress echocardiogram so if this information is clinically important, it may be necessary to obtain both a TTE and a stress echocardiogram. Dobutamine stress echocardiography is used for patients who cannot exercise and can be particularly useful for evaluation of myocardial viability (**Table 5**) and to evaluate aortic stenosis in patients with a low ejection fraction.

TABLE 5. Interpretation of Myocardial Viability Studies

SPECT Viability Testing		
Initial Study (at rest)	**Rest Study Repeated After 4-24 h (with thallium)**	**Interpretation**
Perfusion defect	Perfusion defect	Fixed defect: infarct, no viability
Perfusion defect	Reperfusion of area	Viable myocardium
PET Viability Testing		
Baseline	**Metabolism**	**Interpretation**
Perfusion defect	Metabolically active	Mismatch indicative of viable myocardium
Echocardiography Viability Testing		
Baseline	**Response to Dobutamine**	**Interpretation**
Wall motion abnormality	Low dose: improvement of function Higher dose: worsening of function	Biphasic response indicative of viable myocardium

SPECT = single-photon emission CT.

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CONT.

SPECT imaging takes advantage of the relative differences in blood flow with stress. Radioactive tracer is injected and taken up by the myocardium with blood flow. Images are obtained at rest. Then, with exercise or vasodilator stress, a second injection is given. Tracer is again distributed with blood flow and, therefore, less tracer is taken up in the left ventricular region supplied by a stenotic vessel. This relative difference in flow between stress and rest tomographic images is seen as a perfusion defect and is indicative of CAD (**Figure 2**). Most commonly, technetium-based radiotracers are used. These have a higher energy and provide good image quality. This is particularly useful when there is potential for soft-tissue attenuation that can interfere with interpretation, such as with breast attenuation in women. Thallium is a potassium analogue and can only be taken up by active myocytes. Like technetium, thallium can be used for myocardial perfusion imaging, but because it requires active metabolism, thallium also can be used to assess viability. Myocytes that on initial stress testing appear to be infarcted may slowly take up thallium tracer, identifying them as viable. The benefits of thallium are balanced against higher radiation exposure because of its long half-life.

Myocardial perfusion imaging can quantify the extent and severity of disease and help direct treatment strategies. High-risk features that may be seen on myocardial perfusion imaging include lack of augmentation of post-stress ejection fraction, cavity dilatation, and new wall motion abnormalities. Unlike stress echocardiography, images are not obtained immediately post stress and are often delayed. If there is evidence of a new wall motion abnormality in these delayed images, it signifies a high degree of stenosis.

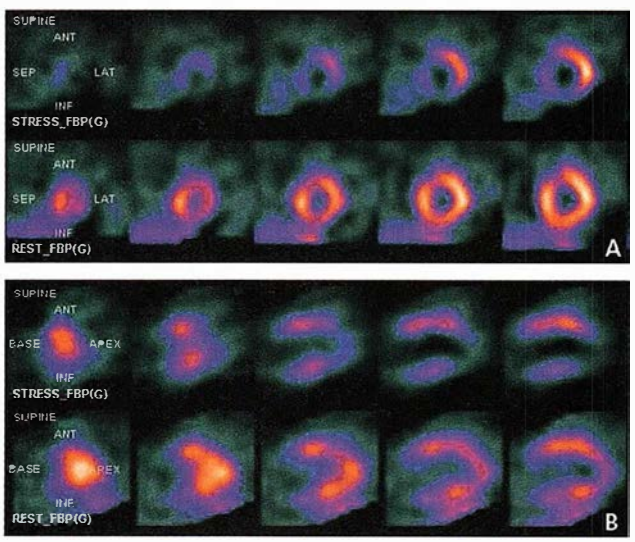

FIGURE 2. Selected images from a nuclear perfusion single-photon emission CT (SPECT) stress study. Short axis views (*panel A*) of the heart with stress (*top row*) and at rest (*bottom row*) show a radiotracer defect in the septum and inferior wall that is filled on the rest images. Long axis views (*panel B*) demonstrate an apical filling defect with stress (*top row*) that is perfused on rest images (*bottom row*).

Like SPECT imaging, cardiac PET can be used to detect ischemia. PET imaging provides improved diagnostic accuracy compared with SPECT and can be particularly useful in patients with nondiagnostic imaging stress tests, obese patients, and patients with diabetes mellitus. Cardiac PET also allows for assessment of peak stress ejection fraction, quantitation of myocardial blood flow, and evaluation of myocardial metabolism. Because some PET radiotracers identify metabolically active myocytes, it is an excellent tool to evaluate for viability. Because cardiac PET uses CT for attenuation correction, limited anatomic information about coronary calcification is also obtained. Because of the short half-life of PET radiotracers, all studies must be performed with vasodilators. The utility of PET/CT scanning is limited by its availability.

CMR imaging can be used for evaluation of myocardial and pericardial disease processes and can be particularly useful for evaluation of infiltrative and inflammatory diseases. It can be utilized to detect the extent and severity of myocardial infarction and viability. Because CMR imaging can be gated, measures of right and left ventricular function can be obtained. Although not widely performed, stress testing with dobutamine to assess wall motion and vasodilators such as adenosine to assess perfusion can be used with CMR imaging to detect ischemia. Limitations of the use of CMR imaging include the length of time needed to acquire images and magnetic interference with cardiac implanted electronic devices.

KEY POINTS

- Stress testing is most efficacious in patients with an intermediate pretest probability of coronary artery disease, because it is these patients who, by the result of their stress test, can be reclassified into higher or lower risk categories. **HVC**
- In patients who are able to exercise and have a normal baseline electrocardiogram, the initial type of stress testing should be exercise stress testing. **HVC**
- Patients with abnormal baseline electrocardiograms (ECGs) that interfere with the interpretation of the exercise ECG (for example, left bundle branch block, left ventricular hypertrophy with ST-segment abnormalities, or a paced rhythm) should undergo stress imaging to identify obstructive coronary artery disease.

Visualization of the Coronary Anatomy

Coronary angiography and coronary CT angiography (CTA) provide anatomic information regarding the coronary vessels (**Figure 3**). Both procedures require iodinated contrast and expose the patient to radiation. Coronary angiography provides a two-dimensional image of the lumen of the vessel filled with contrast. Assessment of the stenotic lesions is made from multiple views of the vessel. Coronary CTA can provide additional information about some of the characteristics of the plaque. If, however, culprit lesions are visualized on coronary CTA, the patient typically requires coronary angiography for

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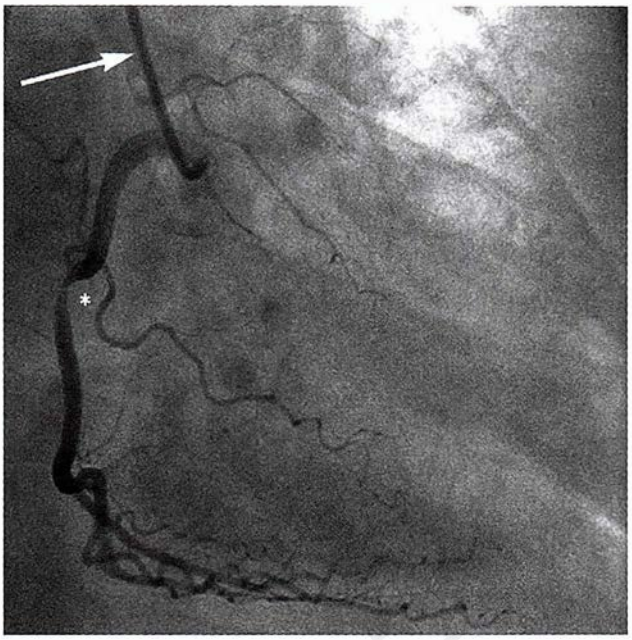

FIGURE 3. Coronary angiogram. Radiocontrast dye is injected via catheter (*arrow*) during coronary angiography, demonstrating 85% to 90% occlusion of the mid right coronary artery (*asterisk*).

CONT.

better definition of the degree of coronary stenosis. Coronary angiography is also required if coronary revascularization is to be performed. If percutaneous coronary intervention is indicated, it may be performed at the time of a patient's diagnostic catheterization. Coronary angiography may be useful as a diagnostic test in patients who, despite maximal medical therapy, have intolerable ischemic symptoms as long as they are candidates for coronary revascularization. Coronary CTA may be used to rule out CAD in symptomatic patients with an intermediate risk of coronary disease. Other limitations of coronary CTA include poor visualization of distal vessels and artifact from calcification that may limit interpretation.

Suspected coronary anomalies, such as anomalous coronary origins, can be evaluated by coronary CTA, CMR imaging, or coronary angiography. These imaging modalities can help identify those abnormalities that are associated with a higher risk of sudden cardiac death.

Coronary Artery Calcium Scoring

Coronary artery calcium (CAC) scoring provides information regarding the burden of atherosclerotic disease but does not provide information regarding the degree of obstruction it may be causing. CAC scoring can be performed with either electron beam or multi-detector CT, and newer technologic advances limit radiation exposure to the patient. It detects the presence of calcification in the walls of the coronary arteries, which is directly proportional to the degree of plaque burden present. CAC scores are categorized as follows: 0, no disease; 1-99, mild disease; 100-399, moderate disease; and above 400, severe disease. Coronary calcium scores greater than 400 are associated with a higher incidence of abnormal perfusion on SPECT imaging. Because of its cost and associated radiation exposure, measurement of coronary artery calcium should be limited to a select group of asymptomatic patients with an intermediate Framingham risk score (10%-20%) in whom results will influence treatment strategy. CAC scoring may be useful particularly if the results will influence treatment strategy, such as initiation of lipid-lowering therapy.

KEY POINT

- Measurement of coronary artery calcium should be limited to a select group of asymptomatic patients with an intermediate Framingham risk score (10%-20%) in whom results will influence treatment strategy because of its associated cost and radiation exposure. HVC

Risks of Coronary Diagnostic Testing

In addition to the physical and societal costs of downstream testing that result from inappropriate testing, each of the modalities used for diagnosis and risk stratification carry specific risks. It is important to determine the pretest probability of disease and to focus additional testing appropriately. For example, ordering an exercise stress test in a patient with a low pretest probability of disease may result in a false-positive stress test and additional downstream testing. Obtaining a CAC score in a low-risk patient may lead to additional tests or procedures for an incidental finding on CT.

Exercise testing is associated with a small risk of myocardial infarction or death (1/2500 tests). Exercise stress testing is contraindicated in patients with unstable cardiac conditions, such as uncontrolled cardiac arrhythmias, severe symptomatic aortic stenosis, uncontrolled heart failure, and unstable angina. Pharmacologic stress agents, including dipyridamole, adenosine, and regadenoson, are associated with development of high-degree atrioventricular block and bronchospasm.

Nuclear stress testing, CAC scoring, coronary CTA, and coronary angiography expose the patient to radiation. The amount of exposure is dependent on factors such as the radiotracer used, equipment, operator technique, complexity of procedure performed, and patient characteristics (such as body size).

Various contrast agents are used for CMR imaging (gadolinium), echocardiography (microbubble contrast agents used for enhancement of endocardial borders), coronary CTA, and coronary angiography (nonionic contrast). Nonionic contrast may be associated with hypersensitivity reactions and acute kidney injury whereas gadolinium is associated with the development of nephrogenic fibrosing dermatopathy in patients with chronic kidney disease.

Cardiac catheterization can result in complications from vascular access, injury to the coronary arteries, dissection of the aorta, or disruption of plaque resulting in peripheral emboli and possible stroke. Vascular access complications include retroperitoneal hematoma from bleeding at the groin access site as well as pseudoaneurysm at the arterial puncture

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CONT. site. Both of these complications require prompt recognition and treatment.

Diagnostic Testing for Structural Heart Disease

Diagnostic testing for structural heart disease should be based on a thorough history and physical examination. New murmurs or a change in examination findings or symptoms in a patient with known structural heart disease should prompt further evaluation. Routine yearly imaging evaluation of structural heart disease in asymptomatic patients is usually not indicated. Benign murmurs, such as grade 1/6 or 2/6 midsystolic murmurs, are common with pregnancy, anemia, and other high-flow states, and do not routinely need echocardiographic evaluation.

Imaging modalities used to evaluate structural heart disease are listed in **Table 6**. Evaluation of structural heart disease typically begins with a TTE. TTE provides information about left and right ventricular cavity size, thickness, and function, as well as quantitative information regarding valvular function, diastolic function, and filling pressures. TTE can be used with intravenous agitated saline contrast, normally cleared by the pulmonary circulation, to document the presence of an intracardiac shunt or a patent foramen ovale. Atrial septal defect is suggested by shunting of microbubbles from the right atrium to the left atrium. TTE is a noninvasive procedure and is the preferred imaging modality for evaluating anterior structures of the heart, such as the aortic valve.

Transesophageal echocardiography (TEE) takes advantage of the proximity of the heart to the esophagus for better image quality. The procedure requires sedation and is contraindicated in patients with esophageal strictures or active esophageal varices or bleeding. Complications include esophageal injury and bleeding. TEE is commonly used to evaluate for endocarditis in patients with a high pretest probability; to assess for diagnostic findings or complications of endocarditis (such as abscess); to better visualize valvular pathology, particularly when planning repair; to evaluate specific structures that cannot be well visualized on TTE (such as prosthetic heart valves); to evaluate acute aortic pathologies; and to rule out left atrial thrombus prior to cardioversion (**Figure 4**).

KEY POINTS

HVC
- Routine yearly imaging evaluation of structural heart disease in asymptomatic patients is usually not indicated; benign murmurs, such as grade 1/6 or 2/6 midsystolic murmurs, are common with pregnancy, anemia, and other high-flow states and do not routinely need echocardiographic evaluation.
- Evaluation of structural heart disease typically begins with transthoracic echocardiography, which provides information about ventricular cavity size, thickness, and function, as well as quantitative information regarding valvular function, diastolic function, and filling pressures.

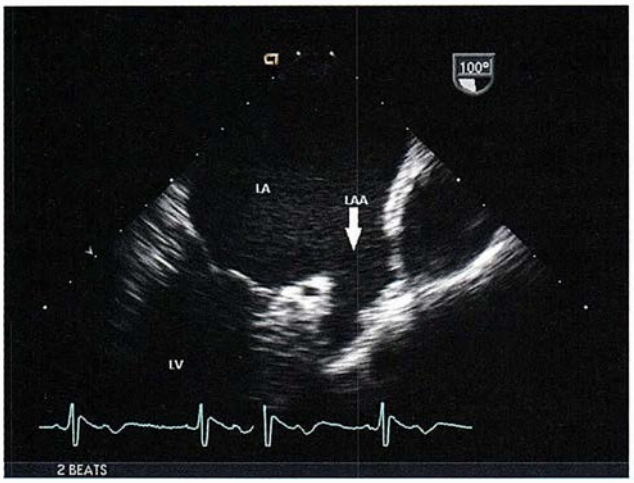

FIGURE 4. Transesophageal echocardiogram. The transducer is posterior to the heart, and the left atrium (*LA*) and left atrial appendage (*LAA, arrow*) are more easily seen than with transthoracic echocardiography, showing absence of thrombus in the appendage. LV = left ventricle.

Diagnostic Testing for Cardiac Arrhythmias

In addition to a careful history and physical examination, the evaluation of a patient with a history of palpitations, presyncope, or syncope in which an arrhythmia is suspected begins with a 12-lead resting ECG. Evidence of preexcitation, ectopic rhythms, atrioventricular block, or intraventricular conduction delay may give insight into the etiology of the symptoms. In patients in whom the presence of structural heart disease is suspected, echocardiography may also be indicated. Because of the intermittent nature of arrhythmias, their diagnosis and documentation can be challenging. Monitoring and diagnostic strategies are based on the frequency of the patient's episodes (**Table 7**, on page 14). Patients with daily symptoms can be evaluated with a 24- or 48-hour ambulatory ECG monitor (Holter monitor), whereas patients with less frequent episodes require other monitoring strategies. For infrequent symptomatic events, an external patient-triggered event recorder can capture the arrhythmia, provided the event lasts long enough for the patient to record it. A looping event recorder captures several seconds of the ECG signal prior to the device being triggered and is useful when episodes are accompanied by syncope or presyncope. For very infrequent events, an implanted loop recorder may be warranted.

Exercise testing is also frequently employed in patients with a suspected or known arrhythmia. Treadmill exercise testing is an important tool for evaluating chronotropic response, ischemia, and exercise-induced or adrenergically induced arrhythmia.

Once a patient is diagnosed with an arrhythmia or arrhythmia-prone cardiovascular condition, diagnostic electrophysiology testing can be helpful for both risk stratification and treatment (such as catheter ablation). Selection of these diagnostic tests is dependent upon the particular patient and the diagnostic concerns, and most patients with arrhythmias do not require an electrophysiology study.

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TABLE 6. Diagnostic Testing for Structural Heart Disease

Diagnostic Test	Major Indications	Advantages	Limitations
Transthoracic echocardiography	Heart failure Cardiomyopathy Valve disease Congenital heart disease Pulmonary hypertension Aortic disease Pericardial disease	Accurate diagnosis of presence and severity of structural heart disease Quantitation of LV size and function, pulmonary pressures, valve function, and intracardiac shunts Widely available, portable, fast	Operator-dependent data acquisition. Interpretation requires expertise. Variability in instrumentation Image quality limits diagnosis in some patients, may require microbubble contrast agents
Transesophageal echocardiography	Endocarditis Prosthetic valve dysfunction Aortic disease Left atrial thrombus	High-quality images, especially of posterior cardiac structures Most accurate test for endocarditis evaluation, prosthetic valves, and left atrial thrombus	Requires esophageal intubation, typically with conscious sedation
Three-dimensional echocardiography	Mitral valve disease ASD (percutaneous ASD closure)	Improved tomographic imaging Used during cardiac procedures for device placement Improved assessment of LV global/regional systolic function	Adjunct to two-dimensional imaging Limited availability and expertise
Radionuclide angiography (MUGA)	Evaluation of LV systolic function	Quantitative EF measurements Accurate for serial LVEF measurements with cardiotoxic drugs	Radiation exposure No data on other cardiac structures
Cardiac catheterization (left and right)	Congenital heart disease Coronary artery disease Valve assessment Shunt assessment	Direct measurement of intracardiac pressures, gradients, and shunts Contrast angiography provides visualization of complex cardiac anatomy Allows percutaneous intervention for structural heart disease	Invasive Radiation and radiocontrast exposure Images not tomographic, limiting evaluation of complex three-dimensional anatomy
Coronary CT angiography	Coronary artery disease Congenital heart disease	Visualization of complex cardiac anatomy High-resolution tomographic images	Invasive Radiation and radiocontrast exposure Image acquisition improved with sinus rhythm and slower heart rate
CMR imaging	Congenital heart disease Aortic disease Myocardial disease (infiltrative disease, myocarditis, hypertrophic cardiomyopathy) RV cardiomyopathy (ARVC) Quantitation of LV mass and function	High-resolution tomographic imaging and blood-flow data Quantitative RV volumes and EF No ionizing radiation or contrast Enables three-dimensional reconstruction of aortic and coronary anatomy	Limited availability and expertise Some patients experience claustrophobia May be contraindicated in patients with pacemaker, ICD, or other implanted devices Gadolinium is contraindicated in kidney failure Sinus rhythm and slower heart rate are needed for improved image quality
Chest CT	Aortic disease Coronary disease Cardiac masses Pericardial disease	High-resolution tomographic images Enables three-dimensional reconstruction of vascular structures	Radiation and radiocontrast exposure

ARVC = arrhythmogenic right ventricular cardiomyopathy; ASD = atrial septal defect; CMR = cardiac magnetic resonance; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LV = left ventricle; LVEF = left ventricular ejection fraction; MUGA = multi-gated acquisition; RV = right ventricle.

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TABLE 7. Diagnostic Tests for Suspected or Known Cardiac Arrhythmias

Diagnostic Test	Utility	Advantages	Limitations
Resting ECG	Initial diagnostic test in all patients	12-lead ECG recorded during the arrhythmia often identifies the specific arrhythmia	Most arrhythmias are intermittent and not recorded on a resting ECG
Ambulatory ECG (Holter monitor)	Frequent (at least daily) asymptomatic or symptomatic arrhythmias	Records every heart beat during a 24- or 48-hour period for later analysis Patient log allows correlation with symptoms	Not helpful when arrhythmia occurs less frequently ECG leads limit patient activities
Exercise ECG	Arrhythmias provoked by exercise	Allows diagnosis of exercise-related arrhythmias Allows assessment of impact of arrhythmia on blood pressure	Physician supervision needed in case a serious arrhythmia occurs Most arrhythmias are not exercise related
Patient-triggered event recorder	Infrequent symptomatic arrhythmias that last more than 1-2 minutes	Small, pocket-sized recorder is held to the chest when symptoms are present Recorded data are transmitted to central monitoring service	Only useful for symptomatic arrhythmias that persist long enough for patient to activate the device Arrhythmia onset not recorded Not useful for syncope or extremely brief arrhythmias
Looping event recorder (wearable)	Infrequent symptomatic brief arrhythmias Syncope	Continuous ECG signal is recorded with the previous 30 seconds to 2 minutes saved when the patient activates the recording mode Arrhythmia onset is recorded	ECG leads limit patient activities Device records only when activated by patient
Implantable loop recorder	Very infrequent asymptomatic or symptomatic arrhythmias	Long-term continuous ECG monitoring with patient-triggered or heart rate-triggered episode storage Specific heart rate or QRS parameters can be set to initiate recording of data	Invasive procedure with minor risks Device must be explanted later
Mobile cardiac outpatient telemetry	Continuous outpatient ECG recording for precise quantification or capture of rare arrhythmia	Auto-triggered and patient-triggered capture of arrhythmia events Up to 96 hours of retrievable memory	ECG leads limit patient activities Resource intensive
Electrophysiology study	Used for both inducing, identifying, and clarifying mechanism of arrhythmia as well as potential treatment (catheter ablation)	The origin and mechanism of an arrhythmia can be precisely defined	Invasive procedure with some risk Some arrhythmias may not be inducible, particularly if the patient is sedated

ECG = electrocardiogram.

KEY POINT

- Patients with a suspected arrhythmia who experience daily symptoms can be evaluated with a 24- or 48-hour ambulatory electrocardiographic monitor (Holter monitor), whereas patients with less frequent episodes require other monitoring strategies, including various types of longer-term event recorders.

Coronary Artery Disease

Stable Angina Pectoris

Diagnosis and Evaluation

The most common manifestation of coronary artery disease (CAD) is stable angina pectoris: chest pain, pressure, or discomfort that develops with exertion and is relieved with rest.

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Symptoms often occur when the burden of atheromatous plaque results in fixed coronary stenosis and limitation of blood flow, leading to an imbalance between myocardial oxygen supply and demand. When patients with cardiovascular risk factors present with chest pain, the location of the pain, quality of symptoms (sharp/dull, transient/persistent, occurring at rest/with exertion), and the age and sex of the patient can help to differentiate stable angina pectoris from other causes of chest pain, such as gastrointestinal, musculoskeletal, or pulmonary causes. These factors are also used to determine a patient's pretest likelihood of CAD (**Table 8**).

The decision to perform exercise or pharmacologic stress testing or coronary CT angiography (CTA) is based on the pretest likelihood of CAD, the patient's baseline electrocardiogram (ECG), the patient's ability to exercise, and the patient's comorbid illnesses, such as asthma or emphysema, that would limit pharmacologic testing (**Figure 5**).The selection of tests for evaluating patients with chest pain is discussed in Diagnostic Testing in Cardiology. Stress testing is most useful in patients at intermediate pretest likelihood of CAD (10% to 90%). In patients with low pretest probability, a normal test result only confirms that the patient is low risk, and an abnormal stress test result is most likely a false-positive, possibly leading to more testing (additional stress testing or invasive angiography). In patients with a high pretest likelihood, the use of stress testing for diagnostic purposes is not indicated, as an abnormal test result only confirms the presence of disease and a normal test result is most likely to indicate a false-negative result.

Stress testing in patients with high pretest likelihood can be used to obtain prognostic information, but the results should not affect the initiation of optimal medical therapy. In patients who have been started on medical therapy for CAD, stress testing can be used to determine a patient's response to optimal medical therapy, measure exercise capacity, and evaluate the extent and severity of ischemia.

The development of coronary CTA is an emerging alternative to stress testing, but coronary CTA does not provide important functional information, such as extent of ischemia, reproduction of symptoms, or exercise capacity. Coronary CTA is useful for diagnostic purposes in patients at intermediate risk for CAD if stress testing is contraindicated or revascularization is unlikely to be performed or change management.

The use of invasive coronary angiography in patients with stable angina pectoris is generally limited to those with persistent or progressive life-limiting symptoms while on optimal medical therapy or those with high-risk criteria on noninvasive stress testing or coronary CTA (see Figure 5).

KEY POINTS

- When patients with cardiovascular risk factors present with chest pain, the quality of symptoms, the age, and the sex of the patient can help to differentiate stable angina pectoris from other causes of chest pain.
- Stress testing is most useful in patients at intermediate pretest likelihood of coronary artery disease (10% to 90%).

HVC

General Approach to Treatment of Stable Angina Pectoris

All patients with ischemic heart disease should be counseled on the importance of risk factor modification, including lifestyle changes, such as smoking cessation, weight management, daily physical activity, and diet modification; as well as control of modifiable risk factors, such as diabetes mellitus, hypertension, and hyperlipidemia. Medical therapy should be initiated in all patients with ischemic heart disease. The combination of risk factor modification and medical therapy is

TABLE 8. Pretest Likelihoods of Coronary Artery Disease in Low-Risk and High-Risk Symptomatic Patients

	Pretest Likelihood					
	Nonanginal Chest Pain[a]		Atypical Angina[b]		Typical Angina[c]	
Age (y)	Men	Women	Men	Women	Men	Women
35	3-35	1-19	8-59	2-39	30-88	10-78
45	9-47	2-22	21-70	5-43	51-92	20-79
55	23-59	4-25	45-79	10-47	80-95	38-82
65	49-69	9-29	71-86	20-51	93-97	56-84

[a]Nonanginal chest pain has one or none of the components for typical chest pain.

[b]Atypical angina has two of the three components for typical angina.

[c]Typical angina has three components: (1) substernal chest pain or discomfort, (2) provoked by exertion or emotional stress, (3) relieved by rest and/or nitroglycerin.

NOTE: Each value represents the percentage with significant coronary artery disease. The first is the percentage for a low-risk, mid-decade patient without diabetes mellitus, smoking, or hyperlipidemia. The second is that of the same-age patient with diabetes mellitus, smoking, and hyperlipidemia. Both high- and low-risk patients have normal results on resting electrocardiography. If ST-T wave changes or Q waves had been present, the likelihood of coronary artery disease would be higher in each entry of the table.

Adapted with permission of Elsevier Science and Technology Journals, from Gibbons RJ, Abrams J, Chatterjee K. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina--summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). J Am Coll Cardiol. 2003 Jan 1;41(1):1S9-68. [PMID: 12S70960]; permission conveyed through Copyright Clearance Center, Inc.

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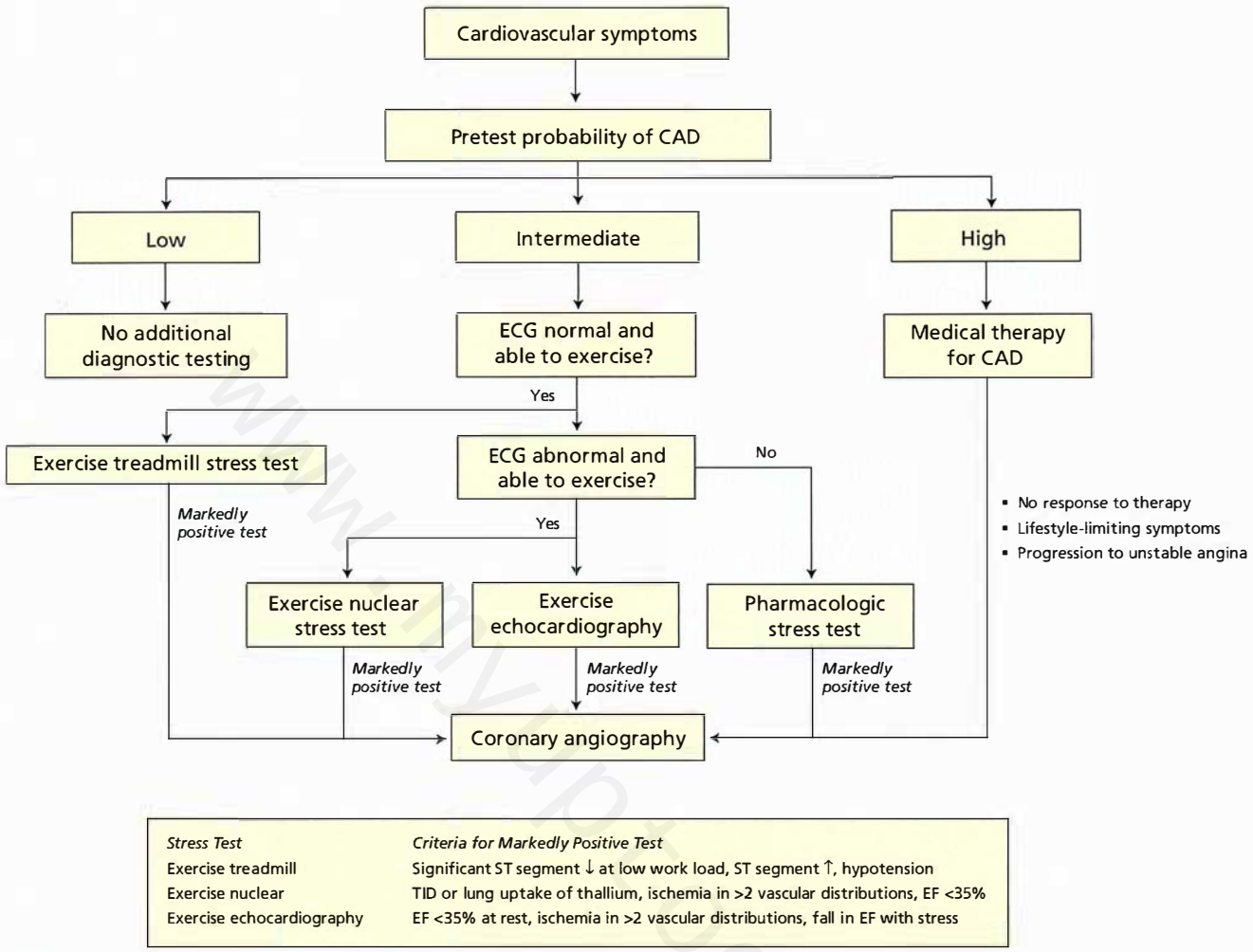

Stress Test	*Criteria for Markedly Positive Test*
Exercise treadmill	Significant ST segment ↓ at low work load, ST segment ↑, hypotension
Exercise nuclear	TID or lung uptake of thallium, ischemia in >2 vascular distributions, EF <35%
Exercise echocardiography	EF <35% at rest, ischemia in >2 vascular distributions, fall in EF with stress

FIGURE 5. Diagnosis of coronary artery disease. CAD = coronary artery disease; ECG = electrocardiogram; EF = ejection fraction; TID = transient ischemic dilation.

referred to as guideline-directed medical therapy (**Figure 6**). Medical therapy is divided into two categories: cardioprotective medications and antianginal medications. Cardioprotective medications improve survival, reduce the occurrence of cardiovascular events, and reduce the progression of systemic atherosclerosis. Antianginal medications vasodilate the coronary vasculature or decrease myocardial oxygen demand, thus reducing the frequency and severity of angina pectoris and improving quality of life.

Cardioprotective Medications

The use of aspirin is associated with a decreased risk of myocardial infarction, stroke, and cardiovascular death in patients with CAD. Aspirin doses of 81 mg to 162 mg daily are recommended in all patients with established CAD unless contraindicated. In patients allergic to aspirin, clopidogrel is recommended as an alternative. The use of newer antiplatelet agents (prasugrel, ticagrelor) as monotherapy has not been tested in patients with stable angina pectoris. Dual antiplatelet therapy (aspirin plus either clopidogrel, prasugrel, or ticagrelor) is currently recommended only following percutaneous coronary intervention (PCI) or an acute coronary event.

Owing to the protective effects of β-blockers, these agents are considered first-line therapy in patients with stable angina pectoris. Dose titration of β-blockers is recommended until the resting heart rate is between 55/min and 60/min. β-Blockers have been associated with fatigue, reduced exercise capacity, symptomatic bradycardia, mood disturbance (depression), and erectile dysfunction. β-Blockers are contraindicated in patients with symptomatic bradycardia, high-grade atrioventricular block, acute decompensated heart failure, and severe reactive airways disease.

ACE inhibitors are indicated in the treatment of patients with stable angina pectoris to reduce cardiovascular and all-cause mortality. This effect on mortality is more profound in patients with concomitant diabetes mellitus and left ventricular systolic dysfunction. Additionally, ACE inhibitors are indicated in patients with concomitant systemic hypertension and proteinuric chronic kidney disease. ACE inhibitors are contraindicated in pregnant women and caution is

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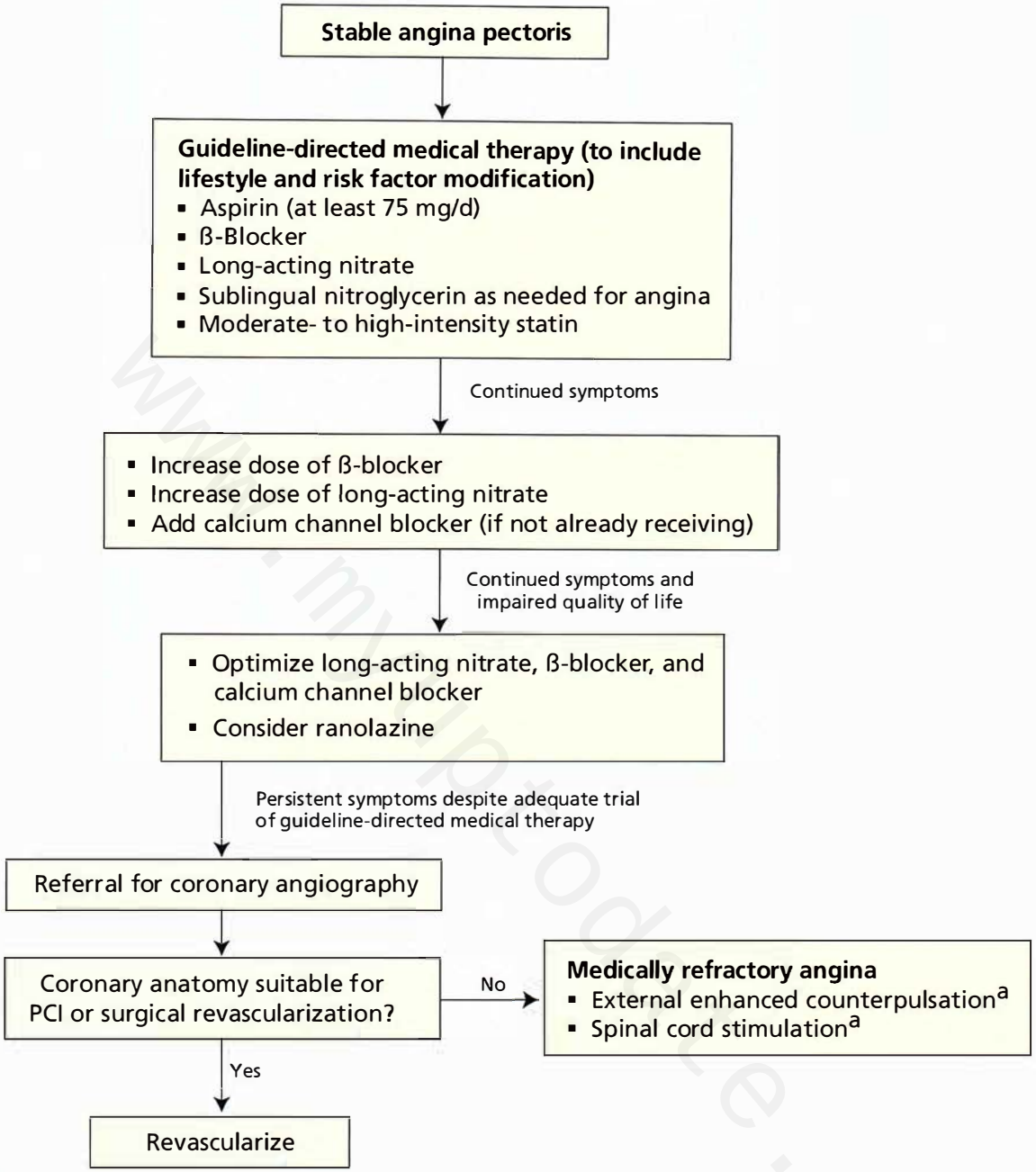

FIGURE 6. Management of stable angina pectoris. PCI = percutaneous coronary intervention.

[a]Not recommended by current guidelines.

Recommendations based on Qaseem A, Fihn SD, Dallas P, Williams S, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Management of stable ischemic heart disease: summary of a clinical practice guideline from the American College of Physicians/American College of Cardiology Foundation/American Heart Association/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons. Ann Intern Med. 2012 Nov 20;157(10):735-43. [PMID: 23165665]

advised in patients with advanced chronic kidney disease. Angiotensin receptor blockers are considered acceptable alternatives in patients who are allergic to or intolerant of ACE inhibitors.

Statins have been shown to reduce the risk of myocardial infarction and death in patients with chronic ischemic heart disease by 25% to 30%. The reduction in cardiovascular events is proportional to the degree of LDL cholesterol reduction; however, statins have been proved to be beneficial in patients regardless of cholesterol level. New cholesterol management guidelines recommend the use of moderate- to high-intensity statins for all patients with (1) LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or greater; (2) diabetes mellitus; or (3) greater than 7.5% estimated 10-year risk of atherosclerotic

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cardiovascular disease (ASCVD). Management of statin therapy is discussed in MKSAP 17 General Internal Medicine.

According to Advisory Committee on Immunization Practices (ACIP) guidelines, all persons aged 6 months or older should have an annual influenza vaccination. In addition, patients at risk for cardiovascular disease warrant influenza vaccination as a preventive measure for cardiovascular disease.

The use of selenium, chromium, β-carotene, vitamin C, vitamin E, and estrogen has not been associated with improved cardiovascular outcomes and is not recommended in patients with ischemic heart disease.

Antianginal Medications

Medications to reduce the frequency and severity of angina pectoris comprise β-blockers, nitrates, calcium channel blockers, and ranolazine.

β-Blockers and nitrates are first-line antianginal agents. In addition to their cardioprotective effects, β-blockers improve angina pectoris by reducing heart rate, myocardial contractility, and blood pressure, resulting in reduced myocardial oxygen demand. Nitrates improve myocardial oxygen supply and reduce myocardial oxygen demand by their effects on coronary and systemic vasodilation, respectively. Nitrates have not been proved to reduce the frequency of cardiovascular events (myocardial infarction, death). Two categories of nitrates are indicated for patients with stable angina pectoris: sublingual or spray nitroglycerin (for emergency use) and topical or oral nitroglycerin (for chronic, daily use). The use of daily nitrates requires periodic nitrate-free intervals (typically at night) to avoid the development of tolerance. The most frequent adverse effect of nitrates is headache. The use of either short- or long-acting nitrates is contraindicated in patients who take phosphodiesterase 5 (PDE-5) inhibitors for erectile dysfunction (sildenafil, vardenafil, tadalafil) owing to the potentiation of hypotension when these drugs are used together.

Calcium channel blockers are second-line therapy in patients with stable angina pectoris who are intolerant of β-blockers or who have continued symptoms on β-blockers and nitrates. All calcium channel blockers cause systemic and coronary vasodilation, and nondihydropyridine calcium channel blockers (diltiazem, verapamil) reduce the heart rate. Because of their vasodilatory properties, calcium channel blockers are first-line agents for the management of patients with Prinzmetal (variant) angina pectoris. The most common adverse effects of calcium channel blockers are peripheral edema, dizziness, constipation, and bradycardia. Calcium channel blockers are contraindicated in patients with left ventricular systolic dysfunction or advanced atrioventricular block.

Ranolazine is a selective inhibitor of the late inward sodium channel in the myocardium. It is generally reserved for patients who remain symptomatic with the use of β-blockers, nitrates, and calcium channel blockers. Ranolazine is an effective antianginal medication; however, its use is limited by cost and adverse effects such as dizziness, headache, nausea, and constipation. Ranolazine should be used with caution in patients with advanced kidney or liver disease and in those taking medications that are potent inhibitors of the CYP3A4 pathway. Examples of strong inhibitors of the CYP3A4 pathway include ketoconazole, clarithromycin, tacrolimus, and cyclosporine.

KEY POINTS

- Aspirin or clopidogrel (if aspirin-allergic) is recommended in all patients with established coronary artery disease unless contraindicated; the use of newer antiplatelet agents (prasugrel, ticagrelor) as monotherapy has not been tested in patients with stable angina pectoris.
- All patients with stable angina pectoris should receive a statin and a β-blocker.
- ACE inhibitors are indicated in the treatment of stable angina pectoris, particularly in patients with concomitant diabetes mellitus and left ventricular systolic dysfunction.

Coronary Revascularization

Decision to Revascularize

In patients with stable angina pectoris whose symptoms are not improved with optimal medical therapy, invasive angiography is warranted to define coronary artery anatomy and prepare for revascularization via PCI or coronary artery bypass graft surgery (CABG). All patients should be counseled on the risks, benefits, and alternatives to angiography and revascularization before diagnostic angiography is pursued.

In patients found to have significant CAD on angiography that would benefit from revascularization, multiple factors are considered in deciding which technique (PCI or CABG) would be best for the patient. These include the degree of left ventricular systolic dysfunction, whether the patient has had a prior CABG, and the patient's ability to adhere to a medication treatment regimen. The SYNTAX score is an anatomic scoring system based on the results of angiography that quantifies lesion complexity in patients with multi-vessel and/or left main coronary artery disease and is useful in helping predict the outcome of different revascularization strategies. The development of appropriate use criteria (AUC), a collection of clinical scenarios that mimic frequently encountered patient presentations, has assisted clinicians in making treatment decisions for patients with all forms of ischemic heart disease.

Percutaneous Coronary Intervention

PCI has not been shown to be superior to optimal medical therapy in patients with stable angina pectoris for reduction of cardiovascular endpoints such as mortality and myocardial infarction. However, PCI has been associated with improvement in quality of life by reducing the severity and frequency of angina. Current guidelines recommend that diagnostic angiography and PCI be reserved for patients with refractory symptoms while on optimal medical therapy, those who are unable to tolerate optimal medical therapy owing to side

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effects, or those with high-risk features on noninvasive exercise and imaging tests.

Coronary Artery Bypass Graft Surgery

The use of CABG in patients with stable angina is generally indicated only for those who remain symptomatic with optimal medical therapy and have specific angiographic findings (either left main disease or multivessel disease with involvement of the proximal left anterior descending artery), concomitant reduced systolic function, or diabetes mellitus. CABG is typically performed via median sternotomy incision and institution of cardiopulmonary bypass; however, recent advances with off-pump CABG allow patients to avoid the need for cardiopulmonary bypass. Off-pump CABG is associated with adverse event and graft patency rates similar to traditional CABG. This less invasive procedure may be more suitable for patients with significant comorbid medical conditions as it may reduce operative risk and shorten hospital and recovery times, but definitive proof is lacking.

After Revascularization

The long-term goals of therapy for ischemic heart disease are to maximize quality of life and exercise function and minimize morbidity and mortality. Clinical practice guidelines do not recommend the routine use of ECG monitoring, stress testing, or anatomic testing (coronary CTA or invasive angiography) in asymptomatic patients after PCI or CABG.

All patients with stable angina pectoris who undergo PCI or CABG should be treated with aspirin (81-162 mg/d) indefinitely. In patients who undergo PCI, dual antiplatelet therapy (aspirin plus clopidogrel) is recommended for at least 1 month after bare metal stent (BMS) implantation and at least 1 year after drug-eluting stent (DES) implantation, although extended use can be considered on an individual basis if a patient's ischemic risk is high and bleeding risk is low (**Table 9**). A major risk with premature discontinuation of dual antiplatelet therapy is the occurrence of stent thrombosis, a complication with high morbidity and mortality.

In patients who undergo CABG, preoperative cardioprotective and antianginal medications should be continued indefinitely. The benefit of cardioprotective medications (aspirin, β-blockers, ACE inhibitors, statins) is greatest in patients with high-risk features such as reduced left ventricular systolic function, prior myocardial infarction, chronic kidney disease, or diabetes.

KEY POINTS

- Percutaneous coronary intervention improves angina symptoms and quality of life in patients with stable angina pectoris but does not increase survival or reduce future cardiovascular events.
- For stable angina pectoris, percutaneous coronary intervention is reserved for patients with refractory symptoms while on optimal medical therapy, those who are unable to tolerate optimal medical therapy owing to side effects, or those with high-risk features on noninvasive imaging. HVC
- Clinical practice guidelines do not recommend the routine use of ECG monitoring, stress testing, or anatomic testing (coronary CT angiography or invasive angiography) in asymptomatic patients after percutaneous coronary intervention or coronary artery bypass graft surgery. HVC
- In patients with stable angina pectoris who undergo percutaneous coronary intervention, dual antiplatelet therapy (aspirin plus clopidogrel) is recommended for at least 1 month after bare metal stent implantation and at least 1 year after drug-eluting stent implantation.

TABLE 9. Duration of Dual Antiplatelet Therapy[a]

Condition	No Stent	Bare Metal Stent	Drug-Eluting Stent	C BG
Stable angina pectoris	Clopidogrel, only if aspirin is contraindicated	Clopidogrel 1 month	Clopidogrel 1 year	Not indicated[b]
UA/NSTEMI	Clopidogrel or ticagrelor 1 year	Clopidogrel, prasugrel, or ticagrelor At least 4 weeks, up to 1 year	Clopidogrel, prasugrel, or ticagrelor 1 year	Clopidogrel or ticagrelor 1 year
STEMI	Clopidogrel or ticagrelor 1 year	Clopidogrel, prasugrel, or ticagrelor At least 4 weeks, up to 1 year	Clopidogrel, prasugrel, or ticagrelor 1 year	Clopidogrel or ticagrelor 1 year

CABG = coronary artery bypass grafting; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; UA = unstable angina.

[a]Dual antiplatelet therapy consists of aspirin and another antiplatelet agent, with aspirin taken indefinitely unless contraindicated.

[b]Preliminary data suggest clopidogrel improves patency of bypass grafts after CABG.

NOTE: Extended dual antiplatelet therapy can be considered if the risk-benefit ratio is favorable.

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Acute Coronary Syndromes

General Considerations

Acute coronary syndrome (ACS) encompasses ST-elevation myocardial infarction (STEMI) and non-ST-elevation acute coronary syndromes (NSTE-ACSs), which comprise non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) (**Figure 7**). The pathophysiology of ACS is most commonly characterized by plaque rupture (75% of cases) and plaque erosion (25% of cases). STEMI is caused by a complete occlusion of an epicardial coronary artery by thrombus at the site of plaque disruption and is defined by the presence of ischemic chest pain (or an equivalent) and the presence of greater than 1-mm ST-segment elevation in two or more consecutive leads or new left bundle branch block on ECG. ST-segment depression in two or more precordial leads (V_1 through V_4) may indicate transmural posterior injury. In UA and NSTEMI, the occlusion is incomplete. NSTE-ACSs are characterized by the presence of ischemic chest pain (or an equivalent), the notable absence of ST-segment elevation on ECG, and the presence of either ST-segment depression or T-wave inversion on ECG. In NSTEMI, cardiac biomarkers (serum creatine kinase MB and troponin) are abnormal, whereas in UA, cardiac biomarkers are normal.

Because the affected artery is completely occluded in STEMI, its diagnosis and treatment are markedly different from those of UA or NSTEMI. For this reason, an initial ECG is imperative in all patients presenting with symptoms consistent with ischemic chest pain, and once diagnosis of STEMI occurs, emphasis is placed on immediate reperfusion of the vessel via thrombolytic therapy or PCI. Patients with ischemic chest pain but without ST-segment elevation on initial ECG are typically classified as having NSTE-ACS and then undergo laboratory testing for cardiac biomarkers. Because these patients do not have an ECG consistent with complete occlusion of a coronary artery and because this group of patients is heterogeneous, risk stratification should occur prior to consideration of coronary angiography and subsequent coronary revascularization with PCI or CABG.

ST-Elevation Myocardial Infarction

Recognition

Optimal management and improved outcomes in patients with STEMI depend on early recognition and institution of reperfusion therapy with either thrombolysis or primary PCI (**Figure 8**). Over the past decade, various systems-based interventions have proved effective in increasing the percentage of patients diagnosed at the time of hospital presentation, reducing the time required to reperfuse an occluded blood vessel with either thrombolysis or PCI and reducing transfer time to a facility capable of thrombolysis or PCI.

STEMI is diagnosed clinically based on the initial ECG and the presence of ischemic chest pain. Several conditions should be considered in the differential diagnosis at the time of presentation, particularly acute aortic dissection, pulmonary embolism, and pericarditis. A focused history should be taken to determine the patient's quality and duration of symptoms, risk factors for CAD, prior history of PCI or CABG, and bleeding risk as it pertains to reperfusion therapy. Physical examination is imperative to evaluate for conditions that mimic STEMI, including acute aortic dissection (asymmetric arm pressures) and pericarditis (pericardial rub). Physical examination should also look for signs of STEMI complications, such as hypotension (ventricular wall rupture, cardiogenic shock) and heart murmur (acute mitral regurgitation). Finally, the physical examination is important to assess for factors that may influence treatment options (gastrointestinal bleeding, neurologic deficits, heart failure, coagulopathy).

Reperfusion

Reperfusion for patients with STEMI occurs primarily via thrombolytic therapy and primary PCI. Despite early success with thrombolytic therapy, some studies suggest that 30% to 50% of patients receiving thrombolysis do not achieve complete reperfusion. Factors that must be considered when deciding to administer thrombolysis or perform primary PCI include the availability of a PCI-capable facility, time from onset of

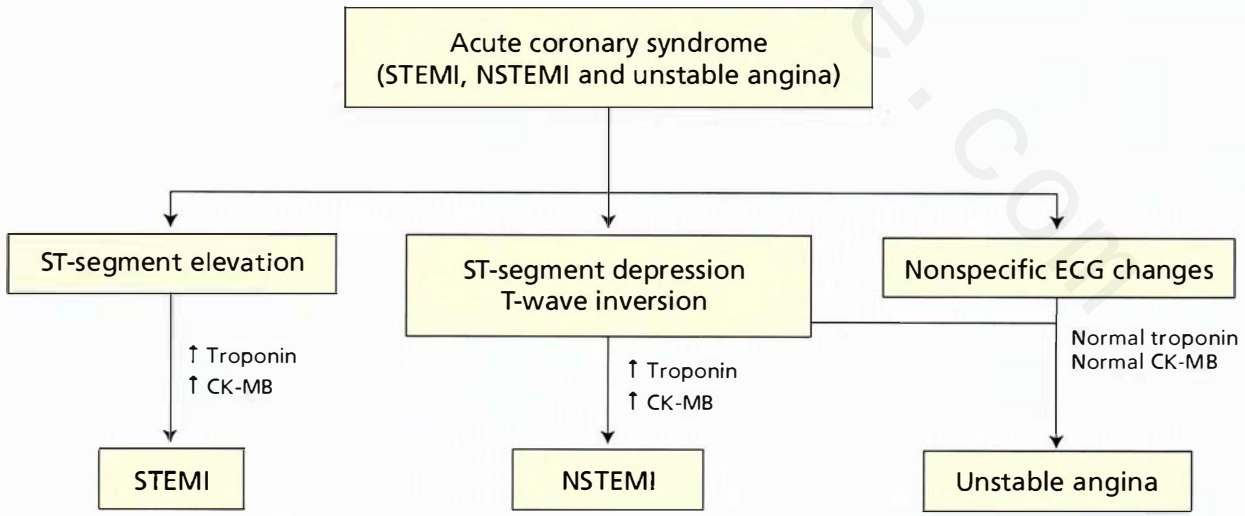

FIGURE 7. Diagnosis of acute coronary syndromes. CK-MB = creatine kinase MB; ECG = electrocardiographic; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

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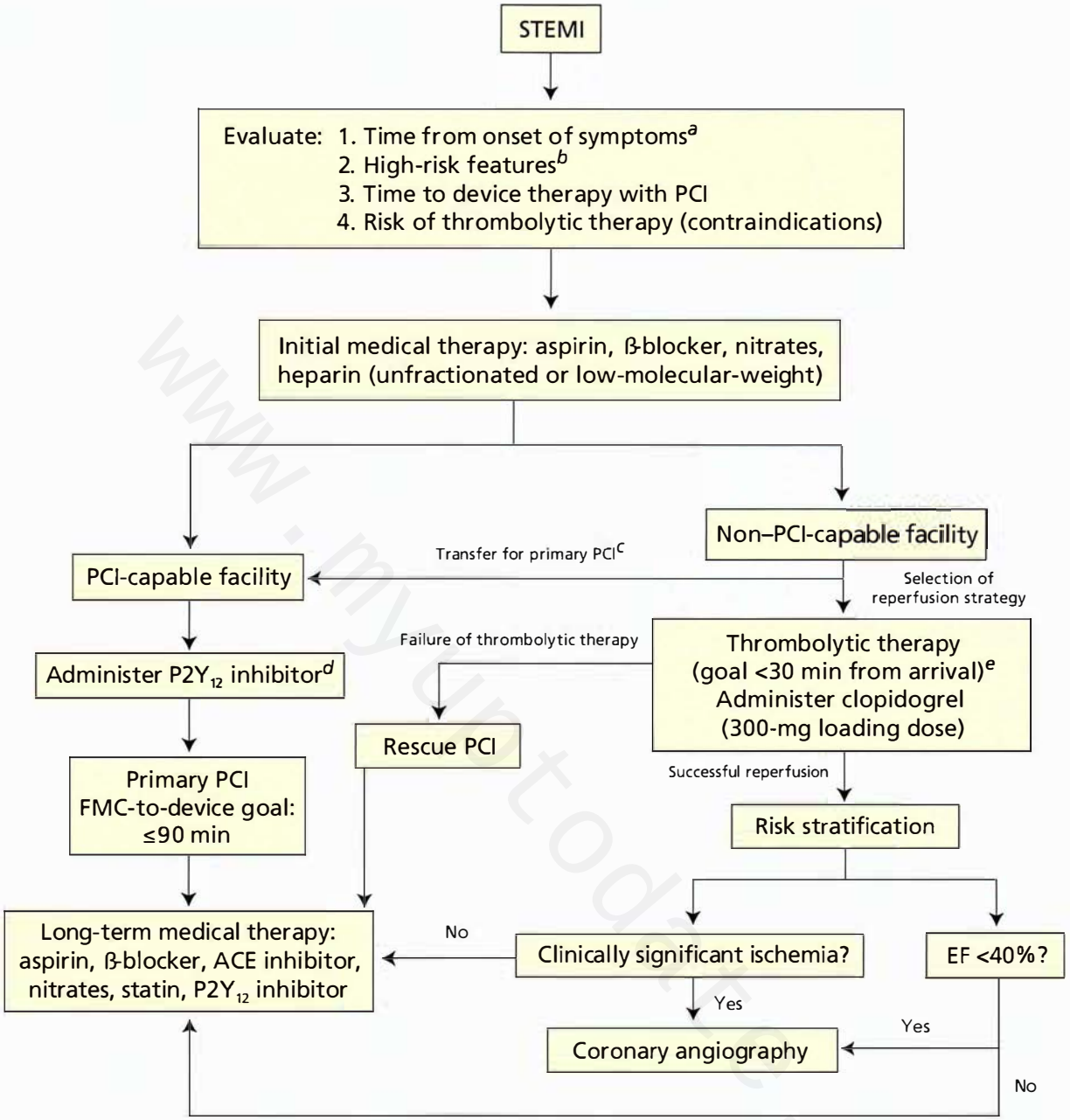

FIGURE 8. Management of ST-elevation myocardial infarction. EF = ejection fraction; FMC= first medical contact; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

[a]If 4 or more hours have elapsed since symptom onset, PCI is preferred.

[b]High-risk features such as cardiogenic shock and heart failure favor PCI.

[c]FMC-to-device ("door-to-balloon") goal for patients being transferred for primary PCI is as soon as possible and ≤120 minutes.

[d]$P2Y_{12}$ inhibitors: clopidogrel, prasugrel, ticagrelor.

[e]STEMI patients presenting to a hospital without PCI capability and who cannot be transferred to a PCI center and undergo PCI within 120 minutes of first medical contact ("door-to-balloon time") should be treated with thrombolytic therapy within 30 minutes of hospital presentation ("door-to-needle time") as a systems goal unless thrombolytic therapy is contraindicated.

O'Gara PT, Kushner FG, Ascheim DD, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Jan 29;127(4):e362-425. Erratum in: Circulation. 2013 Dec 24;128(25):e481. [PMID: 23247304]

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symptoms to presentation, the presence of high-risk features, and relative or absolute contraindications to thrombolytic therapy (Table 10). The preferred method of reperfusion is primary PCI, especially for patients presenting to hospitals with onsite PCI facilities. Because many patients with STEMI present to hospitals without onsite PCI facilities, a treatment algorithm is typically in place to emergently transfer patients to a PCI-capable facility or administer full-dose thrombolytic therapy. Even when thrombolytic therapy is administered, treatment guidelines recommend that patients be transferred to a PCI-capable facility because of the potential for thrombolytic failure.

In patients who undergo primary PCI, the time from patient presentation to device delivery (balloon inflation or thrombectomy catheter activation) is a major determinant of improved outcomes observed in primary PCI when compared with thrombolysis. Several studies have demonstrated superior efficacy of transfer for primary PCI versus thrombolytic therapy; however, observational studies have reported that patients often experience delays in transfer for primary PCI that exceed 1 hour. When PCI cannot be readily achieved within 120 minutes, thrombolytic therapy is recommended in those patients without contraindications. Regional and national efforts have improved these transfer procedures to include the ability of emergency medical services (EMS) to perform ECG in the field, immediate transfer of patients to PCI-capable facilities when STEMI is recognized, and improved communication between non-PCI facilities and PCI facilities.

Table 11 shows the characteristics of the most commonly used thrombolytic agents that are currently available. Although life-threatening bleeding events, such as intracerebral hemorrhage, are rare, they carry an extremely high mortality rate (50%–60%). Patients treated with thrombolytic therapy should

TABLE 10. Contraindications to Thrombolytic Therapy for ST-Elevation Myocardial Infarction

Absolute Contraindications
Any previous intracerebral hemorrhage
Known cerebrovascular lesion (e.g., arteriovenous malformation)
Ischemic stroke within 3 months
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed head or facial trauma within 3 months
Relative Contraindications
History of chronic, severe, poorly controlled hypertension
Severe uncontrolled hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)[a]
History of ischemic stroke (>3 months), dementia, or known intracranial pathology
Traumatic or prolonged (>10 minutes) CPR or major surgery (<3 weeks)
Recent (within 2-4 weeks) internal bleeding
Noncompressible vascular puncture site
For streptokinase/anistreplase: previous exposure (>5 days) or previous allergic reaction to these agents
Pregnancy
Active peptic ulcer disease
Current use of anticoagulants: the higher the INR, the higher the bleeding risk

CPR = cardiopulmonary resuscitation; DBP = diastolic blood pressure; SBP = systolic blood pressure.

[a]Thrombolytic therapy can be considered if SBP can be reduced to <140 mm Hg and DBP to <90 mm Hg with initial medical therapy.

TABLE 11. Characteristics of Thrombolytic Agents Used in the Treatment of STEMI

Characteristic	Streptokinase	Alteplase	Reteplase	Tenecteplase
Dose	1.5 million units over 30-60 min	Up to 100 mg in 90 min[a]	10 units x 2 (30 min apart) each over 2 min	30-50 mg[a]
Bolus administration	No	No	Yes	Yes
Allergic reaction possible on repeat exposure	Yes	No	No	No
TIMI flow grade 2/3[b]	~55%	~75%	~83%	~83%
Rate of intracerebral hemorrhage	~0.4%	~0.4-0.7%	~0.8%	~0.9%
Fibrin specificity	None	+++	+	++++

STEMI = ST-elevation myocardial infarction.

[a]Based on body weight.

[b]*TIMI flow grade 2/3* refers to mildly impaired flow through the coronary artery involved in the myocardial infarction. The higher the percentage of TIMI 2/3 flow, the more effective the thrombolytic agent.

Adapted from Boden WE, Eagle K, Granger CB. Reperfusion strategies in acute ST-segment elevation myocardial infarction: a comprehensive review of contemporary management options. J Am Coll Cardiol. 2007;50(10):917-929. [PMID: 17765117]

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CONT.

be closely observed clinically for symptom resolution and reperfusion arrhythmias, especially an accelerated idioventricular rhythm (AIVR); AIVR is considered a benign rhythm when it occurs within 24 hours of reperfusion. A repeat ECG should be obtained 60 minutes after thrombolysis to determine if ST-segment resolution has occurred.

Thrombolytic failure occurs in approximately 30% of patients, and typically presents with failure to fully resolve chest pain or improve ST-segment elevation by 50%; some patients may show hemodynamic instability or ventricular arrhythmias. In these circumstances, rescue PCI is indicated. Rescue PCI is associated with improved cardiovascular outcomes when compared with conservative medical therapy in patients with failure of thrombolytic therapy. Facilitated PCI is the administration of full- or half-dose thrombolytic therapy (with or without a glycoprotein IIb/IIIa inhibitor) followed by planned, immediate PCI. Adverse events (especially bleeding) have limited the safety and overall use of facilitated PCI.

Medical Therapy

At the time of initial presentation, all patients with STEMI should be given a 325-mg loading dose of aspirin, supplemental oxygen, therapy to improve symptoms (nitrates, analgesics), therapy to reduce infarct size (β-blockers, ACE inhibitors), and antithrombotic therapy (antiplatelet agents, anticoagulants). Aspirin should be administered immediately; however, the administration of other agents should not delay the plan to reperfuse the infarct-related artery.

In many patients with STEMI, control of chest pain can be achieved with sublingual or intravenous nitrates. Morphine and other opioid analgesics are also effective for reducing chest pain by decreasing the body's sympathetic response to STEMI. Caution should be used in patients with inferior STEMI and evidence of right ventricular infarction because nitrates and analgesics can lead to reduced preload and significant hypotension.

In the treatment of STEMI, β-blockers are recommended at the time of initial presentation except in patients with evidence of heart failure, hypotension, bradycardia, advanced atrioventricular block, or other contraindications to β-blockers. Intravenous metoprolol is the most widely used β-blocker for STEMI treatment; it is dosed in 5-mg increments every 5 minutes, for a total dose of 15 mg. Following reperfusion, an oral β-blocker is recommended to reduce myocardial oxygen demand and reduce mortality.

ACE inhibitors should be administered after reperfusion in all patients without contraindications (systolic blood pressure <90 mm Hg, advanced kidney dysfunction, hyperkalemia). Angiotensin receptor blockers may be substituted in patients who are allergic or intolerant to ACE inhibitors.

The use of antiplatelet agents in the setting of STEMI has changed over the past decade with the availability of several new agents. Aspirin remains a mainstay in the treatment of ACS and should be administered to all patients unless allergic or intolerant. Platelet $P2Y_{12}$ receptor inhibitors impair platelet aggregation, and this effect is additive to aspirin. Available agents include clopidogrel, ticagrelor, and prasugrel. Clopidogrel has been the most widely studied, and its use with concomitant thrombolytic therapy and primary PCI is associated with improved outcomes and no apparent increase in the risk of bleeding. For patients for whom primary PCI for treatment of STEMI is planned, both ticagrelor and prasugrel demonstrated superior efficacy when compared with clopidogrel; however, very few patients in these studies were treated with thrombolytic therapy, and little evidence exists to recommend the use of either ticagrelor or prasugrel in patients receiving thrombolytic therapy. Dual antiplatelet therapy should be continued in STEMI patients for a full year, regardless of intervention or stent used; however, if dual antiplatelet therapy cannot be maintained for a full year (for example, because of bleeding, need for surgery, or problems with adherence) and the patient has a bare metal stent implanted, a minimum of 4 weeks of dual antiplatelet therapy is advised.

Platelet glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide) further inhibit platelet aggregation and impair platelet activation. They are useful in patients with STEMI who undergo primary PCI; however, the use of glycoprotein IIb/IIIa inhibitors should be reserved for administration in the catheterization laboratory rather than up-front in the emergency department owing to the increased risk of bleeding and no clear benefit when administered prior to primary PCI. Routine glycoprotein IIb/IIIa inhibitor use in patients who receive thrombolytic treatment without PCI is controversial and not currently recommended.

The choice of anticoagulant for treatment of STEMI is dependent on the reperfusion strategy available for the patient. Unfractionated heparin (UFH) has been thoroughly studied in patients receiving thrombolytic agents, and its use is associated with a reduced incidence of reocclusion of the infarct-related artery. Low-molecular-weight heparin (LMWH) has also been associated with improved outcomes in patients who receive thrombolytic therapy. In patients undergoing primary PCI, the use of UFH is favored over LMWH owing to the ability to monitor the degree of anticoagulation (by measurement of activated clotting times). When a heparin-based strategy is utilized for primary PCI, guidelines recommend the concomitant administration of a glycoprotein IIb/IIIa inhibitor. Recent studies of bivalirudin, a direct thrombin inhibitor, have shown that its use at the time of primary PCI is associated with a similar rate of ischemic events (death, myocardial infarction, stroke, stent thrombosis) and fewer bleeding events when compared with a heparin plus glycoprotein IIb/IIIa inhibitor. In general, therapies that reduce bleeding complications may improve survival but with concern for greater risk of nonfatal ischemic events, such as early stent thrombosis.

In patients with diabetes mellitus who present with STEMI, plasma glucose levels should be maintained below 180 mg/dL (10.0 mmol/L) while avoiding hypoglycemia. Intravenous insulin has been tested in multiple trials, but neither intravenous insulin nor glucose-insulin-potassium infusions are recommended currently.

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Complications of STEMI CONT.

The most common complications during the early management period after STEMI are arrhythmias, heart failure, and vascular access issues in patients who undergo primary PCI. As many as 75% of patients with STEMI have an arrhythmia during hospitalization, including atrial and ventricular arrhythmias, sinus bradycardia (after inferior wall myocardial infarction), atrioventricular block, and sinus tachycardia (after anterior wall myocardial infarction). Approximately 10% to 15% of patients have atrial fibrillation or flutter during hospitalization, and this is associated with poorer long-term outcomes. The presence of atrial fibrillation or heart block is often transient in patients with inferior wall myocardial infarction and suggestive of more extensive infarction in patients with anterior wall myocardial infarction. Ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation) that occur in the first 24 hours after STEMI diagnosis do not typically affect prognosis, require antiarrhythmic medications, or require defibrillator implantation. The occurrence of recurrent ventricular arrhythmias later in hospitalization is associated with a larger infarct and higher short- and long-term morbidity and mortality. In patients with persistent high-degree atrioventricular block or symptomatic bradycardia, placement of a temporary transcutaneous or transvenous pacemaker may be needed to determine reversibility or benefit of permanent pacemaker implantation.

The severity of heart failure (ranging from asymptomatic left ventricular systolic dysfunction to cardiogenic shock) is dependent on the extent of myocardial infarction, severity of obstructive CAD, time from symptom onset to reperfusion, and patient-specific factors (age, comorbid conditions). Patients who develop cardiogenic shock after STEMI often have more extensive left ventricular infarction and an elevated inpatient mortality rate greater than 60%, thus prompting aggressive medical therapy and hemodynamic support with intra-aortic balloon counterpulsation. The initiation of therapy to reduce preload (diuretics) and afterload (nitrates, ACE inhibitors) is indicated in all patients with symptoms of heart failure; however, caution is advised if systolic blood pressure is less than 90 mm Hg or kidney dysfunction exists.

Vascular access complications include hematoma, pseudoaneurysm, arteriovenous fistula, and retroperitoneal hemorrhage.

Mechanical complications in STEMI patients (**Table 12**) are much less frequent in the reperfusion era. Right ventricular infarction, which most commonly results from occlusion of the proximal right coronary artery, should be considered in all patients with inferior wall myocardial

TABLE 12. Potential Mechanical Complications of Myocardial Infarction

Complication	Physical Examination Findings	Electrocardiography Findings	Echocardiography Findings	Pulmonary Artery Catheter Findings
Right ventricular infarction	Hypotension, jugular venous distention, clear lung fields	>1 mm ST-segment elevation in leads V_3R and V_4R	Dilated right ventricle with reduced systolic function	Elevated right atrial and right ventricular pressures, low wedge pressure
Extensive left ventricular infarction	Systolic blood pressure <90 mm Hg	Extensive ST-segment elevation, usually in anterior leads	Severe left ventricular systolic dysfunction	CI <2.0 L/min/m^2, wedge pressure >18 mm Hg
Ventricular septal defect	Holosystolic murmur along left sternal border, often with thrill	Nonspecific; approximately 50% of ventricular septal defects occur in anterior wall MI	High-velocity left-to-right systolic jet within ventricular septum, systolic turbulence on right ventricle side of ventricular septum	Prominent, large *v* waves in wedge pressure tracing; step-up in oxygen saturation from right atrium to right ventricle
Papillary muscle rupture	Holosystolic murmur at left sternal border and apex, may radiate to axillae; pulmonary edema	Usually associated with inferior and inferior-posterior wall MI	Flail mitral valve leaflet with attached mass (papillary muscle head), severe mitral regurgitation	Prominent, large *v* waves in wedge pressure tracing
Left ventricular free wall rupture	Hypotension, jugular venous distention, distant heart sounds	Nonspecific; pulseless electrical activity	Diffuse or localized pericardial effusion with tamponade; discrete wall motion abnormality; defect in myocardium may be seen	Equalization of diastolic pressures, CI <2.0 L/min/m^2

CI = cardiac index; MI = myocardial infarction.

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CONT.

infarction and hypotension. Right ventricular infarction leads to decreased pulmonary blood flow and left atrial return, decreased preload, and impaired filling of the left ventricle. This results in the triad of hypotension, clear lung examination, and elevated jugular venous pressure. Diagnosis is often made clinically and can be confirmed by either ECG (leads V_4R through V_6R) or echocardiography (often used to exclude other causes of cardiogenic shock). Treatment consists of reperfusion, aggressive volume resuscitation, and the use of inotropes (dopamine or dobutamine) until right ventricular function improves (often 2 to 3 days after myocardial infarction).

A ventricular septal defect is an infrequent complication of STEMI. It manifests as hemodynamic compromise in the setting of a new loud holosystolic murmur and often a palpable thrill 3 to 7 days after the initial myocardial infarction. Diagnosis is most commonly made by transthoracic echocardiography. Medical stabilization generally requires the administration of vasopressor agents and placement of an intra-aortic balloon pump. Although surgical mortality is high, inpatient mortality for patients who do not undergo surgery is nearly 100%. Percutaneous ventricular septal defect closure devices are sometimes used in nonsurgical patients, but their use is limited by anatomy and operator expertise.

Mitral regurgitation occurs commonly after STEMI. Mechanisms include severe left ventricular dysfunction with annulus dilatation, worsening of pre-existing mitral regurgitation, and compromise of the mitral apparatus (rupture of papillary muscle or chordae tendineae). Papillary muscle rupture often presents 3 to 7 days after initial myocardial infarction with hemodynamic compromise, pulmonary edema, and a loud systolic murmur. Diagnosis is most often made by transthoracic echocardiography, and transesophageal echocardiography may be required to plan surgical reconstruction. Treatment consists of the administration of vasodilators to reduce afterload and diuretics to decrease preload. If patients become hemodynamically compromised, the administration of vasopressors, placement of an intra-aortic balloon pump, and/or surgical intervention are required.

Left ventricular free wall rupture is the most ominous mechanical complication of STEMI and has a high mortality rate. It often occurs 3 to 7 days after initial myocardial infarction. Risk factors for left ventricular rupture include advanced age, female sex, anterior myocardial infarction, and incomplete reperfusion of STEMI. Patients most commonly present with pericardial tamponade (due to hemopericardium), pulseless electrical activity, and death. Early recognition, emergent pericardiocentesis, and subsequent surgical reconstruction can improve survival.

Left ventricular thrombus occurs in approximately 10% to 20% of patients after anterior myocardial infarction despite reperfusion and aggressive treatment. Transthoracic echocardiography is the most common diagnostic modality, and thrombus is detected as an echo-dense structure, often at the apex of the left ventricle (**Figure 9**). Treatment involves the use of therapeutic warfarin for 3 to 6 months following myocardial infarction to reduce the risk of stroke or systemic embolization.

KEY POINTS

- In patients with ST-elevation myocardial infarction, when percutaneous coronary intervention cannot be readily achieved within 120 minutes, thrombolytic therapy is recommended in the absence of contraindications.
- Patients with ST-elevation myocardial infarction who receive thrombolytic therapy should be transferred to a percutaneous coronary intervention–capable facility because of the potential for thrombolytic failure.

Non-ST-Elevation Acute Coronary Syndromes

The most common pathophysiology of NSTE-ACS is nonocclusive coronary atherosclerosis with or without thrombus formation. The treatment of UA and NSTEMI patients is focused on improvement in epicardial blood flow with medications and revascularization. Because the link between revascularization and clinical outcomes is less clear than in STEMI patients, NSTE-ACS patients should undergo risk stratification prior to invasive treatment.

Risk Stratification

The TIMI risk score is the most commonly used tool for estimating the short-term risk for death and nonfatal myocardial infarction in patients with a NSTE-ACS (**Table 13**). The TIMI risk score is most useful to assist in deciding whether patients will benefit from an early invasive

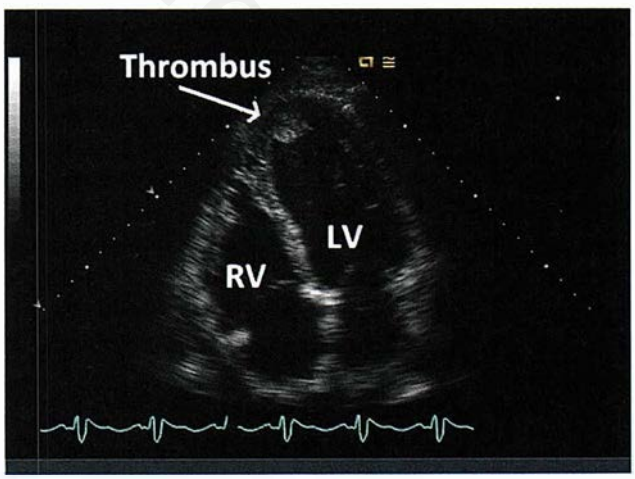

FIGURE 9. Echocardiographic image showing a left ventricular thrombus in a patient with a recent myocardial infarction. LV = left ventricle; RV = right ventricle.

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TABLE 13. TIMI Risk Score for Non-ST-Elevation Acute Coronary Syndromes

Prognostic Variables
(1) Age ≥65 years
(2) ≥3 Traditional CAD risk factors[a]
(3) Documented CAD with ≥50% diameter stenosis
(4) ST-segment deviation
(5) ≥2 Anginal episodes in the past 24 hours
(6) Aspirin use in the past week
(7) Elevated cardiac biomarkers (creatine kinase MB or troponin)
TIMI Risk Score (Sum of Prognostic Variables)
0-2 Low risk
3-4 Intermediate risk
5-7 High risk

CAD = coronary artery disease.

[a]Hypertension, hypercholesterolemia, diabetes mellitus, being a current smoker, family history of CAD.

Adapted from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000;284(7):835-842. [PMID: 10938172]

CONT.

treatment strategy (**Figure 10**). The estimated rates of death and nonfatal myocardial infarction also are useful to counsel patients regarding their risk. In patients at low risk (TIMI score of 0-2), practice guidelines recommend an ischemia-guided strategy that utilizes invasive treatment only if medical therapy is ineffective. Patients at higher risk (TIMI score ≥3) are more likely to benefit from an early invasive approach.

Medical Therapy

All patients who present with ischemic chest pain should be treated initially with aspirin, β-blockers, and nitrates. However, compared with STEMI, in which reperfusion is the primary goal of therapy, once the diagnosis of UA or NSTEMI has been established (through the ECG and biomarkers), risk stratification can be used to guide the clinical use of additional therapies (**Table 14**, on pages 28-29). All NSTE-ACS patients should receive a statin and a $P2Y_{12}$ inhibitor (such as clopidogrel). In patients at intermediate or high risk (TIMI score ≥3), additional therapies, such as anticoagulant agents or a glycoprotein IIb/IIIa inhibitor, should be considered.

Antiplatelet Medications

The initial aspirin dose should be 325 mg at the time of presentation for ischemic chest pain. Patients who are allergic to aspirin should be administered clopidogrel at the time of presentation. Although there remains debate about subsequent aspirin dosing based on patient risk and whether revascularization with PCI or CABG occurs, most patients can be treated with a dose of 81 mg daily indefinitely (especially when dual antiplatelet therapy is being used).

Dual antiplatelet therapy (aspirin plus clopidogrel, prasugrel, or ticagrelor) is recommended in all patients with NSTE-ACS, regardless of TIMI risk score, unless an increased risk of bleeding exists (see Table 9). The use of clopidogrel, in addition to aspirin, is the best-studied combination. Clopidogrel should be given as a loading dose (300 mg or 600 mg) at hospital admission and administered as a 75-mg daily dose for at least 1 year regardless of the need for PCI or CABG. Patients with a bare metal stent who cannot tolerate dual antiplatelet therapy for the full year (for example, because of bleeding, need for surgery, or problems with adherence) should remain on the therapy for at least 4 weeks. If CABG is ultimately required, clopidogrel should be discontinued and CABG should be postponed for 5 to 7 days in order to avoid perioperative bleeding.

Two oral $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, have been developed, and when tested, were superior to clopidogrel in UA and NSTEMI patients. Ticagrelor and prasugrel do not require hepatic metabolism, are more potent, and have a faster onset of action when compared with clopidogrel. These agents also should be discontinued 5 to 7 days or more prior to CABG.

Administration of glycoprotein IIb/IIIa inhibitors in patients with NSTE-ACS does not appear to be of net clinical benefit unless high-risk features, such as ongoing angina or evidence of ischemia after the initiation of standard antiplatelet and antianginal medications, reinfarction, or heart failure, are present. However, these agents, in combination with UFH or bivalirudin, are indicated at the time of PCI in patients with NSTE-ACS who ultimately require revascularization. Because of their potent antiplatelet activity, the main adverse effect of glycoprotein IIb/IIIa inhibitors is increased risk of major and minor bleeding events.

Anticoagulant Medications

The use of anticoagulant medications (UFH, LMWH, fondaparinux, and bivalirudin) has been a cornerstone of therapy for NSTE-ACSs for more than three decades. The choice of a particular agent is based on the patient's bleeding risk, TIMI risk score, comorbid conditions (such as chronic kidney disease), plan for an early invasive versus a conservative strategy, timing of coronary angiography, and physician preference.

UFH and LMWH are the most widely used anticoagulants for NSTE-ACSs. In patients in whom an early invasive approach is planned and in patients with chronic kidney disease, UFH is preferred over LMWH. In patients in whom a conservative strategy is planned, both LMWH and fondaparinux have been proved to be safe and effective. Advantages of fondaparinux and LMWH include the ability to dose once or twice daily rather than continuously and no requirement to monitor therapeutic levels. Because of a significantly increased bleeding risk, the use of the anticoagulant bivalirudin is currently not recommended by clinical guidelines other than during PCI or in patients who are allergic to heparin-based products.

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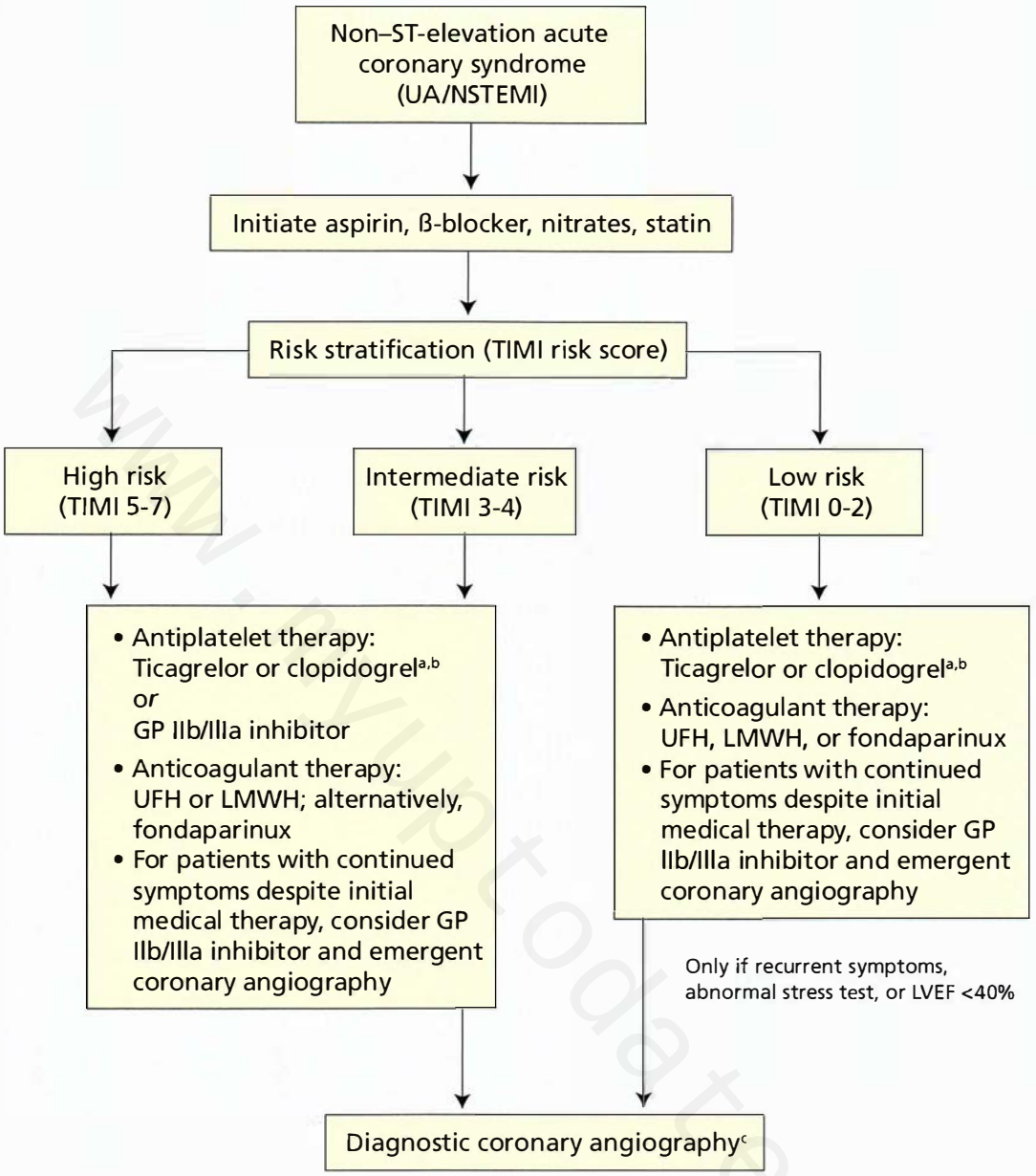

FIGURE 10. Initial management of non-ST-elevation acute coronary syndromes. GP = glycoprotein; LMWH = low-molecular-weight heparin; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina; UFH = unfractionated heparin.

[a]Clopidogrel or ticagrelor may be dosed at the time of hospital admission and acute coronary syndrome diagnosis.

[b]If coronary artery bypass grafting is required, clopidogrel or ticagrelor should be stopped and surgery delayed for at least 5 days.

[c]If the decision is made to withhold a $P2Y_{12}$ inhibitor until time of angiography and a $P2Y_{12}$ inhibitor is desired, clopidogrel, ticagrelor, or prasugrel can be initiated.

Recommendations based on Amsterdam EA, Wenger NK, Brindis RG, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Dec 23;130(25):2354-94. [PMID: 25249586]

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Antianginal Medications

Unless contraindicated, oral β-blockers should be initiated in all patients who present with a NSTE-ACS. Intravenous β-blockers can also be administered; however, caution should be used in patients with heart failure, advanced age, advanced atrioventricular block, and hypotension.

Nitrates that can be administered to NSTE-ACS patients include intravenous, topical, oral, and sublingual formulations. Intravenous nitrates are typically used in patients with ongoing chest pain or borderline blood pressure or hemodynamics. In patients without active symptoms, topical and oral formulations should be prescribed in order to prevent recurrent symptoms. Sublingual nitroglycerin is often prescribed on an as-needed basis for new or worsening angina. All forms of nitrates should be avoided in patients who have taken a PDE-5 inhibitor (such as sildenafil or vardenafil) within 24 hours.

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TABLE 14. Long-Term Medical Therapy for Coronary Artery Disease

Medication	Drugs in This Class	Dosage	Indication[a]	Comment
Antiplatelet Medications				
Aspirin	N/A	75-162 mg/d	All patients, unless intolerant or allergic	
Clopidogrel	N/A	75 mg/d	$P2Y_{12}$ inhibitor in combination with aspirin is indicated in all patients after ACS or PCI	Clopidogrel is recommended as an alternative for patients with intolerance or allergy to aspirin[b]
Prasugrel	N/A	10 mg/d	$P2Y_{12}$ inhibitor in combination with aspirin is indicated in all patients after ACS or PCI	Contraindicated in patients >75 years of age, low body weight (<60 kg [132 lb]), or history of stroke/TIA
Ticagrelor	N/A	90 mg/d	$P2Y_{12}$ inhibitor in combination with aspirin is indicated in all patients after ACS or PCI	More rapid onset of action; does not require first-pass hepatic metabolism; no known genetic polymorphisms. Decreased effectiveness with aspirin dosages ≥100 mg
Cardioprotective Medications				
β-Blockers	Atenolol, metoprolol, carvedilol, nebivolol	Variable	All patients with prior MI or LV systolic dysfunction	Caution is advised in patients with significant obstructive lung disease (e.g., COPD) or advanced atrioventricular block
ACE inhibitors	Benazepril, captopril, enalapril, fosinopril, perindopril, trandolapril, lisinopril, ramipril, quinapril	Variable	All patients with LV systolic dysfunction, hypertension, diabetes, or proteinuric chronic kidney disease	
Angiotensin receptor blockers	Losartan, valsartan, olmesartan, candesartan, irbesartan, telmisartan	Variable	ACE inhibitor-intolerant patients	The use of angiotensin receptor blockers in combination with ACE inhibitors is not well established (class IIb recommendation)
Aldosterone blockade	Spironolactone, eplerenone	Variable	ACS patients with LV systolic dysfunction on therapeutic doses of β-blockers and ACE inhibitors	Caution is advised in patients with significant kidney dysfunction or hyperkalemia
High-intensity statin therapy	Atorvastatin	40-80 mg/d	For all patients with evidence of coronary artery disease and age ≤75 years	
	Rosuvastatin	20-40 mg/d		
Moderate-intensity statin therapy	Atorvastatin	10-20 mg/d	For all patients with evidence of coronary artery disease and age >75 years or otherwise intolerant of high-intensity statin therapy	
	Rosuvastatin	5-10 mg/d		
	Simvastatin	20-40 mg/d		
	Pravastatin	40-80 mg/d		
	Lovastatin	40 mg/d		
	Fluvastatin	40 mg BID		

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TABLE 14. Long-Term Medical Therapy for Coronary Artery Disease *(Continued)*

Medication	Drugs in This Class	Dosage	Indication[a]	Comment
Antianginal Medications				
β-blockers	Atenolol, metoprolol, carvedilol, nebivolol	Variable	All patients with prior MI or LV systolic dysfunction	Caution is advised in patients with significant obstructive lung disease or advanced atrioventricular block
Long-acting nitrates	Isosorbide, transdermal patch, ointment	Variable	Useful for relief of symptoms when maximal, tolerated dose of β-blocker has been achieved[b]	Nitrates are contraindicated in patients taking PDE-5 inhibitors for erectile dysfunction
Short-acting nitrates	Sublingual, spray, or aerosol	Variable	Useful for relief of symptoms, usually prescribed on an as-needed basis	Nitrates are contraindicated in patients taking PDE-5 inhibitors for erectile dysfunction
Calcium channel blockers	Amlodipine, diltiazem, verapamil, nifedipine, nicardipine	Variable	Useful for relief of symptoms when maximal, tolerated dose of β-blocker has been achieved[b]	
Ranolazine	N/A	500-1000 mg BID	Useful for relief of symptoms when maximal, tolerated dose of β-blocker has been achieved[c]	Caution is advised in patients with advanced kidney disease, liver disease, and in those taking potent inhibitors of CYP3A4 pathway

ACS = acute coronary syndrome; BID = twice daily; LV = left ventricular; MI = myocardial infarction; N/A = not applicable; PCI = percutaneous coronary intervention; PDE-5 = phosphodiesterase S; TIA = transient ischemic attack.

[a]Level of evidence: All are class I, level A, except as noted.

[b]Level of evidence: class I, level B.

[c]Level of evidence: class IIa, level B.

CONT.

Calcium channel blockers and ranolazine do not have clear indications for use in patients presenting with an ACS. Opioids, such as morphine, may be administered for symptomatic relief of patients with ongoing chest pain, although caution is advised because of their blood pressure–lowering effects.

Lipid-Lowering Medications

The benefits of statin therapy in ACS patients are well established; however, the timing of initiation (hospital admission versus at the time of PCI versus hospital discharge) is less clear. Recent studies suggest that high-intensity dosing of atorvastatin or rosuvastatin is associated with improved 2-year survival after ACS. Current treatment guidelines recommend the initiation of a high-intensity statin in patients at very high cardiovascular risk, including those patients with an ACS.

Invasive Versus Ischemia-Guided Treatment

Once medical therapy has been initiated and risk stratification has occurred, guidelines recommend that patients with a low-risk NSTE-ACS be treated conservatively with an ischemia-guided strategy and that intermediate- to high-risk patients be considered for early invasive treatment. Patients treated with an ischemia-guided strategy should undergo noninvasive stress testing before hospital discharge; coronary angiography and subsequent PCI or CABG should be reserved for those with recurrent symptoms or high-risk features on stress testing. High-risk patients assigned to an early invasive strategy (coronary angiography and subsequent PCI or CABG within 24 hours of initial hospitalization) have been shown to have improved outcomes when compared with high-risk patients treated conservatively. For patients who are appropriate for an early invasive strategy, there is no evidence that very early angiography (<6 hours or at hospital admission) offers incremental benefit.

Clinical guidelines recommend the use of early invasive treatment in NSTE-ACS patients regardless of risk stratification who have recurrent symptoms, hemodynamic instability, or electrical instability.

CABG is often recommended for ACS patients with specific angiographic criteria (that is, left main disease and multivessel CAD with or without proximal left anterior descending stenosis) with concomitant left ventricular systolic dysfunction and/or diabetes mellitus.

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KEY POINTS

- All patients who present with ischemic chest pain should be treated initially with aspirin, β-blockers, and nitrates; once the diagnosis of a non–ST-elevation acute coronary syndrome has been established, risk stratification can be used to guide the clinical use of additional therapies.
- All patients with a non–ST-elevation acute coronary syndrome should receive a statin and dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor; in patients at intermediate or high risk, additional therapies (anticoagulant agents, glycoprotein IIb/IIIa inhibitor) should be considered.
- Dual antiplatelet therapy is recommended for at least 1 year in all patients with a non–ST-elevation acute coronary syndrome, unless an increased risk of bleeding exists.
- Once medical therapy has been initiated and risk stratification has occurred, guidelines recommend that low-risk patients with a non–ST-elevation acute coronary syndrome be treated conservatively and that intermediate- to high-risk patients be considered for early invasive treatment.

Acute Coronary Syndromes Not Associated with Obstructive Coronary Disease

Although plaque rupture at the site of atherosclerotic plaque deposition is the most common cause of ACS, other disease entities may cause patients to present with chest pain, transient ECG changes, and elevated cardiac biomarkers. The diagnosis of these diseases is generally made once diagnostic coronary angiography has confirmed the absence of obstructive coronary stenoses.

Coronary vasospasm often occurs in normal or near-normal coronary arteries, and spasm can be triggered by the use of illicit drugs, such as cocaine or methamphetamine. In patients who present with ischemic chest pain at rest and transient ST-segment elevation or depression, the diagnosis of vasospasm is often one of exclusion once angiography confirms the absence of obstructive CAD. Vasospasm is most frequently treated with long-term nitrates and calcium channel blockers and avoidance of triggers such as illicit drugs.

Takotsubo cardiomyopathy, often temporally associated with a stressful event, can mimic an ACS with the presence of chest pain, ECG changes, and elevated cardiac biomarkers (see Heart Failure). However, coronary angiography is usually normal or shows only minimal atherosclerotic disease, and left ventriculography is classically defined by the presence of midwall and apical wall motion abnormalities with sparing of the basal segments. Treatment is supportive, and more than 95% of patients have resolution of symptoms and recovery of left ventricular function within 7 days.

Owing to the improved sensitivity of troponin assays, other systemic diseases (such as chronic kidney disease, sepsis, and rhabdomyolysis) and cardiac conditions (such as heart failure, atrial fibrillation, and myocarditis) can lead to a diagnosis of ACS without obstructive coronary artery stenosis on coronary angiography. In most cases, the etiology of ACS is presumed to be demand ischemia (myocardial oxygen demand surpasses oxygen supply); it is termed secondary myocardial infarction when cardiac biomarkers are abnormal. Management of these patients typically includes treatment of the underlying condition in addition to medical therapy (aspirin, statin) and preventive measures for heart disease.

Long-Term Care After an Acute Coronary Syndrome

All patients who are diagnosed with an ACS should continue aspirin (81 mg/d) indefinitely. Patients treated medically without PCI should receive an oral $P2Y_{12}$ inhibitor for up to 12 months. The optimal duration of dual antiplatelet therapy in patients with an ACS who undergo PCI with drug-eluting stent implantation is at least 12 months (see Table 9). In patients who undergo PCI with bare metal stent implantation, the duration of dual antiplatelet therapy is at least 4 weeks but up to 12 months as tolerated. In the absence of contraindications, ACE inhibitors and statins should be continued indefinitely in all patients with an ACS. There is evidence of benefit for treatment with a β-blocker for at least 3 years following an ACS, although many clinicians choose to continue these medications indefinitely if they are well tolerated.

Current guidelines recommend that patients who are entering cardiac rehabilitation programs after ACS should undergo routine exercise ECG testing. Routine stress testing is not currently recommended for asymptomatic patients who are not entering a cardiac rehabilitation program. For patients with an ACS who are symptomatic after hospital discharge, the use of stress testing is acceptable and should be determined by the patient's symptoms (for example, unstable angina, stable angina), ability to exercise, and interpretability of ECG.

KEY POINT

- Routine stress testing is not currently recommended for asymptomatic patients following an acute coronary syndrome who are not entering a cardiac rehabilitation program. HVC

Management of Coronary Artery Disease in Women

Clinical Presentation

Women typically develop ischemic heart disease at a later age in life than men. Unlike men, women present more frequently with stable angina pectoris rather than an ACS or sudden cardiac death. More than 50% of women who present with typical angina are diagnosed with nonobstructive coronary stenoses, and the presence of microvascular disease is thought to be significantly higher in women than in men.

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In women presenting with acute myocardial infarction, chest pain remains the predominant symptom; however, the likelihood of atypical symptoms, such as fatigue, dyspnea, nausea, and abdominal complaints, is significantly higher than in men. In women without significant obstruction on invasive angiography, microvascular dysfunction (either endothelium-dependent or endothelium-independent) is thought to be the cause of symptoms.

Evaluation and Treatment

The sensitivity and specificity of noninvasive stress testing for the evaluation of chest pain are lower in women than in men. ST-segment deviation is less accurate in women than in men. Clinical guidelines report an improved diagnostic test accuracy with the use of stress testing with imaging (see Diagnostic Testing in Cardiology). However, no specific diagnostic evaluation guidelines exist for women, and the same guidelines apply to men and women.

In the COURAGE trial, women with stable angina pectoris had reduced overall mortality or nonfatal myocardial infarction with revascularization therapy as compared with men. However, women have a higher complication rate, particularly bleeding and vascular complications, surrounding revascularization procedures. For these reasons, it is recommended that guideline-directed medical therapy be initiated in women prior to consideration for revascularization. In women undergoing PCI, a trend toward fewer such complications has been found with the use of radial rather than femoral arterial access. Overall, treatment guidelines do not currently differ between men and women. The use of estrogen is not recommended to reduce the occurrence of future cardiovascular events in post-menopausal women.

KEY POINTS

- In women presenting with acute myocardial infarction, chest pain remains the predominant symptom; however, atypical symptoms, such as fatigue, dyspnea, nausea, and abdominal complaints, are more likely than in men.
- In women with coronary artery disease, it is recommended that guideline-directed medical therapy be initiated prior to consideration for revascularization; otherwise, treatment guidelines do not currently differ between men and women.

Management of Coronary Artery Disease in Patients with Diabetes Mellitus

Risk and Evaluation

Patients with diabetes mellitus are at increased risk of developing CAD, and cardiovascular mortality is significantly higher in this population. Additionally, patients with diabetes mellitus often do not experience classic angina pectoris and can present with atypical cardiac symptoms, such as dyspnea, nausea, or hyperglycemic symptoms. Sudden cardiac death occurs significantly more frequently in persons with diabetes compared with those without the disease. The diagnostic accuracy of noninvasive stress testing in symptomatic patients with diabetes is similar to that in patients without diabetes; however, the assessment of CAD in asymptomatic persons with diabetes is controversial. Currently, the American Heart Association recommends stress testing in patients with diabetes who are (1) symptomatic, (2) initiating an exercise program, or (3) known to have CAD and have not had a recent (>2 years) stress test.

Invasive Treatment

In patients with diabetes who are candidates for revascularization, the decision to pursue PCI or CABG remains controversial and depends on a multitude of factors, including severit and extent of CAD, the presence of comorbid conditions, and the degree of atherosclerotic narrowing of small, distal vessels. Multiple studies have analyzed outcomes of patients with diabetes undergoing PCI or CABG. Although CABG is gener lly associated with fewer repeat revascularization procedures, mortalit is similar between the two procedures. When a decision is made to pursue PCI, the use of a drug-eluting stent is recommended to reduce the occurrence of target vessel revascularization because of the more extensive coronary artery disease and higher rate of restenosis in patients with diabetes.

Medical Therapy and Secondary Prevention

Aggressive risk factor reduction, control of plasma glucose levels, and medical therapy are essential in patients with diabetes. In most patients with diabetes and CAD, high-intensity statin therapy and antihypertensive treatment with a target blood pressure below 140/90 mm Hg are recommended. Because of the protective renal effects of ACE inhibitors and angiotensin receptor blockers in patients with proteinuric nephropathy, these agents are preferred over other antihypertensive agents, such as thiazide diuretics.

Common medications used for the treatment of diabetes are of special concern in patients with CAD. In a meta-analysis, thiazolidinediones, specifically rosiglitazone, had been associated with an elevated risk of cardiovascular events, especially myocardial ischemia. However, a more recent clinical trial demonstrated no elevated risk of myocardial infarction or death in patients being treated with rosiglitazone when compared with standard-of-care diabetes drugs. The use of metformin at the time of coronary angiography, after myocardial infarction, and in patients with heart failure should be avoided because of a rare but potentially fatal risk of lactic acidosis.

KEY POINT

- In patients with diabetes, stress testing is recommended by the American Heart Association for those who are (1) symptomatic, (2) initiating an exercise program, or (3) known to have coronary artery disease and have not had a recent (>2 years) stress test.

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Heart Failure

Pathophysiology of Heart Failure

Heart failure is a complex clinical syndrome in which cardiac output is insufficient for meeting the demands of the body, causing symptoms of exertional dyspnea and fatigue. Approximately one half of patients with heart failure have left ventricular systolic dysfunction, or heart failure with reduced ejection fraction (HFrEF); the other half have normal systolic function, or heart failure with preserved ejection fraction (HFpEF). Regardless of whether left ventricular ejection fraction is reduced or preserved, symptoms of exertional dyspnea and fatigue are the same, and assessment of ejection fraction is required to differentiate between these two entities.

Common causes of HFrEF include hypertension, coronary artery disease, myocarditis, certain drugs (for example, doxorubicin, trastuzumab, cyclophosphamide), and toxins, including alcohol, cocaine, amphetamines, cobalt, and lead. Systemic diseases that may cause HFrEF include hypo- and hyperthyroidism, HIV infection, systemic lupus erythematosus, scleroderma, and neuromuscular diseases such as Duchenne and Becker muscular dystrophy. A high percentage of HFrEF cases are idiopathic. The most common causes of HFpEF are hypertension and coronary artery disease; less common causes include infiltrative diseases such as amyloidosis and hemochromatosis. In general, patients with HFpEF tend to be older, heavier women who have a history of hypertension, coronary disease, and diabetes mellitus.

Although the symptoms of exertional dyspnea and fatigue and hemodynamic abnormalities of reduced stroke volume and elevated ventricular filling pressures are similar between HFpEF and HFrEF, there are significant differences in the pathophysiology between the two disease processes. In patients with HFrEF, the common defect is an abnormality of myocardial contraction. Reduced systolic function results in progressive ventricular dilation. In contrast, patients with HFpEF have similar symptoms but normal systolic contraction and an abnormality in diastolic relaxation. This results in restricted filling and high filling pressures. To maintain a normal cardiac output (heart rate × stroke volume), patients with HFpEF tend to have a higher heart rate. Clinically, because these patients have a very small left ventricular size, they are usually much more sensitive to volume loading than patients with HFrEF.

Diagnosis and Evaluation of Heart Failure

Clinical Evaluation

Approximately half of all heart failure hospital admissions result from HFpEF. There is no difference in mortality between patients with HFpEF and HFrEF. For both groups of patients, there is about a 50% survival rate at 3 years after presenting with symptoms of heart failure.

Classic symptoms of acute heart failure include exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and peripheral edema. In patients with stable chronic heart failure, symptoms are typically similar to those of new-onset heart failure but less intense. A patient may normally sleep on two or three pillows owing to nocturnal dyspnea, but with decompensation will sleep on more pillows or move to sleeping in a recliner. Similarly, a patient at baseline may become short of breath walking up one flight of stairs, but with decompensation may have dyspnea putting on his or her clothes. Patients with previously diagnosed heart failure often do not present with classic findings. These patients may present with increased abdominal girth rather than peripheral edema, or with nausea and anorexia caused by gut edema rather than with exertional dyspnea. Educating patients to weigh themselves daily and report changes in weight or baseline symptoms may reduce heart failure hospital admissions if acted on quickly enough.

The first step in the evaluation of a patient with signs and symptoms of heart failure is a thorough history and physical examination, which should be performed to evaluate for possible causes of heart failure and assess cardiovascular risk factors. A detailed history, including alcohol and illicit drug use, alternative therapies, family history, and any history of chemotherapy, should be obtained. Features that increase the likelihood of heart failure include the presence of paroxysmal nocturnal dyspnea (>2-fold likelihood) and the presence of an S_3 (11 times greater likelihood). The likelihood of heart failure is decreased 50% by the absence of dyspnea on exertion and by the absence of crackles on pulmonary auscultation. Elevated jugular venous pressure and an S_3 are independently associated with adverse outcomes, including progression of heart failure.

Diagnosis

In patients who present with acute dyspnea of undetermined etiology, B-type natriuretic peptide (BNP) levels can be used to quickly differentiate between dyspnea secondary to heart failure (elevated BNP) and dyspnea related to pulmonary disease (low to normal BNP). The Breathing Not Properly study evaluated patients who presented to the emergency department with dyspnea. Patients who had heart failure had a mean BNP level greater than 600 pg/mL (600 ng/L), whereas those with noncardiac causes of dyspnea had levels of approximately 50 pg/mL (50 ng/L). Patients with a history of left ventricular dysfunction but not an acute exacerbation had a BNP level of approximately 200 pg/mL (200 ng/L). BNP levels increase with age and worsening kidney function and are reduced in patients with an elevated BMI.

BNP levels alone are not diagnostic for heart failure but should be used only as an initial test to guide the diagnostic evaluation in patients with dyspnea of uncertain etiology. BNP levels should not be used to follow a patient's clinical

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course. There is no benefit to following BNP levels during a hospitalization to determine if diuresis has been adequate. Additionally, routine use of BNP measurement in outpatients with heart failure is not helpful for determining if a patient is fluid overloaded.

A 12-lead electrocardiogram (ECG) should be obtained for all patients with heart failure. An ECG can be helpful to evaluate for possible myocardial infarction, tachyarrhythmia, or left ventricular hypertrophy. A chest radiograph should be obtained to evaluate for concomitant pulmonary disease. Chest radiography can also be helpful for identifying vascular congestion indicating volume overload or pleural effusions.

The initial laboratory assessment of heart failure should include electrolyte levels, urinalysis and kidney function, glucose and lipid levels, liver chemistry tests, and thyroid-stimulating hormone levels. Although thyroid disease is an uncommon cause of heart failure, hypothyroidism and hyperthyroidism are potentially reversible causes of heart failure with appropriate treatment. Coronary disease causes approximately two thirds of cases of heart failure, and an acute coronary syndrome should be suspected as a cause of new heart failure or an exacerbating factor in patients with preexisting heart failure. If an acute coronary syndrome is suspected as precipitating heart failure, measurement of troponin levels may be useful. However, troponin levels are occasionally mildly elevated in patients with an exacerbation of heart failure owing to wall stress and subendocardial ischemia or with acute myocarditis. An elevated troponin level does not guide therapy in this setting but can be used as a marker of more progressive heart failure and worse prognosis. Routine evaluation for unusual causes of heart failure, including hemochromatosis, Wilson disease, multiple myeloma, and myocarditis, should not be performed. An evaluation for other unusual causes of heart failure should not be performed routinely in all patients but should only be performed when there are suggestions of specific diseases by history or physical examination.

The most important diagnostic test in the evaluation of heart failure is transthoracic echocardiography. An echocardiogram will give an assessment of ejection fraction as well as information about possible causes. For example, identification of wall motion abnormalities increases suspicion for coronary artery disease and myocardial ischemia. Echocardiography also allows assessment for aortic and mitral valve disease, with the caveat that mitral regurgitation is often caused by the remodeling process of heart failure and is therefore secondary to the heart failure rather than the primary cause (functional mitral regurgitation). Additionally, the left ventricular end-diastolic dimension can be helpful for evaluating the chronicity of the disease process as well as prognosis. Patients with acute heart failure syndromes and a dilated left ventricle likely have a chronic disease process with delayed onset or recognition of symptoms. A small left ventricle (particularly without wall thinning) is associated with a greater chance of recovery of ejection fraction compared with a markedly dilated left ventricle. Also, a combination of findings on echocardiography may provide a clue to the cause of heart failure. For example, left ventricular hypertrophy and bi-atrial enlargement in a patient with reduced ejection fraction suggests a restrictive cardiomyopathy. The left ventricular hypertrophy of HFpEF is usually secondary to hypertension and should not be confused with the severe hypertrophy characteristic of hypertrophic cardiomyopathy (see Myocardial Disease). Patients with HFpEF often have mild to moderate left ventricular hypertrophy (<15 mm in any region).

Cardiac magnetic resonance (CMR) imaging is used increasingly in the evaluation of patients with heart failure. CMR imaging can be used to assess wall motion abnormalities, global wall function, and viability. Additionally, it can be used to assess tissue perfusion, tissue injury (inflammation or necrosis), fibrosis, infiltration (sarcoid or amyloid), or iron deposition.

Endomyocardial biopsy is rarely indicated for the evaluation of acute heart failure. Patients with progressive heart failure on medical therapy who have malignant arrhythmias should undergo biopsy to evaluate for giant cell myocarditis. Biopsy is also reasonable for patients with new-onset heart failure unresponsive to standard medical therapy. Endomyocardial biopsy can assist in the diagnosis of amyloidosis and hemochromatosis, which are diffuse processes amenable to diagnosis by biopsy techniques; sarcoidosis, on the other hand, can be quite patchy and is less likely to be discovered on endomyocardial biopsy.

There is no role for routine right heart catheterization for the diagnosis or management of patients with heart failure. In patients admitted to the hospital with heart failure, routine right heart catheterization has not been demonstrated to decrease either mortality or rehospitalization rates compared with usual care. Right heart monitoring can be helpful in patients with advanced heart failure who are refractory to medical therapy. Symptomatic hypotension and worsening kidney function may be suggestive of low cardiac output but could also be caused by infection or progression of disease. A right heart catheterization directly measuring cardiac output and filling pressures can guide therapy toward improving hemodynamics (higher stroke volume and lower filling pressures) with inotropic agents and/or more aggressive diuresis if the filling pressures are high. Right heart catheterization is also indicated in patients being evaluated for heart transplantation. Pulmonary hypertension is a risk factor for poor outcomes following heart transplantation because the right ventricle of the donor heart is not accustomed to pumping against high pulmonary pressures and may fail.

Evaluation for Ischemia

Although coronary artery disease is the most common cause of heart failure, owing to expense and radiation exposure, the routine investigation for coronary disease by stress testing or cardiac catheterization or other imaging modalities (such as CMR imaging, PET, or CT) is no longer considered part of the

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CONT. routine evaluation of all patients with newly diagnosed heart failure. Cardiac catheterization should be performed in patients presenting with angina or significant ischemia. Additionally, cardiac catheterization is recommended for patients presenting with chest pain that may or may not be of cardiac origin and those with previously diagnosed coronary artery disease without chest pain if they are eligible for revascularization. Noninvasive stress testing is reasonable in patients with a history of coronary artery disease to evaluate for reversible ischemia, as revascularization can dramatically improve left ventricular function. Additionally, patients with multiple risk factors for coronary disease should undergo noninvasive testing to evaluate for signs of ischemia. If stress testing identifies significant ischemic myocardium, coronary angiography should be considered.

KEY POINTS

- B-type natriuretic peptide levels can be useful to distinguish cardiac from noncardiac causes of dyspnea in the urgent care setting.
- HVC In patients with heart failure, with the exception of thyroid disease, an extensive evaluation of unusual causes of heart failure should not be performed unless there are suggestions of specific diseases by history or physical examination.
- The most important diagnostic test in the evaluation of heart failure is transthoracic echocardiography, which allows assessment of left ventricular ejection fraction as well as information regarding potential causes, clinical course, and prognosis.

Medical Therapy for Systolic Heart Failure

The treatment of patients with HFrEF (systolic heart failure) comprises treatment of the acute exacerbation followed by institution of long-term therapy to decrease morbidity and mortality and improve symptoms in patients with chronic heart failure. The initial therapy for patients presenting with acute heart failure and volume overload is a diuretic. An ACE inhibitor or angiotensin receptor blocker (ARB) should also be started unless the patient has symptomatic hypotension. Once the acute heart failure episode has stabilized, all patients should be treated with a β-blocker.

The long-term therapy of heart failure is based on the patient's functional status as measured by New York Heart Association (NYHA) functional class (**Table 15**) and signs and symptoms of volume overload. In addition to ACE inhibitors and β-blockers, other treatments for heart failure that have been shown to decrease mortality and future hospitalizations include aldosterone antagonists and, specifically for black patients, hydralazine-isosorbide dinitrate (**Table 16**). Several additional medications have been shown to improve symptoms but have no effect on mortality.

TABLE 15. New York Heart Association (NYHA) Functional Class

Class	Description
I	No limitations of physical activity
II	Slight limitation of physical activity
III	Marked limitation of physical activity
IIIA	Symptoms with less than ordinary activity
IIIB	Symptoms with minimal exertion
IV	Unable to carry on any physical activity without symptoms

TABLE 16. Medical Therapy for Heart Failure with Reduced Ejection Fraction

Therapies that Decrease Mortality
ACE inhibitors/angiotensin receptor blockers
β-Blockers
Aldosterone antagonists (if NYHA class II to IV)
Hydralazine/isosorbide dinitrate (black patients with NYHA class III/IV symptoms)
Therapies that Improve Symptoms
Digoxin
Diuretics
Inotropic agents
Vasodilators

NYHA = New York Heart Association.

ACE Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors have been shown to decrease mortality, decrease symptoms of heart failure, improve functional capacity, and improve left ventricular ejection fraction. All patients with HFrEF should be started on an ACE inhibitor. The patient should be started on a low dose, which can be up-titrated as tolerated based on blood pressure and symptoms. Higher doses of ACE inhibitors compared with lower doses have been shown to decrease heart failure hospital admissions but not mortality. In patients with baseline hypotension, it is important to initiate ACE inhibitor therapy, but the dose should not be maximized prior to initiating β-blockade because the combination of both agents is superior to therapy with either one alone. Caution should be used when initiating ACE inhibitor therapy in patients with chronic kidney disease, and the patient's kidney function should be monitored closely. However, the presence of kidney dysfunction should not be considered a contraindication to the initiation of these agents; recent guidelines suggest initiating therapy in patients with a serum creatinine level below 3.0 mg/dL (265.2 µmol/L).

A common adverse effect of ACE inhibitors is a dry, nonproductive cough, which occurs in up to 20% of patients. For

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these patients, it is reasonable to switch to an ARB instead. Less information regarding mortality is available for ARBs, so they should not be used as first-line therapy. Other common adverse effects of both drugs include hyperkalemia and, occasionally, worsening kidney function. In patients with angioedema while taking ACE inhibitors, ARBs should not be used as an alternative because there are reports of angioedema also occurring with these agents.

β-Blockers

β-Blockers should be started in all patients with HFrEF after acute decompensation is treated and the patient is hemodynamically stable. These drugs block the adverse effects of chronic neurohormonal activation on cardiac function. Three β-blockers have been shown to decrease mortality, reduce heart failure symptoms, and improve left ventricular ejection fraction in patients with HFrEF: metoprolol succinate, carvedilol, and bisoprolol. It is important to use one of these three agents because they are the only ones that have a demonstrated benefit in patients with heart failure. Other β-blockers, including short-acting metoprolol (metoprolol tartrate), have not shown similar benefit. Some patients experience increased fatigue on β-blockade, but the vast majority experience an improvement in heart failure symptoms.

Initiating and Managing ACE Inhibitor and β-Blocker Therapy

Patients with acute heart failure and volume overload should initially be started on an ACE inhibitor. Typically, a short-acting agent such as captopril should be used in divided daily doses so that if the patient experiences symptomatic hypotension, the effect will be transient. ACE inhibitors should be titrated based on blood pressure and the presence or absence of adverse effects. For patients with new-onset heart failure and volume overload, a β-blocker should not be initiated until the patient is euvolemic or close to euvolemic.

In contrast to ACE inhibitors, in which the dose can be rapidly titrated upward, β-blockers should be started at a very low dose once patients are euvolemic because these agents have a negative inotropic effect. Instead of up-titrating the drug on a daily basis, titration of a β-blocker should be performed slowly at 1- to 2-week intervals, on an outpatient basis. A number of studies have demonstrated a dose-response effect with β-blockers. High doses compared with low doses of β-blockers have been shown to be more beneficial for both mortality reduction and the reduction of heart failure symptoms. Although patients are often discharged on low doses, these agents should be up-titrated to the maximal tolerated doses after the patient has been discharged (**Table 17**). Limitations to maximal up-titration include symptomatic hypotension and bradycardia. Once the heart rate is below 60/min, the current dose can be maintained. A history of COPD is not a contraindication to initiating β-blocker therapy, and there is no evidence that the nonselective β-blockers are not tolerated in these patients.

TABLE 17. Therapeutic Doses of β-Blockers for Treatment of Heart Failure with Reduced Ejection Fraction

Agent	Target Dosage
Carvedilol	25 mg BID (50 mg BID if >85 kg [187 lb])
Metoprolol succinate	200 mg daily
Bisoprolol	10 mg daily

BID = twice daily.

Diuretics

Diuretics are the mainstay of therapy for symptoms of heart failure associated with volume overload. To avoid hypovolemia, the lowest dose of diuretic necessary should be used. Loop diuretics are the most commonly used agents. In patients with refractory heart failure, the addition of a thiazide diuretic is occasionally used to augment the effects of the loop diuretic. There is no advantage to a continuous intravenous infusion versus bolus therapy in decompensated heart failure. Adverse effects of diuretics include hypokalemia, hypomagnesemia, and worsening kidney function. As electrolyte abnormalities can lead to malignant arrhythmias, electrolytes should be frequently measured in patients receiving high doses. Additionally, patients should be counseled to restrict their sodium and fluid intake.

Digoxin

Digoxin has been used for decades for the treatment of heart failure. Digoxin has not been shown to reduce mortality but does decrease hospitalizations for HFrEF in comparison with placebo. In short-term trials, digoxin has been shown to improve heart failure symptoms, quality of life, and exercise tolerance. The withdrawal of digoxin in patients is associated with increasing heart failure symptoms.

Therapy with digoxin should be closely followed. It is reasonable to check a serum digoxin level when a patient is stable. Patients with kidney impairment, low body mass, and older age have reduced metabolism of digoxin and can quickly develop a toxic level. It is important to check a digoxin level in patients with worsening kidney function. Retrospective analyses have shown that serum levels greater than 1 ng/mL (1.28 nmol/L) are associated with increased risk of mortality, most commonly related to arrhythmias.

Aldosterone Antagonists

Aldosterone antagonists (spironolactone, eplerenone) have been studied in patients with heart failure and NYHA functional class II to IV symptoms and have been shown to reduce mortality and morbidity. For patients with class II symptoms, the benefit has been shown only in those with a history of prior hospitalization or an elevated BNP level. The principal side effect of these agents is hyperkalemia. Spironolactone and eplerenone have not been compared

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with one another, but in clinical trials, gynecomastia occurs specifically with spironolactone. Because of the risk of kidney dysfunction and hyperkalemia, these drugs should be used only in patients with a serum creatinine level below 2.5 mg/dL (221 µmol/L) in men or below 2.0 mg/dL (176.8 µmol/L) in women, and with a serum potassium level below 5.0 mEq/L (5.0 mmol/L). Additionally, if the patient is on potassium supplementation, this should be discontinued when therapy is initiated. Electrolytes and kidney function should be checked 1 week after initiation of therapy and be closely monitored over time. Aldosterone antagonists should be used very cautiously in elderly patients. These drugs are not effective as diuretics at the doses used in heart failure therapy (12.5-25 mg/d for spironolactone, 25-50 mg/d for eplerenone).

Isosorbide Dinitrate and Hydralazine

The combination of isosorbide dinitrate and hydralazine is an alternative therapy for patients with heart failure who have kidney dysfunction that limits therapy with either ACE inhibitors or ARBs. In this setting, this combination is used for its vasodilating properties. More recently, based on retrospective data from earlier clinical trials, a clinical trial in black patients with heart failure and reduced ejection fraction and NYHA class III and IV symptoms was performed that demonstrated a reduction in mortality with a specific formulation of this combination compared with placebo. There was a high incidence of adverse effects (primarily peripheral edema, dizziness, gastrointestinal symptoms, and headaches) and drug withdrawal. For black patients, studies have demonstrated improvements in quality of life in addition to a mortality benefit. Note that this combination was studied as an additional therapy for patients already on an ACE inhibitor or an ARB and a β-blocker, not as a replacement therapy, and should only be instituted after these agents have been maximized.

Calcium Channel Blockers

Because of their vasodilating effects, calcium channel blockers have been closely studied for their potential role in the management of heart failure. Unfortunately, the non-dihydropyridine calcium channel blockers (for example, diltiazem or verapamil) also have myocardial depression activity and have been demonstrated to either have no benefit or worse outcomes in patients with heart failure. Patients who have been treated for hypertension with diltiazem or verapamil should have those agents discontinued once a diagnosis of heart failure has been made. The second-generation dihydropyridine calcium channel blockers, such as amlodipine and felodipine, have been shown to be safe in patients with heart failure, but do not reduce morbidity or mortality. For patients who are still hypertensive on high doses of ACE inhibitors and β-blockers, a peripherally acting dihydropyridine calcium channel blocker can be used as an antihypertensive agent.

KEY POINTS

- Initial therapy for all patients with heart failure with reduced ejection fraction should include an ACE inhibitor; those with volume overload should be given a diuretic, and once the acute heart failure episode has stabilized, all patients should be placed on a β-blocker.
- β-Blockers in the treatment of heart failure should be started at a very low dose and up-titrated slowly, at 1- to 2-week intervals.
- Aldosterone antagonists should be started in patients with New York Heart Association class II to IV symptoms with appropriate kidney function and a potassium level below 5.0 mEq/L (5.0 mmol/L).
- The addition of isosorbide dinitrate and hydralazine to standard heart failure therapy is associated with improvements in quality of life and a mortality benefit in black patients.

Management of Heart Failure with Preserved Ejection Fraction

ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists have been studied in patients with HFpEF. Unfortunately, none of these agents have demonstrated any clinical benefit compared with placebo. At this time, no medications have demonstrated a reduction in mortality in this patient population. Therapy for HFpEF should instead be based on treating the causes and symptoms of the heart failure. Hypertension is a common cause of HFpEF, and aggressive control of blood pressure is necessary. Additionally, controlling tachycardia can be helpful in patients with atrial arrhythmias.

Patients with HFpEF are often quite volume sensitive, with a small therapeutic window between hypovolemia and hypervolemia. Judicious use of diuretics to maintain euvolemia is important. These patients should be encouraged to monitor their weight closely, as small differences in volume can quickly cause volume overload and subsequent hospital admissions.

Device Therapy

Sudden cardiac death is the cause of death in approximately 50% of patients with heart failure. The only reliable predictor of an arrhythmic event is left ventricular ejection fraction. For this reason, implantable cardioverter-defibrillators (ICDs) are used for primary prevention of sudden cardiac death in patients with heart failure and low ejection fraction.

Implantable Cardioverter-Defibrillator for Prevention of Sudden Cardiac Death

In patients with mild to moderate heart failure symptoms and left ventricular ejection fraction less than or equal to 35%, placement of an ICD reduces mortality compared with medical therapy or placebo in patients with both ischemic and

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nonischemic etiologies (**Table 18**). ICDs are indicated for patients with NYHA functional class II and III symptoms, ejection fraction less than or equal to 35% on guideline-directed medical therapy, and a life expectancy of at least 1 year. As patients with class IV symptoms have a reduced life expectancy, ICDs are not indicated in this population except in patients who are awaiting transplantation or undergo placement of a mechanical circulatory device.

ICDs should only be placed after patients are on guideline-directed medical therapy. For patients with recent onset of heart failure who have a reasonable chance of recovery of function, one should wait upwards of 6 months with the patient on adequate medical therapy and then reassess ventricular function to determine if the ejection fraction is still less than 35% prior to implantation. Specifically, patients treated with revascularization for coronary artery disease may have improvement in ejection fraction, which should be re-measured after revascularization.

Cardiac Resynchronization Therapy

In approximately 30% of patients, heart failure progression is accompanied by dyssynchrony (dysfunctional ventricular electromechanical coordination) manifested by prolongation of the QRS duration or a left bundle branch block. Biventricular pacing, or cardiac resynchronization therapy (CRT), involves pacing the right and left ventricles simultaneously. In addition to the usual placement of a pacer lead in the apex of the right ventricle, an additional lead is placed through the coronary sinus down a coronary vein on the lateral wall of the left ventricle. This simultaneous pacing has been demonstrated to increase ejection fraction, decrease heart failure symptoms, and reduce mortality in patients with HFrEF and ECG evidence of dyssynchrony. The 2013 American College of Cardiology Foundation/American Heart Association heart failure management guideline makes a strong recommendation with strong supporting evidence for CRT therapy in patients with an ejection fraction less than or equal to 35%, NYHA functional class III to IV symptoms on guideline-directed medical therapy, and left bundle branch block with QRS duration greater than or equal to 150 msec (see Table 18). A strong recommendation with weaker evidence is provided for patients with NYHA functional class II symptoms.

Patients with NYHA class I symptoms caused by ischemia and a left bundle branch block with a QRS duration greater than 150 msec have shown some benefit with CRT therapy, but the risk-benefit ratio is high owing to adverse effects of the therapy, and it is currently a class IIb recommendation. Adverse effects include infection at the site of the device, inappropriate firings, and occasional tricuspid valve regurgitation.

TABLE 18. Indications for Device Therapy in Heart Failure

Implantable Cardioverter-Defibrillator (for primary prevention)
NYHA class II or III while taking guideline-directed medical therapy[a] *and*
Expectation of survival >1 year *and*
Either of the following:
Ischemic cardiomyopathy ≥40 days post MI or nonischemic cardiomyopathy with ejection fraction ≤35% (primary prevention)
History of hemodynamically significant ventricular arrhythmia or cardiac arrest (secondary prevention)
Biventricular Pacemaker (cardiac resynchronization therapy)
All of the following:
NYHA class II to IV
Ejection fraction ≤35%
On guideline-directed medical therapy
Ventricular dyssynchrony (LBBB with a QRS duration ≥150 msec)

LBBB = left bundle branch block; MI = myocardial infarction; NYHA = New York Heart Association.

[a]Also NYHA class I in patients with ischemic cardiomyopathy and ejection fraction <30% (MADIT-II criteria: Moss AJ, Zareba W, Hall WJ, et al; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346(12):877-883. [PMID: 11907286])

Recommendations from Yancy CW, Jessup M, Bozkurt B, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239. [PMID: 23747642]

KEY POINTS

- An implantable cardioverter-defibrillator is recommended for patients with New York Heart Association class II or III heart failure, a left ventricular ejection fraction less than or equal to 35% after treatment with guideline-directed medical therapy, and a life expectancy of at least 1 year.
- Cardiac resynchronization therapy is recommended for patients with New York Heart Association class II to IV heart failure, a left ventricular ejection fraction less than or equal to 35% on guideline-directed medical therapy, and a left bundle branch block with QRS duration greater than or equal to 150 msec.

Assessment of Chronic Heart Failure

Patients with chronic heart failure should be serially assessed for progression of disease in the outpatient setting. At each visit, it is important to assess current symptoms and functional capacity, volume status, and the adequacy of the medical therapy (both appropriate doses and the appropriate medications as heart failure progresses). Of equal or greater importance is repeated patient education, including reminding patients to take their medications as prescribed, measure their weight daily, avoid dietary sodium, watch their fluid

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intake, and exercise regularly. Patients who appropriately take their medications and avoid sodium and excess fluid intake can greatly improve their functional status.

Despite multiple studies demonstrating the benefit of medical therapies in heart failure, fewer than 60% of patients are discharged from the hospital on ACE inhibitor and β-blocker therapy. It is important to review medications at every visit to ensure that patients are on the appropriate therapy.

Serial B-Type Natriuretic Peptide Assessment

Serial assessment of BNP levels in patients with chronic heart failure have been evaluated in a number of studies. Although higher BNP levels are associated with increased mortality, change in level in an individual patient does not predict progression of disease. Additionally, there is no evidence of benefit to using BNP for serially following patients to assess volume status or for dose adjustment of medications.

Echocardiography in Chronic Heart Failure

Echocardiography should be performed in patients with severe left ventricular dysfunction after optimization of medical therapy to determine if the left ventricular ejection fraction has improved to above 35% before consideration of ICD implantation. For patients with chronic heart failure who are clinically stable, echocardiography rarely provides diagnostic benefit, and obtaining annual echocardiograms is not likely to change therapy or outcome. For patients hospitalized with acute heart failure, obtaining a repeat echocardiogram to evaluate left ventricular function or for worsening valvular abnormalities is reasonable. If a patient has progressive heart failure symptoms as an outpatient, a repeat echocardiogram can be helpful to evaluate for progressive valvular abnormalities, new wall motion abnormalities, or an increase in left ventricular size that may alter treatment and affect prognosis.

Assessing Prognosis

Multiple retrospective studies have been performed looking at methods to evaluate prognosis in patients with heart failure. Current 1-year survival rates for patients undergoing heart transplantation or placement of a left ventricular assist device are between 85% and 90%. Patients with a higher risk of death should be considered for these therapies. Important risk factors for death include NYHA class IV symptoms, repeat hospitalizations, hyponatremia (serum sodium <133 mEq/L [133 mmol/L]), worsening kidney function, higher doses of diuretics, intolerance of ACE inhibitors or β-blockers, and arrhythmias resulting in ICD firings. Patients with multiple risk factors should be referred to a heart failure cardiologist for further evaluation. Additionally, occasional discussions with patients regarding end-of-life issues and their wishes for advanced heart failure therapy should be initiated while the patient is still stable. Patients' advanced care plans often change over time.

Cardiopulmonary exercise testing is routinely performed to assess prognosis in patients being evaluated for transplantation. Patients with a low oxygen consumption (peak O_2 consumption <14 mL/kg/min) or a high ratio of ventilation-to-carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ >34) have a poor 1-year prognosis.

The Seattle Heart Failure model (www.SeattleHeartFailureModel.org) is an online program that uses clinical characteristics to predict outcomes in patients with heart failure. This model can be used to help assess prognosis based on clinical characteristics and can be used to guide patients as they ask questions about their prognosis.

KEY POINTS

- Patients with chronic heart failure should be seen regularly for assessment of clinical status as well as ongoing patient education regarding taking medications as prescribed, measuring their weight daily, reducing dietary sodium and avoiding excess fluid intake, and exercising regularly.
- In patients with chronic heart failure who are clinically stable, annual or more frequent follow-up echocardiography rarely provides therapeutic or diagnostic benefit and is not recommended. **HVC**

Inpatient Management of Heart Failure

Acute Decompensated Heart Failure

Patients with heart failure admitted to the hospital usually have symptoms of volume overload as the primary concern. Reasons to admit patients include progressive heart failure symptoms with dyspnea at rest, an inability to respond to oral diuretics, recurrent ICD firings, symptoms of ischemia, worsening kidney function, and signs of poor perfusion (such as cool extremities, a low pulse pressure, or pulsus alternans). Therapy is primarily focused on diuresis. Additional evaluation should be performed to determine the reasons for the decompensation, including a review of medications and whether the patient was taking his or her medications properly, an echocardiogram to look for reversible causes of worsening function, and, if appropriate, an evaluation for ischemia. Generally, the initial dose of intravenous diuretic should be at least equivalent to the total daily oral dose. If the patient does not respond appropriately to that dose, rapid up-titration should be performed to assist in fluid removal. The patient's usual outpatient medications (for example, ACE inhibitor, β-blocker) should be continued unless the patient is hypotensive or demonstrates signs of poor perfusion, in which case dose reduction or discontinuation of both the ACE inhibitor and β-blocker should be considered. In patients with signs of low-output heart failure (hypotension, worsening kidney or liver function, cool extremities), the β-blocker should be discontinued.

Patients should be adequately diuresed during the hospitalization. Orthopnea and an elevated central venous pressure are suggestive of elevated filling pressures. Patients often have symptomatic improvement before they are euvolemic, and striving to achieve euvolemia may result in a reduction in readmission rates. Volume status can be difficult to assess and a

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careful physical examination is required. Patients should be assessed for signs of volume overload even if they have reached a goal or "dry" weight, as this is not a reliable measure of euvolemia. Findings supportive of euvolemia include an estimated central venous pressure below 10 cm H_2O, no orthopnea, absence of peripheral edema, and reduced dyspnea. Despite the use of high-dose intravenous diuretic therapy and improvement in volume status during hospitalization, many patients are discharged before achieving euvolemic or decongested status. Objective markers of decongestion include net urine output, weight loss, evidence of hemoconcentration (increase in hematocrit and hemoglobin levels), and reduction in BNP level. These markers have been associated with lower rates of rehospitalization for heart failure in short-term follow-up.

Ultrafiltration can occasionally be used in patients admitted with volume overload when routine diuresis fails or patients are unresponsive to diuretic therapy. A recent randomized trial of ultrafiltration versus intravenous diuretics in patients with decompensated heart failure and worsening kidney function showed no difference in weight loss but worsened kidney function in patients treated with ultrafiltration.

Worsening kidney function, typically defined as a serum creatinine increase of 0.3 mg/dL (26.52 µmol/L) or greater during hospitalization for heart failure, is a common complication, occurring in up to 25% of patients. This event often triggers changes in medical therapy, including reduction or cessation of diuretics, ACE inhibitors or ARBs, or aldosterone antagonists. Retrospective studies have found that this complication is associated with worse survival long-term, but no therapies have been shown to prevent or reduce worsening kidney function in patients with heart failure.

Vasopressin antagonists can be used for the treatment of patients with hypervolemic or euvolemic hyponatremia. They are beneficial for correcting hyponatremia but have not demonstrated any mortality benefits.

Cardiogenic Shock

Cardiogenic shock is defined by persistent, symptomatic hypotension and end-organ dysfunction. Patients have acute kidney failure, evidence of liver dysfunction with elevated aminotransferase levels, poor peripheral perfusion with cool extremities, and decreased mental status. Cardiogenic shock requires intensive therapy with intravenous vasopressors. Patients who remain in shock despite intravenous therapy and with worsening organ function should be considered for mechanical support.

It is important to quickly rule out reversible causes in patients with cardiogenic shock. Reversible causes include acute myocardial infarction; ventricular septal or free wall rupture; and acute valvular regurgitation, possibly related to papillary muscle rupture, infection, or ascending aortic arch aneurysm with dissection of the aortic valve. Bedside echocardiography can be helpful in identifying structural causes of cardiogenic shock.

The initial therapy for cardiogenic shock includes vasoactive medications to increase cardiac output and raise blood pressure through peripheral vasoconstriction (**Table 19**). Patients with cardiogenic shock secondary to progressive heart failure are generally given an inotropic agent, such as dobutamine or milrinone (cleared by the kidneys). Patients with peripheral vasoconstriction (increased systemic vascular resistance) often benefit from the addition of a pure vasodilator such as sodium nitroprusside. Placement of a right heart catheter can be helpful to assess filling pressures, cardiac output, and systemic vascular resistance to help choose the appropriate medical regimen. Although the routine placement of a right heart catheter for patients admitted with heart failure has not been shown to improve outcomes, it should be considered to assist in therapeutic decision-making in patients with cardiogenic shock.

For patients with symptomatic hypotension and end-organ dysfunction despite vasopressor therapy, mechanical therapy should be considered. Mechanical support options

TABLE 19. Intravenous Vasoactive Medications Used for Treatment of Cardiogenic Shock

Medication	Mechanism	Inotropy	Vasodilation
Milrinone	Phosphodiesterase inhibitor	++	+
Dobutamine	β_1, β_2 receptors	++	(+) (at low dose) – (vasoconstriction, at high dose)
Nesiritide	Natriuretic peptide receptors	0	++
Sodium nitroprusside	Nitric oxide	0	++
Nitroglycerin	Nitric oxide	0	++ (mainly venous)
Vasopressin	V receptor	–	– (vasoconstriction)
Dopamine	D receptor β_1 receptors at intermediate dose α_1 receptor at high dose	+	– (vasoconstriction, at high dose)
Norepinephrine	Affinity for α_1, α_2 receptors greater than for β_1 receptors	+	– (vasoconstriction)

Strength of effect: ++ indicates very strong; + indicates strong; (+) indicates weak; 0 indicates neutral; – indicates opposite effect.

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CONT. include intra-aortic balloon pumps and percutaneous or surgically implanted short-term mechanical ventricular assist devices (VADs). These assist devices have catheters that are placed into the vascular system (left atrium or ventricle); they then pump the blood into the aorta, essentially assisting the failing left ventricle. These devices augment cardiac output and improve end-organ perfusion. Because all of these devices require large catheters, a common complication is vascular compromise at the point of insertion.

Strategies to Prevent Readmission

At many U.S. hospitals, heart failure is the most common discharge diagnosis. Currently, 30-day readmission rates are greater than 20%, and reducing these admissions is a major focus of study and resources. Studies evaluating diuresis have shown that greater fluid removal during the hospitalization is associated with a lengthening of the time to readmission. Additionally, it is important that patients are discharged on appropriate medical therapy, including an ACE inhibitor and a β-blocker. Early physician follow-up, ideally within 7 days of discharge, has also been associated with a reduction in readmissions.

Because it is often difficult to schedule patients for an office visit within 1 week of discharge, multidisciplinary heart failure clinics have been created by a number of hospitals. These programs often include telephone monitoring of signs and symptoms, evaluating whether patients are actually taking their medications, educating patients on salt and fluid restriction, and providing a mechanism for early follow-up after hospitalization.

KEY POINTS

- In hospitalized patients with acute volume overload, the initial dose of intravenous diuretic should be at least equivalent to the total daily oral dose; rapid up-titration should be performed if needed to assist in fluid removal.
- Reversible causes of cardiogenic shock include acute myocardial infarction, ventricular septal or free wall rupture, and acute valvular regurgitation.

HVC
- In patients discharged with a diagnosis of heart failure, early physician follow-up, ideally within 7 days of discharge, has been associated with a reduction in hospital readmissions.

Advanced Refractory Heart Failure

Once patients have progressed to advanced heart failure, the therapeutic options are limited to inotropic therapy, heart transplantation, mechanical circulatory support, and palliative care. Heart transplantation is the best option for patients with end-stage heart failure, with 50% survival rates approaching 13 years, but is limited by donor availability such that only 2000 transplants are performed in the United States annually. Candidates for transplant are therefore thoroughly evaluated for comorbidities that may limit survival. The upper age limit for heart transplant is 65 to 70 years. Patients with kidney dysfunction, diabetes with end-organ manifestations, malignancy, chronic infection, or other comorbidities are often denied transplant. Options for patients who are not candidates for heart transplantation include mechanical circulatory support as destination therapy and inotropic therapy. However, inotropic therapy does not decrease mortality and may actually increase it. The survival of inotropic-dependent patients is less than 10% at 1 year.

Mechanical Circulatory Support

With the development of continuous-flow left ventricular assist devices (LVADs), the survival of patients with advanced heart failure after implantation of these devices has dramatically improved. The pumps are surgically inserted into the left ventricle, and the blood is pumped through the device from the left ventricle to the aorta. The patients have a line (driveline) coming through the skin through which the power is transmitted to the pump. Ninety percent of patients receiving an LVAD as a bridge to heart transplantation are alive at 1 year. For patients who are not candidates for transplant and have an LVAD placed as destination therapy, the survival at 2 years is more than 60% and improving. Complications related to these devices include ischemic and hemorrhagic stroke (>10% of patients), driveline-related infections (approximately 30%), and gastrointestinal bleeding related to arteriovenous malformations (20% in some reports).

Management of Post-Transplant Patients

The prognosis of heart transplant recipients has improved greatly in recent years. Most patients have no functional limitations and return to a normal quality of life. Patients typically begin on a three-drug immunosuppression regimen early after transplantation that includes a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative agent (mycophenolate mofetil, sirolimus, or everolimus), and prednisone. Most centers try to wean patients off of prednisone by 1 year. Immunosuppressive medications are associated with a number of adverse effects, including hypertension (>90% of patients) and new-onset diabetes (20% of patients). During the first year post-transplant, while doses of immunosuppressants are high, patients have an increased risk for infection. Rejection occurs in approximately 20% of patients in the first year but is almost nonexistent after the first year unless a patient stops taking immunosuppressants. Signs of rejection include heart failure and atrial arrhythmias (typically atrial flutter). However, most patients with rejection manifest no clinical symptoms, necessitating routine surveillance with endomyocardial biopsy. The surveillance interval varies; however, most centers perform biopsies between 1 and 5 years after transplant.

The long-term complications of heart transplant include cardiac allograft vasculopathy and malignancy. Cardiac allograft vasculopathy occurs in more than 50% of the patients by the fifth year after transplant. It is characterized by diffuse intimal thickening of the coronary arteries that starts distally and progresses proximally. For this reason, the usual therapies for coronary disease, such as percutaneous coronary

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intervention and coronary artery bypass grafting, are usually not beneficial. Lymphoproliferative disorders and skin cancer are the most common malignancies.

Because the heart in transplant patients is denervated, they usually do not experience typical ischemic chest pain, leading to atypical presentations of coronary artery disease and acute coronary syndromes. Additionally, without vagal innervation, heart rates tend to run between 90/min and 110/min. Heart transplant patients have a marked response to adenosine but are not responsive to digoxin or atropine. For transplant patients presenting with atrial arrhythmias, caution should be used before giving adenosine to diagnose the arrhythmia because it may cause prolonged atrioventricular conduction block.

KEY POINTS

- Cardiac allograft vasculopathy occurs in more than 50% of heart transplant recipients by the fifth year after transplant; because of its diffuse nature, revascularization is usually not beneficial.
- Because the heart in transplant patients is denervated, they usually do not experience typical ischemic chest pain, leading to atypical presentations of coronary artery disease and acute coronary syndromes.

Specific Cardiomyopathies

The most common cause of heart failure is coronary artery disease. Other common causes include hypertension and idiopathic cardiomyopathy. Approximately 10% of patients with heart failure have heart failure related to a specific etiology. This includes medication-induced cardiomyopathies (primarily chemotherapeutic agents), myocarditis, amyloidosis, sarcoidosis, infectious etiologies such as HIV, peripartum cardiomyopathies, and alcohol or other drug-induced cardiomyopathies. Others will be discussed later. Restrictive cardiomyopathies with such causes as chemotherapeutic agents, amyloidosis, and sarcoidosis are discussed in Myocardial Disease. Peripartum cardiomyopathy is discussed in Pregnancy and Cardiovascular Disease.

Takotsubo Cardiomyopathy

Takotsubo, or stress-induced, cardiomyopathy is a syndrome of reversible ventricular systolic dysfunction usually precipitated by an acute emotional or physiologic stress. Although takotsubo cardiomyopathy was initially described in elderly women following intense emotional stress, the syndrome may occur in men and in some patients an antecedent stress may not be identifiable. It is believed to be caused by sympathetic-mediated myocyte injury, but the precise pathogenesis is unknown. It often mimics an acute myocardial infarction with elevated troponin levels and electrocardiographic changes, but it is usually associated with normal coronary arteries. The hallmark is wall motion abnormalities that extend beyond a single coronary territory, identified by echocardiography or other imaging study. For example, on left ventriculogram, the apex of the heart will be hypokinetic and the mid heart will contract normally. Characteristic electrocardiographic changes include ST-segment elevation and diffuse deep T-wave inversions with some prolongation of the QTc interval. Takotsubo cardiomyopathy is usually associated with recovery of systolic function in the acute period. Nevertheless, these patients should be treated with ACE inhibitors and β-blockers acutely. There is no accepted length of time to continue this therapy in patients whose left ventricular function returns to normal. For the rare patient who does not recover, this therapy should be continued.

Acute Myocarditis

Myocarditis usually presents with heart failure symptoms over a few days to weeks. Occasionally, patients have symptoms for several months before heart failure is discovered. The classic presentation of viral myocarditis includes a viral prodrome with fever, myalgia, and upper respiratory symptoms, but a prodrome is not required for the diagnosis. Patients present with dyspnea, chest pain, and arrhythmias. ECG abnormalities are often present, along with evidence of myocardial damage with elevated troponin levels.

Various infectious pathogens can cause myocarditis. The most common causes are adenovirus, coxsackievirus, and enterovirus. The pathogenesis of myocarditis is unclear and may involve direct infection of the myocardium with the virus or an immune system response to the infection.

Endomyocardial biopsy can define myocarditis with evidence of myocardial necrosis, degeneration, or both, with an adjacent inflammatory infiltrate. Indications for endomyocardial biopsy include ventricular arrhythmia, high-grade conduction block (type II or III) or lack of response to usual heart failure therapy.

Therapy for acute myocarditis is supportive and consists of usual heart failure therapy. Placebo-controlled immunosuppressive trials have not demonstrated improvements in mortality or ejection fraction. Patients often take months (6-12) to recover left ventricular function. Approximately 50% of patients eventually recover cardiac function; therefore, it is important to wait and not place an ICD for the usual indications (ejection fraction <35% and NYHA class II or III symptoms) until at least 6 months of heart failure therapy.

Giant Cell Myocarditis

Giant cell myocarditis is an acute, rapidly progressive form of myocarditis associated with ventricular arrhythmias and progressive cardiac dysfunction despite medical therapy. For unclear reasons, this process usually occurs in persons younger than 40 years. The underlying mechanism is unknown but is thought to be autoimmune. On endomyocardial biopsy, the pathognomonic "giant cell" is seen. Unlike other forms of myocarditis, aggressive immunosuppressive therapy has been shown to improve survival but this process is still often fatal. These patients should be considered for cardiac transplantation but often need to be bridged with VADs. There are case reports of giant cell myocarditis recurring post-transplantation.

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Tachycardia-Mediated Cardiomyopathy

Sustained tachyarrhythmia for weeks to months can produce cardiomyopathy. The most common arrhythmias implicated are atrial fibrillation, atrial flutter, and tachycardia. Patients with very frequent premature ventricular contractions (≥10,000/d) can develop cardiomyopathy. Controlling heart rate with medications or ablation often results in improvement and resolution of heart failure for these patients. Patients with tachycardia should be evaluated for hyperthyroidism.

Myocardial Disease

Hypertrophic Cardiomyopathy

Clinical Presentation and Evaluation

Hypertrophic cardiomyopathy (HCM) is an inheritable cardiac disorder with a prevalence of 1 in 500 persons. More than 1400 sarcomeric mutations involving at least 11 different genes have been identified. The mutations demonstrate an autosomal dominant pattern of inheritance with high disease penetrance. Sporadic cases may also occur.

The major pathophysiologic mechanisms contributing to signs and symptoms of HCM are diastolic dysfunction and dynamic left ventricular outflow tract (LVOT) obstruction. Diastolic dysfunction arises from abnormal relaxation and poor myocardial compliance, leading to an increase in left ventricular filling pressures. Dynamic LVOT obstruction, present in approximately two thirds of patients, results from septal hypertrophy and anterior displacement of the mitral valve apparatus; this displacement also is associated with decreased coaptation of the valve leaflets and resultant mitral regurgitation (**Figure 11**, **Figure 12**). Dynamic LVOT obstruction is exacerbated by any drug therapy that increases contractility, such as digoxin or other inotropic agents. Obstruction is also

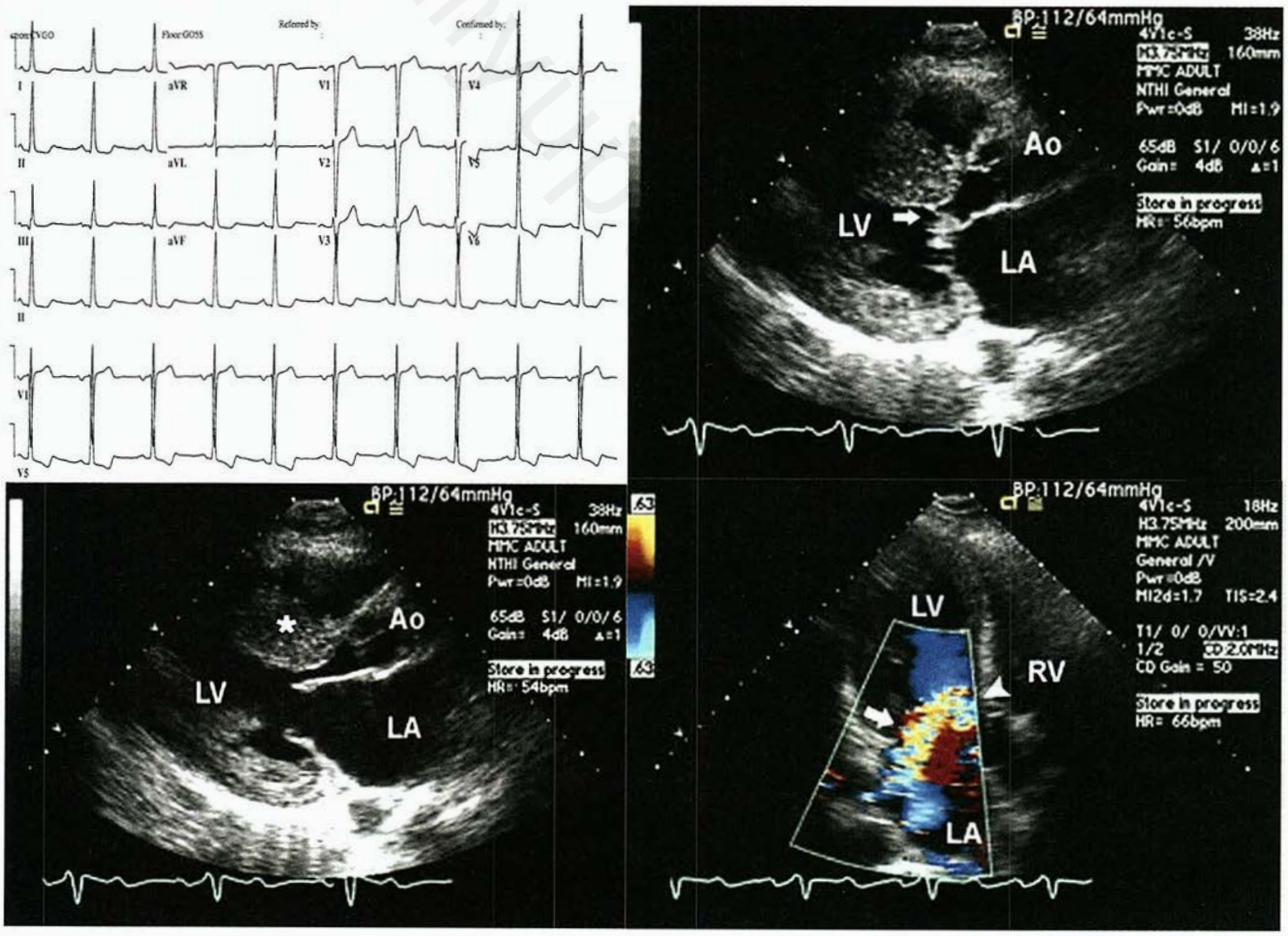

FIGURE 11. A patient with hypertrophic cardiomyopathy. Resting 12-lead electrocardiogram (*top left panel*) demonstrating findings of left ventricular hypertrophy and secondary ST-segment changes. Echocardiography (parasternal view) (*bottom left panel*) demonstrating severe myocardial hypertrophy of the ventricular septum (*asterisk*). Systolic anterior motion of the mitral valve is present (*arrow*) (*top right panel*). Apical long axis view of the left ventricle (*bottom right panel*). Systolic anterior motion of the mitral valve (*arrowhead*) leads to decreased coaptation of the mitral valve and secondary mitral regurgitation (*arrow*). Ao = ascending aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.

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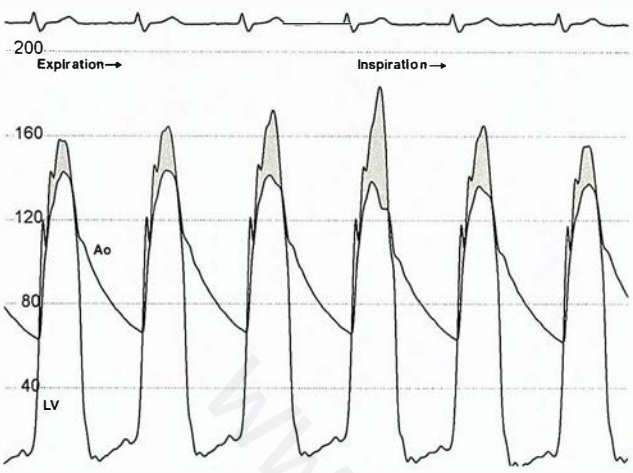

FIGURE 12. Dynamic changes in the left ventricular outflow tract (LVOT) gradient from obstructive hypertrophic cardiomyopathy during respiration. These hemodynamic tracings were taken during quiet respiration. Note that the LVOT gradient (*shaded*) increases significantly with expiration. These changes are mediated by respiratory-induced variation in ventricular afterload and have been described as *reversed pulsus paradoxus*. Ao = ascending aorta; LV = left ventricle.

worsened by reduced ventricular preload, such as from dehydration, or afterload, such as from vasodilator therapy.

Most patients with HCM have minimal or no symptoms. However, a subset develop exertional dyspnea, angina, presyncope, or syncope. Sudden cardiac arrest may be the initial manifestation of the disorder. HCM accounts for approximately 35% of sudden deaths among all persons younger than 35 years and is the leading cause of sudden death in this age group.

Several physical signs are helpful in diagnosing HCM in patients in whom it is suspected. The carotid upstroke typically is rapid and may be bifid (pulsus bisferiens—"twice beating") in those with LVOT obstruction. The jugular venous pulse may demonstrate a heightened *a* wave when there is significant infundibular hypertrophy. The apical impulse typically is sustained, localized, and may be bifid or trifid. An S_4 is frequently present, especially in younger patients. Paradoxical splitting of the S_2 also may occur with significant LVOT obstruction.

The murmur of dynamic LVOT obstruction is systolic with an ejection quality, frequently heard best at the left lower sternal border. Augmentation of the murmur occurs during maneuvers that decrease preload (squat-to-stand, Valsalva strain) and afterload (amyl nitrite inhalation). These maneuvers can help distinguish HCM from other causes of systolic murmurs, such as aortic stenosis and mitral regurgitation. Contrary to HCM, the murmurs of aortic stenosis and mitral regurgitation diminish with maneuvers that reduce preload.

The diagnosis of HCM typically is made by two-dimensional echocardiography and visualization of severe myocardial hypertrophy in the absence of a local or systemic etiology (**Figure 13**). The pattern of myocardial hypertrophy classically is described as asymmetric and involving principally the ventricular septum, but concentric, apical, and eccentric forms also are common. Cardiac magnetic resonance (CMR) imaging also may be used for diagnosis, particularly when there is eccentric or apical hypertrophy that may be difficult to visualize on echocardiography. Doppler echocardiography can accurately diagnose and quantify LVOT obstruction in most instances, with examinations performed at rest, with provocation (such as with amyl nitrite or dobutamine), or during exercise. LVOT obstruction is considered significant when the calculated pressure gradient is either 30 mm Hg or greater at rest, or 50 mm Hg or greater with provocation. In 80% to 90% of patients with HCM, electrocardiography (ECG) demonstrates findings of left ventricular hypertrophy.

Dynamic LVOT obstruction is present in approximately 25% of HCM patients at rest, with another 30% to 40% demonstrating obstruction only after provocative maneuvers. Patients can suffer from debilitating symptoms regardless of the presence of dynamic LVOT obstruction. However, because of the high prevalence of dynamic obstruction in patients with HCM and the availability of specific strategies that can reduce symptoms by alleviating it, clinicians should thoroughly evaluate for the presence and degree of obstruction.

HCM must be distinguished from other disorders that are associated with myocardial hypertrophy or increased wall thickness. These disorders include hypertensive heart disease, aortic stenosis, cardiac amyloidosis, Noonan syndrome, Fabry disease, and mitochondrial cardiomyopathy. Athlete's heart is a syndrome of myocardial hypertrophy that can be difficult to differentiate from HCM. Several clinical features are suggestive of athlete's heart, although a period of deconditioning (6 months or more) may be required to diagnose the presence of physiologic hypertrophy (**Table 20**, on page 45).

KEY POINT

- The systolic murmur of obstructive hypertrophic cardiomyopathy is augmented by maneuvers that decrease preload (squat-to-stand, Valsalva strain); in contrast, the systolic murmurs of aortic stenosis and mitral regurgitation diminish with maneuvers that reduce preload.

Clinical Course and Risk Stratification

Although symptoms of HCM can be debilitating and sudden cardiac death is a devastating complication, symptoms are minimal or absent and lifespan is normal in approximately 90% of patients with HCM. Atrial fibrillation occurs in 20% to 25% of patients with or without symptoms of obstruction. In some patients, owing to the underlying diastolic dysfunction, the loss of atrial systole from these arrhythmias can precipitate significant hemodynamic deterioration in addition to embolic risk. Contemporary investigations of unselected HCM populations demonstrate an incidence of sudden cardiac death of 0.5% to 0.8% per year. All patients with HCM should undergo

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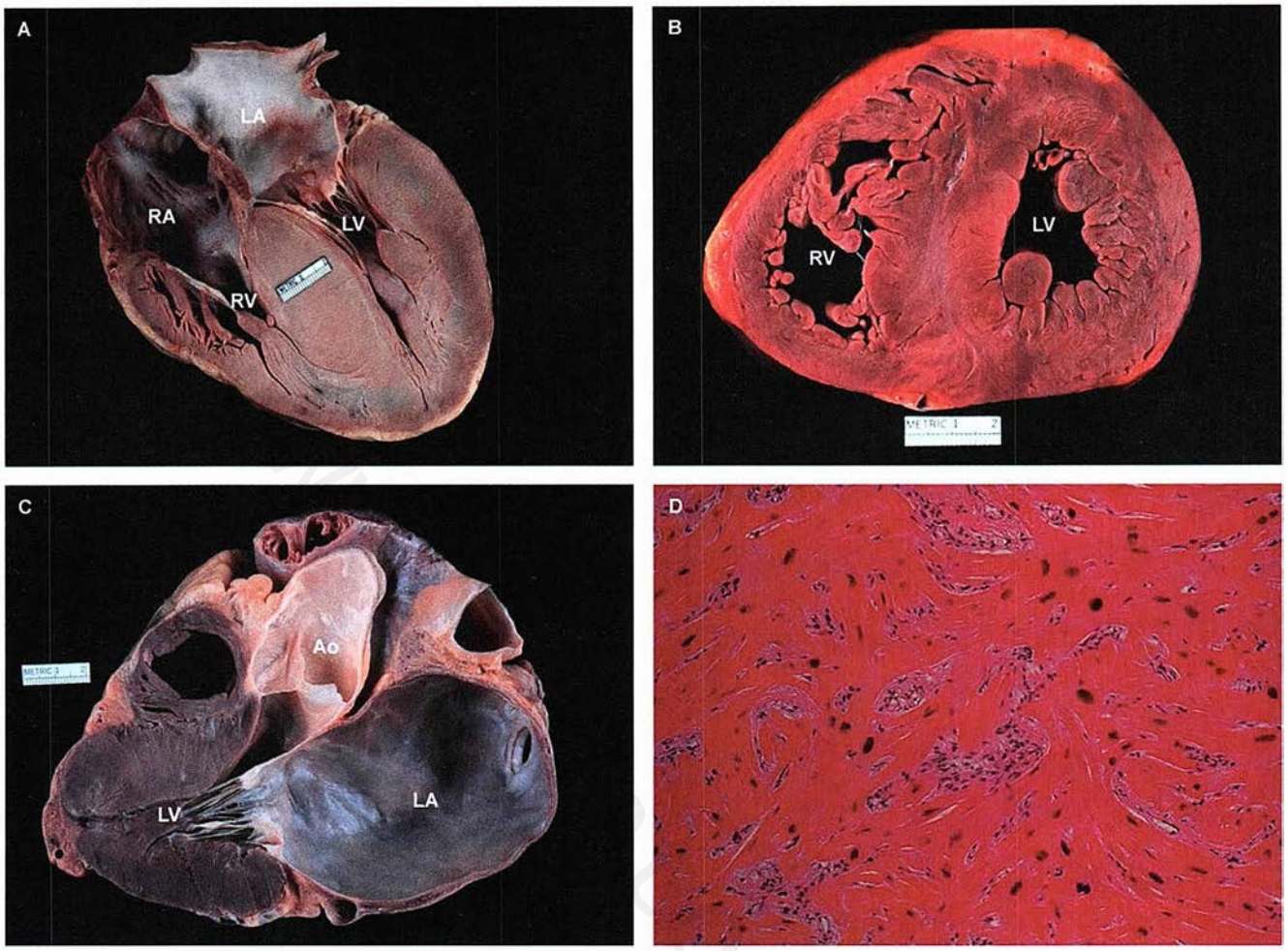

FIGURE 13. Pathology of hypertrophic cardiomyopathy. Gross specimens demonstrate severe myocardial hypertrophy due to hypertrophic cardiomyopathy with concentric hypertrophy (*A* and *B*) and apical hypertrophy (*C*). Microscopy demonstrates myocyte disarray, the histologic hallmark of hypertrophic cardiomyopathy (*D*). Ao = ascending aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Images courtesy of Dr. William D. Edwards, Department of Pathology, Mayo Clinic.

risk stratification for sudden cardiac death (**Table 21**). Therapy with an implantable cardioverter-defibrillator (ICD) should be considered in patients with one or more risk factors. The clinical efficacy of ICDs for prevention of sudden cardiac death in HCM has been demonstrated in several large registries.

KEY POINT

- Placement of an implantable cardioverter-defibrillator should be considered in patients with hypertrophic cardiomyopathy with one or more major risk factors for sudden cardiac death: prior cardiac arrest, massive myocardial hypertrophy, family history of sudden cardiac death, ventricular tachycardia, blunted blood pressure response to exercise, unexplained syncope.

Management

The major management goals for patients with HCM are alleviation of symptoms, risk stratification for sudden cardiac death, ICD implantation for those at high risk, and family counseling. Because a significant number of sudden deaths occur during or following exercise, abstention from competitive sports or strenuous aerobic activities is advised for all patients. Patients with HCM also should be counseled on the need to avoid dehydration and states of severe peripheral vasodilatation, such as from hot baths or saunas. Pregnancy generally is well tolerated, although precautions should be taken to minimize peripheral vasodilatation as for all patients with HCM.

Pharmacologic Treatment

Negative inotropic agents are the cornerstone of medical therapy for patients with symptomatic obstructive HCM. Negative inotropes (β-blockers, nondihydropyridine calcium channel blockers [verapamil], and disopyramide) depress contractility, thereby reducing the intraventricular flow velocities that predispose to LVOT obstruction. These agents also lengthen diastole, facilitating more time for ventricular filling. Appropriate drug therapy suffices for most patients with symptomatic obstructive HCM, although high doses may be required.

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TABLE 20. Clinical Features Distinguishing Hypertrophic Cardiomyopathy from Athlete's Heart

Feature	Hypertrophic Cardiomyopathy	Athlete's Heart
Family history	Positive	Negative
Electrocardiography	Pathologic Q waves, T-wave inversions, conduction defects	Absence of these features
Doppler echocardiography	Diastolic filling abnormalities	Normal diastolic filling
Extent of hypertrophy	>15 mm	Often ≤12 mm
Pattern of hypertrophy	Asymmetric, concentric, or eccentric	Concentric
Left ventricular end-diastolic dimension	<45 mm	>55 mm
Gadolinium hyperenhancement on cardiac magnetic resonance imaging	Present	Absent
Objective exercise testing	% Predicted peak Vo_2 <100%	% Predicted peak Vo_2 >120% or >50 mL/kg/min
Genetic testing	Positive	Negative
Evaluation after period of deconditioning	No regression in hypertrophy	Regression >2 mm

Vo_2 = oxygen consumption.

TABLE 21. Risk Factors for Sudden Death in Patients with Hypertrophic Cardiomyopathy

Risk Factors	Comments
Major[a]	
Cardiac arrest (ventricular fibrillation)	Portends high rate of recurrence or death (11% per year)
Spontaneous sustained VT	
Family history of premature sudden death	Most predictive if occurs in a close relative or multiple relatives
Unexplained syncope	Most predictive if occurs in young patients, is exertional, or is recurrent
Left ventricular diastolic wall thickness ≥30 mm	
Blunted increase (<20 mm Hg) or decrease in systolic blood pressure on exercise	More predictive in patients <50 years of age
Nonsustained spontaneous VT	Less predictive if very brief (≤3 beats) and asymptomatic
Heart failure that has progressed to dilated cardiomyopathy with ejection fraction ≤35% and NYHA class II or III symptoms	Occurs in 5% to 10% of patients with hypertrophic cardiomyopathy
Possible Risk Factors in Individual Patients[a]	
Myocardial ischemia	May be a trigger for sustained ventricular arrhythmia in select patients
Left ventricular outflow obstruction	Gradient is modifiable with therapy
Delayed hyperenhancement with gadolinium on CMR imaging	Is common and is not an independent risk factor. However, severe extent is likely important and can be considered to be an arbitrating risk factor
Factors Not Predictive	
Ventricular arrhythmias inducible by electrophysiologic stimulation	Generally not considered to be of incremental value above noninvasive risk factors

CMR = cardiac magnetic resonance; NYHA = New York Heart Association; VT = ventricular tachycardia.

[a]Risk factors from Gersh BJ, Maron BJ, Bonow RO, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011 Dec 13;58(25):e212-60. [PMID: 22075469]

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Positive inotropes (such as digoxin), vasodilators, and high-dose diuretics should be avoided, as these drugs exacerbate LVOT obstruction. Patients with atrial fibrillation and HCM should receive anticoagulation therapy with warfarin for stroke prevention, independent of cardiovascular risk factors. Although β-blockers are commonly prescribed in these patients, their use in the absence of symptoms or for prevention of sudden cardiac death is generally not recommended.

Septal Reduction Therapy

For patients with persistent, severe, drug-refractory symptoms caused by obstructive HCM, septal reduction therapy with surgical septal myectomy or percutaneous alcohol septal ablation should be considered.

Surgical myectomy is the gold standard therapy for relief of LVOT obstruction. In this procedure, a transaortic approach is typically used to resect the ventricular septum, often extending the resection to the base of the papillary muscles (**Figure 14**). In experienced centers, symptom relief with surgical myectomy occurs in more than 90% of patients with a low perioperative mortality rate (<1%). Long-term survival following myectomy has been found to be comparable to the expected survival of the general population.

Percutaneous alcohol septal ablation is an alternative therapy for septal reduction and may be particularly considered as an option for patients with high surgical risk. In this technique, a slightly oversized angioplasty balloon is placed in a septal perforating artery. The perfusion bed is delineated with contrast, followed by injection of desiccated alcohol. The alcohol results in a controlled infarction, which decreases ventricular systole and thereby ameliorates LVOT obstruction. A major limitation of alcohol ablation is the risk of pacemaker dependency. Pacemaker dependency occurs more frequently in patients with preexistent conduction disease. Incidence is 10% to 15% in patients with a normal ECG but up to 50% in patients with preprocedural left bundle branch block or a wide QRS interval. The decision to implant a pacemaker or ICD in the event of heart block with septal reduction therapy is based primarily on risk factors for sudden death.

In comparison to surgical myectomy, alcohol septal ablation has been associated with similar rates of clinical improvement, as measured by symptoms of heart failure and objective measures of peak myocardial oxygen consumption on treadmill testing. Few data on long-term follow-up after alcohol septal ablation are available, leading to recommendations that this procedure be restricted to relatively older patients as the long-term consequences of the therapeutic infarction of septal ablation are relatively unknown. Current national guidelines recommend that surgical myectomy and alcohol septal ablation should only be performed in centers of expertise, in the context of a longitudinal, comprehensive care program dedicated to patients with HCM.

Role of Genetic Testing and Screening

All first-degree relatives of patients with HCM should undergo screening for the disease. This recommendation is based on the inheritable nature of HCM, the potential for sudden cardiac death, and the demonstrated efficacy of ICDs. Screening consists of physical examination, ECG, and two-dimensional echocardiography (or CMR imaging), with screening intervals recommended according to age, symptoms, and family history (**Table 22**). Ongoing screening of first-degree relatives who are initially free of the disease is recommended throughout adulthood because of the possibility of disease expression at any age.

Genetic testing of patients with HCM can identify pathologic mutations, which can then be used to screen family members for HCM. Genetic counseling is an important facet of the care of patients with HCM, regardless of whether genetic testing is performed. Counseling enables informed decision-making about the risks and benefits of testing and facilitates

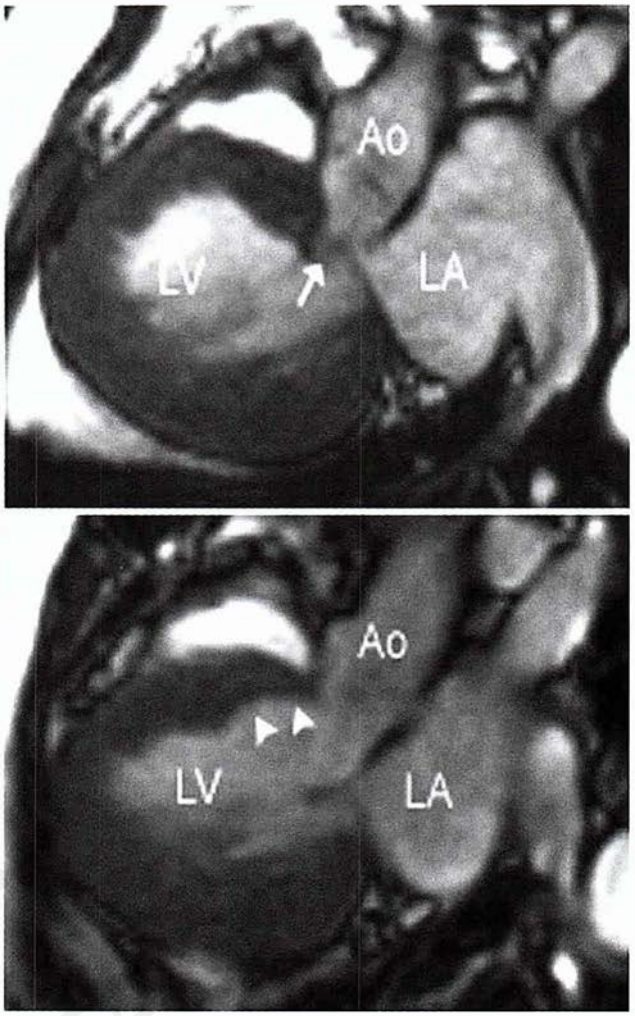

FIGURE 14. Cardiac magnetic resonance (CMR) imaging of hypertrophic cardiomyopathy before and after surgical myectomy. Prior to surgery, there is systolic anterior motion of the mitral valve owing to ventricular septal hypertrophy (*arrow*) (*top panel*). Surgery facilitates direct resection of the basal ventricular septum (*arrowheads*), leading to reconstruction of the left ventricular outflow tract and relief of obstruction (*bottom panel*). Ao = ascending aorta; LA = left atrium; LV = left ventricle.

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TABLE 22. Recommended Screening Intervals for Evaluation of First-Degree Relatives of Patients with Hypertrophic Cardiomyopathy

Age Group	Recommendation
<12 years	Screening optional unless:
	Presence of symptoms
	Family history of malignant ventricular tachyarrhythmias
	Patient is competitive athlete in an intense training program
	Other clinical suspicion of early LV hypertrophy
12 to 18-21 years	Every 12 to 18 months
>18-21 years	At symptom onset or at least every 5 years (more frequently in families with malignant tachyarrhythmias or late onset)

LV = left ventricular.

NOTE: These recommendations are for relatives of patients with hypertrophic cardiomyopathy in whom genetic testing is negative, inconclusive, or not performed.

Recommendations from Gersh BJ, Maron BJ, Bonow RO, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011 Dec 13;58(25):e212-60. [PMID: 22075469]

the interpretation of the results, which can include known pathologic mutations and likely pathogenic mutations, as well as variants of unknown significance.

Genetic testing is performed as a panel, with the mutations associated with the greatest likelihood of pathologic consequences being β-myosin heavy chain, myosin-binding protein C, troponin T, troponin I, α-tropomyosin, actin, regulatory light chain, and essential light chain. A negative genetic test result does not rule out HCM in patients with phenotypic evidence of disease, so their immediate family members still should undergo interval screening. Whereas all patients with HCM can be considered for genetic testing to facilitate diagnosis in family members, the decision to pursue testing is individualized based on likelihood of detecting mutations, patient and family desire, and reimbursement concerns. The likelihood of detecting mutations is increased with a positive family history and a reversed curvature morphology of the ventricular septum. In reversed curvature, the hypertrophy of the septum is maximal in the mid-portion, with relatively less hypertrophy in the apical and basal segments. To date, genetic test results have not been strongly linked to risk of sudden cardiac death, so they should not be used for risk stratification.

KEY POINT

- All first-degree relatives of patients with hypertrophic cardiomyopathy should undergo screening for the disease, with screening intervals recommended according to age, symptoms, and family history.

Restrictive Cardiomyopathy

Clinical Presentation and Evaluation

Primary restrictive cardiomyopathy is an idiopathic disorder characterized by nondilated, poorly compliant ventricles, leading to severe diastolic dysfunction, elevated filling pressures, and heart failure. In rare cases, restrictive cardiomyopathy is familial, with an autosomal dominant pattern of inheritance. Restrictive cardiomyopathy is a diagnosis of exclusion and must be distinguished from constrictive pericarditis (see later), eosinophilic syndromes, radiation-induced disease, storage diseases (such as Fabry disease, hemochromatosis), as well as infiltrative cardiomyopathies, such as amyloidosis and sarcoidosis. Patients with other forms of heart failure can also have restrictive patterns of diastolic ventricular filling but are not defined as having a primary restrictive cardiomyopathy.

Patients with restrictive cardiomyopathy may present at any age, with symptoms and signs of pulmonary and systemic congestion. The diagnosis can be considered when there is severe diastolic dysfunction and dilated atria in the absence of ventricular hypertrophy or cavity dilatation. Systolic function is preserved in most patients or, at least, is disproportionately high given the degree of diastolic dysfunction. Pulmonary hypertension, secondary to diastolic dysfunction, is common.

Endomyocardial biopsy can be performed for patients with suspected restrictive cardiomyopathy to evaluate for infiltrative disease, such as storage diseases or amyloidosis, when clinical assessment or less invasive testing (such as protein electrophoresis or fat biopsy) is inconclusive. The yield of biopsy is low in disorders with patchy myocardial involvement such as sarcoidosis.

Differentiating Restrictive Cardiomyopathy from Constrictive Pericarditis

Both restrictive cardiomyopathy and constrictive pericarditis present with elevation of diastolic pressures and heart failure that is disproportionate to the degree of systolic dysfunction. Distinction of the two disorders is important, as pericardiectomy will result in symptom relief and improvement in longevity in patients with constriction. Imaging and hemodynamic evaluation are most useful for differentiating these entities.

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CONT.

Distinguishing constrictive pericarditis and restrictive cardiomyopathy with physical examination can be challenging, as these conditions have similar signs. In both conditions, peripheral edema with elevation of the jugular venous pulse can be evident. The contour of the jugular venous pulse demonstrates prominent *y* descents owing to accentuation of early ventricular filling, and may rise (or fail to fall) with inspiration because of poor effective operative compliance (Kussmaul sign). In both disorders, if systolic function is preserved, the apical impulse characteristically is not displaced nor diffusely enlarged. In constriction, the apical impulse may be diminished. An early diastolic filling sound may be present in both disorders, attributable to either a "knock" in constrictive pericarditis or an S_3 (right- or left-sided) in restrictive cardiomyopathy. Because of severe diastolic abnormalities, physical findings of pulmonary hypertension are relatively more common in restrictive cardiomyopathy.

Measurement of B-type natriuretic peptide may be useful, as this biomarker is released at high levels in response to wall tension with restrictive cardiomyopathy (≥400 pg/mL [400 ng/L]) but is usually normal or only mildly elevated in constriction (<100 pg/mL [100 ng/L]). CT imaging may demonstrate pericardial thickening and possibly calcification in constrictive pericarditis, although the pericardium can also be normal in thickness in a small subset of patients.

A hemodynamic evaluation is frequently required to distinguish restrictive cardiomyopathy from constriction. As a myocardial disease, restrictive cardiomyopathy may predominantly affect left ventricular filling, resulting in elevated left ventricular end-diastolic pressure and resultant pulmonary hypertension. In patients with constriction, the total cardiac volume is fixed by the rigid pericardium. As a result, there is enhancement of ventricular interdependence and resultant equalization of right and left ventricular diastolic pressures and reciprocal changes in the filling and stroke volume of the right and left ventricles during inspiration (see Pericardial Disease). These reciprocal changes during inspiration can be detected by either echocardiography or cardiac catheterization and are not present in patients with restrictive cardiomyopathy.

Management

The primary goals in the management of restrictive cardiomyopathy are optimization of diastolic filling and relief of pulmonary and systemic congestion. Negative chronotropic agents, such as calcium channel blockers and β-blockers, are beneficial, as they lengthen the diastolic filling period and improve myocardial relaxation. Loop diuretics may be utilized; however, these agents should be used judiciously owing to the underlying poor ventricular compliance, which leads to the need for a relatively high ventricular filling pressure to maintain forward cardiac output. ACE inhibitors (or angiotensin receptor blockers) may improve diastolic function, but the benefit of these drugs in patients with heart failure due to restrictive cardiomyopathy is less certain than in patients with systolic dysfunction. Digoxin, which increases intracellular calcium, should not be used in patients with restrictive cardiomyopathy. Atrial fibrillation, with loss of atrial contractile function, may lead to decompensated heart failure in patients with restrictive cardiomyopathy, but rhythm control may be challenging because of chronic left atrial pressure elevation and dilation.

The overall prognosis is generally poor in patients with idiopathic restrictive cardiomyopathy, with a 5-year survival of approximately 64%. Prognosis is affected by functional status, and cardiac transplantation should be considered in patients with severe refractory symptoms.

KEY POINTS

- Restrictive cardiomyopathy is characterized by severe diastolic dysfunction and, frequently, pulmonary hypertension.
- Restrictive cardiomyopathy is a diagnosis of exclusion and must be distinguished from constrictive pericarditis, eosinophilic syndromes, and infiltrative diseases.

Cardiac Tumors

Tumor Types

Cardiac tumors are usually metastatic, arising from carcinoma of the lung, breast, kidney, esophagus, or liver, or from blood dyscrasias, such as leukemia or lymphoma. Malignant melanoma is commonly associated with cardiac metastases. In autopsy series, cardiac involvement occurs in 10% to 15% of all patients with metastatic malignancy.

Primary cardiac tumors are exceedingly rare (0.02% to 0.06%) and are mostly benign. The most common primary cardiac tumors in adults are myxomas, followed by lipomas and papillary fibroelastomas. Myxomas are connective tissue tumors with cells encompassed within mucopolysaccharide stroma, with an appearance that may be villous, smooth, or friable. Myxomas may arise as part of the Carney complex, an autosomal dominant disorder associated with pigmentation abnormalities (blue nevi), cardiac and extracardiac myxomas, schwannomas, and endocrine tumors. Lipomas are fatty cell tumors that typically arise in the subendocardial layer. Papillary fibroelastomas are pedunculated tumors with frond-like arms, usually present on the left-sided valves of the heart. Malignant sarcomas of various types (angiosarcoma, fibroma, rhabdomyosarcoma, leiomyosarcoma) also have been described with cardiac involvement, accounting for approximately 15% of primary cardiac tumors.

Clinical Presentation and Evaluation

Manifestations of cardiac tumors depend on their location and size. Cardiac tumors that arise near or involve valves may obstruct blood flow or cause regurgitation, leading to pulmonary or systemic congestion. The auscultatory findings associated with left atrial myxoma are classically described as resembling those of a mitral stenosis murmur with an accompanying sound of a "tumor plop"; this finding, however, occurs in the minority of patients (10% to 15%). Patients

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with a myxoma may report constitutional symptoms, such as fever, anorexia, and weight loss, which are likely related to tumor cytokine production. Embolization, from either tumor fragments or associated thrombi, may cause neurologic symptoms or other systemic sequelae. Such embolization is relatively more common with villous or friable myxomas and papillary fibroelastomas. In a series of 74 patients with left atrial myxoma, systemic embolization occurred in 12%. Cardiac tumors, particularly lipomas and malignant sarcomas, may either directly invade or be located within myocardium, causing heart block or impairment of contractility. Pericardial effusion with or without tamponade also is a common manifestation.

Imaging (echocardiography, CT, or CMR imaging) is needed for the detection and evaluation of cardiac tumors. Myxomas characteristically are pedunculated and gelatinous, arising most commonly in the left atrium with the stalk adherent to the fossa ovalis (85% of cases) (**Figure 15**). Papillary fibroelastomas, whose origin may be related to trauma, typically involve left-sided cardiac valves or the left ventricular outflow tract. Papillary fibroelastomas have a central core stalk with fronds and often are mobile, with an appearance resembling a sea anemone (**Figure 16**). Lipomas typically are found within the subendocardium, although involvement of valves has been reported. Sarcomas frequently infiltrate the myocardium. Although sarcomas may occur in the right atrium, myxomas predominate as the cause of primary cardiac tumors in both atria.

Management

The need for surgical resection is dependent on the size, location, and malignant nature of the cardiac tumor, in addition to symptoms and risk of embolization. Myxomas should be resected after diagnosis owing to the risk of embolization and cardiovascular complications, including the potential for sudden death. Survival for patients after surgical resection of myxoma is comparable to that of healthy individuals. Myxomas may recur, with a reported incidence varying between 5% and 13%, with recurrence being more common in younger patients and those with Carney complex or a positive family history. Routine surveillance with imaging is indicated to monitor for recurrence, which usually occurs at the original site of the tumor.

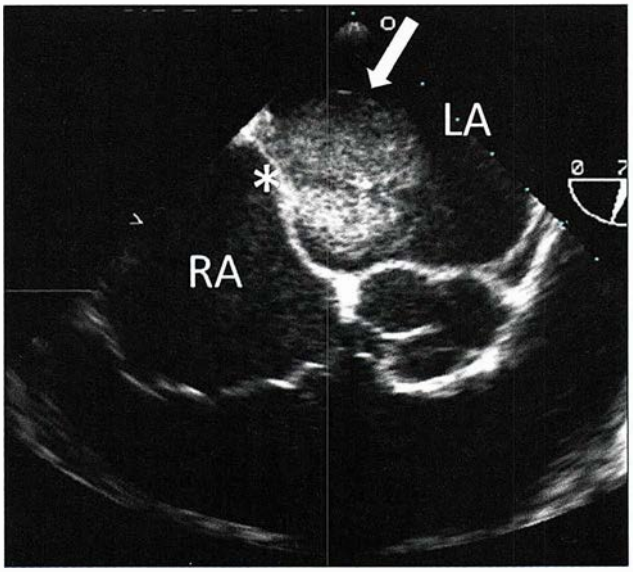

FIGURE 15. Transesophageal echocardiography across the right atrium (RA) and left atrium (LA) demonstrates a large mass (*arrow*) attached to the atrial septum in proximity of the fossa ovalis (*asterisk*); the mass was surgically removed and proved to be a left atrial myxoma.

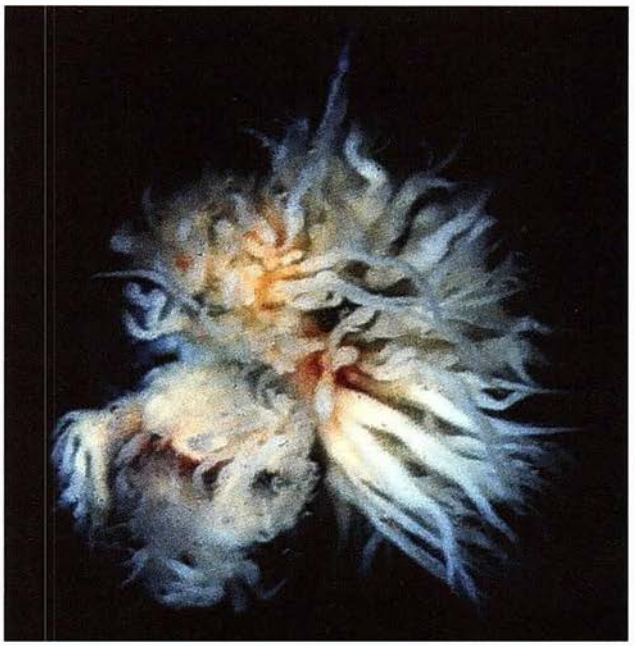

FIGURE 16. Gross pathologic specimen of a papillary fibroelastoma.

Image courtesy of Dr. William D. Edwards, Department of Pathology, Mayo Clinic.

Surgical resection is often considered for papillary fibroelastoma, particularly if the lesion is large (>10 mm), highly mobile, or associated with systemic embolization.

Treatment of tumors with myocardial involvement is challenging. In particular, sarcomas are difficult to treat owing to their widespread, invasive nature and the high recurrence rates despite surgical resection. Survival is improved when there is complete resection and no metastatic involvement (median survival, 15 to 18 months versus 2 to 5 months). Cardiac transplantation using an allograft or autograft may be a therapeutic option in selected patients. In the autograft procedure, the tumor is resected from an excised heart, followed by reconstruction and auto-implantation of the heart into the patient.

KEY POINT

- Myxomas should be resected after diagnosis owing to the risk of embolization and cardiovascular complications, including the potential for sudden death.

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Arrhythmias

Antiarrhythmic Medications

Antiarrhythmic medications are used to prevent recurrent arrhythmias and maintain sinus rhythm. Although antiarrhythmic medications have historically been organized according to their predominant mechanism of action using the Vaughan-Williams classification system (**Table 23**), it is increasingly recognized that this nomenclature system has limitations because most antiarrhythmic drugs have several mechanistic actions.

The membrane-active antiarrhythmic agents (class I and class III) principally affect ion channels. Class I agents decrease impulse formation and speed of depolarization and are often used in patients with atrial arrhythmias and no structural heart disease. Several class IA agents are used less frequently, although they are helpful in specific situations (see Table 23), including the use of procainamide in patients with preexcited atrial fibrillation. Class IC agents are avoided in patients with coronary artery disease and structural heart disease as they have been shown to cause proarrhythmic activity (ventricular arrhythmias) and increase mortality. Class II agents (β-blockers) and class IV agents (nondihydropyridine calcium channel blockers) are frequently used to slow heart rates in patients with supraventricular or atrial arrhythmias; however, they should be avoided in patients who have atrial fibrillation with preexcitation. Class III agents are used to treat atrial and ventricular arrhythmias. These agents are cleared by the kidneys and should be avoided in patients with significant chronic kidney disease owing to increased toxicity and proarrhythmia. Because class III agents lead to QTc-interval prolongation, initiation of this therapy is usually done on an inpatient basis

TABLE 23. Antiarrhythmic Medications

Classification	Mechanism of Action	Individual Agents/ Examples	Effects	Use
Class IA	Sodium channel blockade with some potassium channel blockade	Quinidine, procainamide, disopyramide	Decreases speed of depolarization and prolongs repolarization	Pre-excited atrial fibrillation (procainamide), Brugada syndrome (quinidine), SVT, atrial fibrillation, and ventricular arrhythmias
Class IB	Sodium channel blockade	Lidocaine, mexiletine, phenytoin	Decreases speed of depolarization	Ventricular arrhythmias
Class IC	Sodium channel blockade	Flecainide, propafenone	Decreases speed of depolarization and shortens repolarization	Atrial fibrillation, SVT, ventricular arrhythmias; avoid with CAD or structural heart disease.
Class II	β-adrenergic blockade	Metoprolol, propranolol, carvedilol, atenolol, bisoprolol	Decreases sympathetic tone; suppresses automaticity, sinoatrial conduction, and AV conduction	Rate control of atrial arrhythmias, SVT, ventricular arrhythmias; avoid if pre-excitation is present.
Class III	Potassium channel blockade	Sotalol, dofetilide	Prolongs action potential duration	Atrial fibrillation, atrial flutter, ventricular arrhythmias; avoid in CKD.
Class IV	Calcium channel blockade (nondihydropyridines)	Verapamil, diltiazem	Suppresses sinoatrial and AV conduction	SVT, rate control of atrial arrhythmias, triggered arrhythmias (e.g., outflow tract VT); avoid if pre-excitation is present.
Multichannel blockers	Several, including potassium, sodium, and calcium channel blockade	Amiodarone, dronedarone	Multiple mechanisms, although they act principally by extending repolarization	Atrial arrhythmias, ventricular arrhythmias
Adenosine receptor agonists	A_1-receptor agonist	Adenosine	Slows or blocks sinoatrial and AV nodal conduction	Termination of SVT
Cardiac glycoside	Increasing vagal activity	Digoxin	Slows AV nodal conduction	Rate control of atrial fibrillation

AV = atrioventricular; CAD = coronary artery disease; CKD = chronic kidney disease; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

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with regular assessment of the QTc interval. Patients taking class III agents should avoid other QT-prolonging medications, and serum potassium and magnesium levels should be checked regularly.

Amiodarone, a multichannel blocker, is among the most commonly used antiarrhythmic medications. It is frequently used to treat atrial fibrillation in older persons and to prevent recurrent ventricular tachycardia. Amiodarone is the preferred antiarrhythmic agent in patients with structural heart disease and heart failure. Although highly effective, amiodarone has multiple toxicities. Amiodarone therapy is associated with risks for thyroid toxicity, hepatotoxicity, lung toxicity, photosensitivity, corneal and lenticular deposits, optic neuropathy, and other neurologic adverse effects. Patients on amiodarone require routine monitoring of thyroid and liver function, pulmonary function testing at baseline and with symptoms, and periodic ophthalmologic evaluation. Amiodarone interacts with several medications. Patients on amiodarone require lower doses of warfarin, statins, and digoxin. Dronedarone is a multichannel blocker used to treat atrial fibrillation. Owing to increased mortality in patients with heart failure or permanent atrial fibrillation, its use should be restricted to patients with intermittent atrial fibrillation and no overt heart failure.

Digoxin is an oral positive inotropic agent that acts on the sodium-potassium exchanger and has vagal properties that lead to decreased atrioventricular (AV) nodal conduction. As a result of its vagal mechanism, it primarily controls the heart rate at rest and is less effective during activity. Adenosine is an A_1-receptor blocker that can inhibit AV conduction. Adenosine is frequently used as a therapeutic agent to terminate supraventricular tachycardia.

KEY POINT

- Calcium channel blockers and β-blockers are often used to treat supraventricular and atrial arrhythmias; however, these agents should be avoided in patients who have atrial fibrillation with preexcitation.

Approach to the Patient with Bradycardia

Clinical Presentation

Symptoms of bradycardia (heart rate less than 60/min) include fatigue, exertional intolerance, dyspnea, lightheadedness, and syncope. Bradycardia can result from pathology in the sinus node, the AV node, or the His-Purkinje system. Physicians should maintain a high suspicion for reversible causes of bradycardia, including elevated intracranial pressure, hypothyroidism, hyperkalemia, Lyme disease, and medication effects (most commonly AV nodal blockers, especially β-blockers and digoxin).

The diagnostic evaluation of bradycardia includes (1) establishing a correlation between the rhythm (bradycardia) and symptoms and (2) excluding severe conduction abnormalities that require urgent intervention. Evaluation includes a careful history, a focused laboratory evaluation (including an assessment of thyroid function), resting 12-lead electrocardiogram (ECG), exercise treadmill testing to assess the heart rate response to exercise (chronotropic competence), and ambulatory ECG monitoring based on the nature and frequency of the patient's episodes or symptoms (see Diagnostic Testing in Cardiology). Rarely, electrophysiologic testing can be used to help ascertain if sinus node dysfunction is present.

Sinus Bradycardia

Sinus bradycardia (sinus rhythm with a heart rate <60/min) may be appropriate in several situations, including in trained athletes or during sleep, when the heart rate may fall as low as 30/min. The most common intrinsic cause of inappropriate or pathologic sinus bradycardia (sinus node dysfunction) is age-related myocardial fibrosis in the vicinity of the sinus node. The most common extrinsic cause of sinus bradycardia is medication effect. Sinus node dysfunction can also present with chronotropic incompetence, and this is frequently overlooked. Other, less common, causes of sinus node dysfunction include right coronary ischemia, intracranial hypertension, postsurgical scarring after cardiothoracic surgery, and infiltrative or inflammatory disorders (such as sarcoidosis).

Atrioventricular Block

AV block is classified as first degree, second degree, or third degree. First-degree AV block is characterized by prolonged AV conduction, which manifests on the ECG as a PR interval greater than 200 msec. First-degree AV block is not a true block because all P waves conduct to the ventricles. It has been associated with an increased risk of atrial fibrillation, pacemaker implantation, and all-cause mortality in long-term follow-up.

In second-degree AV block, some P waves conduct to the ventricle and some do not. There are two forms of second-degree AV block. When progressive PR prolongation is observed prior to a blocked beat, second-degree Mobitz type 1 (Wenckebach block) is present. Second-degree Mobitz type 1 block is characterized by grouped beating and progressive shortening of the R-R intervals. Mobitz type 1 block is almost always localized to the AV node. It generally carries a benign prognosis and frequently improves with exercise or increased sympathetic tone.

When the PR interval is constant prior to nonconducted P waves, the second-degree block is termed Mobitz type 2 block. When 2:1 block is present, Mobitz type 1 versus type 2 block cannot be differentiated. Mobitz type 2 block usually represents block lower in the conduction system and has a higher risk of progression to complete heart block.

Third-degree AV block, or complete heart block, is defined as the failure of any P waves to conduct to the ventricles, and it is characterized by AV dissociation on the ECG.

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Pacemakers

Pacemakers are indicated in patients with symptomatic bradycardia in the absence of a reversible cause, hence the importance of establishing symptoms when evaluating patients with bradycardia. In patients with minimal symptoms, a persistent resting heart rate below 40/min is also considered an indication for permanent pacing. Pacemakers also are indicated in patients with evidence of AV conduction disturbances that have a high likelihood of progressing to complete heart block or life-threatening sudden asystole. Indications for permanent pacemaker implantation are shown in **Table 24**.

TABLE 24. Selected Indications for Permanent Pacing

Symptomatic bradycardia without reversible cause
Asymptomatic bradycardia with significant pauses (>3 seconds in sinus rhythm) or persistent heart rate <40/min
Atrial fibrillation with 5-second pauses
Asymptomatic complete heart block or Mobitz type 2 second-degree atrioventricular block
Alternating bundle branch block

Patients with intraventricular conduction delays have a low risk of progression to complete heart block (1%–3% annually) and do not require permanent pacing. When a patient develops new-onset conduction disease in the setting of an acute coronary syndrome, temporary pacing may be required, but decisions on permanent pacing should be delayed until a patient has been revascularized and stabilized to determine whether the arrhythmia persists.

Patients with pacemakers who require surgery should have a preoperative device evaluation to determine whether preoperative reprogramming of the device is necessary. Although "MRI conditional" pacemakers are now available, the presence of a pacemaker remains a contraindication to MRI scanning for most patients.

There are several types of implanted cardiac devices, with various capabilities. Implanted cardiac electronic devices include implanted loop monitors, pacemakers, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization devices. With the exception of subcutaneous ICDs, which do not utilize intracardiac leads, all ICDs also have pacemaker functions. **Table 25** reviews the various types of implanted

TABLE 25. Cardiac Implantable Electronic Devices for Treatment of Cardiac Rhythm Disorders

			Functions		
Device	**Components**	**Indications**	**Pacemaker Function**	**Antitachycardia Pacing**	**Defibrillation**
Pacemaker	Pulse generator and intravascular leads (single- or dual-chamber)	Sinus node dysfunction, atrioventricular block, or other causes of non-reversible symptomatic bradycardia	Yes	No	No
Implantable cardioverter-defibrillator	Defibrillator and intravascular leads (single- or dual-chamber)	To provide continuous monitoring and treatment of ventricular arrhythmias	Yes	Yes	Yes
Subcutaneous implantable cardioverter-defibrillator	Defibrillator and a single lead that are entirely under the skin (extravascular); no transvenous leads	To provide continuous monitoring and treatment of ventricular arrhythmias	No	No	Yes
Cardiac resynchronization therapy-pacing (CRT-P)	Pulse generator and intravascular leads, including a pacing lead in the coronary sinus to pace the left ventricle	To restore electrical synchrony between the ventricles in patients with heart failure	Yes	No	No
Cardiac resynchronization therapy-defibrillator (CRT-D)	Defibrillator and intravascular leads, including a pacing lead in the coronary sinus to pace the left ventricle	To restore electrical synchrony between the ventricles in patients with heart failure and to monitor and treat ventricular arrhythmias	Yes	Yes	Yes

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CONT. cardiac electronic devices, their functions, and their general indications.

KEY POINT

- A pacemaker is indicated for symptomatic bradycardia without a reversible cause as well as for atrioventricular conduction abnormalities that are likely to progress to complete heart block.

Approach to the Patient with Tachycardia

Patients with symptomatic tachycardia often report palpitations, lightheadedness or dizziness, chest discomfort, dyspnea, exertional intolerance, or syncope. Some patients are asymptomatic and are found to have arrhythmias incidentally during monitoring in the setting of hospitalization or other medical care. The most important part of the evaluation is the documentation of tachycardia and correlation with symptoms (see Diagnostic Testing in Cardiology). In addition to a history and physical examination, all patients with tachycardia should have a resting 12-lead ECG. Most patients with tachycardia should undergo echocardiography to exclude the presence of structural heart disease and thyroid function evaluation.

In both hospital and ambulatory settings, sinus tachycardia (sinus rhythm with heart rate >100/min) is the most commonly encountered tachycardia. Sinus tachycardia is usually caused by physiologic distress, including pain, fever, anemia, or anxiety. The evaluation and treatment of sinus tachycardia are directed at the underlying etiology. Significant sinus tachycardia in a critically ill patient is a worrisome finding as it usually indicates advanced physiologic compromise, including respiratory failure, insufficient cardiac output, or severe infection.

Older patients with palpitations are more likely to have atrial fibrillation, atrial flutter, or ventricular tachycardia (VT). Although VT is often associated with hemodynamic compromise, VT is often well tolerated, whereas many patients have hemodynamically significant supraventricular tachycardia or atrial arrhythmias. Therefore, vital signs are not helpful in determining the nature of an arrhythmia.

In younger persons with tachycardic symptoms, supraventricular tachycardias are more common, including AV nodal reentrant tachycardia (AVNRT) and accessory pathway–mediated tachycardia. Patients with an accessory pathway often have evidence of anterograde conduction and a delta wave on ECG.

Atrial and ventricular ectopy are present in many—if not most—persons. The frequency of ectopy and symptoms usually dictate both the work-up and subsequent management.

KEY POINT

- In addition to a resting electrocardiogram, diagnostic testing for most patients with tachycardia should include an echocardiogram and evaluation of thyroid function.

Supraventricular Tachycardias

Clinical Presentation

Supraventricular tachycardias (SVTs) are a group of arrhythmias that arise in atrial tissue or the AV node. Because conduction of supraventricular impulses below the AV node is conducted normally, the ECG in SVT usually reveals a narrow-complex tachycardia, although the QRS complexes can be wide (>120 msec) in the presence of bundle branch block, aberrancy, pacing, or anterograde accessory pathway conduction (antidromic tachycardia).

SVTs include abnormal electrical activity arising in the atrium (premature atrial contractions, tachycardia, atrial fibrillation and flutter, multifocal atrial tachycardia) or AV node (junctional tachycardia, AVNRT, atrioventricular reciprocating tachycardia [AVRT]). Because they are so common and for the purpose of this review, atrial fibrillation and atrial flutter are discussed separately; the rest of this section will focus exclusively on the other SVTs.

SVT can occur in all age groups but is frequently encountered in younger patients. SVT is more common in women than men and usually occurs without structural heart disease, although this should be evaluated with an echocardiogram. Patients with SVT often have repeated episodes of tachycardia. Patients may have palpitations, a sensation of pounding in the neck, fatigue, lightheadedness, chest discomfort, dyspnea, presyncope, and, less commonly, syncope.

The ECG classification of SVT is usually based on the relationship of the P wave and the QRS complex. In short-RP tachycardias (RP interval < PR interval), the P wave closely follows the QRS complex. In long-RP tachycardias (RP interval > PR interval), the P wave is more than half the distance between the QRS complexes. Short-RP tachycardias include typical AVNRT, AVRT, and junctional tachycardia. Junctional tachycardias are less common in adults, but they can occur in patients with digoxin intoxication and other conditions. Long-RP tachycardias include atypical AVNRT, sinus tachycardia, atrial tachycardia, and the permanent form of junctional reciprocating tachycardia.

Episodes of SVT can often be terminated with Valsalva maneuvers (bearing down), carotid sinus massage, or facial immersion in cold water. Adenosine can be used to terminate SVT and to help diagnose the etiology. Termination with adenosine often suggests AV node dependence (AVNRT and AVRT), whereas continued atrial activity (P waves) during AV block can help identify atrial flutter and atrial tachycardia.

Premature Atrial Contractions and Atrial Tachycardia

Atrial ectopy can be isolated (premature atrial contractions [PACs]), occur in salvos, or be sustained (atrial tachycardia). PACs are extremely common, and the frequency increases with age. Only 1% of persons in the general population have no PACs during ambulatory ECG monitoring. However, PAC burden is associated with increased risk of atrial fibrillation.

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Symptomatic PACs are typically treated with β-blockers or calcium channel blockers.

Atrial tachycardia can occur in patients with or without structural heart disease; when symptomatic, first-line treatment is a β-blocker or nondihydropyridine calcium channel blocker (diltiazem or verapamil). Second-line treatment includes catheter ablation or antiarrhythmic drug therapy. In general, success rates for ablation of atrial tachycardia are lower than those for other SVTs.

Multifocal atrial tachycardia, characterized by multiple (≥3) P-wave morphologies and a heart rate greater than 100/min, is frequently seen in patients with end-stage COPD. Treatment is usually directed at the underlying etiology and electrolyte disturbances, although β-blockers and calcium nondihydropyridine calcium channel blockers can be used cautiously.

Atrioventricular Nodal Reentrant Tachycardia

AVNRT is the most common type of SVT, accounting for two thirds of all patients with SVT (excluding atrial fibrillation and atrial flutter). AVNRT is caused by reentrant conduction within the AV node, utilizing both the fast and slow pathways (**Figure 17**). In *typical* AVNRT, the electrical conduction goes down the slow pathway and conducts back up toward the atrium over the fast pathway (slow-fast). This leads to a short RP interval with a retrograde P wave inscribed very close to the QRS complex. The closely coupled retrograde P waves may be buried in the QRS complexes and may not be visible, or they may appear as a pseudo R′ wave in lead V_1 and a pseudo S wave in the inferior leads. In *atypical* AVNRT, conduction goes down the fast pathway and returns to the atrium via the slow pathway (fast-slow); this leads to a long RP interval. Rarely, AVNRT can involve conduction over more than one slow pathway (slow-slow AVNRT).

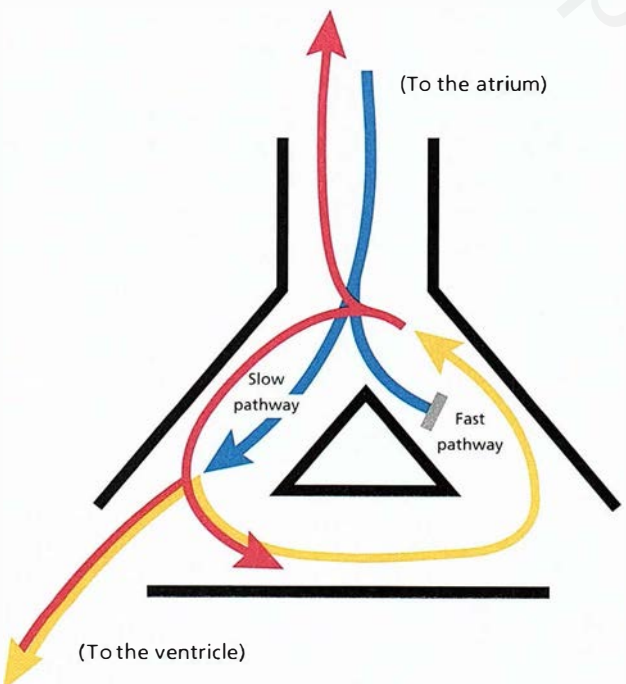

FIGURE 17. Mechanism of typical atrioventricular nodal reentrant tachycardia. The slow pathway has a short refractory period, and the fast pathway has a long refractory period. The *blue line* represents anterograde conduction down the slow pathway; conduction does not occur down the fast pathway because it is refractory. The *yellow line* represents impulse conduction into the ventricle and retrograde up the fast pathway, which is no longer refractory. The *red line* represents completion of the circuit with activation of the atria and ventricles.

Beyond acute termination with physical maneuvers or adenosine, treatment to prevent recurrent AVNRT includes AV nodal blocking therapy with β-blockers or nondihydropyridine calcium channel blockers. Patients who have recurrent AVNRT or do not tolerate or prefer to avoid long-term medical therapy are usually referred for catheter ablation, which has a high success rate. The major risk of ablation is a 1% risk of injury to the AV node requiring pacemaker implantation.

Atrioventricular Reciprocating Tachycardia

AVRT is an accessory pathway (bypass tract)–mediated tachycardia. Accessory pathway conduction is often observed as preexcitation on ECG. Because of early ventricular activation over the accessory pathway, the PR interval is shortened and the initial part of the QRS complex is slurred (delta wave) because of ventricular depolarization adjacent to the pathway. In AVRT, conduction is anterograde over the AV node (orthodromic AVRT) or anterograde over the accessory pathway (antidromic AVRT). Orthodromic AVNRT, the most common type of AVRT (more than 90% to 95% of cases) is characterized by a narrow QRS complex resulting from conduction over the AV node and the His-Purkinje system. Antidromic AVRT is characterized by a wide, slurred QRS complex resulting from conduction over the bypass tract and activation of the ventricle without use of the specialized conduction system. Adenosine can be given to terminate orthodromic AVRT; however, adenosine or other AV nodal blockers are contraindicated in preexcited atrial fibrillation and antidromic AVRT. AV nodal blockade in patients with these rhythms can promote rapid conduction down the bypass tract and induction of ventricular fibrillation (VF).

Patients with evidence of preexcitation on their resting ECG (delta wave) and symptomatic SVT have Wolff-Parkinson-White (WPW) syndrome. Up to one third of patients with WPW syndrome have or will develop atrial fibrillation. Rapid conduction over an accessory pathway in atrial fibrillation can lead to VF and sudden cardiac death (SCD), although this is a relatively rare event. Risk factors for VF in WPW syndrome include documented AVRT, multiple bypass tracts, Ebstein anomaly (right heart enlargement and severe tricuspid valve regurgitation), and a rapidly conducting accessory pathway. WPW syndrome is often seen in patients with Ebstein anomaly.

In general, evaluation of a patient with preexcitation includes a 12-lead ECG, echocardiogram, ambulatory ECG monitoring, and an exercise stress test. Stress testing is an

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effective means of noninvasive risk stratification for patients with preexcitation. Loss of preexcitation during exercise generally indicates low risk. Electrophysiology (EP) testing can help determine rapidity of conduction and risk for sudden death; it also can help localize the pathway and facilitate catheter ablation, which has a high success rate (although success depends on the location of the bypass tract). In general, catheter ablation is first-line therapy for patients with preexcitation and symptoms. Antiarrhythmic agents are reserved for second-line therapy, particularly in patients with accessory pathways in close vicinity to the AV node.

Management of asymptomatic preexcitation on ECG is controversial. In the absence of symptoms, however, invasive testing is generally not required, unless the patient has a high-risk occupation, such as an airline pilot or bus driver.

KEY POINTS

- Therapeutic options for prevention of recurrence of atrioventricular nodal reentrant tachycardia include atrioventricular nodal blocking drugs and catheter ablation.
- First-line therapy for Wolff-Parkinson-White syndrome (preexcitation with symptoms) is catheter ablation.

Atrial Fibrillation

Atrial fibrillation is the most common sustained cardiac arrhythmia. The diagnosis of atrial fibrillation is based upon the demonstration of disorganized atrial activity, seen as an irregularly irregular ventricular response on ECG. Fibrillation of the atrial myocardium can lead to stasis and intracardiac thrombus formation. In patients older than 40 years, the lifetime risk of atrial fibrillation is 1 in 4. The incidence of atrial fibrillation is age-related, and more than 10% of persons aged 80 years and older have atrial fibrillation. Atrial fibrillation is associated with a fivefold increased risk of stroke as well as an increased risk of heart failure and dementia. Atrial fibrillation can occur secondary to reversible or acute physiologic insults, including hyperthyroidism, cardiac surgery, and pulmonary embolism. More commonly, atrial fibrillation is the result of long-standing disease affecting the heart, particularly hypertension, structural heart disease, and obstructive sleep apnea.

Clinical Presentation

As with most arrhythmias, patients with atrial fibrillation can experience a wide range of symptoms, including palpitations, lightheadedness or dizziness, dyspnea, exercise intolerance, chest pain, and syncope. Some patients are asymptomatic and are found to have atrial fibrillation as an incidental finding on ECG. In its most severe forms, particularly in patients with advanced diastolic dysfunction or restrictive cardiomyopathy, atrial fibrillation can result in hemodynamic compromise. Some patients initially present with heart failure caused by tachycardia-induced cardiomyopathy.

Atrial fibrillation is classified as first-detected, paroxysmal, persistent, or long-standing persistent atrial fibrillation. Paroxysmal atrial fibrillation starts and stops spontaneously. Persistent atrial fibrillation lasts for 7 days or more and requires electrical or pharmacologic cardioversion. Long-standing persistent atrial fibrillation is persistent atrial fibrillation that is more than 1 year in duration.

Acute Management

Both acute and chronic management of atrial fibrillation are based on three therapeutic goals: (1) preventing stroke, (2) controlling the heart rate (preventing tachycardia/rapid ventricular rates), and (3) symptom relief. Once a diagnosis of atrial fibrillation is made, a search for reversible causes should be completed, including an evaluation of thyroid function. Patients with atrial fibrillation should undergo screening for sleep apnea with more extensive testing if the clinical history is suggestive. An echocardiogram should be obtained to investigate potential valvular or other structural heart disease.

Acute Anticoagulation

In patients with newly discovered atrial fibrillation in whom cardioversion will not be performed, institution of intravenous anticoagulation is usually not necessary. In these patients, oral anticoagulation can be started based on risk factors (see Long-Term Management). If cardioversion is planned, anticoagulation therapy is based on the duration of atrial fibrillation. For patients who are known to have been in atrial fibrillation for less than 48 hours, preprocedural anticoagulation is not necessary as the risk of thrombus formation is low. Patients with atrial fibrillation of unclear duration or those with atrial fibrillation for more than 48 hours require preprocedural anticoagulation. These patients should receive 3 weeks of therapeutic anticoagulation prior to cardioversion. Alternatively, transesophageal echocardiography (TEE) can be performed to look for an intracardiac thrombus. If TEE is negative for thrombus, acute cardioversion can be performed immediately. All patients (regardless of the duration of atrial fibrillation) must be anticoagulated at the time of cardioversion and after cardioversion for a minimum of 4 weeks owing to an increased risk of thromboembolic events after restoration of sinus rhythm.

Cardioversion and Acute Rate Control

Many patients who present with an initial episode of atrial fibrillation convert spontaneously, often within hours. However, the presence of hypotension, myocardial ischemia, or heart failure is an indication for immediate cardioversion regardless of the duration of atrial fibrillation. Acute cardioversion of atrial fibrillation should be synchronized to the R wave so as to avoid an "R-on-T" event and provocation of VF.

Patients with rapid ventricular conduction require heart rate control in order to improve cardiac function and symptoms. Target heart rates should be between 60/min and 110/min in the acute setting. Acute rate control is most

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often achieved with β-blockers or nondihydropyridine calcium channel blockers. Intravenous medications, including metoprolol, esmolol, diltiazem, and verapamil, can be used, with subsequent transition to oral formulations. In patients with mild symptoms, oral agents can be considered without initial intravenous therapy. Calcium channel blockers should be avoided in patients with left ventricular dysfunction. Digoxin can be added to improve rate control, especially in patients with heart failure. Patients with evidence of preexcitation should not be treated with β-blockers or calcium channel blockers. In patients with preexcited atrial fibrillation, procainamide is the treatment of choice.

If cardioversion is favored because of significant symptoms despite rate control, pharmacologic or electrical cardioversion can be pursued. Class IC agents (flecainide, propafenone) or ibutilide (an intravenous class III medication) can be considered for pharmacologic cardioversion in patients without structural heart disease.

Long-Term Management

Anticoagulation

Stroke is the most concerning consequence of atrial fibrillation. The absolute risk of stroke is 4% per year among patients with nonvalvular atrial fibrillation, but comorbidities can increase the risk 15 to 20 times. Hypertension is an important risk factor for both atrial fibrillation and stroke; therefore, aggressive blood pressure control is paramount in the management of atrial fibrillation.

Stroke prevention with antithrombotic therapies is predicated on a patient's aggregate risk profile. Several risk stratification scores are available to clinicians. In patients with nonvalvular atrial fibrillation, the $CHADS_2$ score was, until recently, the basis for most guideline and consensus documents. Owing to the limited ability of the $CHADS_2$ score to discern between low and intermediate risk, the CHA_2DS_2-VASc risk score was developed and now is the recommended score to assess risk of stroke in patients with nonvalvular atrial fibrillation (**Table 26**). The CHA_2DS_2-VASc score is particularly

TABLE 26. Risk Stratification Scores, Adjusted Stroke Rates, and Antithrombotic Therapy Recommendations

Score	Incidence of Ischemic Stroke (per 100 patient-years)[a]	Antithrombotic Therapy[b]
$CHADS_2$ Score[c]		
0	0.6	Aspirin or no therapy
1	3.0	Aspirin or OAC
2	4.2	OAC
3	7.1	OAC
4	11.1	OAC
5	12.5	OAC
6	13.0	OAC
CHA_2DS_2-VASc Score[d]		
0	0.2	None
1	0.6	None or aspirin or OAC
2	2.2	OAC
3	3.2	OAC
4	4.8	OAC
5	7.2	OAC
6+	10.3	OAC

OAC = oral anticoagulation.

[a]Data from Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012 Jun;33(12):1500-10. [PMID: 22246443]

[b]$CHADS_2$ recommendations from Fuster V, Rydén LE, Cannom DS, et al; American College of Cardiology; American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace. 2006 Sep;8(9):651-745. Erratum in: Europace. 2007 Sep;9(9):856. [PMID: 16987906]. CHA_2DS_2-VASc recommendations from January CT, Wann LS, Alpert JS, et al; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014 Dec 2;130(23):e199-267. [PMID: 24682347]

[c]$CHADS_2$ scoring (maximum 6 points): One point each is given for heart failure, hypertension, age ≥75 years, and diabetes mellitus. Two points are given for previous stroke/transient ischemic attack.

[d]CHA_2DS_2-VASc scoring (maximum 9 points): One point each is given for heart failure, hypertension, diabetes mellitus, vascular disease (prior myocardial infarction, peripheral arterial disease, aortic plaque), female sex, and age 65 to 74 years. Two points each are given for previous stroke/transient ischemic attack/thromboembolic disease and age ≥75 years.

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helpful in patients with 0 or 1 $CHADS_2$ risk factors. In addition to the $CHADS_2$ points, this score gives an additional point for age 65 to 74 years, female sex, and the presence of atherosclerotic disease, and gives 2 points for age 75 or older. Patients with a $CHADS_2$ score of 0 or 1 who have a CHA_2DS_2-VASc score of 2 or more may benefit from oral anticoagulation. Certain high-risk features, such as mitral stenosis or rheumatic heart disease, prior systemic embolism, a prosthetic heart valve, left atrial appendage thrombus, and hypertrophic cardiomyopathy require oral anticoagulation regardless of risk score.

For patients who are treated with aspirin, the recommended dose is 81 to 325 mg daily. For patients who require oral anticoagulation, several agents are now available. Dose-adjusted warfarin (a vitamin K antagonist) remains an effective low-cost alternative for stroke prevention in patients with a higher risk of stroke. The efficacy and safety of warfarin therapy are closely associated with the amount of time in the therapeutic range (INR 2-3). The chief limitations of warfarin are its need for frequent INR monitoring and adjustment and its numerous food and drug interactions. Recently, several new oral anticoagulants have been approved by the FDA for the prevention of stroke in patients with nonvalvular atrial fibrillation, including dabigatran, rivaroxaban, and apixaban (**Table 27**). Warfarin remains the agent of choice in patients with valvular atrial fibrillation, generally defined as atrial fibrillation with mitral stenosis or mitral valve replacement.

Dabigatran is superior to warfarin for the prevention of stroke and is associated with less intracranial bleeding, but carries a higher risk of gastrointestinal bleeding. Rivaroxaban is noninferior to warfarin for the prevention of stroke or systemic embolism and is associated with less intracranial and fatal bleeding. Similar to patients receiving dabigatran, patients on rivaroxaban have a higher risk of gastrointestinal bleeding compared with warfarin. Apixaban also is superior to warfarin for the prevention of stroke and is associated with less bleeding overall, including intracranial bleeding, but similar rates of gastrointestinal bleeding. All of the novel oral anticoagulants are cleared by the kidneys. Thus, dose adjustment is required based on estimated glomerular filtration rate (eGFR), and these agents are contraindicated in patients with end-stage kidney disease. For this reason, annual measurement of serum creatinine level is recommended for patients treated with these drugs. All of the novel oral anticoagulants have shorter half-lives relative to warfarin; however, there are no quick, readily available serum assays to accurately determine anticoagulant activity. Furthermore, currently there is no antidote for these agents in patients with severe hemorrhage.

In patients with concomitant coronary artery disease and atrial fibrillation, antithrombotic therapy presents significant challenges. For most patients with stable coronary artery disease, single-agent therapy with an oral anticoagulant is sufficient for prevention of both acute coronary syndromes and stroke events. Combination antiplatelet and oral anticoagulant therapy increases the risk of bleeding, including intracranial hemorrhage. However, patients with an acute coronary syndrome or revascularization in the previous 12 months are thought to benefit from combination therapy with low-dose aspirin (<100 mg/d) and oral anticoagulation. In patients who receive a coronary stent, triple therapy with low-dose aspirin (<100 mg/d), a thienopyridine (such as clopidogrel), and warfarin is indicated for as short a period as possible. In patients with a drug-eluting stent, this period may extend to 6 months or a year. Ongoing clinical trials are evaluating the combination of anticoagulant therapy for atrial fibrillation and antiplatelet agents for coronary artery disease.

TABLE 27. Anticoagulants FDA-Approved for Stroke Prevention in Atrial Fibrillation

Medication	Reversibility	Frequency	Type of AF	Cautions
Warfarin (vitamin K antagonist)	Yes	Dosing adjusted to INR	Valvular or nonvalvular	Avoid in pregnancy. Caution with idiopathic thrombocytopenic purpura, HIT, hepatic disease, protein C or S deficiency. Many drug interactions.
Dabigatran (direct thrombin inhibitor)	No	Twice daily	Nonvalvular	Decrease dose if CrCl 15-30. Caution with P-glycoprotein inhibition.
Rivaroxaban (factor Xa inhibitor)	No[a]	Once daily	Nonvalvular	Avoid with CrCl <30, moderate hepatic disease. Caution with mild hepatic disease
Apixaban (factor Xa inhibitor)	No[a]	Twice daily	Nonvalvular	Avoid with severe hepatic disease, strong dual inhibitors or inducers of CYP3A4 and P-glycoprotein. Caution with moderate hepatic disease.

AF = atrial fibrillation; CrCl = creatinine clearance (mL/min/1.73 m^2); HIT = heparin-induced thrombocytopenia.

[a]Early data suggest that factor Xa inhibitors may be able to be reversed with prothrombin complex concentrates. Additionally, several "antidotes" are in development for the factor Xa inhibitors.

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Rate Versus Rhythm Control

There is no evidence of a survival advantage or reduction in stroke with restoration and maintenance of sinus rhythm in patients with atrial fibrillation, including those with heart failure. Therefore, the decision to institute a rate or rhythm control strategy largely depends on symptoms and patient preference. Patients who are asymptomatic can be managed with rate control only, with a resting heart rate goal of less than 110/min. Patients with tachycardia-induced cardiomyopathy, heart failure, or left ventricular ejection fraction of less than 40% may require more stringent rate control (heart rate 60-80/min at rest). AV nodal blockers, including β-blockers and nondihydropyridine calcium channel blockers, can be used to control the heart rate. Combination therapy is often required to adequately control the heart rate. In addition to assessing the resting heart rate, assessment of the heart rate with activity should be considered, either with ambulatory ECG monitoring, a stress test, or a 6-minute walk test.

In patients who continue to have symptoms despite adequate rate control, a rhythm control strategy should be considered to improve quality of life. Rhythm control may require cardioversion followed by antiarrhythmic therapy. Antiarrhythmic drug selection is based on patient comorbidities and the safety profile of the antiarrhythmic drugs. Some patients with infrequent symptomatic atrial fibrillation may not require daily therapy. Patients with infrequent atrial fibrillation and neither structural heart disease nor conduction disease may benefit from a "pill-in-the pocket" approach, whereby patients take a class IC drug (flecainide or propafenone) only when they develop an episode of atrial fibrillation. Patients who follow this approach should be taking an AV nodal blocker or should take one before taking their "pill in the pocket." The first time this approach is used, it should take place in a monitored setting to ensure that the patient can safely tolerate the therapy without development of proarrhythmia or conduction disturbance (for example, post-termination pause). Regardless of the rate or rhythm control strategy used, stroke prevention should be guided by patient risk (CHA_2DS_2-VASc score).

Nonpharmacologic Strategies

In patients who have refractory symptomatic atrial fibrillation despite antiarrhythmic drug therapy, catheter ablation with pulmonary vein isolation is an effective rhythm control therapy. Atrial fibrillation ablation is best reserved for patients with early atrial fibrillation without evidence of significant left atrial enlargement and those without multiple comorbidities. The success rates for atrial fibrillation ablation are variable, but in patients with paroxysmal atrial fibrillation, between 70% and 90% are symptom-free at 1 year. Complications can include intraprocedural or late tamponade, vascular complications, and a 0.5% to 1% risk of stroke. Patients who develop dyspnea months to years after an atrial fibrillation ablation may have pulmonary vein stenosis. Anticoagulation is mandatory for the first 2 to 3 months after ablation, and thereafter is guided by risk factors. In patients with symptomatic atrial fibrillation who are undergoing cardiac surgery for other reasons, the maze procedure can be performed as a means of maintaining sinus rhythm.

Patients with refractory symptomatic tachycardia despite attempts at rate and rhythm control may be candidates for AV node ablation. In this approach, patients receive a pacemaker and undergo therapeutic ablation of the AV node, rendering them pacemaker-dependent but no longer tachycardic. These patients remain in atrial fibrillation and still require stroke prevention therapy.

KEY POINTS

- All patients with atrial fibrillation who undergo cardioversion require anticoagulation therapy for a minimum for 4 weeks following the procedure.
- The CHA_2DS_2-VASc score for estimating stroke risk in atrial fibrillation is similar to the $CHADS_2$ score but better differentiates low- and intermediate-risk patients; in addition to heart failure, hypertension, age, diabetes mellitus, and previous stroke, the CHA_2DS_2-VASc score incorporates lower age (65-74 years), sex, and the presence of atherosclerotic disease.
- Options for long-term anticoagulation in patients with atrial fibrillation include warfarin, dabigatran, rivaroxaban, and apixaban; the latter three agents do not require blood monitoring and lack the food and drug interactions of warfarin, but they are substantially more expensive.

Atrial Flutter

Unlike atrial fibrillation, atrial flutter is an organized macro-reentrant rhythm with discrete and organized atrial activity on the ECG, usually with an atrial rate of 250/min to 300/min. Although they are distinct rhythms, atrial fibrillation and atrial flutter are often found in the same patients because of similar risk factors and pathophysiology. Episodes of atrial flutter can induce atrial fibrillation and vice-versa.

Typical atrial flutter has a sawtooth appearance on ECG, with negative flutter waves in the inferior leads and positive flutter waves in lead V_1 (**Figure 18**). Typical atrial flutter is caused by counterclockwise reentry around the tricuspid annulus. Atypical flutter can be clockwise or can occur in other locations in the atria, including the left atrium after atrial fibrillation ablation.

In many respects, atrial flutter is managed similar to atrial fibrillation, including stroke prevention. However, owing to the atrial rate and the ratio of conduction through the AV node (for example, 2:1 or 4:1), rate control of atrial flutter can be difficult and often requires large doses of AV nodal blockers. Therefore, atrial flutter is usually managed with a rhythm control strategy. Catheter ablation of typical atrial flutter is often preferred owing

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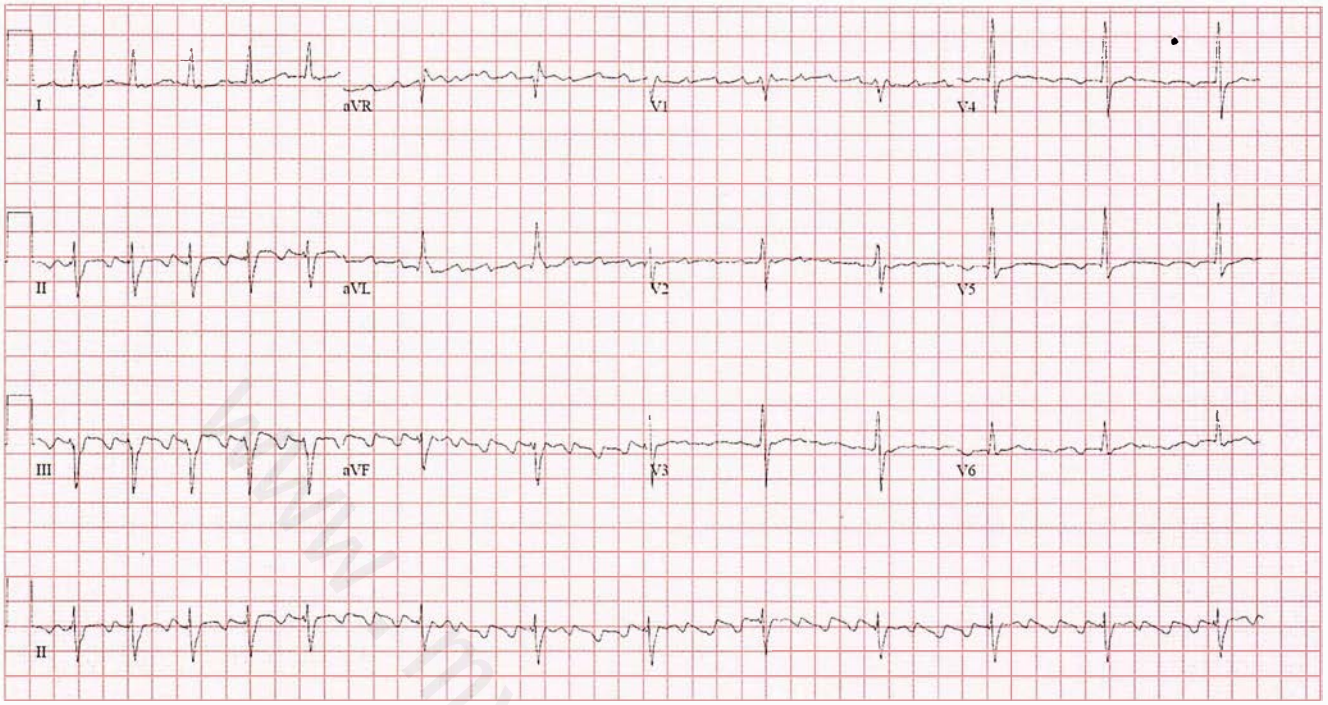

FIGURE 18. In this electrocardiogram demonstrating typical atrial flutter, negative sawtooth waves are seen in the inferior leads and positive waves are seen in lead V_1. In the bottom rhythm strip, 2:1 and 4:1 conduction patterns are seen.

to a high success rate and lower complication rate relative to other ablation procedures. In asymptomatic patients in whom rate control can be achieved, a medical rate control strategy is acceptable.

Wide-Complex Tachycardias

A wide-complex tachycardia is any tachycardia (heart rate ≥100/min) with a QRS complex of 120 msec or greater. The differential diagnosis includes supraventricular rhythms with aberrant conduction (such as underlying bundle branch block), preexcitation, paced rhythms, and ventricular tachycardia.

Often, patients present with a wide-complex tachycardia of unknown etiology. In adults with structural heart disease, 95% of wide-complex tachycardias are VT. Wide-complex tachycardias that are positive in lead aVR, have a QRS morphology that is concordant in the precordial leads (monophasic with the same polarity), have a QRS morphology other than typical right or left bundle branch block, and exhibit extreme axis deviation (-90° to ±180°, sometimes called a northwest axis), are usually VT. The presence of AV dissociation, fusion beats (QRS complex created by fusion between a sinus capture beat and a VT beat), and capture beats (sinus beat that captures the myocardium in between VT beats) are all highly suggestive of VT.

When the origin of a wide-complex tachycardia cannot be determined, VT should be assumed until expert consultation can be obtained.

Ventricular Arrhythmias

Premature Ventricular Contractions

Premature ventricular contractions (PVCs) are common and can occur in up to 75% of healthy persons. Patients with PVCs generally report palpitations and a sensation of skipped beats. Forceful palpitations with PVCs are usually caused by exaggerated cardiac filling during the pause after the PVC. PVCs are more common in patients with hypertension, left ventricular hypertrophy, prior myocardial infarction, and other forms of structural heart disease. For patients with bothersome palpitations, the first diagnostic test is an ECG. If the diagnosis is not established, 24- to 48-hour ambulatory monitoring is used to diagnose and quantify the frequency of PVCs and determine if they are monomorphic or polymorphic. Frequent PVCs (>10% of all beats or ≥10,000 PVCs in a 24-hour period) can lead to tachycardia-induced myopathy. Patients with frequent PVCs or polymorphic PVCs should undergo echocardiography or other cardiovascular imaging (such as cardiac magnetic resonance [CMR] imaging) to evaluate for the presence of structural heart disease.

In patients without high-risk features (such as syncope, a family history of premature SCD, coronary artery disease, or structural heart disease), PVCs (including ventricular bigeminy and trigeminy) are generally benign and do not require additional testing or treatment. Treatment should be limited to those with symptoms or a high burden of PVCs (≥10,000 in a 24-hour period). Treatment for PVCs usually begins with β-blocker or nondihydropyridine calcium channel blocker

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therapy. Antiarrhythmic drug therapy can also be used when PVCs persist despite β-blockade or calcium channel blockade. EP study and catheter ablation can be considered in patients who cannot tolerate medical therapy or if medical therapy fails to suppress the PVCs.

Ventricular Tachycardia with Structural Heart Disease

In structural heart disease, including both ischemic and nonischemic cardiomyopathy, the presence of myocardial scar tissue facilitates reentry and the development of VT. VT can present as nonsustained or sustained VT (>30 seconds). In patients with ventricular scarring, VT is usually regular and monomorphic. **Figure 19** shows ECG findings of monomorphic VT in a patient with cardiac sarcoidosis. In patients with structural heart disease, VT may lead to hypotension, syncope, degeneration into VF, and cardiac arrest. Alternatively, short runs of VT or slow sustained VT may be well tolerated or asymptomatic.

All patients with VT should undergo resting ECG, exercise treadmill testing to provoke the arrhythmia, and cardiac imaging to evaluate for structural heart disease. Patients with ischemic cardiomyopathy who present with VT should undergo an ischemia evaluation and revascularization if indicated. Patients with cardiomyopathy and heart failure should receive optimal medical therapy in order to reduce their risk of ventricular arrhythmia. Patients with structural heart disease or cardiomyopathy and sustained VT/VF should undergo ICD implantation for secondary prevention. In patients with an ICD, if VT recurs despite β-blocker therapy, antiarrhythmic drug therapy should be considered. In most patients with structural heart disease, amiodarone is first-line antiarrhythmic drug therapy. Patients with recurrent VT despite medical therapy should be considered for EP study and catheter ablation, which has been shown to reduce ICD shocks and thus improve quality of life.

Idiopathic Ventricular Tachycardia

VT in patients without structural heart disease is considered idiopathic. Patients often present with palpitations in early adulthood (20-40 years of age). Episodes are often provoked by stress, emotion, or exercise. Syncope is uncommon. Idiopathic VT usually arises from the outflow tracts, the fascicles, or the papillary muscles. Outflow tract tachycardias, the most common type, are triggered arrhythmias that can arise from the right or left ventricular outflow tracts. They are adenosine-sensitive and often exhibit repetitive salvos. Right ventricular outflow tract tachycardia has a left bundle branch block appearance with tall R waves in the inferior leads. Pharmacologic therapy for idiopathic VT includes calcium channel blockers (especially verapamil) or β-blockers. When symptoms continue despite these measures, catheter ablation can be considered. ICDs are rarely indicated in patients with idiopathic VT owing to the benign prognosis and efficacy of other therapies.

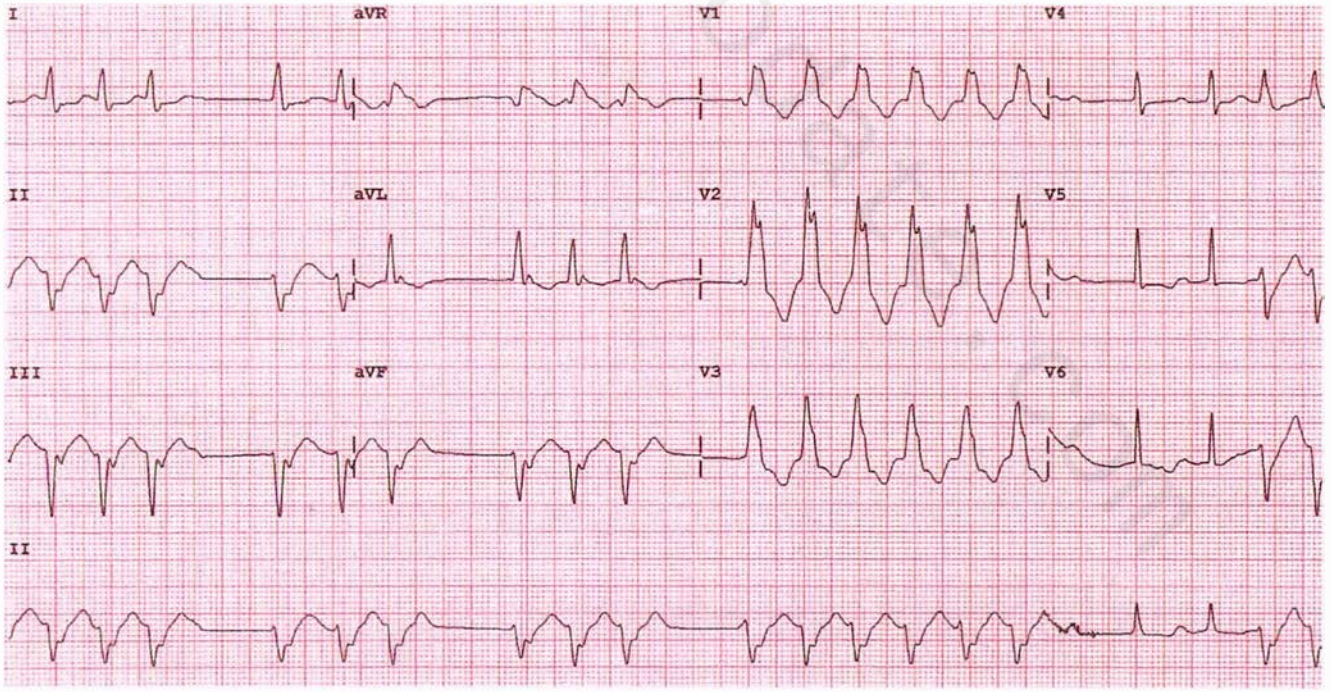

FIGURE 19. An electrocardiogram demonstrating episodes of monomorphic ventricular tachycardia in a patient with cardiac sarcoidosis. Note that the repeated wide-complex beats do not resemble a typical bundle branch block pattern. There are several sinus beats (narrow complexes) that help ascertain the etiology of the wide beats as ventricular tachycardia.

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KEY POINT

- In patients with premature ventricular contractions without high-risk features, reassurance is usually sufficient; treatment should be limited to those with symptoms or frequent episodes.

Inherited Arrhythmia Syndromes

The diagnosis and management of inherited arrhythmia syndromes are complicated by the variable penetrance and variable expressivity often observed. Characteristics and treatment of the most important inherited syndromes are reviewed in **Table 28**. The presence of unexplained premature (younger than 35 years) death or sudden death in a first-degree family member should raise suspicion for the possible presence of an inherited arrhythmia syndrome and referral to a cardiovascular specialist. Genetic testing has facilitated the diagnostic evaluation of these disorders, particularly when an affected family member has a known pathogenic mutation. Patients with a family history of SCD and unexplained syncope are particularly at high risk and merit aggressive evaluation.

Long QT syndrome is one of the most common inherited arrhythmias and is defined by the presence of a prolonged QTc interval (>440 msec in men and >460 msec in women) accompanied by unexplained syncope or ventricular arrhythmia. The presence of a prolonged QTc interval alone is not sufficient for a diagnosis of long QT syndrome. The diagnostic criteria include ECG findings, symptoms, and in some cases, results of genetic testing. There are many causes of a prolonged QTc interval, most of them are acquired, including medications such as antiarrhythmic agents, antibiotics (macrolides and fluoroquinolones), antipsychotic drugs, and antidepressants (a list can be accessed at http://crediblemeds.org/); structural heart disease; and electrolyte abnormalities. Patients with a QTc interval greater than 500 msec are at greatest risk for SCD. First-line therapy for long QT syndrome is β-blocker therapy. Patients with cardiac arrest or those who have recurrent events (syncope or VT) despite β-blocker therapy should undergo ICD implantation. Patients with documented long QT syndrome should avoid participation in competitive athletics.

Short QT syndrome is a rare and genetically heterogeneous disorder characterized by a short QT interval, usually less than 340 msec (or QTc <350 msec). It is inherited in an autosomal dominant pattern. Patients can present with atrial and ventricular arrhythmias and syncope. Short QT syndrome carries a high risk for SCD, and ICD placement is recommended for all patients.

Brugada syndrome, an autosomal dominant disorder associated with mutations in the sodium channel gene, is characterized by right precordial ECG abnormalities, including ST-segment coving (ST-segment elevation that descends into an inverted T wave) in leads V_1 through V_3 with or without right bundle branch block (**Figure 20**), VF, and cardiac arrest. Brugada syndrome is more common in men and in persons of Asian descent. Arrhythmic events often occur at night during sleep. The ECG abnormalities can be variable and may be unmasked by fever or pharmacologic challenge with sodium channel blockade (for example, procainamide infusion). Risk stratification in patients with Brugada syndrome is principally based upon the presence or absence of syncope; those with syncope or ventricular arrhythmia should undergo ICD placement. Patients with recurrent ventricular arrhythmias and/or ICD shocks often benefit from quinidine antiarrhythmic drug therapy.

Catecholaminergic polymorphic VT is a rare disorder characterized by polymorphic ventricular arrhythmias and

TABLE 28. Inherited Arrhythmia Syndromes

Disorder	Characteristic Findings	Treatment[a]
Long QT syndrome	Syncope, QTc interval usually >460 msec, torsades de pointes	β-Blockers, ICD, exercise restriction
Short QT syndrome	Syncope, QT interval <340 msec, atrial fibrillation, VT, VF	ICD in all patients
Brugada syndrome	Syncope, VF, coved ST-segment elevation in early precordial leads (V_1-V_3)	ICD
Catecholaminergic polymorphic VT	Syncope, polymorphic or bidirectional VT during exercise or emotional distress	β-Blockers, ICD, exercise abstinence
Early repolarization syndrome	Syncope, inferior and lateral early repolarization on ECG, VF	ICD
ARVC/D	Syncope, T-wave inversions in leads V_1 to at least V_3, monomorphic VT, abnormal signal-averaged ECG, frequent PVCs, and abnormal right ventricular size and function on echocardiography or CMR imaging	ICD, β-blockers, antiarrhythmic medications, exercise abstinence

ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia; CMR = cardiac magnetic resonance; ECG = electrocardiography; ICD = implantable cardioverter-defibrillator; PVCs = premature ventricular contractions; QTc = corrected QT interval; VF = ventricular fibrillation; VT = ventricular tachycardia.

[a]Treatment recommendations for ICDs in inherited arrhythmia syndromes are guided by risk stratification with criteria that are often disease specific. Additionally, antiarrhythmic drugs are often required in several syndromes for recurrent ventricular arrhythmias.

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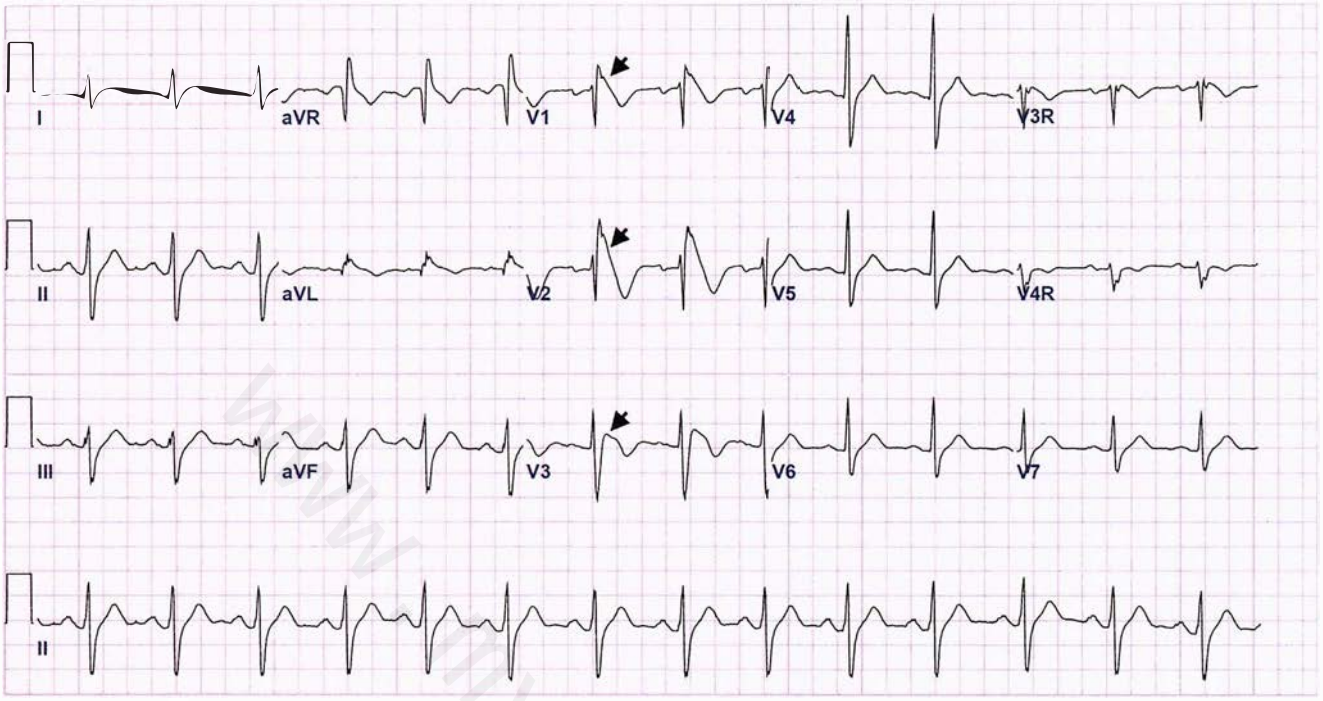

FIGURE 20. In this electrocardiogram demonstrating a type 1 Brugada pattern, ≥2 mm J-point elevation, coved ST-segment elevation (*arrowheads*), and T-wave inversions are seen in leads V_1 to V_3.

cardiac arrest usually provoked by high-adrenergic states, including strong emotion and exercise. Patients with this disorder usually have provocable arrhythmias with exercise or epinephrine infusion. Treatment includes β-blocker therapy and often ICD placement. Patients with the disorder should abstain from exercise.

In patients with unexplained VF arrest, particularly when provoked during exercise, early repolarization syndrome should be considered. Whereas early repolarization (J-point elevation) is a common and benign finding on ECG, the presence of inferior and lateral early repolarization more than 1 mm in a patient with VF or cardiac arrest should be considered early repolarization syndrome. In patients with VF or cardiac arrest, ICD implantation is indicated.

Hereditary structural heart disease, such as hypertrophic cardiomyopathy (see Myocardial Disease) or arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), often manifests as sudden cardiac arrest in a young person. ARVC/D is characterized by fibrous and fibro-fatty changes of the right ventricle and subsequent ventricular arrhythmias. Penetrance is variable and age-related, with many patients presenting between puberty and young adulthood. Patients with ARVC/D usually have ventricular ectopy or monomorphic VT, although patients with severe disease may have heart failure. The diagnosis of ARVC/D is guided by diagnostic criteria that include ECG abnormalities, family history, the presence of arrhythmias, and structural abnormalities of the right ventricle as seen on cardiac imaging. ARVC/D is usually progressive, and those with ARVC/D should abstain from exercise, as it may accelerate disease progression and arrhythmogenesis. Patients with ARVC/D and cardiac arrest or risk factors (nonsustained VT, inducible VT) are offered ICD placement. β-Blockers are first-line therapy for ventricular arrhythmia; however, antiarrhythmic therapy with sotalol or amiodarone or catheter ablation is often required for recurrent VT.

Sudden Cardiac Arrest

Epidemiology and Risk Factors

SCD is defined as instantaneous death or sudden collapse within 1 hour of symptoms. Unwitnessed death is considered SCD if the patient was known to be well within 24 hours of the event. Most episodes of SCD are caused by ventricular arrhythmias (VT/VF arrest). In the general population, the risk of SCD is 1/1000 per year. The incidence is greatest in patients with preexisting structural heart disease; however, most episodes of SCD occur in patients with normal left ventricular function. Risk factors for SCD include (but are not limited to) heart failure, diminished left ventricular function, prior myocardial infarction, unexplained syncope, left ventricular hypertrophy, nonsustained ventricular arrhythmia, chronic kidney disease, and obstructive sleep apnea.

Acute Management

Patients with cardiac arrest require immediate cardiopulmonary resuscitation (CPR) and advanced cardiac life support. The two most important interventions for patients in cardiac arrest are high-quality CPR chest compressions and rapid

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defibrillation in patients with VT/VF arrest. Basic life support guidelines now emphasize the acronym CAB (Chest compressions, Airway, Breathing) to highlight the importance of immediate, rapid, and sustained chest compressions and de-emphasizing assisted breathing. Once a code has been called or the emergency medical system has been activated and an automated external defibrillator has been requested, the patient's pulse should be checked immediately. If no definite pulse is detected within 10 seconds, chest compressions should begin without delay. In patients with VT/VF, time to defibrillation is an important determinant of the likelihood of survival to hospital discharge. Therefore, when a shockable rhythm is present, defibrillation should be performed as rapidly as possible.

Once CPR has been started, the 2010 American Heart Association guidelines on CPR and emergency cardiovascular care dictate management based upon the presence or absence of a shockable rhythm. In patients with asystole or pulseless electrical activity (PEA), CPR is continued with reassessment of rhythm status for a shockable rhythm every 2 minutes. Epinephrine (1 mg intravenously) should be given every 3 to 5 minutes, although vasopressin (40 units intravenously) can replace the first or second dose of epinephrine. Atropine is not recommended for the treatment of asystole or PEA arrest. Further management of PEA arrest should include ascertainment and treatment of any correctable etiology (for example, tamponade). In patients with VT/VF, a shock is advised with immediate resumption of CPR and reassessment of the rhythm in 2 minutes. Epinephrine should be given after the second shock and every 3 to 5 minutes thereafter. If VT/VF continues despite three shocks and epinephrine, amiodarone should be given as a bolus.

Patients with symptomatic bradycardia and hemodynamic distress should first be treated with atropine. If atropine is ineffective, dopamine or epinephrine infusions can be attempted until transcutaneous pacing or a temporary pacing wire (preferred) can be implemented.

Post-resuscitation care includes therapeutic hypothermia in patients who remain comatose. Complications of therapeutic hypothermia include ventricular arrhythmias during rewarming and infectious complications, including sepsis. Hemodynamics and oxygenation should be optimized in the post-arrest setting. Moderate glycemic control is also recommended. Patients with evidence of acute coronary syndrome should undergo immediate catheterization and revascularization provided there are no contraindications.

Device Therapy for Prevention of Sudden Cardiac Death

Patients with sustained ventricular arrhythmias or cardiac arrest without a reversible etiology have a class I recommendation for secondary prevention ICD placement. In patients with structural heart disease who meet specific criteria, ICDs are indicated for primary prevention (see Heart Failure). ICD battery life is approximately 7 to 10 years but is variable. Although ICD malfunction is rare, when it occurs, it is often due to a problem with the intracardiac leads.

Patients with modern ICDs have few limitations. In general, light to moderate exercise, including sexual intercourse, is permissible and is associated with improvement in cardiovascular health and quality of life. However, some disorders carry specific restrictions (see Table 28). Patients with ICDs should avoid strenuous upper extremity exercises, including weight lifting, because these activities can damage the leads coursing through the chest. Electromagnetic interference can lead to inappropriate detection of VT/VF and shocks; therefore, patients should avoid large sources of electromagnetic interference, including arc welding and high-voltage machinery. During surgery, ICDs may need to be reprogrammed or have a magnet applied to avoid false detection of VT/VF due to electrocautery. For this reason, patients with ICDs should have an evaluation or device programming recommendation from their electrophysiologist before undergoing invasive procedures or surgery.

Patients who experience shocks need to contact their ICD physician. Patients who experience more than one shock in 24 hours or any shock accompanied by dyspnea, chest pain, syncope, or heart failure symptoms require emergency medical care.

KEY POINT

- Implantable cardioverter-defibrillator placement is indicated for secondary prevention in patients with sustained ventricular arrhythmias (>30 sec) or cardiac arrest without a reversible etiology.

Device Infection

Between 1993 and 2008, the use of cardiac implanted electronic devices increased by 96%. As a result, the number of patients susceptible to device infection seen in clinical practice has increased dramatically. Device infections range from infections involving the site of device placement (pocket infection) to infective endocarditis. Most device infections are due to staphylococcal infections, particularly *Staphylococcus epidermidis* and *S. aureus*. When caring for patients with cardiac implanted electronic devices who present with symptoms of infection, clinicians must have a high suspicion for device infection.

Patients with cardiac device infection can present with fever, chills, and malaise. The physical examination may reveal erythema, pocket swelling, and drainage from the pocket. Laboratory findings frequently include anemia, leukocytosis, and an elevated erythrocyte sedimentation rate. In patients with suspected device infection, multiple blood cultures should be drawn. Echocardiography (most often with transesophageal echocardiography) should be performed to identify intracardiac or lead vegetations. The device pocket should never be aspirated for diagnostic purposes because puncturing the pocket can damage the leads or introduce infection.

Once a cardiac device infection is diagnosed, treatment includes complete removal of all hardware, debridement of the pocket, sustained antibiotic therapy, and reimplantation at a new site (if and when appropriate). Suppressive antibiotic therapy without complete removal of the device is not curative and is associated with a high fatality rate.

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KEY POINTS

- In a patient with suspected implanted cardiac device infection, the device pocket should never be aspirated for diagnostic purposes because puncturing the pocket can damage the leads or introduce infection.
- Treatment of implanted cardiac device infection comprises complete hardware removal and pocket debridement, sustained antibiotic therapy, and reimplantation at a new site if appropriate.

Pericardial Disease

Acute Pericarditis

Clinical Presentation

Acute pericarditis may occur as part of a systemic disorder or in isolation. Although there are many potential causes of acute pericarditis, most cases are idiopathic or presumed to be viral or autoimmune in origin. In developing countries and susceptible individuals, tuberculosis and HIV infection are common causes of acute pericarditis. Other causes include neoplasm, trauma, uremia, thoracic irradiation, and certain medications (hydralazine, penicillin, chemotherapeutic agents).

Acute pericarditis may be diagnosed on the basis of typical symptoms of chest pain, a pericardial friction rub, distinctive electrocardiographic (ECG) abnormalities, and supportive data from noninvasive testing. Chest pain characterizes the clinical presentation in 90% to 95% of patients, with additional symptoms related to the underlying cause. Chest pain due to acute pericarditis typically is sharp, anterior, and positional, and it is aggravated by maneuvers that increase pericardial pressure (cough, inspiration) and orthostasis (decreased pain in the upright position). These characteristics may be useful in distinguishing pericarditis from acute myocardial ischemia; however, these features also are frequently present in other chest pain syndromes, such as aortic dissection, costochondritis, and pulmonary embolism. Fever may also be present with acute pericarditis.

A pericardial friction rub is considered to be a hallmark of acute pericarditis. A pericardial rub occurs in 35% to 80% of patients, with or without a pericardial effusion. Three components may be auscultated, attributable to atrial systole, ventricular systole, and early rapid ventricular diastolic filling. Pericardial rub intensity and location can vary, but it is characteristically heard at the left lower sternal border. It is best heard during a held end-expiration with the patient leaning forward. This maneuver allows distinction from a pleuropericardial or pleural rub, which are present only during respiration.

Evaluation

ECG changes frequently occur in patients with acute pericarditis owing to inflammation of the visceral pericardium (or epicardium). Typical ECG changes are concave upward ST-segment elevation and PR-segment abnormalities, with elevation in lead aVR and depression in all other leads. PR-segment abnormalities are due to atrial involvement (**Figure 21**). Although the ECG abnormalities typically are diffuse, certain causes (such as cardiac perforation, trauma, or

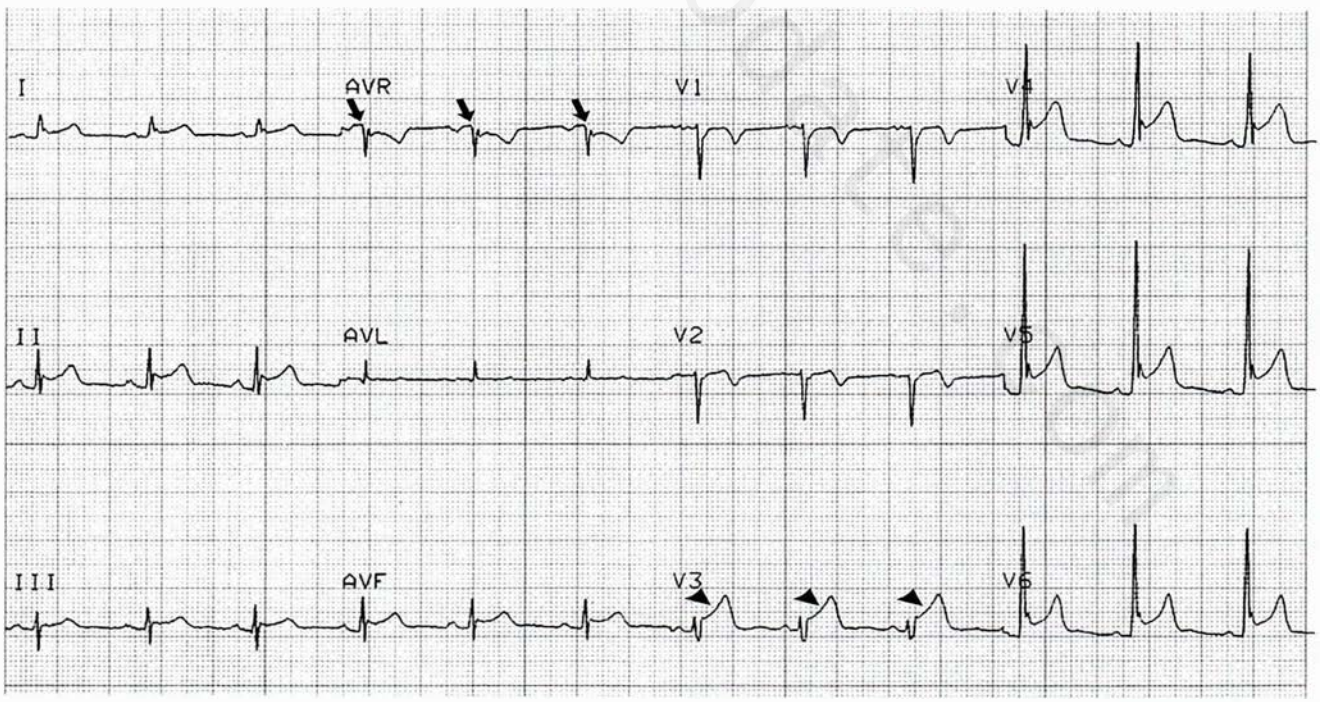

FIGURE 21. Electrocardiographic changes of acute pericarditis. Concave ST-segment elevation is present in most of the leads (*arrowheads*). The PR segment is depressed in all leads except aVR (*arrows*).

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segmental myocardial infarction) may result in localized changes. Sinus tachycardia and electrical alternans also are frequently seen. Several ECG features should be routinely considered to help to distinguish the changes of acute pericarditis from myocardial ischemia and early repolarization (**Table 29**).

Other noninvasive tests can be used to support the diagnosis of acute pericarditis but are limited in their sensitivity and specificity. Inflammatory markers, such as erythrocyte sedimentation rate, leukocyte count, and C-reactive protein level, may be elevated. Increases in biomarkers of cardiac injury (cardiac troponin T or troponin I) indicate concomitant myocarditis (that is, myopericarditis). Cardiomegaly may be seen on chest radiographs if a large pericardial effusion in present.

Echocardiography should be performed in all patients with suspected acute pericarditis to evaluate for the presence of a hemodynamically significant pericardial effusion. Although a pericardial effusion occurs in 50% to 60% of patients, its absence does not rule out the diagnosis of acute pericarditis.

Although evaluation for a cause is usually warranted in patients with acute pericarditis, the diagnostic yield of standard testing is low, with an etiology identified in fewer than 20% of cases. Important causes to consider for further evaluation are those that require specific therapy, such as neoplastic disorders, autoimmune disease, trauma (for example, postsurgical pericarditis), and infection (such as tuberculosis). Evaluation for specific causes of acute pericarditis should be considered according to the degree of clinical suspicion for disorders that would require therapy beyond treatment of the acute episode of pericarditis (for example, malignancy or autoimmune disease). Most cases of acute pericarditis are viral or idiopathic and responsive to anti-inflammatory drugs.

Pericardiocentesis can assist in diagnosis when other testing is inconclusive and is also indicated for obtaining a tissue sample if tuberculosis is suspected.

Management

Management goals for a patient with acute pericarditis are the identification and treatment of potential underlying causes, symptom relief with anti-inflammatory agents, and the recognition and treatment of pericardial effusions that are hemodynamically significant. Most patients with acute pericarditis can be managed as outpatients. Patients with acute pericarditis are at increased risk for developing atrial fibrillation and flutter, which may require treatment for symptom management and reversion to sinus rhythm. Life-threatening complications due to effusion are rare but may develop rapidly. Clinical features indicative of increased risk and a potential need for hospitalization are the presence of fever, leukocytosis, acute trauma, abnormal cardiac biomarkers, immunocompromise, oral anticoagulant use (which may increase the risk of bleeding and tamponade), and large or hemodynamically significant pericardial effusions.

For analgesia and treatment of pericardial inflammation, NSAIDs provide effective relief in 70% to 80% of patients. The efficacy of medical therapy varies according to the underlying cause, with response rates greatest among those with idiopathic or presumed viral causes. Relatively high doses of these medications are required (aspirin, 650-1000 mg every 6 to 8 hours; ibuprofen, 400-800 mg every 8 hours; indomethacin, 50 mg every 8 hours). Slow tapering over a period of 2 to 4 weeks is recommended to reduce the risk of recurrent inflammation. In patients with pericarditis associated with myocardial infarction, NSAIDs other than aspirin should not be used. These agents can impair myocardial healing and increase the risk of mechanical complications in these patients.

Colchicine (0.5 to 1.2 mg/d for 3 months), in addition to NSAIDs, is an effective adjunctive therapy for acute pericarditis. The efficacy of colchicine has been demonstrated in several randomized and retrospective studies, which have shown significantly lower rates of treatment failure and recurrent pericarditis when used in conjunction with standard NSAID therapy. Colchicine is generally well tolerated; side effects include gastrointestinal distress and, less commonly, bone marrow suppression, myositis, and liver toxicity.

Glucocorticoids are not considered first-line therapy for acute pericarditis and are reserved for patients with contraindications to NSAIDs and those with refractory pericarditis. Glucocorticoids also may be considered in specific disease

TABLE 29. Electrocardiographic Features for Differentiating Acute Pericarditis from Myocardial Ischemia

Feature	Acute Pericarditis	Myocardial Ischemia
ST-segment contour	Concave upwards	Convex upwards
ST-segment lead involvement	Diffuse	Localized
Reciprocal ST-T wave changes	No	Yes
PR-segment abnormalities	Yes	No
Hyperacute T waves	No	Yes
Pathologic Q waves	No	Yes
Evolution	ST-segment change initially, then T-wave change	T-wave change initially, then ST-segment change
QT prolongation	No	Yes

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states that are potentially amenable to such therapy (for example, autoimmune disorders, uremic pericarditis). A 3-month course of prednisone (0.25 to 0.50 mg/kg daily starting dose) may be used in these circumstances, with a slow taper beginning at 2 to 4 weeks. Recurrent pericarditis has been reported to be more common among patients prescribed glucocorticoids, but these reports have been hampered by the tendency to use these agents in patients whose pericarditis has been refractory to other therapies. Thus, glucocorticoids are still considered to be an effective alternative therapy for these patients.

After an episode of acute pericarditis, as many as 30% of patients develop recurrent pericarditis. There is a low (<1%) risk of developing constrictive pericarditis. Recurrent pericarditis can be treated with anti-inflammatory agents with a slower, longer taper (for example, 4 months), the addition of colchicine, or the use of glucocorticoids. Etiologies of acute pericarditis other than viral or idiopathic causes should be suspected.

KEY POINTS

- Echocardiography should be performed in patients with suspected acute pericarditis to evaluate for the presence of a hemodynamically significant pericardial effusion; however, the absence of an effusion does not rule out the diagnosis.
- First-line therapy for acute pericarditis is high-dose NSAIDs; colchicine can be used in conjunction with standard NSAID therapy.
- Glucocorticoids in the treatment of acute pericarditis are reserved for patients with contraindications to NSAIDs and those with refractory pericarditis.

Constrictive Pericarditis

Clinical Presentation and Evaluation

Constrictive pericarditis is a chronic disorder that results from pericardial inflammation, fibrosis, and possibly calcification, leading to a loss of elasticity. Although many cases are idiopathic, causes of constrictive pericarditis include chest radiation therapy, cardiac surgery, trauma, post-myocardial infarction syndromes, and systemic diseases that affect the pericardium, such as connective tissue disease, malignancy, tuberculosis, and other infections.

The pericardium in constrictive pericarditis is rigid and noncompliant, resulting in a total cardiac volume that is largely fixed. Ventricular filling occurs rapidly in early diastole and terminates abruptly near mid-diastole owing to the pericardial restraint. With disease progression, the impairment in diastolic filling and increased intracardiac filling pressures leads to reduced end-diastolic ventricular volume and stroke volume. As a result, symptoms and signs of diminished cardiac output (such as fatigue) and evidence of volume overload characterize the clinical presentation of constrictive pericarditis. The jugular venous pressure is elevated in nearly all patients, with prominent *x* and *y* descents. Physical findings that also may be present include a Kussmaul sign (jugular vein engorgement with inspiration), pericardial knock, pulsus paradoxus, pleural effusion, congestive hepatomegaly, and peripheral edema or ascites. In patients with long-standing constrictive pericarditis, hepatic failure and cirrhosis may be present.

The diagnosis of constrictive pericarditis can be made with a detailed hemodynamic evaluation using either Doppler echocardiography or cardiac catheterization. The basis for the diagnostic hemodynamic findings in constrictive pericarditis is the concept of enhanced ventricular interdependence, which classically results in equalization of diastolic pressures in all heart chambers. The noncompliant pericardium also prevents the complete transmission of respiratory changes in thoracic pressure to the cardiac chambers. Filling of the right and left ventricles varies significantly with respiration owing to marked changes in the early diastolic gradient emptying into these chambers (that is, dissociation of thoracic-cavitary pressures). During inspiration, the decrease in thoracic pressure leads to relatively less left ventricular filling, while the increase in caval blood flow augments right ventricular preload. Reciprocal changes in ventricular loading occur during expiration (**Figure 22**). Because

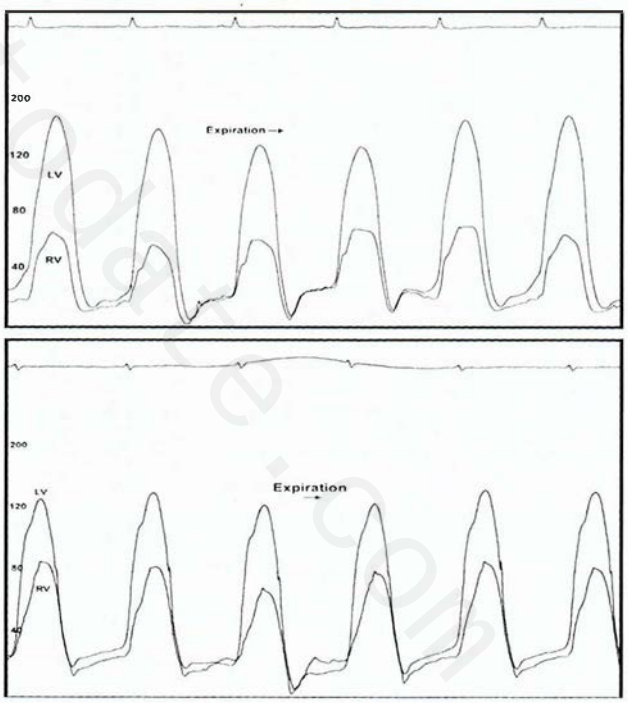

FIGURE 22. Comparison of hemodynamics of constrictive pericarditis versus restrictive cardiomyopathy. In constrictive pericarditis (*top panel*), there is significant enhancement of ventricular interdependence leading to discordance of the left ventricular and right ventricular pressures during respiration. Arrows indicate onset of expiration and subsequent respective changes in left ventricular and right ventricular systolic pressures. In restrictive cardiomyopathy (*bottom panel*), there is evidence of early rapid ventricular filling, but the ventricular pressures concordantly rise and fall during respiration. LV = left ventricle; RV = right ventricle.

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CONT. constrictive pericarditis does not involve the ventricular septum, bulging of the septum towards the left occurs during inspiration and returns towards the right during expiration, leading to marked enhancement of ventricular interdependence. The dissociation of thoracic and intracavitary pressures and the enhanced ventricular interdependence lead to reciprocal changes in filling and emptying of the right and left ventricles, which manifest as alterations in right- and left-sided forward stroke volumes during respiration (see Figure 22). These findings are distinct from restrictive cardiomyopathy, in which there is not significant enhancement of ventricular interdependence or dissociation of intracavitary-intrathoracic pressures (**Table 30**). Restrictive cardiomyopathy is characterized by severe left ventricular diastolic dysfunction due to myocardial abnormalities or infiltration. Differentiation of constrictive pericarditis from restrictive cardiomyopathy is clinically important because surgical treatment of constrictive pericarditis may be curative of the condition, but there are no therapies that significantly improve the natural history of restrictive cardiomyopathy.

Other echocardiographic findings supportive of the diagnosis of constrictive pericarditis are increased pericardial thickness and plethora of the inferior vena cava. Pericardial thickening, with or without calcification, can also be detected with cardiac CT or cardiac magnetic resonance (CMR) imaging (**Figure 23**).

A subset of patients with chronic constrictive pericarditis develop effusive constrictive pericarditis. There typically is minimal pericardial fluid present in constrictive pericarditis; in some patients, however, pericardial inflammation

TABLE 30. Characteristics of Constrictive Pericarditis, Restrictive Cardiomyopathy, and Cardiac Tamponade

Characteristic	Constrictive Pericarditis	Restrictive Cardiomyopathy	Cardiac Tamponade
Mechanism	Rigid, inelastic pericardium resulting in fixed cardiac volume	Myocardial disease with severe diastolic dysfunction	Increased intrapericardial pressure compromises ventricular filling
Hemodynamic implications	Rapid and limited diastolic filling due to pericardial restraint; increased intracardiac filling pressures, diminished cardiac output, and volume overload	Diastolic abnormalities lead to elevated ventricular filling pressures and pulmonary hypertension	Ventricular filling is impaired with a reduction in cardiac output; jugular venous and pulmonary venous pressures increased
Physical examination	↑ JVP, Kussmaul sign, pericardial knock, diminished apical impulse, congestion (peripheral edema, pleural effusion, congestive hepatopathy)	↑ JVP, Kussmaul sign, pericardial knock, diminished apical impulse, congestion (peripheral edema, pleural effusion, congestive hepatopathy)	↑ JVP, pulsus paradoxus, hypotension, reflex tachycardia
Electrocardiography	No characteristic findings	No characteristic findings	Decreased voltage, sinus tachycardia, electrical alternans
Chest radiography	Pericardial calcification	Atrial enlargement	Enlarged cardiac silhouette ("water-bottle" heart)
Echocardiography	Pericardial thickening/calcification; respiratory variation in filling of right and left ventricles; ventricular septal shift during respiration; plethora of inferior vena cava	Markedly dilated atria with preserved systolic function; severe impairment of myocardial relaxation	Pericardial effusion, diastolic collapse of right atrium and ventricle, enlargement of inferior vena cava, ventricular septal shifting during respiration, respiratory changes in mitral inflow
CMR imaging/CT	Pericardial thickening/calcification	Normal pericardium	Pericardial effusion
Hemodynamic right and left heart catheterization	Prominent *x* and *y* descents; elevated atrial pressures; elevated and equalized diastolic LV and RV pressures (within 5 mm Hg); decreased transmission of intrathoracic pressure causes discordance of LV and RV pressures and stroke volume during respiration (enhanced ventricular interdependence)	Prominent *x* and *y* descents; elevated atrial pressures; concordance of LV and RV pressures during respiration	Prominent *x* descents and blunted *y* descents; elevated atrial pressures; blunting/loss of early ventricular diastolic filling wave
BNP	Normal or minimally elevated	Elevated	Normal or low

BNP = B-type natriuretic peptide; CMR = cardiac magnetic resonance; JVP = jugular venous pressure; LV = left ventricular; RV= right ventricular.

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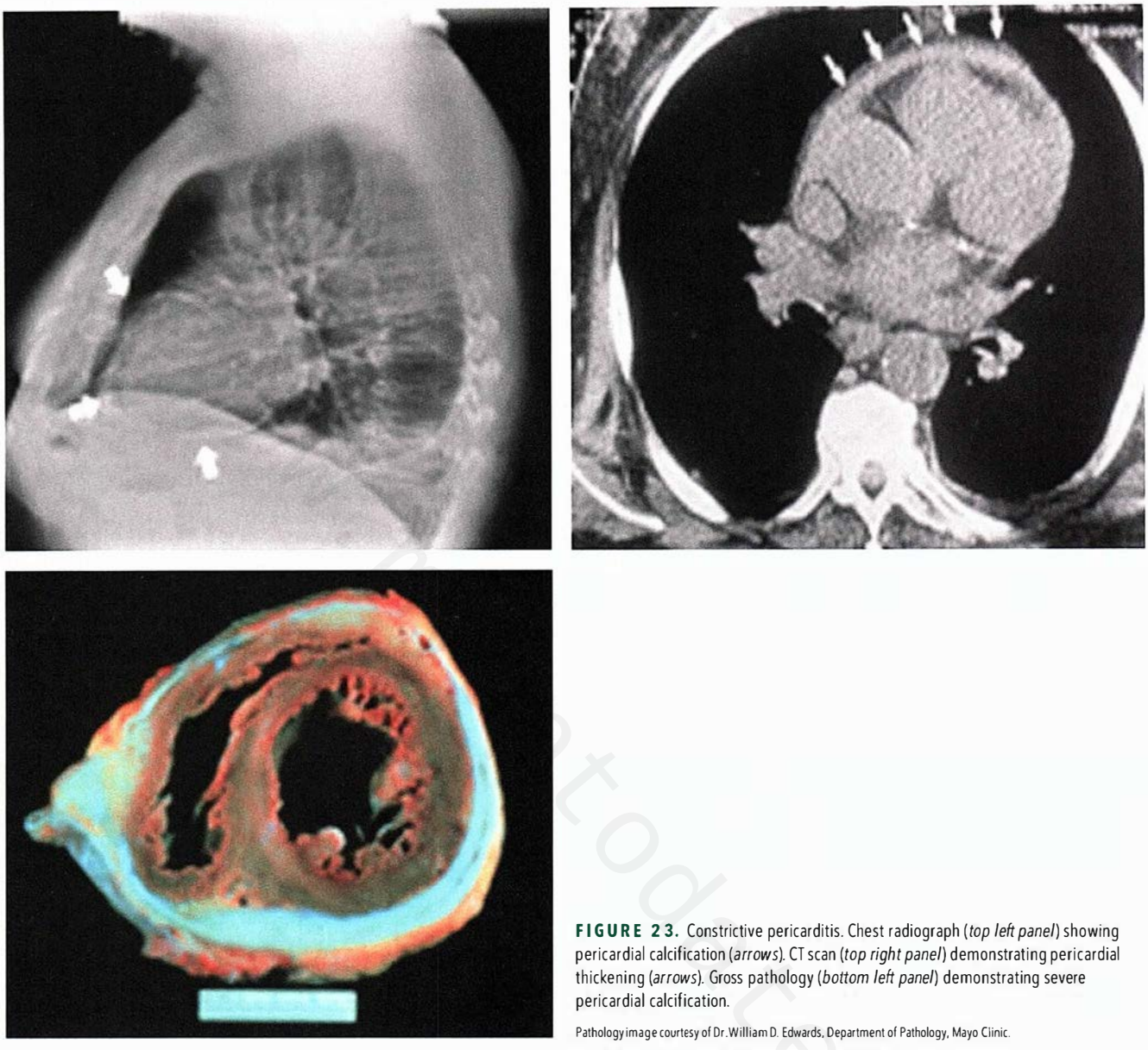

FIGURE 23. Constrictive pericarditis. Chest radiograph (*top left panel*) showing pericardial calcification (*arrows*). CT scan (*top right panel*) demonstrating pericardial thickening (*arrows*). Gross pathology (*bottom left panel*) demonstrating severe pericardial calcification.

Pathology image courtesy of Dr. William D. Edwards, Department of Pathology, Mayo Clinic.

CONT. results in an effusion that is placed under pressure by the inelastic pericardium. Although this does not typically cause the hemodynamic changes seen with cardiac tamponade, it may change the clinical presentation. Symptoms of low cardiac output, systemic congestion, and an elevated jugular venous pulse occur, as in constrictive pericarditis; however, a pericardial knock may be absent and the *y* descent of the jugular venous pulse may be less prominent. The etiology is similar to that of chronic constriction, although tuberculous pericarditis is particularly prone to this clinical presentation. Effusive constrictive pericarditis should be suspected in a patient with residual symptoms and signs of persistent atrial pressure elevation after successful pericardiocentesis. The diagnosis can be made with either echocardiography or cardiac catheterization.

Management

Some patients with constrictive pericarditis can have reversible or transient inflammation, such as post-pericardiotomy syndrome after cardiac surgery, that responds to anti-inflammatory agents. Thus, it may be reasonable to perform a trial of medical therapy (such as NSAIDs) before pericardiectomy surgery in some patients presenting with constrictive pericarditis, particularly those with mild symptoms, a potentially reversible cause of acute inflammation, and no evidence of chronic constriction. Diuretic therapy may reduce volume overload and improve symptoms transiently.

Cardiac surgery with pericardiectomy is the definitive treatment for relief of heart failure in patients with constrictive pericarditis. Because of the complexity of the procedure, this surgery is best performed in experienced centers where a

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total pericardiectomy, with removal of as much of the pericardium as is technically possible, may be achieved. Patients treated with total pericardiectomy have been shown to have improved outcomes relative to those who undergo more limited procedures. Predictors of poor outcome after surgical pericardiectomy include advanced age, severe symptoms, chronic kidney disease, pulmonary hypertension, left ventricular dysfunction, and radiation therapy as the underlying cause of constrictive pericarditis. In one study, the 7-year survival after pericardiectomy was 27%, 66%, and 88%, respectively, for patients with constrictive pericarditis due to radiation, prior cardiac surgery, and an idiopathic cause. Medical therapy with diuretics can improve symptoms or be palliative in patients who are not surgical candidates, but the chronic nature of the disorder can prove to be drug-refractory.

KEY POINTS

- In some patients with constrictive pericarditis, particularly those with mild symptoms, a potentially reversible cause of acute inflammation, and no evidence of chronic constriction, it may be reasonable to perform a trial of medical therapy before surgery.
- Cardiac surgery with pericardiectomy is the definitive treatment for relief of heart failure in patients with constrictive pericarditis.

Cardiac Tamponade

Clinical Presentation and Evaluation

The normal pericardium contains 15 to 50 mL of plasma ultrafiltrate. The rate of accumulation and the absolute amount of pericardial fluid surrounding the heart above the normal baseline level determine the hemodynamic effects of an effusion. Cardiac tamponade occurs when intrapericardial pressure exceeds intracardiac pressure, leading to impairment of ventricular filling throughout the entire diastolic period.

Virtually any disorder that causes a pericardial effusion can result in cardiac tamponade. Malignancy is the most common atraumatic etiology, with breast and lung cancer being the most frequent. Other important causes are idiopathic or viral pericarditis, complications of invasive cardiac procedures, aortic dissection with disruption of the aortic valve annulus, tuberculosis, uremia, and pericarditis or ventricular rupture from a myocardial infarction.

During cardiac tamponade, venous return and ventricular filling become impaired owing to excess intrapericardial pressure. This impairment precipitates elevation and equalization of diastolic pressures in the heart, including increased pulmonary venous and right atrial pressures, and ultimately, a reduction in cardiac output. With inspiration, filling pressure to the left ventricle falls, leading to a reduction in the stroke volume. The fall in left ventricular stroke volume during inspiration manifests as a relative decrease in pulse pressure or peak systolic pressure and is the hallmark finding of pulsus paradoxus (a decrease in the systolic pressure of >10 mm Hg with inspiration) in these patients. As compensation for the reduced stroke volume and hypotension, tachycardia is usually present.

Less common presentations of cardiac tamponade also need to be considered in some patients. A loculated pericardial effusion may occur after cardiac surgery or in other postoperative settings. It may occur in the posterior pericardial space adjacent to the atria, posing challenges for detection by echocardiography. Posterior loculated effusions should be suspected in postoperative patients with hemodynamic instability. Low-pressure cardiac tamponade occurs without elevated jugular venous pressure because the intracardiac filling pressures are low. Examples include patients with malignancy or tuberculosis complicated by severe dehydration. Pneumopericardium with cardiac tamponade may result from gas-forming bacterial pericarditis after penetrating chest trauma.

Cardiac tamponade should be suspected when there is a compatible history, hypotension, and an elevated jugular venous pressure and pulsus paradoxus. An enlarged cardiac silhouette may be seen on chest radiograph ("water-bottle heart"). The ECG typically demonstrates sinus tachycardia and electrical alternans. Echocardiography readily detects pericardial effusions and is the primary modality for diagnosing cardiac tamponade (**Figure 24**). Signs of cardiac tamponade include diastolic collapse of the right atrium and right ventricle, ventricular septal shifting with respiration, and enlargement of the inferior vena cava. With Doppler echocardiography, respiratory variation in mitral inflow can be detected early in the evolution of tamponade. Moreover, the changes in mitral inflow are highly sensitive, and may precede changes in cardiac output, blood pressure, and other echocardiographic evidence of tamponade. Respiratory changes in mitral inflow resolve after pericardiocentesis unless an effusive-constrictive physiology is present.

The signs of cardiac tamponade also can be evident with invasive hemodynamic catheterization. Characteristic findings include prominent *x* descents and blunted *y* descents on the atrial tracings (**Figure 25**) and elevated ventricular diastolic pressures with blunting or loss of the early rapid ventricular filling wave, which is the hallmark of cardiac tamponade that distinguishes it from other diastolic disorders. Other hemodynamic findings include equalization of left- and right-sided end-diastolic pressures, reduced cardiac output, and alterations in the systolic ejection period or pulse pressure that result from decreased stroke volume (analogous to pulsus paradoxus).

Management

Intravenous normal saline and, if needed, vasopressors should be administered to stabilize the hemodynamics in a patient with cardiac tamponade. Although the presentation includes symptoms and signs of heart failure, reduction of intravascular volume by diuresis may exacerbate the hemodynamic abnormalities of tamponade.

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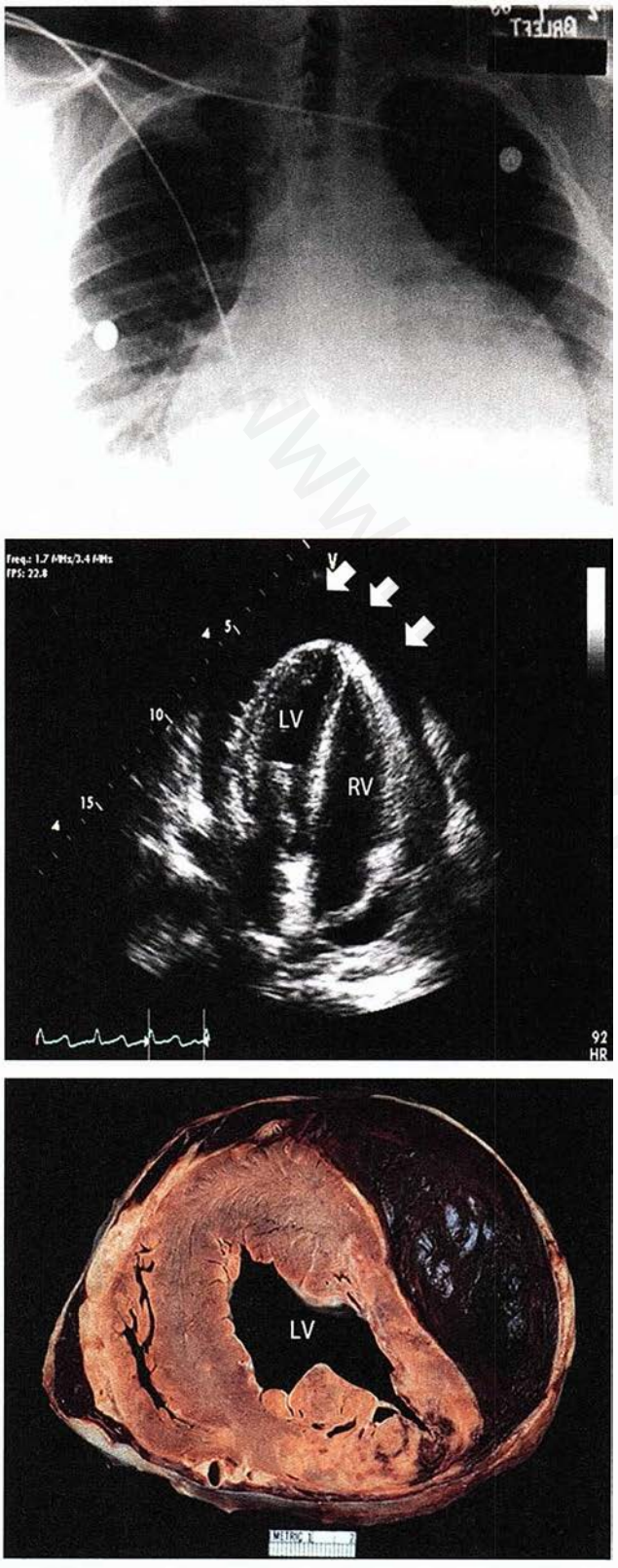

FIGURE 24. Cardiac tamponade. Chest radiograph (*top panel*) showing "water-bottle heart." Transthoracic echocardiogram (*middle panel*) showing a large pericardial effusion (*arrows*). Gross pathology (*bottom panel*) of cardiac tamponade. LV = left ventricle; RV = right ventricle.
Pathology image courtesy of Dr. William D. Edwards, Department of Pathology, Mayo Clinic.

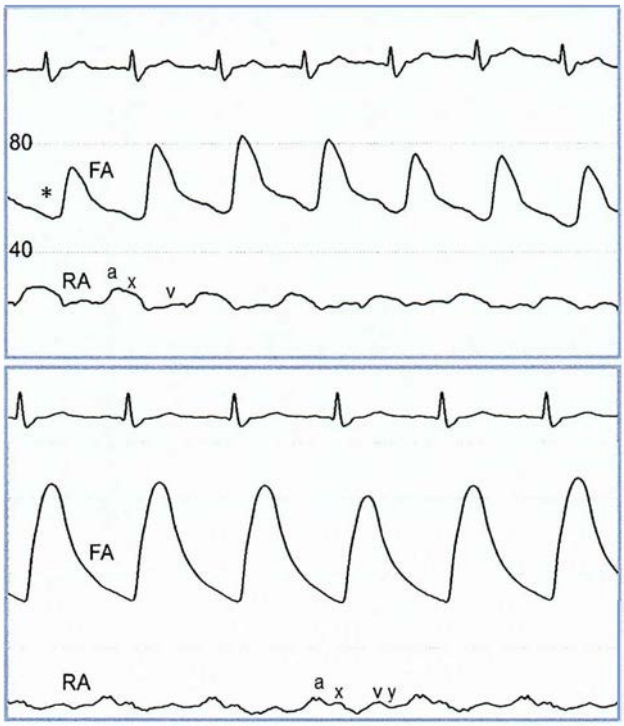

FIGURE 25. Invasive hemodynamic features of cardiac tamponade. Y-axis indicates pressure (mm Hg). Hypotension and pulsus paradoxus (*asterisk*) in the femoral artery (FA) pressure tracing and loss of the *y* descent in the right atrial (RA) pressure tracing are evident (*top panel*). Following pericardiocentesis, there is a rise in arterial pressure and return of the *y* descent in the RA pressure tracing (*bottom panel*).

Pericardiocentesis with echocardiographic guidance is the most expeditious treatment for cardiac tamponade, with a lower complication rate than blind or ECG-guided pericardiocentesis. Pericardiocentesis should be avoided when treating tamponade associated with aortic dissection. In these patients, abrupt return of ventricular ejection may exacerbate the dissection and precipitate acute decompensation. During attempts at needle passage with pericardiocentesis, the tense pericardium may discharge fluid from the pericardial effusion into the pleural space. This effect can be immediately recognized on echocardiography and may obviate further attempts at pericardiocentesis, as acute relief of tamponade may occur.

Although the vast majority of pericardial effusions can be treated percutaneously, some still require surgical drainage. A surgical approach also may be required for viscous or loculated effusions, those resulting from bacterial infections, posterior effusions that can be difficult to approach from any thoracic approach, and malignant effusions with a high likelihood of recurrence. In addition, recent hemorrhage into the pericardium may result in pericardial clot formation that can be difficult to remove with a catheter. Pericardiocentesis in the setting of aortic dissection may exacerbate the intimal tear owing to the abrupt increase in stroke volume that occurs with relief of cardiac tamponade. Surgical therapy most commonly consists of a pericardial window to allow drainage of fluid; some

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CONT. patients require an open pericardiectomy. Open pericardiectomy can be beneficial when there is a diagnostic need for pericardial tissue.

KEY POINT

- Pericardiocentesis with echocardiographic guidance is the most expeditious treatment for cardiac tamponade.

Valvular Heart Disease

Pathophysiology of Valvular Heart Disease

Valvular heart disease (VHD) comprises cardiac dysfunction due to structural or functional abnormalities of the cardiac valves. Dysfunction results from either failure of the valves to competently close (regurgitation) or to effectively open (stenosis). Causes of VHD have changed markedly in developed countries over the past 50 years, with a shift away from rheumatic disease and toward calcific, degenerative, and congenital causes. Rheumatic heart disease continues to be the primary cause of VHD in the developing world.

The effect of VHD on the heart and on the patient varies based on the affected valve and the mechanism of dysfunction:

- Aortic stenosis causes chronic pressure overload that typically leads to concentric left ventricular (LV) hypertrophy with increased wall thickness and normal chamber size to compensate for increased LV afterload.
- Chronic aortic regurgitation causes increased LV preload and afterload, leading to increased LV volume and mass.
- Mitral stenosis causes increased pressure within the left atrium (LA), leading to increased pulmonary venous pressure, pulmonary hypertension, and atrial dilation.
- Chronic mitral regurgitation causes volume overload (increased preload) of the LV and LA, leading to increased LA size and pressure and LV dilation.

Many of these changes in cardiac structure occur gradually because of physiologic mechanisms that compensate for the increased loading conditions. For this reason, patients remain asymptomatic for some time even in the setting of significant valve disease. The exception to this is acute valve lesions, in which the compensatory changes do not have sufficient time to develop.

Diagnostic Evaluation of Valvular Heart Disease

History and Physical Examination

The initial evaluation of the patient with possible VHD serves to diagnose, quantify, and assess mechanisms of valve dysfunction. The evaluation should focus on disease severity, symptoms, quality of life, expected benefits of intervention compared with medical therapy or expectant management, patient desires, and local resources for surgery or intervention.

In many patients with chronic VHD, the development of symptoms is insidious and their onset may go unnoticed. Typical symptoms include exertional dyspnea, edema, and orthopnea. A thorough history provides the opportunity to assess daily activity and lifestyle changes that may effectively "mask" symptoms. This is important as the presence or absence of symptoms may play a pivotal role in deciding timing of intervention.

The physical examination, including cardiac auscultation, is the key first step in identifying the presence of VHD and the likely valve or valves involved and in helping to guide an appropriate diagnostic and therapeutic approach (**Figure 26**). A thorough cardiac examination entails determining the intensity of the murmur as well as specific characteristics that help define whether it is a clinically significant murmur. Not all murmurs require further evaluation (specifically echocardiography).

The clinical grading of both systolic and diastolic murmurs is based on a scale of 1 to 6 (**Table 31**). Diastolic murmurs are always considered abnormal and require further evaluation. Systolic murmurs may be either innocent or indicative of significant valve disease. Some murmurs are associated with normal valves but abnormal systemic processes (for example, anemia and other high-output states, such as hyperthyroidism) or increased flow (for example, a systolic murmur in the setting of aortic regurgitation). Innocent murmurs are characteristically brief and are associated with normal heart sounds and no hemodynamic abnormalities. Patients with grade 1 or 2 midsystolic murmurs who are asymptomatic with no associated findings and those with continuous murmurs suggestive of a venous hum or mammary souffle (a continuous murmur heard over the breast in lactating women) do not warrant echocardiographic evaluation.

The character of a murmur in response to clinical maneuvers is helpful in localizing the flow disturbance to a specific valve. For example, in general, right-sided murmurs increase with inspiration and left-sided murmurs increase with expiration. A Valsalva maneuver decreases the length and intensity of most murmurs, except for systolic murmurs associated with hypertrophic obstructive cardiomyopathy and mitral valve prolapse. Exercise causes the murmur of mitral stenosis to get louder, whereas isometric maneuvers, such as handgrip, increase the intensity of regurgitant murmurs such as aortic and mitral regurgitation. Postural maneuvers are ideal for differentiating hypertrophic obstructive cardiomyopathy and mitral valve prolapse from other murmurs as they are louder with standing and softer with squatting. Physical examination findings, such as an enlarged or displaced apical impulse, abnormal peripheral pulses, and timing and intensity of heart sounds (including extra heart

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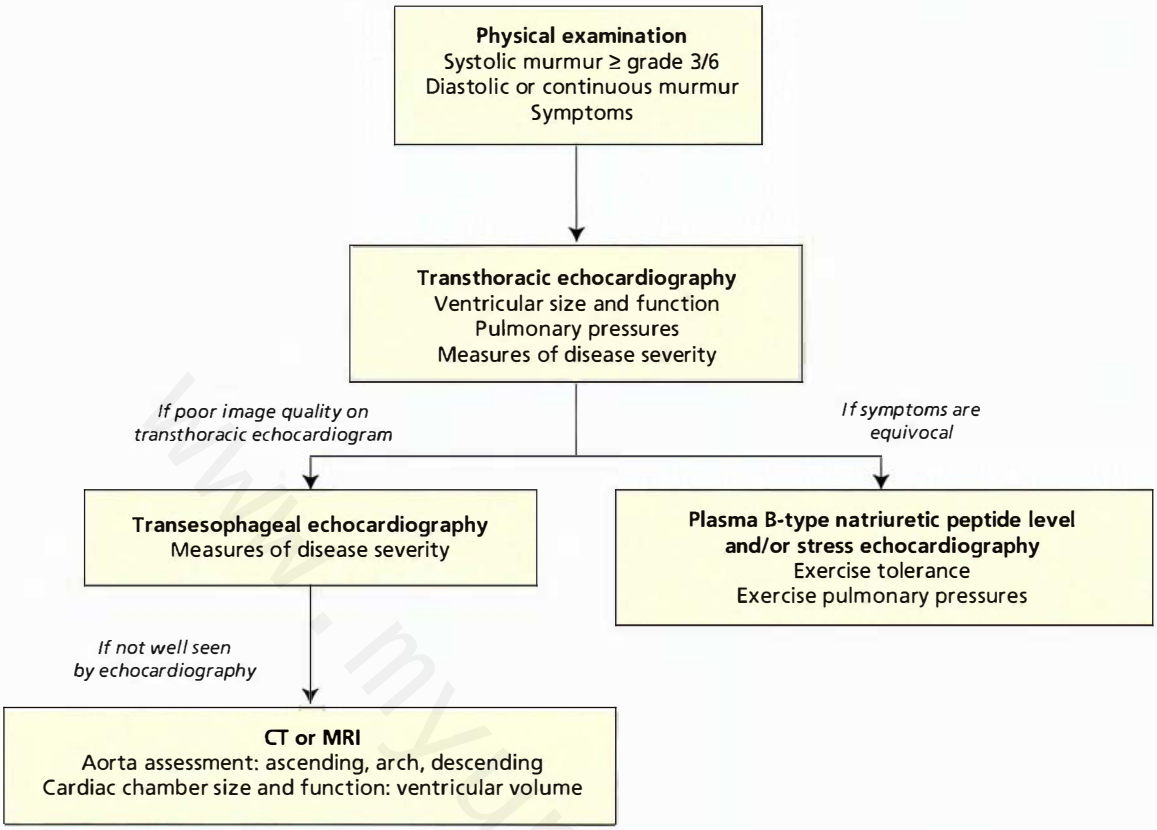

FIGURE 26. Diagnostic evaluation of valvular heart disease.

TABLE 31. Clinical Grading of Murmurs

Grade	Description
1	Faintest murmur that can be heard (with difficulty)
2	Faint murmur but can be identified immediately
3	Moderately loud murmur
4	Loud murmur associated with a palpable thrill
5	Very loud murmur but cannot be heard without the stethoscope
6	Loudest murmur; can be heard without a stethoscope

sounds such as an S_3 or S_4 or a systolic ejection click) may help identify specific valve lesions as well. Common valve lesions and heart murmurs are further described in **Table 32**.

Laboratory and Imaging Tests

Electrocardiography (ECG) and chest radiography are often performed during the initial evaluation. ECG provides valuable insight into rhythm (such as the presence of atrial fibrillation) and cardiac chamber enlargement. Chest radiography is essential when interpreting dyspnea or clinical signs of heart failure with evidence of cardiac enlargement and pulmonary vascular redistribution. Chest radiography may also provide secondary clues (such as a dilated left ventricle in the setting of chronic aortic regurgitation), but its utility in the evaluation of VHD is less than other modalities, especially echocardiography.

Transthoracic echocardiography (TTE) with color flow and spectral Doppler imaging is the primary noninvasive means of evaluating cardiac murmurs as well as the primary means for following the course of VHD. TTE is indicated for patients with the following (see Figure 26):

- Systolic murmurs ≥grade 3/6 or late or holosystolic murmurs
- Diastolic or continuous murmurs
- Murmurs with accompanying symptoms

TTE permits assessment of LV size and function (systolic and diastolic), estimation of pulmonary artery pressure (an indirect estimate based on the tricuspid regurgitant jet velocity), and determination of disease severity. Echocardiography also helps establish a reference point for future comparisons if significant abnormalities are detected. Transesophageal echocardiography (TEE) provides improved image quality over TTE as the probe has only the thin tissue of the esophagus through which to image. TEE is indicated for patients with severe disease who need further quantification, better identification of leaflet involvement (particularly for patients with mitral regurgitation), or when poor image quality on TTE limits

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TABLE 32. Valvular and Other Cardiac Lesions and Their Associated Examination Findings

Cardiac Condition	Characteristic Murmur	Location	Radiation	Associated Findings	Severity and Pitfalls
Aortic stenosis	Mid-systolic; crescendo-decrescendo	RUSB	Right clavicle, carotid, apex	Enlarged, nondisplaced apical impulse; S_4; bicuspid valve without calcification will have systolic ejection click followed by murmur	Severe aortic stenosis may include decreased A_2; high-pitched, late peaking murmur; diminished and delayed carotid upstroke Radiation of murmur down the descending thoracic aorta may mimic mitral regurgitation
Aortic regurgitation	Diastolic; decrescendo	LLSB (valvular) or RLSB (dilated aorta)	None	Enlarged, displaced apical impulse; S_3 or S_4; increased pulse pressure; bounding carotid and peripheral pulse	Acute, severe regurgitation murmur may be masked by tachycardia, short duration of murmur Severity in chronic regurgitation is difficult to assess by auscultation
Mitral stenosis	Diastolic; low pitched, decrescendo	Apex (heard best in left lateral decubitus position)	None	Opening snap after S_2 if leaflets mobile; irregular pulse if atrial fibrillation present	Interval between S_2 and opening snap is short in severe mitral stenosis Intensity of murmur correlates with transvalvular gradient P_2 may be loud if pulmonary hypertension present
Mitral regurgitation	Systolic; holo- or late systolic	Apex	To axilla or back; occasionally anteriorly to precordium	Systolic click in mitral valve prolapse; S_3; apical impulse hyperdynamic and may be displaced if dilated left ventricle; in mitral valve prolapse, Valsalva maneuver moves onset of clicks and murmur closer to S_1; handgrip increases murmur intensity	Acute, severe regurgitation may have soft or no holosystolic murmur, mitral inflow rumble, S_3
Tricuspid stenosis	Diastolic; low pitched, decrescendo; increased intensity during inspiration	LLSB	Nonradiating	Elevated central venous pressure with prominent *a* wave, signs of venous congestion (hepatomegaly, ascites, edema)	Low-pitched frequency may be difficult to auscultate, especially at higher heart rate

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TABLE 32. Valvular and Other Cardiac Lesions and Their Associated Examination Findings *(Continued)*

Cardiac Condition	Characteristic Murmur	Location	Radiation	Associated Findings	Severity and Pitfalls
Tricuspid regurgitation	Holosystolic	LLSB	LUSB	Merged and prominent *c* and *v* waves in jugular venous pulse; murmur increases during inspiration	Right ventricular impulse below sternum Pulsatile, enlarged liver with possible ascites May be higher pitched if associated with severe pulmonary hypertension
Pulmonary stenosis	Systolic; crescendo-decrescendo	LUSB	Left clavicle	Pulmonic ejection click after S_1 (diminishes with inspiration)	Increased intensity of murmur with late peaking
Pulmonary regurgitation	Diastolic; decrescendo	LLSB	None	Loud P_2 if pulmonary hypertension present	Murmur may be minimal or absent if severe due to minimal difference in pulmonary artery and right ventricular diastolic pressures
Innocent flow murmur	Midsystolic; grade 1/6 or 2/6 in intensity	RUSB	None	Normal intensity of A_2; normal splitting of S_2; no radiation	May be present in conditions with increased flow (e.g., pregnancy, fever, anemia, hyperthyroidism)
Hypertrophic obstructive cardiomyopathy	Systolic; crescendo-decrescendo	LLSB	None	Enlarged, hyperdynamic apical impulse; bifid carotid impulse with delay; increased intensity during Valsalva maneuver or with squatting to standing	Murmur may not be present in nonobstructive hypertrophic cardiomyopathy
Atrial septal defect	Systolic; crescendo-decrescendo	RUSB	None	Fixed, split S_2; right ventricular heave; rarely, tricuspid inflow murmur	May be associated with pulmonary hypertension, including increased intensity of P_2, pulmonary valve regurgitation
Ventricular septal defect	Holosystolic	LLSB	None	Palpable thrill; murmur increases with hand-grip, decreases with amyl nitrite	Murmur intensity and duration decrease as pulmonary hypertension develops (Eisenmenger syndrome) Cyanosis if Eisenmenger syndrome develops

A_2 = aortic valve component of S_2; LLSB = left lower sternal border; LUSB = left upper sternal border; P_2 = pulmonary valve component of S_2; RLSB = right lower sternal border; RUSB = right upper sternal border.

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image interpretation. The disadvantage compared with TTE is that it is invasive, requiring sedation and technical expertise distinct from TTE.

For stenotic lesions, Doppler-derived velocities across the affected valve allow calculation of pressure gradients and valve area. Based on the conservation of mass principle, the measured flow through one heart chamber region and measured velocity of blood across the region (stenotic valve) of interest can be used to calculate the area of the stenotic valve.

Assessment of severity for regurgitant valves includes color Doppler jet size and the width of the narrowest segment of the regurgitant jet (vena contracta). Additional quantitative measures for regurgitant lesions, such as effective regurgitant orifice area, regurgitant volume, and proximal isovolumic surface area, although technically more demanding to acquire, are strongly associated with prognosis and should be measured routinely in patients with moderate or severe regurgitation by color Doppler jet size. Three-dimensional echocardiography, both transthoracic and transesophageal, provides additional information such as feasibility of repair (rather than replacement) and location of paravalvular leaks. Additional imaging, such as cardiac magnetic resonance (CMR) imaging or multidetector CT (MDCT), may provide information on LV function, aortic dimensions, chamber sizes and volumes, and coronary anatomy. Consistency of quantitative evaluation is important. Simple measurements, such as LV outflow tract diameter, may vary greatly in the same patient when obtained at different times and by different operators. These differences may affect valve area calculations and influence timing of surgery.

Cardiac catheterization can provide important hemodynamic information, especially when the severity of the valve disease as measured by noninvasive testing is not consistent with symptoms or physical examination severity, or when accurate assessment of pulmonary pressures or detection of intracardiac shunts is needed. Coronary angiography is recommended before valve surgery in patients with severe VHD and a history of coronary artery disease, suspected myocardial ischemia, or LV systolic dysfunction; in men older than 40 years and postmenopausal women; in patients with one or more cardiovascular risk factors; and in patients in whom mitral regurgitation is thought to be caused by LV dysfunction. These patients may require concomitant revascularization at the time of surgery.

For patients in whom symptoms are equivocal, adjunctive evaluation (such as B-type natriuretic peptide measurement, exercise evaluation for tolerance/symptoms, and blood pressure response to exercise), assessment of pulmonary artery pressures, and LV outflow tract gradient (by TTE or cardiac catheterization) may be helpful.

KEY POINTS

- Patients with grade 1 or 2 midsystolic murmurs who are asymptomatic with no associated findings and those with continuous murmurs suggestive of a venous hum or mammary souffle do not warrant echocardiographic evaluation. HVC
- Transthoracic echocardiography is indicated for the evaluation of valve disease in patients with systolic murmurs grade 3/6 intensity or greater; late or holosystolic murmurs; diastolic or continuous murmurs; or any murmur with accompanying symptoms.

General Principles of Management of Valvular Heart Disease

Treatment is guided by valve lesion severity, which can be classified into four stages (A to D) in a system similar to that used for patients with heart failure (**Table 33**). The mainstay of treatment for VHD, both stenosis and regurgitation, is centered on interventions to treat the mechanical problem. The goals of treatment are both to improve symptoms and reduce the risk of complications such as irreversible ventricular dysfunction, pulmonary hypertension, and death. The most

TABLE 33. Stages of Progression of Valvular Heart Disease

Stage	Definition	Description
A	At risk	Patients with risk factors for development of VHD
B	Progressive	Patients with progressive VHD (mild-to-moderate severity and asymptomatic)
C	Asymptomatic severe	Asymptomatic patients who meet criteria for severe VHD:
		C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated
		C2: Asymptomatic patients with severe VHD, with decompensation of the left or right ventricle
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD

VHD = valvular heart disease.

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common indication for treatment is symptoms (**Table 34**) but other factors, including chamber dysfunction, chamber enlargement, and pulmonary hypertension may be indications for treatment. In general, for both stenotic and regurgitant lesions, symptoms occur before the development of ventricular dysfunction; however, some patients may have asymptomatic ventricular dysfunction. Medical therapy does not stall the progression of disease but is indicated for patients with symptoms and LV dysfunction who are awaiting valve repair or replacement, as well as for those who are not operative candidates. Preventive measures, such as statins for preventing progression of aortic stenosis, have not been shown to be useful.

The primary therapy for patients with severe VHD is valve repair or valve replacement with either bioprosthetic or mechanical valves. For patients with high surgical risks, percutaneous techniques for aortic valve replacement and mitral valve repair are now available.

Follow-up is essential in asymptomatic patients, as disease progression may occur over time (**Table 35**). After valve repair or replacement, patients should ideally be followed in conjunction with a cardiovascular specialist.

TABLE 34. Indications for Interventions for Valvular Heart Conditions

Valve Lesion	Indications to Intervene[a]	Interventions
Aortic stenosis	Symptoms (class I) LVEF <50% (class I) Moderate (class IIa) or severe (class I) aortic stenosis at time of other cardiac surgery Abnormal blood pressure response (decrease in systolic blood pressure) during exercise (class IIa) Asymptomatic patients with very severe aortic stenosis (class IIa)	Aortic valve replacement
Aortic regurgitation	Symptoms (class I) LVEF <50% (class I) Moderate (class IIa) or severe (class I) aortic regurgitation at time of other cardiac surgery LV dilatation (end-systolic dimension >50 mm) (class IIa)	Aortic valve replacement
Mitral stenosis	Symptoms (class I) Very severe mitral stenosis (MVA <1.0 cm^2) and no symptoms if valve morphology favorable for balloon valvotomy (class IIa) Severe mitral stenosis at time of other cardiac surgery (class I)	Percutaneous balloon valvotomy (if anatomy favorable by echocardiography with less than moderate mitral regurgitation and no left atrial thrombus)[b] Mitral valve replacement
Mitral regurgitation	Symptoms (class I) LVEF 30%-60% (class I) LV end-systolic diameter ≥40 mm (class I) Moderate (class IIa) or severe (class I) mitral regurgitation at time of other cardiac surgery Pulmonary hypertension (PA systolic pressure ≥50 mm Hg) (class IIa) New-onset atrial fibrillation (class IIa)	Mitral valve repair if anatomy favorable (presence of annular dilation, mitral leaflet prolapse, or myxomatous changes without calcification or stenosis) Mitral valve replacement
Tricuspid regurgitation	Severe tricuspid regurgitation at time of surgery for left-sided valve (class I) Symptoms due to severe, primary tricuspid regurgitation not responsive to medical therapy (class IIa)	Tricuspid valve repair if anatomy favorable Tricuspid valve replacement (bioprosthetic)

LV = left ventricle; LVEF = left ventricular ejection fraction; MVA = mitral valve area; PA = pulmonary artery.

[a]Strength of recommendation: class I: procedure should be performed; class IIa: procedure is reasonable.

[b]All patients considered for percutaneous balloon mitral valvotomy should undergo transesophageal echocardiography to assess for left atrial appendage clot and mitral regurgitation severity regardless of whether patient has sinus rhythm or atrial fibrillation.

Recommendations from Nishimura RA, Otto CM, Bonow RO, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):2438-88. Erratum in: J Am Coll Cardiol. 2014 Jun 10;63(22):2489. [PMID: 24603192]

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TABLE 35. Serial Evaluation of Asymptomatic Patients with Left-Sided Valvular Conditions

Factors Considered	Lesion Severity	Frequency
Aortic Stenosis		
Stenosis severity; rate of progression; LV systolic function; ascending aorta dilation if bicuspid aortic valve	At risk (V_{max} <2 m/s)	
	Mild (V_{max} 2.0-2.9 m/s or mean gradient <20 mm Hg)	Clinical eval yearly; echo every 3-5 y
	Moderate (V_{max} 3.0-3.9 m/s or mean gradient 20-39 mm Hg)	Clinical eval yearly; echo every 1-2 y
	Severe (V_{max} ≥4 m/s or mean gradient ≥40 mm Hg, AVA ≤1.0 cm^2)	Clinical eval yearly; echo every 6-12 mo
	Very severe (V_{max} ≥5 m/s or mean gradient ≥60 mm Hg)	Clinical eval yearly; echo every 6-12 mo
Mitral Stenosis		
Stenosis severity	Mild and moderate (MVA >1.5 cm^2, diastolic pressure half-time <150 msec)	Clinical eval yearly; echo every 3-5 y
	Severe (MVA ≤1.5 cm^2, diastolic pressure half-time ≥150 msec or ≥220 msec with very severe stenosis, PASP >30 mm Hg)	Clinical eval yearly; echo every 1-2 y for MVA 1.0-1.5 cm^2, every year for MVA <1.0 cm^2
Aortic Regurgitation		
Regurgitation severity; rate of progression; LV ejection fraction; LV chamber size; ascending aorta dilation if bicuspid aortic valve	Mild (VC <0.3 cm, ERO <0.10 cm^2, RV <30 mL/beat, RF <30%); normal EF	Clinical eval yearly; echo every 3-5 y
	Moderate (VC 0.3-0.6 cm, ERO 0.10-0.29 cm^2, RV 30-59 mL/beat, RF 30%-49%)	Clinical eval yearly; echo every 1-2 y
	Severe (VC >0.6 cm, ERO >0.3 cm^2, RV ≥60 mL/beat, RF ≥50%)	
	EF ≥50%; LVESD ≤50 mm	Clinical eval every 6-12 mo; echo every 6-12 mo, more frequently for dilating LV
	EF <50%; LVESD >50 mm	Clinical eval every 6-12 mo; echo every 6-12 mo, more frequently for dilating LV
Mitral Regurgitation		
Regurgitation severity; rate of progression; EF; LV chamber size	At risk (VC <0.3 cm)	Clinical eval yearly; echo only if symptomatic
	Mild and moderate (VC <0.7 cm, ERO <0.40 cm^2, RV <60 mL/beat, RF <50%)	Clinical eval yearly; echo every 3-5 y for mild severity, every 1-2 y for moderate severity
	Severe (VC ≥0.7 cm, ERO ≥0.4 cm^2, RV ≥60 mL/beat, RF ≥50%)	Clinical eval every 6-12 mo; echo every 6-12 mo, more frequently for dilating LV

AVA = aortic valve area; echo = echocardiography; EF = ejection fraction; ERO = effective regurgitant orifice; eval = evaluation; LV = left ventricle; LVESD = left ventricular end-systolic dimension; MVA = mitral valve area; PASP = pulmonary artery systolic pressure; RF = regurgitant fraction; RV = regurgitant volume; VC = vena contracta width; V_{max} = maximum aortic jet velocity.

Recommendations based on Nishimura RA, Otto CM, Bonow RO, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):2438-88. Erratum in: J Am Coll Cardiol. 2014 Jun 10;63(22):2489. [PMID: 24603192]

KEY POINTS

- Medical therapy does not stall the progression of valvular heart disease but is indicated for patients with symptoms and left ventricular dysfunction who are awaiting valve repair or replacement, as well as for those who are not operative candidates.
- The mainstay of therapy for patients with severe valvular heart disease is either valve repair or valve replacement with bioprosthetic or mechanical valves.

Aortic Stenosis

Clinical Presentation and Evaluation

Aortic stenosis is the most common type of valvular heart disease in the United States and is typically caused by calcific degeneration of an otherwise normal aortic valve. Other causes include bicuspid aortic valve and rheumatic valve disease, the latter of which remains common worldwide and is almost always accompanied by mitral valve disease.

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Calcific aortic stenosis is a disease of the elderly, and coronary artery disease and hypertension are common in these patients. Patients may present with heart failure symptoms, usually associated with preserved ejection fraction. Some patients present with decompensated heart failure associated with reduced cardiac output. The chronic increase in LV systolic pressure results in a compensatory increase in myocardial cell mass; interstitial fibrosis may follow, leading first to diastolic dysfunction and then to systolic dysfunction. Increased LV end-diastolic pressure results in pulmonary congestion. These and other adaptive and pathologic processes contribute to the three cardinal symptoms of aortic stenosis: angina, dyspnea, and syncope. Identification of the symptomatic patient is crucial; in the absence of symptoms, patients with aortic stenosis—even severe aortic stenosis—have a low risk of mortality, with a risk of sudden death estimated to be less than 1%. The rate of progression is approximately 0.1 cm^2 annually. Although variable, symptoms of heart failure, angina, or syncope generally begin once the valve area is below 1.0 cm^2. Once symptoms develop, prognosis is poor without valve replacement, with an average survival of less than 10% over the next 2 to 3 years.

TTE is essential in the initial diagnosis and follow-up of aortic stenosis, permitting quantification of valve area and gradients (see Table 35), chamber size, wall thickness, ventricular function, and coexistent valve disease. Echocardiographic findings for severe aortic stenosis include a heavily calcified aortic valve with restrictive leaflets, possibly a bicuspid aortic valve, and associated aortic regurgitation. TEE can provide additional information regarding leaflet anatomy (bicuspid, unicuspid) when TTE images are inadequate as well as information about concomitant aortic root abnormalities. If echocardiographic data conflict with clinical data or echocardiographic images are suboptimal, CMR imaging may be useful. It can assess leaflet anatomy, measure gradients, and, in patients with a bicuspid aortic valve, assess aorta and aortic root anatomy. Cardiac CT can be used to measure valve area when echocardiographic images are inadequate and to quantify calcification, a marker for risk of disease progression.

Some patients with calcific aortic stenosis have severe aortic stenosis based on valve area but a gradient that is less than 30 mm Hg. Whether symptoms in this "low-flow/low-gradient aortic stenosis" are caused primarily by aortic valve disease with resultant LV dysfunction or the effective valve is reduced owing to poor leaflet excursion ("pseudosevere aortic stenosis") can be best determined with dobutamine stress echocardiography. Key to this evaluation is the understanding of contractile reserve. Contractile reserve is defined as an increase in transaortic stroke volume of greater than 20% with dobutamine infusion. In patients with severe aortic stenosis and resultant LV dysfunction but with contractile reserve, the mean gradient will increase with dobutamine stress and the aortic valve area will remain below 1.0 cm^2; these patients will benefit from aortic valve replacement. Those with an increase in aortic valve area to greater than 1.0 cm^2 or with a maximum aortic jet velocity (V_{max}) below 4 m/s have moderate aortic stenosis and medical therapy is appropriate. Some patients with true aortic stenosis do not have contractile reserve and no change in LV function or aortic valve gradients is seen with dobutamine stress. These patients have a worse prognosis. A lack of contractile reserve is an indicator of higher surgical mortality but is not in itself a contraindication to surgery.

Paradoxic low-gradient aortic stenosis is a more recently described entity in which the measured aortic valve area is reduced in a setting of preserved ejection fraction (>50%) but reduced stroke volume (<35 mL/m^2). Typically encountered in the elderly, it is associated with factors related to reduced stroke volume, such as small LV size and marked LV hypertrophy. This may cause the severity of aortic stenosis to be underestimated by echocardiography owing to the low gradient. Identifying these patients—who are usually symptomatic—is important, as these are patients who may benefit from aortic valve replacement.

Management

In asymptomatic patients with aortic stenosis, identifying those who are in higher risk subgroups is important, as these patients may benefit from earlier intervention. Exercise treadmill testing is reasonable in asymptomatic patients to identify those who actually do have symptoms with exercise, have ST-segment changes on ECG, or have an abnormal blood pressure response (lack of increase in systolic blood pressure by at least 20 mm Hg above baseline), as these patients may benefit from earlier surgery. Patients must be closely monitored during exercise testing. Additional factors that may predict more rapid progression and thus indicate closer follow-up include elevated B-type natriuretic peptide level, LV ejection fraction below 50%, pulmonary hypertension, and moderate to severe valve calcification. Appropriate follow-up of asymptomatic patients is based on lesion severity (see Table 35).

Aortic valve replacement is indicated for asymptomatic patients with severe aortic stenosis and LV systolic dysfunction (LV ejection fraction <50%) as well as for those patients with severe aortic stenosis who are undergoing coronary artery bypass grafting or surgery on the aorta or other heart valves.

Surgical aortic valve replacement is the treatment of choice for most patients with symptomatic severe aortic stenosis. It is associated with low mortality for patients younger than 70 years (1%-3%) and for selected patients who are older than 80 years. Balloon aortic valvuloplasty (BAV) has a limited role in the treatment of adult aortic stenosis. Whereas BAV does result in reduction in gradient and increase in valve area, these results typically last only for a few months. Recently, BAV in the adult has been used successfully as a bridge to definitive treatment (surgical or transcatheter aortic valve replacement [TAVR]) or to differentiate symptoms in high-risk patients with comorbid conditions such as COPD.

Medical therapy has limited benefit in the treatment of aortic stenosis. Statins do not delay the progression of aortic stenosis but should be prescribed as indicated to patients with

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CONT.

hyperlipidemia or atherosclerotic risk factors. In patients with heart failure, ACE inhibitors, diuretics, angiotensin receptor blockers, and digoxin may be used as appropriate but have not been shown to be helpful in changing the natural history of aortic stenosis.

It is estimated that fewer than half of patients with symptomatic, severe aortic stenosis undergo surgical aortic valve replacement because of comorbid medical conditions that increase surgical risk. This population has become the target for TAVR. The 3-year follow-up results of the PARTNER trial indicate that TAVR has a survival benefit similar to that of surgical replacement for high-risk patients (PARTNER A cohort). TAVR is superior to medical therapy in patients thought not to be surgical candidates (PARTNER B cohort), as 1-year mortality was 30.7% in the TAVR arm versus 50.7% in the medical therapy arm. Complications include stroke and paravalvular aortic regurgitation. Currently, TAVR is indicated for patients who have been determined by a cardiac surgeon to be inoperable or at high risk for death or major morbidity with open aortic valve replacement and in whom existing comorbidities would not preclude the expected benefit from correction of the aortic stenosis. For high-risk patients who are surgical candidates, risk should be determined by a team of cardiologists and cardiac surgeons, with the use of objective measurements, such as the Society of Thoracic Surgeons adult cardiac risk score (STS score) (http://riskcalc.sts.org/STSWebRiskCalc273/de.aspx). Patients with an STS risk score of greater than or equal to 8% may be candidates for TAVR. TAVR is not approved in patients with a bicuspid aortic valve, significant aortic regurgitation, or mitral valve disease.

KEY POINTS

- Once symptoms of aortic stenosis develop, prognosis is poor without intervention (valve replacement), with an average survival of only 2 to 3 years and a high risk of sudden death.
- Transcatheter aortic valve replacement is a treatment option for patients with aortic stenosis who are inoperable or at high risk for death or major morbidity with open aortic valve replacement.

Aortic Regurgitation

Clinical Presentation and Evaluation

Acute severe aortic regurgitation usually is caused by infective endocarditis or aortic dissection (typically in a setting of hypertension or Marfan syndrome). Chronic severe aortic regurgitation is most commonly associated with a dilated ascending aorta from hypertension or primary aortic disease, calcific aortic sclerosis, bicuspid aortic valve, or rheumatic disease. Calcific aortic sclerosis can progress to significant stenosis and is associated with a mild degree of aortic regurgitation.

Symptoms from acute aortic regurgitation result from the sudden large volume in a previously normal LV, resulting in a rapid increase in LV end-diastolic pressure and compensatory increase in heart rate and contractility to maintain cardiac output. When this compensation becomes inadequate, pulmonary edema, myocardial ischemia (due to decreased diastolic perfusion), and cardiogenic shock ensue. Conversely, chronic aortic regurgitation permits a compensatory increase in LV size with increased LV diastolic volume and LV hypertrophy (eccentric and concentric) due to increased volume and afterload. These compensatory mechanisms help maintain stroke volume and cardiac output, but eventually, the increase in volume leads to cardiac dysfunction and heart failure symptoms due to increased LV filling pressure as well as angina due to decreased coronary perfusion pressure and marked LV hypertrophy.

Quantifying the severity of aortic regurgitation is most often done with TTE. Markers of severe aortic regurgitation include wide vena contracta (or diameter of the regurgitant jet orifice), rapid equilibration of aortic and LV pressures during diastole, early mitral valve closure, and diastolic mitral regurgitation. TEE is useful in identifying leaflet anatomy, in further assessment of severity of aortic regurgitation and aortic root pathology, and in evaluation of subvalvular (for example, subaortic membrane) or supravalvular stenosis, and can aid in intraoperative repair and replacement. CMR imaging, including magnetic resonance angiography (MRA), can quantify severity of aortic regurgitation and assess aortic root and ascending aorta dilation. Cardiac CT may provide information such as coronary anomalies and leaflet anatomy.

Management

Urgent or emergent surgical valve replacement is indicated for acute severe aortic regurgitation. For chronic severe aortic regurgitation, valve replacement is indicated for symptomatic patients regardless of LV systolic function (see Table 34). Valve replacement also is indicated for asymptomatic patients with chronic severe aortic regurgitation and LV systolic dysfunction and for patients with chronic severe aortic regurgitation undergoing coronary artery bypass graft surgery or surgery on the aorta or other heart valves. Combined aortic root replacement with aortic valve replacement is used when there is an associated aortic root aneurysm. Follow-up of asymptomatic patients is based on severity of regurgitation and other factors (see Table 35).

Vasodilators and inotropic agents may benefit patients with acute severe aortic regurgitation and concomitant heart failure as short-term therapy before proceeding with surgery. ACE inhibitors or angiotensin receptor blockers may be used in patients with chronic severe aortic regurgitation and heart failure and in patients with hypertension; however, these agents, as well as dihydropyridine calcium channel blockers, have not been shown to delay need for surgery in asymptomatic patients without hypertension.

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KEY POINTS

- Urgent or emergent surgical valve replacement is indicated for patients with acute severe aortic regurgitation.
- Valve replacement is indicated for symptomatic patients with chronic severe aortic regurgitation regardless of left ventricular systolic function.

Bicuspid Aortic Valve

Bicuspid aortic valve is the most common congenital heart abnormality, affecting 0.5% to 2% of the total population. Although a bicuspid aortic valve may be suspected in patients with classic auscultatory findings (systolic ejection click at the left lower sternal border; murmur of aortic stenosis or aortic regurgitation in a young patient), it is most often diagnosed by TTE performed for some other indication. A bicuspid aortic valve may be diagnosed initially in a patient presenting with a complication, such as bacterial endocarditis or aortic dissection. Features that may raise suspicion include eccentric aortic regurgitation, enlarged sinuses of Valsalva, a dilated ascending aorta, or an elliptical valve opening. Calcification may obscure valve leaflets and make the diagnosis difficult. TEE may provide confirmatory information as to leaflet anatomy as well as the presence of associated conditions, including aortic aneurysms and aortic coarctation, and is appropriate when the diagnosis is uncertain.

The clinical course of patients with a bicuspid aortic valve varies widely. Although overall survival is similar to that of age-matched controls, approximately one in three patients with a bicuspid aortic valve may eventually require valve surgery for either stenosis or regurgitation. Stenosis proceeds at a faster rate when the aortic valve is bicuspid, and valve replacement may be required in the fifth or sixth decade of life. Some degree of regurgitation is common with a bicuspid aortic valve but is less likely than stenosis to lead to valve replacement. The presence of a bicuspid aortic valve carries an increased risk of infective endocarditis, and good dental care is important in these patients. Current guidelines no longer recommend antibiotic prophylaxis for this patient population (see Infective Endocarditis, later). The timing of follow-up TTE depends on many factors, including patient age and severity of the valve lesion. In general, older, asymptomatic patients with a bicuspid aortic valve and severe aortic valve stenosis or regurgitation require yearly echocardiography; those with mild stenosis or regurgitation should have echocardiography every 3 to 5 years.

A bicuspid aortic valve may occur with other cardiovascular and systemic abnormalities, such as aortic coarctation, aneurysm of the sinuses of Valsalva, and patent ductus arteriosus. Patients with a bicuspid aortic valve are predisposed to aortic aneurysm and dissection owing to aortic connective tissue abnormalities. For this reason, the ascending aortic diameter should be reassessed by echocardiography if the aortic root or ascending aorta dimension is greater than or equal to 4.0 cm, with the evaluation interval determined by degree and rate of aortic dilation and by family history. Annual evaluation should occur if the aortic diameter is greater than 4.5 cm. Multidetector CT or CMR imaging is appropriate for further assessment of aortic pathology when TTE or TEE is not conclusive and for long-term follow up of aortic dimensions when TEE images are inadequate. A bicuspid aortic valve may be present in patients with other thoracic aneurysm syndromes as well, such as Loeys-Dietz syndrome (hypertelorism, split uvula or cleft palate, and aortic aneurysms). Echocardiography of first-degree relatives of patients with a bicuspid aortic valve is indicated to screen for bicuspid aortic valve or aortic aneurysms.

As with calcific aortic stenosis, medical therapies for bicuspid aortic valve stenosis are limited. Aortic valve replacement is the only therapeutic option for adult patients with a stenotic bicuspid aortic valve, and recommendations regarding when to intervene are the same as for tricuspid aortic valves (see Table 34).

For patients with a regurgitant bicuspid aortic valve, valve replacement is the treatment of choice when regurgitation is clinically significant; however, repair may be performed in selected patients by experienced surgeons.

Surgery to repair the aortic root or replace the ascending aorta is indicated in patients with a bicuspid aortic valve when the aortic root diameter is greater than 5.5 cm. Surgery is reasonable if the diameter of the ascending aorta or aortic root is greater than 5.0 cm and a risk factor for dissection is present (family history of aortic dissection or if the rate of increase in diameter is ≥0.5 cm per year). Ascending aorta replacement is reasonable in patients who are undergoing aortic valve surgery because of severe aortic stenosis or aortic regurgitation if the diameter of the ascending aorta is greater than 4.5 cm. H

KEY POINTS

- In general, older, asymptomatic patients with a bicuspid aortic valve and severe aortic valve stenosis or regurgitation require yearly echocardiography; those with mild aortic stenosis or regurgitation require echocardiography every 3 to 5 years. HVC
- Echocardiography of first-degree relatives of patients with a bicuspid aortic valve is indicated to screen for bicuspid aortic valve or aortic aneurysms.
- Patients with a bicuspid aortic valve are predisposed to aortopathy, and aortic surgery is indicated when the aortic root diameter is greater than 5.5 cm.

Mitral Stenosis

Clinical Presentation and Evaluation

The primary cause of mitral stenosis is rheumatic carditis. Improved hygiene and the routine use of antibiotics for group A streptococcal pharyngitis have greatly reduced the incidence of rheumatic heart disease in the United States and developed countries. Rarely, functional mitral stenosis occurs as a result

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of outflow obstruction from tumor (such as myxoma) or left atrial thrombus. Other causes of mitral stenosis include congenital disease (such as parachute mitral valve, wherein the mitral chordae insert into one instead of two papillary muscles) and mitral annular calcification. Symptoms can be indolent, with patients remaining asymptomatic for years and then presenting with a gradual decrease in activity. Other symptoms include dyspnea, orthopnea, fatigue, and, less commonly, hemoptysis or systemic embolization. Symptoms typically are not present until the mitral valve area is less than 1.5 cm^2, although tachycardia may precipitate symptoms at larger valve areas. The decrease in mitral valve area results in a diastolic pressure gradient between the left atrium and ventricle. This increase in left atrial pressure causes left atrial enlargement, with development of atrial fibrillation and a significantly increased risk of left atrial/left atrial appendage thrombus, as well as exertional dyspnea and eventual pulmonary edema owing to increased pulmonary venous pressure. In addition, chronic pulmonary venous pressure elevation may result in pulmonary hypertension. The risk of thromboembolism increases with age and the presence of atrial fibrillation. Warfarin remains the anticoagulant of choice for these patients with concomitant atrial fibrillation as they were excluded from trials of novel oral anticoagulants.

TTE is used to assess disease severity of mitral stenosis by measuring valve area and transvalvular gradient (see Table 35). Typical echocardiographic findings of rheumatic mitral stenosis include a domed or "hockey stick" appearance to the mitral valve, with thickened, calcified subvalvular apparatus and marked left atrial enlargement. Gradients are heart-rate dependent and can vary greatly in patients who are tachycardic or have atrial fibrillation. Echocardiography is essential for assessment of valve morphology, including factors such as valve calcification and thickening, leaflet motion, and subchordal thickening. These factors, taken together, help predict the likelihood of successful percutaneous mitral balloon valvuloplasty. TEE provides better visualization for assessment of mitral regurgitation severity as well as the presence of left atrial appendage thrombus. Multidetector CT may provide additional information by valve planimetry as well as visualization of the coronary anatomy. This may be helpful for patients whose valve is not well imaged on TTE and are unable to tolerate TEE.

Management

Percutaneous mitral balloon valvotomy is indicated for symptomatic patients (New York Heart Association [NYHA] functional class II, III, or IV) with severe mitral stenosis (see Table 34) and favorable valve morphology. TEE plays an important role in assessment of patients being considered for percutaneous balloon valvotomy to evaluate for potential contraindications, including left atrial appendage clot or significant (moderate to severe) mitral regurgitation. Mitral valve surgery (repair if possible) is indicated in patients with symptomatic (NYHA functional class III–IV) severe mitral stenosis when balloon valvotomy is unavailable, unsuccessful, or contraindicated or when the valve morphology is unfavorable.

Medical therapy for mitral stenosis consists of diuretics or long-acting nitrates, which may help improve symptoms such as dyspnea. In addition, β-blockers or nondihydropyridine calcium channel blockers can lower heart rate and improve LV diastolic filling time.

KEY POINT

- Mitral valvotomy or surgery is indicated for symptomatic patients (New York Heart Association functional class II-IV) with severe mitral stenosis and favorable valve morphology.

Mitral Regurgitation

Clinical Presentation and Evaluation

Abnormalities in any of the structures of the mitral valve apparatus, including anterior and posterior mitral leaflets, the annulus, the papillary muscles, and the chordae tendineae, can result in mitral regurgitation. Organic, or primary, mitral regurgitation refers to processes involving the leaflets, such as mitral valve prolapse, myxomatous degeneration (the abnormal accumulation of proteoglycans), collagen vascular disease, and infective endocarditis. Processes that affect the support structures, such as coronary artery disease and LV remodeling in the setting of LV dysfunction, result in functional, or secondary, mitral regurgitation.

Acute severe mitral regurgitation is associated with papillary muscle rupture following acute myocardial infarction, flail mitral valve (dissociation of the valve leaflet from the chordae), and infective endocarditis with leaflet perforation. The sudden large volume in the left atrium and ventricle results in rapid increases in LV end-diastolic pressure and left atrial pressure, which leads to elevated pulmonary artery pressure and pulmonary edema. The diminished LV stroke volume leads to hypotension and shock.

Patients with chronic mild to moderate mitral regurgitation may remain asymptomatic for many years. Progression is variable and caused by either progression of lesions or increasing mitral annulus size. The increase in volume and subsequent increase in left atrial pressure lead to compensatory dilation of the left atrium and LV. Left atrial dilation predisposes to atrial fibrillation. A chronic increase in preload and resultant eccentric hypertrophy, in the setting of increased stroke volume (normal forward stroke volume and regurgitant volume) lead to contractile dysfunction and increased end-diastolic volume, which lead to pulmonary congestion and pulmonary hypertension. Appropriate follow-up of asymptomatic patients with mitral regurgitation is outlined in Table 35.

TTE serves as the main imaging modality in the evaluation and management of mitral regurgitation. TTE allows diagnosis of the mechanism of mitral regurgitation, qualitative and

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TABLE 37. Empiric Therapy for Infective Endocarditis

Condition	Therapy
Community-acquired native valve IE	Consider vancomycin + gentamicin
Nosocomial-associated IE	Consider vancomycin + gentamicin + rifampin or vancomycin + gentamicin + a carbapenem or cefepime
Prosthetic valve IE	Consider vancomycin + gentamicin + rifampin

IE = infective endocarditis.

CONT.

within 60 days of a hospital admission that was associated with a risk for bacteremia or infective endocarditis. For nosocomial infections, coverage for multidrug-resistant bacteria, particularly coagulase-negative staphylococci, is recommended.

Surgery for native valve endocarditis usually entails resection of the vegetation and valve repair or replacement if appropriate. Early surgery (during initial hospitalization and before completion of a full course of antibiotics) is indicated for patients with acute infective endocarditis presenting with valve stenosis or regurgitation resulting in heart failure; left-sided infective endocarditis caused by *Staphylococcus aureus*, fungal, or other highly resistant organisms; infective endocarditis complicated by heart block, annular or aortic abscess, or destructive penetrating lesion; and infective endocarditis with persistent bacteremia or fever lasting longer than 5 to 7 days after starting antibiotic therapy. Surgery is recommended for patients with relapsing prosthetic valve endocarditis. In patients with infective endocarditis who have documented infection of pacemaker or defibrillator systems, complete removal of these systems (all leads and generator) is indicated. Early surgery is reasonable in patients with infective endocarditis who have recurrent emboli and persistent vegetations on antibiotic therapy, and may be considered in patients with native valve endocarditis who have mobile vegetations greater than 10 mm in length. The Early Surgery versus Conventional Treatment in Infective Endocarditis (EASE) trial compared the clinical outcomes of early surgery with a conventional treatment strategy in patients with left-sided infective endocarditis and a high risk of embolism. In this study, early surgery (within 48 hours after diagnosis and randomization) in patients with large vegetations (>10 mm) significantly reduced embolic events with similar in-hospital and 6-month mortality rates compared with delayed surgery.

Prophylaxis

The significant morbidity and mortality associated with infective endocarditis underscore the importance of appropriate administration of antibiotics before procedures expected to produce bacteremia. The American College of Cardiology/American Heart Association (ACC/AHA) recommendations and the European Society of Cardiology (ESC) recommendations, which changed significantly in recent years, may contradict long-standing expectations of patients and practice patterns of health care providers. However, infective endocarditis is more likely to result from frequent exposure to random bacteremia associated with daily activities than from bacteremia caused by dental, gastrointestinal tract, or genitourinary procedures; additionally, the risk of antibiotic-associated adverse effects may exceed the benefit (if any) from prophylactic antibiotic therapy.

Infective endocarditis prophylaxis is currently recommended for patients with cardiac conditions with the highest risk for adverse outcomes from infective endocarditis (rather than those with an increased lifetime risk for infective endocarditis). Prophylaxis is recommended for patients with (1) a prosthetic cardiac valve; (2) a previous episode of infective endocarditis; (3) congenital heart disease, including unrepaired cyanotic congenital heart disease, a completely repaired congenital heart defect with prosthetic material or device during the first 6 months after the procedure, and repaired congenital heart disease with residual defects; or (4) valvulopathy following cardiac transplantation.

Unless there is a history of infective endocarditis, prophylaxis is not recommended for patients with native valve disease, including rheumatic heart disease, mitral valve prolapse with regurgitation, or a bicuspid aortic valve.

In patients who meet the criteria, prophylaxis should be administered prior to dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa (**Table 38**). Infective endocarditis prophylaxis is not recommended prior to nondental procedures, such as TEE, genitourinary procedures, or gastrointestinal procedures. Antimicrobial prophylaxis is recommended for procedures involving incision or biopsy of the respiratory tract mucosa, such as bronchial biopsy, tonsillectomy, and adenoidectomy.

KEY POINTS

- In patients with a cardiac murmur suggestive of organic valvular or congenital heart disease or patients with a prosthetic heart valve, infective endocarditis should be suspected in the presence of fever, anemia, hematuria, and physical findings suggestive of embolization.
- Early surgery is indicated for patients with acute infective endocarditis presenting with valve stenosis or regurgitation resulting in heart failure; left-sided infective endocarditis caused by *Staphylococcus aureus*, fungal, or other highly resistant organisms; infective endocarditis complicated by heart block, annular or aortic abscess, or destructive penetrating lesion; and infective endocarditis with persistent bacteremia or fever lasting longer than 5 to 7 days after starting antibiotic therapy.
- Surgery is recommended for patients with prosthetic valve endocarditis and relapsing infection.

(Continued)

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TABLE 38. Prophylactic Infective Endocarditis Regimens for Adults Before a Dental Procedure

Situation	Agent[a]	Dosage
Oral	Amoxicillin	2 g
Unable to take oral medication	Ampicillin	2 g IM or IV
	or	
	Cefazolin or ceftriaxone	1 g IM or IV
Allergic to penicillin or ampicillin - oral	Cephalexin	2 g
	or	
	Clindamycin	600 mg
	or	
	Azithromycin or clarithromycin	500 mg
Allergic to penicillin or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone	1 g IM or IV
	or	
	Clindamycin	600 mg IM or IV

IM = intramuscular; IV = intravenous.

[a]Regimen consists of a single dose 30 to 60 minutes before the dental procedure, or, if inadvertently not administered, drug may be given up to 2 hours after the procedure.

Adapted from Wilson W, Taubert KA, Gewitz M, et al; American Heart Association. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. J Am Dent Assoc. 2008 Jan;139 Suppl:3S-24S. Review. Erratum in: J Am Dent Assoc. 2008 Mar;139(3):253. [PMID: 18167394]. Copyright 2008 American Dental Association.

KEY POINTS *(continued)*

HVC
- Infective endocarditis prophylaxis should be limited to those with a prosthetic cardiac valve; a history of infective endocarditis; unrepaired cyanotic congenital heart disease or repaired congenital heart defect with prosthesis or shunt (≤6 months post-procedure) or residual defect; or valvulopathy following cardiac transplantation.

Prosthetic Valves

H The choice of prosthesis for patients requiring valve replacement must account for various considerations, including the patient's age, any comorbid factors, and the patient's preference and ability to adhere to medical therapy post-implantation. The ACC/AHA and ESC have published recommendations regarding valve selection (**Table 39**). In general, patient factors that favor a mechanical prosthesis include younger age, an absence of contraindications to long-term anticoagulation, a risk of accelerated bioprosthetic structural valve deterioration (for example, with pregnancy or kidney failure), and a reasonable life expectancy in patients for whom future redo valve surgery would be high risk. Conversely, factors that would favor a bioprosthetic valve include older age; patients in whom adequate long-term anticoagulation is unlikely (for example, owing to adherence problems or anticoagulation agents not being readily available) or contraindicated because of high bleeding risk (prior major bleed, lifestyle or occupation issues); patients requiring reoperation for mechanical valve thrombosis despite good long-term anticoagulant control; and young women contemplating pregnancy (although a mechanical prosthesis requiring anticoagulation is not a contraindication to pregnancy).

TABLE 39. Summary of Recommendations for Prosthetic Valve Choice

Type of Valve	Recommendation
Bioprosthesis	Recommended: patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired
	Reasonable: patients >70 y of age
Mechanical prosthesis	Reasonable: AVR or MVR in patients <60 y of age who do not have a contraindication to anticoagulation
Either bio- or mechanical prosthesis	Reasonable: patients between 60 y and 70 y of age

AVR = aortic valve replacement; MVR = mitral valve replacement.

NOTE: The guideline recommends that the choice of valve intervention and prosthetic valve type should be a shared decision-making process.

Recommendations from Nishimura RA, Otto CM, Bonow RO, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):2438-88. Erratum in: J Am Coll Cardiol. 2014 Jun 10;63(22):2489. [PMID: 24603192]

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CONT.

Lifelong oral anticoagulation with warfarin is recommended for all patients with a mechanical prosthesis and those with bioprostheses with other indications for anticoagulation. The target INR is based upon prosthesis location, with a target of 2.5 for patients with a mechanical aortic prosthetic valve and 3.0 for patients with a mechanical mitral prosthetic valve and those patients with a mechanical aortic prosthetic valve and risk factors (atrial fibrillation, LV dysfunction, previous thromboembolism, hypercoagulable condition, or older-generation mechanical aortic valve replacement). The addition of aspirin, 75 to 100 mg/d, is recommended as well. Ongoing studies are evaluating various anticoagulation regimens for newer and potentially less thrombogenic valves.

The need for anticoagulation for those with bioprosthetic valves is less clear. Oral anticoagulation should be considered for the first 3 months after implantation of a mitral or tricuspid bioprosthesis and for the first 3 months after bioprosthetic mitral valve repair. Low-dose aspirin or anticoagulation should be considered for the first 3 months after implantation of an aortic bioprosthesis. Long-term aspirin use is reasonable for all patients with bioprosthetic valves.

Patients with prosthetic valves require lifelong cardiology follow-up, including annual clinical examination. For baseline assessment, all patients undergoing valve replacement surgery should have TTE performed 2 to 3 months after implantation as a baseline study. Patients with bioprosthetic valves may be considered for annual echocardiograms after the first 10 years in the absence of a change in clinical status. Routine echocardiography is not recommended for patients with mechanical valves or those with recently implanted biologic valves in the absence of any change in symptoms or examination findings.

KEY POINTS

- Lifelong oral anticoagulation with warfarin is recommended for all patients with a mechanical prosthetic heart valve.
- Oral anticoagulation should be considered for the first 3 months after implantation for patients with a bioprosthetic mitral or tricuspid valve and for the first 3 months after bioprosthetic mitral valve repair.
- Routine echocardiography is not recommended for patients with mechanical valves or those with recently implanted biologic valves in the absence of any change in symptoms or examination findings.

Adult Congenital Heart Disease

Introduction

Advances in care of patients with congenital heart disease over the past six decades have resulted in more adults than children living in North America with these conditions. Cardiovascular residua are common in patients with previous intervention for congenital cardiac lesions, underscoring the importance of periodic informed follow-up by a team consisting ideally of the internist and an adult or pediatric cardiologist trained in adult congenital heart disease. Specialized care is particularly important for patients with complex and cyanotic congenital cardiac disease. Congenital heart conditions may be first identified during pregnancy or symptom status may be worsened by the physiologic changes of pregnancy. Decisions regarding the safety of pregnancy in patients with congenital cardiac disease and management during pregnancy should be made on an individual basis in consultation with a congenital heart disease specialist.

Patent Foramen Ovale

The foramen ovale allows transfer of oxygenated placental blood to the fetal circulation and usually closes within the first few weeks of life. In 25% to 30% of the population, however, the foramen ovale remains patent (**Figure 27**). Patent foramen ovale (PFO) is usually asymptomatic and identified incidentally. No treatment or follow-up is needed for the PFO found incidentally in an asymptomatic patient.

PFO is diagnosed by visualizing the interatrial septum by echocardiography and demonstrating shunting of blood across the defect by color flow Doppler imaging or by using agitated saline injected intravenously and subsequent transfer through the PFO from right to left atrium. If transthoracic echocardiography (TTE) is nondiagnostic, transesophageal echocardiography (TEE) usually provides improved visualization of the atrial septum.

Antiplatelet therapy is recommended as first-line therapy for patients with PFO and cryptogenic stroke. Results of randomized controlled trials of device closure for crytogenic stroke and PFO have not demonstrated benefit compared with medical therapy for secondary stroke prevention. Patients with cryptogenic stroke and PFO may be treated with antiplatelet or anticoagulant therapy and should be encouraged to participate in one of the ongoing trials comparing closure with medical therapy. There is no indication for PFO closure or for antiplatelet therapy in asymptomatic patients.

Observational studies have suggested an association between PFO and migraine. However, randomized studies of PFO closure to prevent migraine recurrence have not shown beneficial effect, and PFO closure should not be performed for the prophylaxis of migraine.

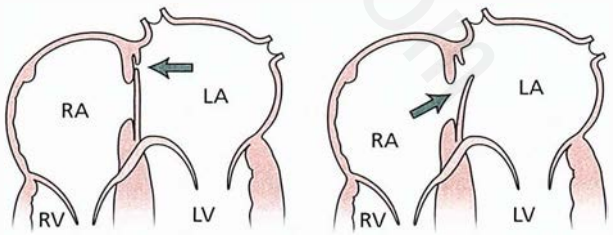

FIGURE 27. Patent foramen ovale. The *arrows* demonstrate the mechanism of right-to-left shunt through the patent foramen ovale. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Redrawn from original supplied courtesy of Dr. William D. Edwards, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.

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Rarely, a PFO may be associated with the platypnea-orthodeoxia syndrome. Platypnea-orthodeoxia syndrome is an acquired disorder characterized by cyanosis and dyspnea in the upright position. These symptoms are related to right-to-left shunting across a PFO or atrial septal defect and are caused by a transient increase in right atrial pressure, which occurs as a complication of right ventricular myocardial infarction, pulmonary embolism, tricuspid regurgitation, or acute right heart failure. Device PFO closure in these patients may decrease hypoxemia and cyanosis.

Atrial septal aneurysm is redundant and mobile atrial septal tissue. No treatment is needed when atrial septal aneurysm is discovered incidentally. Atrial septal aneurysm in conjunction with a PFO reportedly increases the risk of stroke compared with a PFO alone. Antiplatelet therapy is recommended for patients with cryptogenic stroke and an isolated atrial septal aneurysm. In patients with atrial septal aneurysm and recurrent stroke on antiplatelet therapy, anticoagulant therapy is recommended if no other cause of stroke is identified. Rarely, surgical excision of an atrial septal aneurysm and defect closure is considered if antiplatelet or warfarin therapy fails to prevent stroke recurrence.

KEY POINTS

- Antiplatelet therapy is recommended as first-line therapy for patients with patent foramen ovale and cryptogenic stroke.

HVC
- There is no indication for patent foramen ovale closure or for antiplatelet therapy in asymptomatic patients.

HVC
- Randomized trials do not support patent foramen ovale closure to reduce risk of recurrent stroke or migraine.

Atrial Septal Defect

Pathophysiology and Genetics

An atrial septal defect (ASD) is a communication between the atria. Left-to-right shunt occurs and, over time, causes right-sided cardiac chamber dilatation. Defects are classified according to location (**Figure 28**). Ostium secundum ASDs are the most common type (75% of cases). These are located in the middle portion of the atrial septum and are usually isolated anomalies. Ostium primum defects (15%-20% of cases) are located in the lowest portion of the atrial septum; they are commonly associated with a cleft mitral valve, ventricular septal defect, and subaortic stenosis, a collection of abnormalities termed endocardial cushion defect. Sinus venosus defects (5%-10% of cases) are usually located near the superior vena cava or, rarely, near the inferior vena cava. More than 90% of patients with sinus venosus ASD have associated anomalies of pulmonary venous connection. A coronary sinus ASD (<1% of cases) is a communication between the coronary sinus and the left atrium. These defects are commonly associated with complex congenital heart lesions or a persistent left-sided superior vena cava.

Most ASDs occur sporadically; however, several genetic syndromes associated with ASDs are recognized. The Holt-Oram syndrome involves bilateral upper extremity bone abnormalities and congenital heart defects, most commonly an ASD. Familial ostium secundum ASDs have also been described and may be autosomal dominant or are linked to chromosome 5. Down syndrome is commonly associated with congenital heart disease, most commonly a form of atrioventricular septal defect, including ostium primum ASD.

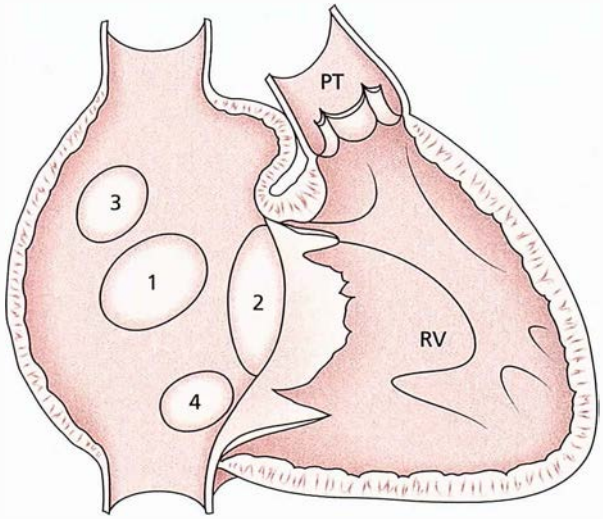

FIGURE 28. Positions of various atrial septal defects viewed from the right side of the heart. (1) ostium secundum; (2) ostium primum; (3) sinus venosus; (4) inferior vena cava. PT = pulmonary trunk; RV = right ventricle.

Redrawn from original supplied courtesy of Dr. William D. Edwards, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.

Clinical Presentation

ASDs may initially be identified in adulthood; the age of presentation depends on the shunt size and associated defects. Common presenting features include fatigue; exertional dyspnea; atrial fibrillation; paradoxical embolism; and abnormalities on the physical examination, including a pulmonary outflow murmur or fixed splitting of S_2 or, less commonly, findings that are consistent with a genetic syndrome involving an ASD. Occasionally, an ASD is identified as the cause for right heart enlargement found incidentally on an echocardiogram. Rarely, patients with isolated ASDs present with pulmonary arterial hypertension (PAH); this usually occurs in young women, suggesting the coexistence of idiopathic PAH.

Clinical findings in ASD include jugular venous distention, a parasternal impulse, and a systolic flow murmur at the second left intercostal space. Large shunts may cause a diastolic flow rumble across the tricuspid valve owing to a large left-to-right shunt. Fixed splitting of the S_2 is the characteristic auscultatory finding in patients with an ASD.

Diagnostic Evaluation

The electrocardiogram (ECG) and chest radiograph findings in patients with ASDs are outlined in **Table 40**. Complete heart block may occur in familial ASD.

TTE is the diagnostic imaging modality of choice for identification of ostium primum and secundum ASDs. Additional

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TABLE 40. Imaging Findings and Late Complications in Adult Congenital Heart Disease

Lesion	ECG and CXR Findings	Late Complications
Patent foramen ovale	Normal	Paradoxical embolism, platypnea-orthodeoxia syndrome
Ostium secundum ASD	ECG: Incomplete RBBB, RA enlargement, right axis deviation	Right heart enlargement, atrial fibrillation, PAH (rare)
	CXR: Right heart enlargement, prominent pulmonary artery, increased pulmonary vascularity	Post repair: residual shunt (rare)
Ostium primum ASD	ECG: Left axis deviation, 1st-degree atrioventricular block	Right heart enlargement, atrial fibrillation, mitral regurgitation (from mitral valve cleft), PAH (rare)
	CXR: Right heart enlargement, prominent pulmonary artery, increased pulmonary vascularity	Post repair: residual shunt (rare), mitral regurgitation (from mitral valve cleft), left ventricular outflow tract obstruction
Sinus venosus ASD	ECG: Abnormal P axis	Right heart enlargement, atrial fibrillation, PAH (rare)
	CXR: Right heart enlargement, prominent pulmonary artery, increased pulmonary vascularity	Post repair: residual shunt (rare), residual anomalous pulmonary venous connection
Small VSD	Normal	Endocarditis
Large VSD	ECG: RV or RV/LV hypertrophy	Left heart enlargement, PAH, Eisenmenger syndrome
	CXR: LA and LV enlargement, increased pulmonary vascular markings; with PAH: prominent central pulmonary arteries, reduced peripheral pulmonary vascular markings	Post repair: residual VSD, residual shunt (rare)
Small PDA	Normal	Endocarditis
Large PDA	ECG: LA enlargement, LV hypertrophy; with PAH: RV hypertrophy	Endocarditis, heart failure, PAH, Eisenmenger syndrome
	CXR: Cardiomegaly, increased pulmonary vascular markings; calcification of PDA (occasional); with PAH: prominent central pulmonary arteries, reduced peripheral pulmonary vascular markings	Post repair: residual shunt (rare)
Pulmonary valve stenosis	ECG: Normal when RV systolic pressure <60 mm Hg; if RV systolic pressure >60 mm Hg: RA enlargement, right axis deviation, RV hypertrophy	Post repair: Severe pulmonary valve regurgitation after pulmonary valvotomy or valvuloplasty
	CXR: Pulmonary artery dilatation, calcification of pulmonary valve (rare); RA enlargement may be noted	
Aortic coarctation	ECG: LV hypertrophy and ST-T wave abnormalities	Hypertension (75% of cases), bicuspid aortic valve (>50% of cases), increased risk of aortic aneurysm and intracranial aneurysm
	CXR: Dilated ascending aorta, "figure 3 sign" beneath aortic arch, rib notching from collateral vessels	Post repair: Recoarctation, hypertension, aortic aneurysm
Repaired tetralogy of Fallot	ECG: RBBB, increased QRS duration (QRS duration reflects degree of RV dilatation)	Post repair: Increased atrial and ventricular arrhythmia risk, pulmonary valve regurgitation or stenosis; tricuspid regurgitation
	CXR: Cardiomegaly with pulmonary or tricuspid valve regurgitation; right aortic arch in 25% of cases	QRS >180 msec increases risk of ventricular tachycardia and sudden death
Eisenmenger syndrome	ECG: Right axis deviation, RA enlargement, RV hypertrophy	Right heart failure, hemoptysis, stroke
	CXR: RV dilatation, prominent pulmonary artery, reduced pulmonary vascularity	

ASD = atrial septal defect; CXR = chest radiograph; ECG = electrocardiogram; LA = left atrium; LV = left ventricle; PAH = pulmonary arterial hypertension; PDA = patent ductus arteriosus; RA = right atrium; RBBB = right bundle branch block; RV = right ventricle; VSD = ventricular septal defect.

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findings on TTE include right-sided cardiac chamber enlargement, tricuspid regurgitation related to annular dilatation, and increased right ventricular systolic pressure. Agitated saline contrast injection may help identify a right-to-left atrial shunt if Eisenmenger syndrome is suspected (see Adults with Cyanotic Congenital Heart Disease, later). Sinus venosus and coronary sinus ASDs are less readily diagnosed by TTE in adults and often require TEE, MRI, or CT imaging.

MRI and CT can be used to quantify right ventricular volumes and ejection fraction. These studies are rarely used as the primary imaging modality when ASD is suspected but may help quantify right heart enlargement in a patient with ASD. In addition, a CT or MRI performed for another reason may be the first imaging study to demonstrate the ASD. MRI, CT, and TEE are useful for identifying anomalous pulmonary veins.

Cardiac catheterization is the only reliable method to calculate the pulmonary-to-systemic blood flow ratio (Qp:Qs) but is rarely required for uncomplicated ASDs. Cardiac catheterization may be recommended in the patient with an ASD and PAH to aid in determining whether ASD closure is indicated.

Treatment

Symptoms and right-sided cardiac chamber enlargement are the main indications for ASD closure. Closure should also be considered for patients with platypnea-orthodeoxia syndrome and patients with intracardiac shunt before pacemaker placement because of the increased risk of systemic thromboembolism. Other considerations include patient age, defect size and location, and associated abnormalities such as right heart enlargement, moderate (or less) hypertension, and tricuspid regurgitation. A small ASD (Qp:Qs <1.5:1.0) with no associated symptoms or right heart enlargement can be followed clinically.

Percutaneous intervention involves closure of the ASD using a device delivered via the venous system in the catheterization laboratory. This is the preferred treatment for patients with an isolated ostium secundum ASD and right-sided cardiac chamber enlargement but no other associated cardiovascular abnormality that requires operative intervention. Surgical closure is indicated for very large ostium secundum ASDs or insufficient septal anatomy for device closure; for all other types of ASDs; and for patients with any type of ASD when there is coexistent cardiovascular disease that requires operative intervention, such as coronary artery disease or tricuspid valve regurgitation.

Patients with severe PAH and an ASD may be considered for closure providing there is persistent left-to-right shunt and no evidence of fixed pulmonary vascular disease. Standard medical therapy for PAH should also be considered.

Patients with an isolated anomalous pulmonary venous connection may present with clinical and TTE features similar to an ASD, but no atrial-level shunt during agitated saline contrast study. A high clinical index of suspicion should prompt focused imaging with TEE, CT, or MRI.

Patients with small ASDs do not need any limitation of physical activity. In patients with large left-to-right shunts, exercise is often self-limited owing to decreased cardiopulmonary function. If pulmonary vascular disease is present, patients should be advised against isometric or competitive exercise.

Pregnancy in patients with ASD is generally well tolerated in the absence of PAH. The risk of congenital heart disease transmission in patients with sporadic ASD is estimated to be less than 10%. Genetic syndromes have variable inheritance; a family history should be taken. Holt-Oram syndrome is inherited in an autosomal dominant fashion.

Follow-up After Atrial Septal Defect Closure

Clinical follow-up is recommended for all adult patients after surgical or device ASD closure; the frequency of follow-up should be individualized. TTE imaging is generally recommended within the first year after closure and then periodically after that. Pre- and post-closure atrial fibrillation occurs more frequently the older the patient is at the time of ASD closure. Rare complications after device closure include device migration, erosion into the aorta or pericardium, and sudden death. Chest pain or syncope after device closure warrants urgent evaluation for device erosion.

KEY POINTS

- Fixed splitting of the S_2 is the characteristic auscultatory finding in patients with an atrial septal defect.
- A small atrial septal defect (pulmonary-to-systemic blood flow ratio [Qp:Qs] <1.5:1) with no associated symptoms or right heart enlargement can be followed clinically. HVC
- Symptoms and right-sided cardiac chamber enlargement are the main indications for atrial septal defect closure.

Ventricular Septal Defect

Pathophysiology

Ventricular septal defects (VSDs) are common at birth, but the frequency decreases by adulthood because of spontaneous closure of small defects. VSDs are defined by their location on the ventricular septum (**Figure 29**). The most common type of VSD is perimembranous, comprising 80% of cases; these are usually isolated abnormalities. Subpulmonary VSDs (also called outlet or supracristal VSDs) account for approximately 6% of defects in the non-Asian population and 33% in Asians. Spontaneous closure of these defects is rare, and progressive aortic valve regurgitation is common owing to aortic cusp distortion. Muscular VSDs (10% of cases) can be located anywhere in the ventricular septum and may be single or multiple; these defects usually close spontaneously. Inlet defects (4%) occur in the superior-posterior portion of the ventricular septum adjacent to the tricuspid valve. These defects occur as

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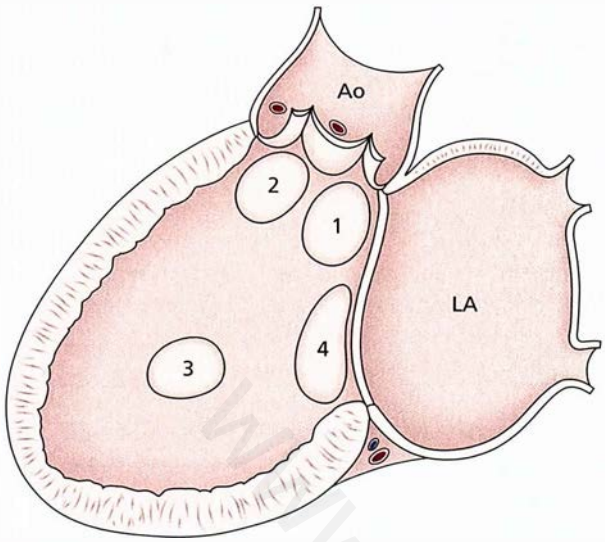

FIGURE 29. Positions of various ventricular septal defects viewed from the left side of the heart. (1) perimembranous; (2) subpulmonary; (3) muscular; (4) inlet. Ao = aorta; LA= left atrium.

Redrawn from original supplied courtesy of Dr. William D. Edwards, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.

part of the atrioventricular septal defect complex and are characteristically seen in patients with Down syndrome.

Clinical Presentation

Clinical presentation of an isolated VSD depends on the defect size and pulmonary vascular resistance. Patients with a small VSD and no PAH present with a loud holosystolic murmur located at the left sternal border that often obliterates the S_2 and may be palpable. Small VSDs do not cause left heart enlargement or PAH.

A moderate-sized VSD with a moderate left-to-right shunt may cause left ventricular volume overload and PAH. Patients remain asymptomatic for many years but eventually present with symptoms of heart failure. The left ventricular impulse may be displaced, suggesting volume overload. A holosystolic murmur is noted at the left sternal border; the duration and quality depend on the pressure gradient between the left and right ventricles. Progressive PAH results in shortening of the murmur.

Large VSDs associated with moderate or large left-to-right shunts are usually detected in childhood by the presence of a murmur, heart failure, and failure to thrive. Unless closure is performed early in life, fixed PAH will ensue within several years, resulting in Eisenmenger syndrome and right-to-left shunt reversal.

Diagnostic Evaluation

The ECG and chest radiograph findings in patients with VSDs are outlined in Table 40. TTE is the primary diagnostic test for patients in whom a VSD is suspected. TTE allows determination of the location, size, and hemodynamic impact of the VSD in most patients, along with the presence or absence of associated valve regurgitation, PAH, and left heart enlargement. MRI or CT imaging may be used in select patients for delineation of cardiac anatomy in patients with limited echocardiographic images and measurement of ventricular volumes. Cardiac catheterization is rarely performed to confirm the diagnosis but is helpful in delineating pulmonary vascular disease and the Qp:Qs ratio.

Treatment

Although percutaneous device closure is possible for select VSDs, most patients are treated surgically. Closure of a VSD is generally indicated when there is a significant shunt (Qp:Qs ratio is 2.0 or greater), and there is evidence of left ventricular volume overload; an additional indication for closure is a history of endocarditis.

For small VSDs with a small left-to-right shunt and no left heart enlargement or valve disease, observation is appropriate with periodic clinical evaluation and imaging. Large VSDs with right-to-left shunt reversal and PAH (Eisenmenger syndrome) should not be closed; closure will result in clinical deterioration due to reduction in cardiac output.

Patients with a small VSD require no activity restrictions. If pulmonary vascular disease is present (pulmonary artery systolic pressure >50 mm Hg), patients should be advised against isometric or competitive exercise.

In the absence of PAH, pregnancy in women with VSDs is generally well tolerated. Women with VSDs and associated PAH should be counseled against pregnancy.

Follow-up After Ventricular Septal Defect Closure

Complications following VSD repair include residual or recurrent VSD, arrhythmias, PAH, endocarditis, and aortic or tricuspid valve regurgitation. Cardiovascular evaluation with TTE imaging is recommended within 1 year of VSD closure. Subsequent clinical and TTE follow-up frequency depends on clinical and cardiac status. Anticoagulation is not routinely recommended following VSD closure.

KEY POINTS HVC

- For small ventricular septal defects with a small left-to-right shunt and no left heart enlargement or valve disease, observation is appropriate with periodic clinical evaluation and imaging.
- Closure of a ventricular septal defect is indicated when the pulmonary-to-systemic blood flow ratio (Qp:Qs) is 2.0 or greater, and there is evidence of left ventricular volume overload or a history of endocarditis.
- Large ventricular septal defects with right-to-left shunt reversal and pulmonary arterial hypertension (Eisenmenger syndrome) should not be closed as closure will result in clinical deterioration.

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Patent Ductus Arteriosus

Pathophysiology

Patent ductus arteriosus (PDA) is the persistence of the arterial duct that connects the aorta and the pulmonary artery in the fetus. Maternal rubella and neonatal prematurity predispose to PDA. The PDA may be an isolated abnormality or associated with other congenital cardiac defects.

Clinical Presentation

A PDA produces an arteriovenous fistula, usually resulting in a continuous murmur that envelops the S_2. A tiny PDA is generally asymptomatic and inaudible. Patients with a moderate-sized PDA may present with symptoms of dyspnea and heart failure. A continuous "machinery" murmur is heard beneath the left clavicle. Bounding pulses and a wide pulse pressure may also be noted.

A large PDA causes a large left-to-right shunt and, if unrepaired, may cause PAH with eventual shunt reversal from right-to-left (Eisenmenger syndrome). A characteristic feature of an Eisenmenger PDA is clubbing and oxygen desaturation that affects the feet but not the hands owing to desaturated blood reaching the lower part of the body preferentially (differential cyanosis).

Diagnostic Evaluation

The ECG and chest radiograph findings in patients with PDA are outlined in Table 40. TTE with color flow Doppler imaging usually confirms the presence of a PDA. In patients with severe PAH, the PDA may be difficult to visualize owing to equalization of pressures in the aorta and pulmonary artery. In patients with a PDA and elevated pulmonary artery pressures, cardiac catheterization is used to determine reversibility and shunt size. Angiography confirms the size and shape of the PDA and helps to determine whether percutaneous closure is feasible. Cardiac CT and MRI may identify a PDA but are not used as primary diagnostic techniques.

Treatment

Closure of a PDA is indicated for left-sided cardiac chamber enlargement in the absence of severe PAH. Closure may be performed surgically or percutaneously; however, surgical closure of a calcified PDA may be challenging. Referral to a congenital cardiac center for consideration of closure options is appropriate for these patients.

A tiny PDA requires no intervention. In patients with a small PDA and prior endocarditis, closure is suggested. A moderate-sized PDA is generally closed percutaneously. A large PDA with severe PAH and shunt reversal should be observed, as closure may be detrimental. In these patients, medical therapy for PAH should be considered.

Patients with a small PDA without PAH do not need any limitation of physical activity. Anticoagulation is not routinely recommended for patients with PDA or following PDA closure.

KEY POINTS

- Closure of a patent ductus arteriosus is indicated for left-sided cardiac chamber enlargement in the absence of severe pulmonary arterial hypertension.
- A large patent ductus arteriosus with severe pulmonary arterial hypertension and shunt reversal should be observed as closure may be detrimental.

Pulmonary Valve Stenosis

Pathophysiology

Pulmonary valve stenosis is usually an isolated congenital cardiac lesion, causing obstruction to right ventricular outflow. Noonan syndrome, an autosomal dominant disorder, is often associated with isolated pulmonary valve stenosis or other congenital cardiac defects. Additional features of Noonan syndrome include short stature, variable intellectual impairment, unique facial features, neck webbing, and hypertelorism.

Clinical Presentation

Patients with mild or moderate pulmonary valve stenosis are generally asymptomatic, whereas those with severe stenosis may have exertional dyspnea. On physical examination, mild pulmonary valve stenosis is characterized by a normal jugular venous waveform and precordial impulse. A pulmonary ejection click decreases with inspiration. Moderate or severe pulmonary valve stenosis results in right ventricular hypertrophy with a resultant prominent *a* wave on the jugular venous pressure waveform and a right ventricular lift. An ejection click may be audible, but as the severity of pulmonary valve stenosis progresses, the click disappears owing to loss of valve pliability. An ejection systolic murmur, heard at the left sternal border, increases in intensity and duration as the severity of pulmonary valve stenosis worsens. The pulmonary valve component of S_2 is delayed and eventually disappears with increasing severity. A right ventricular S_4 is heard in severe pulmonary valve stenosis.

Diagnostic Evaluation

The ECG and chest radiograph findings in patients with pulmonary valve stenosis are outlined in Table 40. TTE with Doppler confirms the presence of pulmonary valve stenosis and allows assessment of its severity. Pulmonary valve stenosis is considered severe if the peak gradient is 60 mm Hg or greater. Pulmonary cusp mobility, calcification, and the effects of obstruction on the right ventricle may affect treatment options. Right ventricular hypertrophy is expected in patients with pulmonary valve stenosis, but when right heart enlargement occurs, an associated lesion, such as pulmonary regurgitation or an ASD, should be suspected. Cardiac catheterization is primarily used when percutaneous intervention is considered. MRI and CT are not routinely used in patients with pulmonary valve stenosis.

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Treatment

Pulmonary balloon valvuloplasty is the treatment of choice for pulmonary valve stenosis and is indicated for asymptomatic patients with appropriate pulmonary valve morphology who have a peak instantaneous Doppler gradient of at least 60 mm Hg or a mean gradient greater than 40 mm Hg and pulmonary valve regurgitation that is less than moderate. Balloon valvuloplasty is also recommended for symptomatic patients with appropriate valve morphology who have a peak instantaneous Doppler gradient of greater than 50 mm Hg or a mean gradient greater than 30 mm Hg. Operative intervention is recommended for pulmonary valve stenosis associated with a small pulmonary annulus, more than moderate pulmonary regurgitation, severe subvalvar or supravalvar pulmonary stenosis, or another cardiac lesion that requires operative intervention.

Patients with previous pulmonary balloon or surgical valvuloplasty rarely have residual pulmonary stenosis but are at increased risk for pulmonary valve regurgitation. Long-term clinical and TTE follow-up is recommended after intervention; the frequency depends on the severity of pulmonary valve regurgitation.

Patients with pulmonary valve stenosis and a peak gradient below 50 mm Hg do not require exercise restriction. Patients with more severe stenosis should participate only in low-intensity sports.

Pregnancy is generally well tolerated in women with pulmonary valve stenosis unless the lesion is severe. Percutaneous valvotomy has been performed during pregnancy.

KEY POINT

- Pulmonary balloon valvuloplasty is the treatment of choice for severe pulmonary valve stenosis.

Aortic Coarctation

Pathophysiology

Aortic coarctation is a discrete aortic narrowing, usually located just beyond the left subclavian artery, causing hypertension proximal and reduced blood pressure distal to the aortic narrowing.

Clinical Presentation

Patients with aortic coarctation may be asymptomatic or present with hypertension, symptoms of exertional leg fatigue, or headaches. Upper extremity hypertension and reduced blood pressure and pulse amplitude in the lower extremities are characteristic findings and cause a radial artery–to–femoral artery pulse delay. More than 50% of patients with aortic coarctation have a bicuspid aortic valve.

Turner syndrome is a chromosomal abnormality (45,X) characterized by a female with short stature, a broad chest with widely spaced nipples, webbed neck, and aortic coarctation. Aortic coarctation is also associated with bicuspid aortic valve, aortic valve and subaortic stenosis, parachute mitral valve, VSD, and cerebral artery aneurysms.

The characteristic murmur of aortic coarctation is a systolic murmur heard in the left infraclavicular region or over the back. When severe, the murmur may be continuous, and a murmur from collateral intercostal vessels may also be audible and palpable over the chest wall. In patients with aortic coarctation and a bicuspid aortic valve, an ejection click or a systolic murmur may be heard. An S_4 is often audible.

Diagnostic Evaluation

The ECG and chest radiograph findings in patients with aortic coarctation are outlined in Table 40. The "figure 3 sign" on chest radiograph (**Figure 30**) is caused by dilatation of the aorta above and below the area of coarctation. Dilatation of intercostal arteries may result in the radiographic appearance of "rib notching."

TTE is usually the initial diagnostic test in patients with suspected aortic coarctation and allows identification of associated features, such as bicuspid aortic valve and left ventricular hypertrophy. MRI and CT are recommended to identify coarctation severity, the presence of collateral vessels, and associated abnormalities such as aortic aneurysm. Cardiac catheterization is reserved for patients who are being considered for percutaneous intervention.

Treatment

Severe aortic coarctation is associated with reduced survival. Common causes of morbidity and mortality include systemic

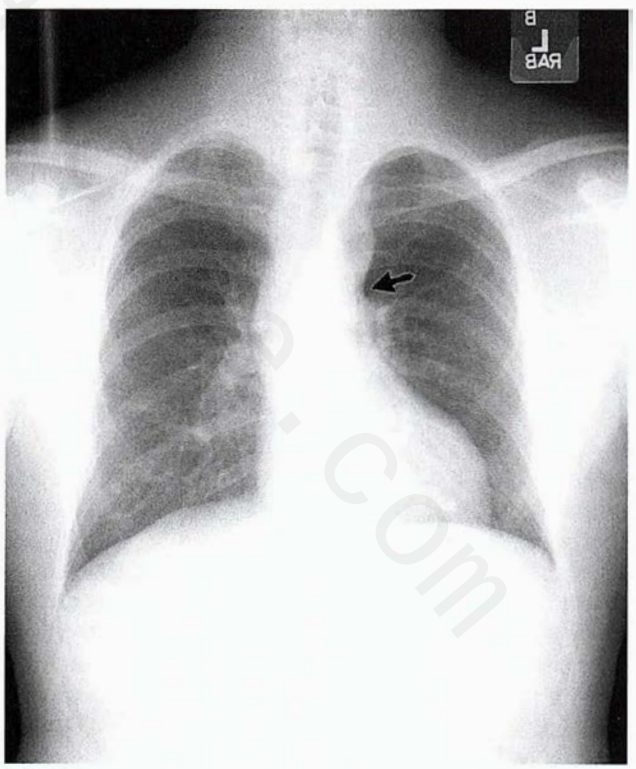

FIGURE 30. Chest radiograph of a patient with aortic coarctation exhibiting the "figure 3 sign," caused by dilatation of the aorta above and below the area of coarctation (*arrow*).

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hypertension, coronary artery disease, stroke, aortic dissection, and heart failure.

Intervention for coarctation is recommended when the coarctation systolic peak (peak-to-peak) pressure gradient is 20 mm Hg or higher (measured by TTE Doppler or cardiac catheterization) or if there is radiologic evidence of severe coarctation with collateral flow. Surgical and percutaneous intervention options are available, and selection depends on the length, location, and severity of the coarctation as well as the presence of associated lesions.

Patients with severe residual or unrepaired coarctation, aortic stenosis, or a dilated aorta should be counseled to avoid contact sports and isometric exercise.

Women with repaired aortic coarctation and no significant residua generally tolerate pregnancy well. A comprehensive prepregnancy evaluation is warranted to evaluate for residua. Women with severe unoperated coarctation should avoid pregnancy prior to intervention. Patients with mild or moderate residual or unoperated coarctation will generally tolerate pregnancy well but should undergo blood pressure monitoring during pregnancy and receive cardiovascular follow-up.

Follow-up After Aortic Coarctation Repair

Hypertension occurs in up to 75% of patients following coarctation repair. Blood pressure control is recommended to reduce hypertension-related morbidity. Intervention is often required for bicuspid aortic valve, aortic aneurysm, aortic dissection, recoarctation, coronary artery disease, systolic or diastolic heart failure, and intracranial aneurysm. Age at the time of repair is the most important predictor of long-term survival. Regular follow-up should include evaluation with a congenital cardiologist as well as TTE and aortic imaging.

KEY POINTS

- Upper extremity hypertension and reduced blood pressure and pulse amplitude in the lower extremities are characteristic findings of aortic coarctation and cause a radial artery–to–femoral artery pulse delay.
- Intervention for aortic coarctation is recommended when the coarctation systolic peak (peak-to-peak) pressure gradient is 20 mm Hg or higher or if there is radiologic evidence of severe coarctation with collateral flow.
- Patients with severe residual or unrepaired aortic coarctation, aortic stenosis, or a dilated aorta should be counseled to avoid pregnancy, contact sports, and isometric exercise.

Tetralogy of Fallot

Tetralogy of Fallot is the most common cyanotic congenital cardiac lesion and includes a large subaortic VSD, infundibular or valvular pulmonary stenosis, aortic override, and right ventricular hypertrophy (**Figure 31**). Unoperated adult patients are rarely encountered.

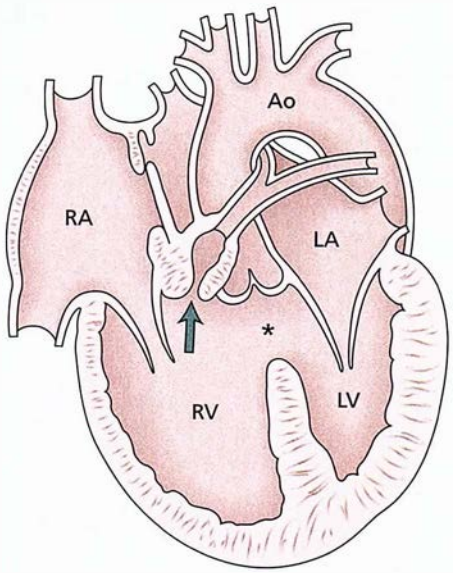

FIGURE 31. Tetralogy of Fallot. A subarterial ventricular septal defect (*asterisk*) and pulmonary stenosis (*arrow*) are associated with secondary aortic override and right ventricular hypertrophy. Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Redrawn from original supplied courtesy of Dr. William D. Edwards, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.

Approximately 15% of patients with tetralogy of Fallot have the 22q11.2 chromosome microdeletion. This increases the chance of congenital heart disease inheritance to approximately 50% compared with 5% in patients without the microdeletion. Genetic testing is recommended for all patients with tetralogy of Fallot who are planning reproduction. Tetralogy of Fallot is also common in persons with Down syndrome.

Surgical repair of tetralogy of Fallot involves patch closure of the VSD and relief of right ventricular outflow tract obstruction by patch enlargement. The transannular patch procedure invariably disrupts the integrity of the pulmonary valve, causing severe pulmonary valve regurgitation, the most common reason for reoperation in patients after repair of tetralogy of Fallot. Over many years, pulmonary regurgitation causes progressive right heart enlargement, tricuspid regurgitation, exercise limitation, and increased risk for arrhythmias. Annual follow-up by a congenital cardiologist is recommended to monitor these sequelae and determine optimal timing for intervention. Current surgical techniques include attempted relief of pulmonary valve stenosis with preservation of native pulmonary valve function.

Diagnostic Evaluation After Repair of Tetralogy of Fallot

The ECG and chest radiograph findings in patients with repaired tetralogy of Fallot are outlined in Table 40. Presence of an arrhythmia should prompt a search for right heart chamber enlargement from pulmonary valve regurgitation. The QRS duration on the ECG reflects the degree of right ventricular dilatation. A QRS duration of 180 msec or longer and non-

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CONT. sustained ventricular tachycardia are risk factors for sudden cardiac death.

TTE can confirm the presence of pulmonary or tricuspid valve regurgitation, right ventricular outflow tract obstruction, residual VSD, aortic regurgitation, and aortic dilatation. MRI is used to assess right ventricular size and function, which helps determine appropriate timing for pulmonary valve replacement. Diagnostic catheterization may be required to assess hemodynamics and residual shunts and delineate coronary artery and pulmonary artery anatomy.

Treatment of Tetralogy of Fallot Residua

Pulmonary valve replacement is recommended in patients with repaired tetralogy of Fallot who have severe pulmonary valve regurgitation with symptoms, decreased exercise tolerance, more than moderate right heart enlargement or dysfunction, or arrhythmias. Long-standing pulmonary valve regurgitation may result in tricuspid regurgitation, and repair of the tricuspid valve may also be needed. Percutaneous pulmonary valve replacement is now available for select patients with previous operative intervention for tetralogy of Fallot.

Patients with repaired tetralogy of Fallot and residual sequelae should be cautioned regarding participation in contact sports and heavy isometric exercise.

KEY POINT

- Pulmonary valve replacement is recommended in patients with repaired tetralogy of Fallot who have severe pulmonary valve regurgitation with symptoms, decreased exercise tolerance, more than moderate right heart enlargement or dysfunction, or arrhythmias.

Adults with Cyanotic Congenital Heart Disease

General Management

Right-to-left cardiac shunts, such as unrepaired or palliated tetralogy of Fallot, truncus arteriosus, tricuspid atresia, and Eisenmenger syndrome, result in hypoxemia, erythrocytosis, and cyanosis. Erythrocyte mass is increased in patients with cyanosis as a compensatory response to improve oxygen transport.

Physical features include central cyanosis and digital clubbing. Patients with cyanotic congenital heart disease are predisposed to scoliosis, arthropathy, gallstones, pulmonary hemorrhage or thrombus, paradoxical cerebral emboli or cerebral abscess, kidney dysfunction, and hemostatic problems. Because of these problems, a congenital cardiac specialist should evaluate patients with cyanotic congenital heart disease at least annually.

Patients with cyanotic or complex congenital heart disease are at increased risk for endocarditis; therefore, antimicrobial prophylaxis is recommended prior to certain nonsterile procedures. In patients who are hospitalized with a right-to-left intracardiac shunt, filters on intravenous lines should be used to prevent paradoxical air embolism. Early ambulation, pneumatic compression devices, or anticoagulation is also recommended for prevention of venous stasis and potential venous thrombosis and paradoxical embolism. Because perioperative cardiac complications are common in these patients, elective operations should be performed at centers that care for such patients with a coordinated multidisciplinary team approach. Consultation with a congenital cardiac specialist is recommended when patients are hospitalized.

Most patients with cyanosis have compensated erythrocytosis and stable hemoglobin levels. Occasionally, hyperviscosity symptoms occur, including headaches and reduced concentration. Phlebotomy is recommended for a hemoglobin level greater than 20 g/dL (200 g/L) and a hematocrit level greater than 65% associated with hyperviscosity symptoms in the absence of dehydration. Phlebotomy should be performed no more than two to three times each year. Dehydration should be excluded before considering the procedure, and it should be followed by intravenous fluid administration. Repeated phlebotomies deplete iron stores and may result in the production of iron-deficient erythrocytes or microcytosis, increasing the risk of stroke. Iron deficiency in a patient with destabilized erythropoiesis is treated with oral iron therapy for a short time. Iron therapy is discontinued when serum ferritin and transferrin saturation values are within the normal range.

Maternal cyanosis impairs normal fetal growth and development and increases the risk of intrauterine growth retardation and miscarriage. Maternal and fetal morbidity and mortality are increased, related to the degree of cyanosis, ventricular function, and pulmonary pressures. If pregnancy occurs in a patient with cyanotic heart disease, physical activity should be curtailed and supplemental oxygen is recommended. Preventive measures to decrease the risk of venous thrombosis and paradoxical embolism also are recommended.

Eisenmenger Syndrome

Eisenmenger syndrome is severe PAH and reversal of a congenital cardiac shunt caused by VSD, PDA, or, less commonly, ASD. Eisenmenger syndrome has become increasingly rare owing to medical screening, including TTE and appropriate intervention.

Conservative medical measures are recommended in the management of Eisenmenger syndrome. Persons with Eisenmenger syndrome should be cautioned regarding iron deficiency, dehydration, acute exposure to excess heat, and moderate or severe strenuous or isometric exercise. Routine phlebotomy based on hemoglobin or hematocrit level is not recommended because iron deficiency and microcytosis may lead to increased symptoms; rather, phlebotomy should be performed only when symptoms of hyperviscosity occur and with saline volume replacement. In addition, chronic high altitude exposure should be avoided, as it further reduces oxygen saturation. Women should be cautioned to avoid pregnancy because of the high risk for maternal mortality.

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All patients with Eisenmenger syndrome should be evaluated annually by a congenital cardiac specialist. Noncardiac surgery should be performed at centers with expertise in the care of patients with complex congenital cardiac disease whenever possible. Meticulous care of intravenous lines with filters to avoid paradoxical air embolism is imperative. Patients with progressive symptoms may benefit from pulmonary vasodilator therapy.

Long-distance air travel should be approached with caution and occur in pressurized aircrafts. Select patients may benefit from supplemental oxygen during prolonged air travel.

KEY POINT

- In patients with Eisenmenger syndrome, meticulous care of intravenous lines with filters to avoid paradoxical air embolism is imperative.

Diseases of the Aorta

Introduction

Aortic disease includes acute life-threatening conditions such as aortic dissection, chronic conditions such as aortic atheroma that may lead to embolism, and aortic aneurysms that carry the risk of rupture. Appropriate surveillance and treatment of aortic disease are crucial to preventing catastrophic vascular events.

Imaging of the Thoracic Aorta

Using imaging to screen asymptomatic patients for abnormalities of the thoracic aorta is not recommended, except in patients with underlying vascular pathology (such as Marfan or Ehlers-Danlos syndrome), a bicuspid aortic valve, or a family history of aortic disease. Abnormalities of the thoracic aorta are sometimes discovered incidentally on chest radiography performed for other purposes. An acute aortic syndrome may produce a widening of the mediastinal silhouette, enlargement of the aortic knob, or displacement of the trachea from midline (**Figure 32**). If an abnormality is identified, additional noninvasive imaging of the aorta may be useful to determine aortic cross-sectional area, which may predict the risk of aneurysm rupture or dissection. Echocardiography, CT, and MRI can be used to cross-sectionally image the aorta (**Table 41**). There is substantial variance in measured aortic dimension according to image technique based on measurement of either internal or external aortic diameter. Care must be taken to measure the dimension perpendicular to the long axis of the aorta because oblique or tangential measurements may overestimate the true aortic diameter.

Maximum aortic diameter at a specific location is generally reported by imaging results. Dilation above the upper limits for normal may represent an aneurysm, but a patient with a larger body size may have a larger absolute aortic diameter. The maximum ascending aortic diameter may be indexed to body surface area (z-score).

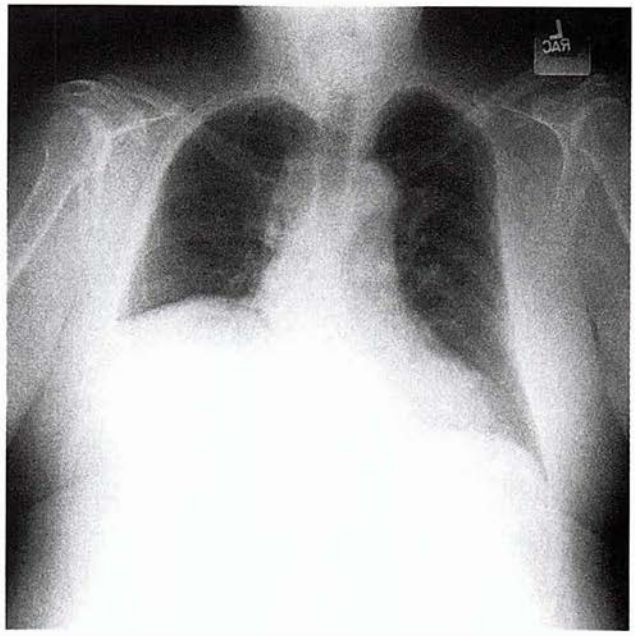

FIGURE 32. Chest radiograph shows a widened superior mediastinum and a right pleural effusion consistent with aortic dissection.

Echocardiography, CT, and MRI have similar sensitivity and specificity for diagnosis of acute thoracic aorta disease, although each has advantages and disadvantages. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) have the advantages of being performed at the patient's bedside and providing results within several minutes. However, although TTE may be useful in identifying an intimal flap, enlarged aortic root, or aortic insufficiency, it is limited in evaluating the mid-distal ascending aorta, transverse aorta, or descending thoracic aorta. TEE overcomes the shortcomings of TTE but requires conscious sedation. The primary advantages of TEE compared with CT imaging of suspected aortic dissection include its portability in the unstable patient and lack of contrast injection.

Invasive imaging of the aorta by angiography is rarely indicated for the diagnosis of acute disease. It may be helpful in determining the length of an aneurysm and involvement of branch vessels and should be reserved for patients in whom a percutaneous intervention is planned.

KEY POINTS

- Screening of asymptomatic patients for abnormalities of the thoracic aorta should be reserved for patients with underlying vascular pathology (such as Marfan or Ehlers-Danlos syndrome), a bicuspid aortic valve, or a family history of aortic disease. HVC
- Invasive imaging of the aorta by angiography is rarely necessary for the diagnosis of acute disease; it should be reserved for patients in whom a percutaneous intervention is planned. HVC

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TABLE 41. Comparison of Thoracic Aortic Imaging Modalities

Modality	Advantages	Disadvantages
Transthoracic echocardiography (TTE)	Good visualization of aortic root/proximal ascending aorta	Limited visualization of the distal ascending aorta and aortic arch with branches of the great vessels
	No exposure to radiation or contrast dye	Requires experienced operator
	Allows definition of valvular pathology, myocardial function, pericardial disease	A negative TTE does not rule out aortic dissection, and other imaging techniques must be considered.
	Bedside diagnosis	
Transesophageal echocardiography (TEE)	TEE has superior imaging quality versus TTE	Requires experienced operator
	Excellent visualization of the aorta from its root to the descending aorta	Invasive procedure
	No exposure to radiation or contrast dye	
	Allows definition of valvular pathology, myocardial function, pericardial disease	
	Bedside diagnosis	
CT	Visualization of entire aorta and side branches	Exposes patient to radiation, iodinated contrast dye
	Rapid imaging	
	Multiplanar reconstruction	
MRI	Visualization of entire aorta and side branches	For acute disease, prolonged image acquisition away from acute care area
	No exposure to radiation or iodinated contrast dye	Contraindicated in patients with implanted pacemaker or defibrillator
		Gadolinium contrast dye contraindicated in patients with kidney disease

Thoracic Aortic Aneurysm

Thoracic aortic aneurysms may involve the aortic root, ascending aorta, aortic arch, or descending aorta. Aneurysms of the aortic root and ascending aorta are most common and usually occur as a consequence of underlying medial degeneration. Thoracic aortic aneurysms often are asymptomatic and are frequently detected incidentally during evaluation for another problem. Rarely, thoracic aortic aneurysms may be discovered because of compressive symptoms, such as hoarseness, stridor, or dysphagia. If rupture occurs, patients may have severe chest pain, back pain, sudden shortness of breath, or sudden death. A diastolic heart murmur or symptoms of heart failure may occur with aneurysmal dilatation of the aortic root and subsequent aortic valve regurgitation.

Causes of thoracic aortic aneurysms are listed in **Table 42**. These aneurysms typically result from cystic medial degeneration that leads to loss of smooth muscle cells and elastic fiber degeneration, resulting in a weakening of the aortic wall. Cystic medial degeneration occurs normally with aging and is exacerbated by hypertension. In younger patients, aneurysm is most often related to a connective tissue disorder (such as Marfan or Ehlers-Danlos syndrome). Bicuspid aortic valve is an important risk factor for aneurysm involving the aortic root and ascending thoracic aorta. Approximately 50% of patients with bicuspid aortic valves have enlargement of the proximal aorta that may be independent of the severity of aortic valve disease. The vast majority of aneurysms affecting the descending thoracic aorta are associated with atherosclerosis. Other causes of thoracic aortic aneurysm include acquired infection and inflammatory conditions, such as syphilis, Takayasu arteritis, and giant cell arteritis.

The leading cause of death in patients with thoracic aortic aneurysm is rupture (60%). Several studies have shown an increasing risk of rupture after the aneurysm has surpassed 5.0 cm in diameter (4.0-5.0 cm in patients with genetically mediated disorders), and a rapid rate of expansion is an independent risk factor for rupture. Pregnancy also is associated with an increased risk of aortic dissection, particularly in women with Marfan syndrome, in whom dissection may occur at aortic diameters that are smaller than would usually be considered for elective repair.

Smaller thoracic aortic aneurysms can be medically managed with aggressive blood pressure control. β-Blockers may be of particular benefit for reducing the rate of aortic growth in patients with Marfan syndrome, although their benefit in treating aneurysms of other etiologies has not been proved. Losartan, an angiotensin receptor blocker, has also been associated with slower progression of aortic root dilation in patients with Marfan syndrome.

In any patient with a thoracic aortic aneurysm that does not require immediate intervention, regular surveillance is important for identifying the development of signs and

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TABLE 42. Causes of Thoracic Aortic Aneurysms

Category	Syndrome
Atherosclerosis	
Connective tissue disorders	Marfan syndrome
	Ehlers-Danlos syndrome, type IV
	Loeys-Dietz syndrome
Other genetic and/or congenital conditions	Familial thoracic aortic aneurysms and aortic dissections (TAAD) syndrome
	Bicuspid aortic valve
	Turner syndrome
Vasculitis	Takayasu arteritis
	Giant cell arteritis
	Nonspecific (idiopathic) aortitis
	Other autoimmune conditions (Behçet syndrome, systemic lupus erythematosus)
Infectious	Septic embolism
	Direct bacterial inoculation
	Bacterial seeding
	Contiguous infection
	Syphilis
Aortic injury	Prior acute aortic syndrome
	Chest trauma

symptoms. Annual echocardiography should be performed to monitor aortic growth. Earlier re-evaluation is indicated for changes in symptoms or physical examination findings and for hemodynamic assessment related to pregnancy. When the aortic dimension nears the threshold for intervention, patients should be referred to an appropriate specialist for evaluation. Because patients with a bicuspid aortic valve have an increased risk of aortic aneurysm and dissection, these patients should undergo echocardiography of the aorta annually if the aortic root or ascending aorta dimension is greater than 4.5 cm. In those with an aortic diameter between 4.0 and 4.5 cm, the examination interval depends on the rate of progression of dilation and the family history.

Familial thoracic aortic aneurysms and aortic dissections (TAAD) is an inherited autosomal dominant condition. Screening is recommended for first-degree relatives of persons with TAAD once a year or at least every few years. If the mutation is known, genetic testing can identify those relatives who should be screened with aortic imaging.

In patients with Marfan syndrome, follow-up imaging is recommended 6 months after diagnosis with annual surveillance thereafter if the aortic root is less than 4.5 cm in diameter and otherwise stable. If the aortic diameter is 4.5 cm or greater or shows significant growth over time, then more frequent surveillance is suggested (for example, twice yearly). Most patients with Marfan syndrome present with enlargement of the ascending aorta; therefore, serial examination is focused mainly on assessing this portion of aorta, and transthoracic ultrasound is the preferred imaging modality in these patients.

The repair of a thoracic aortic aneurysm is often recommended prophylactically to prevent the morbidity and mortality associated with aneurysm rupture. In asymptomatic patients, elective thoracic aortic repair is recommended if the aortic root or ascending aorta is greater than 5.5 cm (5.5–6.0 cm for the descending aorta) or has rapid growth (>0.5 cm/year). For genetically mediated disorders (such as Marfan syndrome), a lower threshold of 5.0 cm (4.0–5.0 cm in certain patients) may be used for repair. For patients with a bicuspid aortic valve, repair is indicated if the aortic diameter is greater than 5.5 cm and is reasonable if the diameter is greater than 5.0 cm and the patient has an increased risk of dissection (family history of dissection or rapid growth).

Repair of ascending aortic and aortic arch aneurysms requires surgery and may include aortic valve replacement or repair in patients with significant annular dilatation or associated aortic valve pathology. A conservative procedure whereby the aneurysm is replaced with a Dacron graft and the aortic valve is preserved has gained widespread use. If the aortic valve needs replacement and the patient has a dilated aortic root, a composite aortic valve and aortic root and ascending aorta graft replacement (Bentall operation) may be performed. The Bentall operation includes re-implantation of the coronary arteries into the ascending aortic graft. Thoracic endovascular aortic repair (TEVAR) with stent grafting has emerged as a promising alternative to open repair for

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CONT.

aneurysm of the descending thoracic aorta. TEVAR has been associated with shorter hospital stays and lower hospital morbidity and has the potential advantages of avoiding thoracotomy, aortic cross-clamping, and extracorporeal support. Adverse events following TEVAR include stroke, spinal ischemia, access complications, and endoleaks.

KEY POINTS

- Patients with a thoracic aortic aneurysm should undergo annual echocardiography to monitor aortic aneurysm growth.
- Patients with a bicuspid aortic valve should undergo annual echocardiography of the aorta if the aortic root or ascending aorta dimension is greater than 4.5 cm.
- In asymptomatic patients, elective thoracic aortic repair is recommended if the aortic root or ascending aorta is greater than 5.5 cm (5.5-6.0 cm for the descending aorta) or has rapid growth (>0.5 cm/year); for patients with genetically mediated disorders, the threshold for repair is lower.

Acute Aortic Syndromes

Acute aortic syndromes include aortic dissection, intramural hematoma, penetrating atherosclerotic ulcer, and trauma induced aortic rupture (**Figure 33**). Acute aortic syndromes threaten central aortic pressure, critical organ perfusion, and survival. Prompt recognition and delivery of appropriate medical and interventional care are critical determinants of outcome.

Pathophysiology

In aortic dissection, blood passes through a tear in the aortic intima, creating a false lumen that separates layers of the aorta. Propagation of the dissection can proceed in an anterograde or retrograde fashion from the initial tear, involving side branches and causing complications such as tamponade, aortic valve insufficiency, or malperfusion syndromes. An intramural hematoma may result from rupture of the vasa vasorum or "microtears" in the intima, resulting in a crescent of hematoma within the media without identifiable interruption of the intima. Penetrating atherosclerotic ulcers are most likely caused by atherosclerosis with subsequent erosion across the internal elastic membrane of the aorta, allowing for a blood-filled false space within the wall of the aorta.

The Stanford classification describes type A dissections as originating within the ascending aorta or arch, whereas type B dissections originate distal to the left subclavian artery. This nomenclature has been generalized to all of the acute aortic syndromes, although most intramural hematomas and penetrating ulcers are type B lesions.

Diagnosis and Evaluation

The diagnosis of an acute aortic syndrome requires a high index of suspicion because of its life-threatening complications. The classic presentation consists of "aortic chest pain" described as severe ripping or tearing pain that may radiate to the anterior chest or back, jaw, or abdomen, depending on which segment of the aorta is involved. Hypertension is the most important risk factor; other risk factors include smoking and atherosclerosis. In the setting of an acute aortic dissection, hypertension and an aortic regurgitation murmur that is faint, short in duration, and low in pitch may be present. Other findings on physical examination that may increase the index of suspicion include pulsus paradoxus, asymmetric blood pressure in the upper extremities, and an asymmetric pulse examination. A low D-dimer level

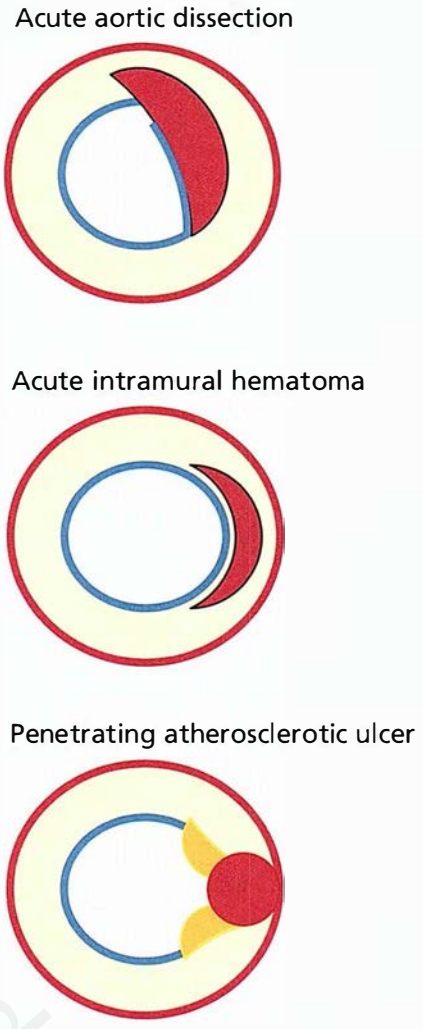

FIGURE 33. Cross-sectional representation of acute aortic syndromes. Acute aortic dissection: interruption of intima (*blue*) with creation of an intimal flap and false lumen formation within the media (*red*). Colorflow by Doppler echocardiography or intravenous (IV) contrast by CT is present within the false lumen in the acute phase. Acute intramural hematoma: crescent-shaped hematoma contained within the media without interruption of the intima (*blue*). No color flow by Doppler echocardiography or IV contrast by CT within crescent. Penetrating atherosclerotic ulcer: atheroma (*yellow*) with plaque rupture disrupting intimal integrity; blood pool contained within intima-medial layer (pseudoaneurysm). Color flow by Doppler echocardiography or IV contrast by CT enters the ulcer crater.

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CONT. (<0.5 μg/mL [0.5 mg/L]) suggests against an acute aortic syndrome. In aortic dissection, chest radiography may demonstrate a widening of the mediastinum. An electrocardiogram is often abnormal, but nondiagnostic. Clinical suspicion should be high, and CT, MRI, or TEE for confirmation of the diagnosis should not be delayed.

Treatment

Patients with a suspected acute aortic syndrome who are not in cardiogenic shock should receive medical therapy to control heart rate and blood pressure. Intravenous β-blockers should be used to target a heart rate of below 70/min. In patients requiring additional blood pressure control, a rapidly titratable antihypertensive medication, such as sodium nitroprusside, labetalol, enalaprilat, hydralazine, or nicardipine, should be given intravenously, with a goal of decreasing the mean arterial pressure to the lowest level that still allows visceral and cerebral perfusion.

Emergency surgery is recommended for all patients with type A aortic dissection as well as for type A intramural hematoma. Any delays to surgery should be avoided or addressed, as type A dissection has a very high short-term mortality rate. Concomitant aortic arch reconstruction, coronary artery reimplantation, aortic valve repair or replacement, or branch vessel repair may be required depending on the anatomy and pathology of the lesion.

Uncomplicated type B aortic syndromes may be treated medically. The INSTEAD trial, which enrolled subjects with uncomplicated chronic type B dissection, showed no difference in clinical or aortic outcomes at 2 years for patients treated with TEVAR versus medical therapy alone. Among patients who survived at 2 years, additional long-term follow-up of the INSTEAD trial demonstrated that TEVAR in addition to optimal medical treatment was associated with improved long-term aorta-specific survival and delayed disease progression. Surgery is indicated for complicated type B aortic dissection defined by refractory pain or hypertension, rapid aneurysmal expansion, rupture, or malperfusion syndrome.

KEY POINTS

- The classic presentation of an acute aortic syndrome consists of "aortic chest pain"—severe ripping or tearing pain that may radiate to the anterior chest or back, jaw, or abdomen, depending on which segment of the aorta is involved.
- Findings that increase the index of suspicion for an acute aortic syndrome include pulsus paradoxus, asymmetric blood pressure in the upper extremities, and an asymmetric pulse examination.
- Type A aortic dissection has a very high short-term mortality rate, and emergency surgery is recommended for all patients without delay.

Aortic Atheroma

Aortic atherosclerotic plaques are a manifestation of systemic atherosclerosis. Aortic atheroma may be detected incidentally during imaging (**Figure 34**). The risk of embolism and stroke in patients with aortic atheroma is significantly increased for plaques that are mobile or protruding, particularly if the plaque is greater than 4 mm in size. Thromboembolism may also result from dislodgment of debris from the aortic wall occurring as a complication of an invasive cardiovascular procedure, such as catheterization, intra-aortic balloon pump placement, or vascular surgery.

Noncoronary atherosclerotic disease, including aortic atheroma, is a coronary heart disease risk equivalent and, therefore, should be aggressively treated to reduce the risk of future cardiovascular events, including treatment with antiplatelet agents and statins. In an observational study, statin therapy was associated with a 17% absolute reduction in thromboembolic events in patients with aortic atheroma.

KEY POINT

- Aortic atheroma is a coronary heart disease risk equivalent, and patients should be aggressively treated with antiplatelet agents and statins to reduce their cardiovascular risk.

Abdominal Aortic Aneurysm

Screening and Surveillance

An abdominal aortic aneurysm (AAA) is considered to be present when the minimum anteroposterior diameter of the aorta reaches 3.0 cm. The most important risk factors for AAA are increasing age, smoking, and male sex (men with AAA outnumber women by up to 6:1). Other risk factors include atherosclerosis, hypertension, and family history of AAA.

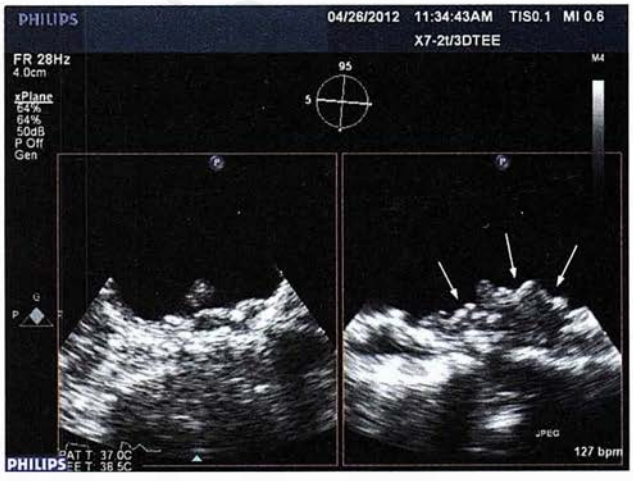

FIGURE 34. Transesophageal echocardiogram demonstrating an aortic atheroma in the descending aorta (*arrows*). *Left panel:* short axis view; *right panel:* long axis view.

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Based on randomized data, the U.S. Preventive Services Task Force guidelines recommend a one-time ultrasonographic screening in men aged 65 to 75 years who are active or former smokers (see MKSAP 17 General Internal Medicine). The sensitivity and specificity of ultrasonography for detection of AAA are excellent.

AAA rupture has an exceedingly high mortality rate, yet most AAAs never rupture. Thus, deciding when and in whom to intervene and electively repair an AAA is of major importance. The strongest risk factor for the rupture of an AAA is maximal aortic diameter; this measurement is the dominant indication for repair. Estimated annual rupture risk according to AAA diameter is shown in **Table 43**.

After AAA has been identified, surveillance imaging results determine the timing of repair. The frequency of surveillance is dependent on baseline aneurysm size; larger aneurysms expand faster than smaller ones and may require more frequent surveillance. If AAA maximum diameter is 3.5 to 4.4 cm, repeat ultrasonography is recommended annually; if maximum diameter is 4.5 to 5.4 cm, repeat ultrasonography should be performed every 6 to 12 months. Elective repair should be considered for AAA of 5.5 cm in diameter, for those that increase in diameter by more than 0.5 cm within a 6-month interval, and for those that are symptomatic (tenderness or abdominal or back pain). For women, elective repair may be considered for an AAA that reaches 5.0 cm in diameter.

Treatment

Medical therapies for AAA focus on targeting modifiable risk factors for AAA and cardiovascular disease with the goals of reducing aneurysm expansion or rupture, reducing morbidity and mortality associated with repair, and reducing cardiovascular morbidity and mortality. Smoking cessation is the cornerstone of therapy for active smokers.

If repair is being considered, the choice between open surgical or endovascular aneurysm repair (EVAR) is individualized based on the patient's age, comorbidities, patient preference, and aortic anatomy. Randomized trials comparing open repair with EVAR have found significantly improved short-term (30-day) morbidity and mortality for EVAR, but no significant differences in long-term mortality. Moreover, in the long term, EVAR was associated with increased complication rates (including endovascular leaks, device migration and failure, and post-implantation syndrome) and the need for reinterventions. Because of these potential complications, patients who have undergone EVAR of AAA require diligent follow-up with imaging studies performed annually to evaluate the status of the graft. Additional long-term data from prospective randomized trials are needed to fully evaluate the benefit/risk profile of open AAA repair versus EVAR. In patients with severe comorbid disease considered not eligible for open surgical correction, a trial of EVAR versus medical therapy demonstrated no difference in all-cause mortality at 8 years, but greater cost and increased complications were associated with endovascular repair.

TABLE 43. Annual Rupture Risk of Abdominal Aortic Aneurysm by Diameter

Aneurysm Diameter	Annual Rupture Risk
<4.0 cm	<0.5%
4.0-4.9 cm	0.5%-5%
5.0-5.9 cm	3%-15%
6.0-6.9 cm	10%-20%
7.0-7.9 cm	20%-40%
≥8.0 cm	30%-50%

Adapted with permission of Elsevier Science and Technology Journals, from Brewster DC, Cronenwett JL, Hallett JW Jr, et al; Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. Guidelines for the treatment of abdominal aortic aneurysms. Report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. J Vasc Surg. 2003 May;37(5):1106-17. [PMID:12756363]; permission conveyed through Copyright Clearance Center, Inc.

KEY POINTS

- The most important risk factors for abdominal aortic aneurysm are increasing age, smoking, and male sex; one-time ultrasonographic screening is recommended for men ages 65 to 75 years who have ever smoked.
- Elective repair should be considered for an abdominal aortic aneurysm of 5.5 cm in diameter, for those that increase in diameter by more than 0.5 cm within a 6-month interval, and for those who are symptomatic.
- Medical therapies for abdominal aortic aneurysm focus on targeting modifiable risk factors for abdominal aortic aneurysm and cardiovascular disease; smoking cessation is the cornerstone of therapy for active smokers.

Peripheral Arterial Disease

Epidemiology and Screening

Lower extremity peripheral arterial disease (PAD) is a disorder of the aortic bifurcation or arteries of the lower limbs. The most common cause of PAD is atherosclerosis, and PAD shares the primary atherosclerotic risk factors of smoking, diabetes mellitus, and increasing age. However, unlike other types of arterial disease, the population burden of PAD is higher in women than in men. PAD is defined noninvasively by calculation of the ankle-brachial index (ABI). PAD is common, with an estimated unselected adult prevalence in the United States of approximately 6% in persons aged 40 years and older.

There is a wide spectrum of clinical manifestations for PAD:

- Asymptomatic patients found to have PAD from a screening ABI (20%-50%)
- Atypical symptoms associated with exercise limitation (40%-50%)

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- Classic intermittent claudication (10%-35%)
- Ischemic pain and ulceration in a lower extremity from chronic limb ischemia (1%-2%)

PAD is associated with reduced exercise capacity and functional status regardless of the symptomatic state. Limb-specific outcomes (such as limb ischemia or amputation) occur less frequently than systemic manifestations of atherosclerosis (myocardial infarction or stroke). Both asymptomatic and symptomatic patients with PAD are at increased risk of cardiovascular morbidity and mortality, and PAD is considered a coronary heart disease risk equivalent. Patients with PAD are likely to have concomitant vascular disease in other arterial beds and have an annual cardiovascular event rate of 5% to 7%. Thus, early recognition of PAD provides a unique opportunity to identify persons at early increased risk for a cardiovascular event and to modify risk factors. However, the U.S. Preventive Services Task Force concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for PAD and cardiovascular disease risk assessment with the ABI in adults. Initial testing may be considered in persons with the following characteristics that signify high risk:

- Exertional leg discomfort
- Nonhealing wounds
- Age 50 years or older with a history of smoking or diabetes

KEY POINTS

- Patients with peripheral arterial disease are likely to have concomitant vascular disease in other arterial beds and have an annual cardiovascular event rate of 5% to 7%.
- Initial testing for peripheral arterial disease may be considered in persons with exertional leg discomfort, nonhealing wounds, or aged 50 years or older with a history of smoking or diabetes mellitus.

Evaluation

History and Physical Examination

Patients at risk for PAD should undergo a vascular review of symptoms to assess walking impairment, claudication, and ischemic pain while at rest. Patients with PAD may have symptoms of leg ischemia, but many are asymptomatic. Among symptomatic patients, the perception of symptoms can vary from minimal to severe and may not necessarily correlate with severity of disease. Discriminating claudication from pseudoclaudication (a result of narrowing of the lumbar spinal canal) is important (**Table 44**). In severe PAD or critical limb ischemia, patients may describe discomfort that worsens with elevation of the leg and improves with dependent positioning, such as dangling the leg off the foot of the bed.

Components of the physical examination of patients with suspected PAD are shown in **Table 45**. Patients at risk for lower extremity PAD should undergo comprehensive pulse examination and inspection of the feet. Shoes and socks are removed and the feet inspected for skin changes. Physical examination may reveal diminished, absent, or asymmetric pulses below the level of stenosis, with occasional bruits over stenotic lesions and evidence of poor wound healing. Other physical findings seen in PAD include a unilaterally cool extremity; a prolonged venous filling time (>20 seconds); shiny atrophied skin; ulceration; and thickened, ridged, and brittle nails. Most patients with upper extremity PAD are asymptomatic, and PAD may be detected only by the finding of asymmetric arm blood pressures, with a typical differential in systolic blood pressures of greater than 15 mm Hg.

Diagnostic Testing

There are several diagnostic modalities to choose from to assess for PAD. Measurement of the ABI is a simple, inexpensive, and noninvasive technique that correlates well with angiographic disease severity and functional symptoms. Patients should rest for 5 to 10 minutes before measuring the ankle pressure and should be lying flat for an accurate ABI measurement, with the head and heels fully supported. The study is performed by applying a blood pressure cuff to the calf and measuring the systolic blood pressure by palpation or Doppler at the ankle. The blood pressure is recorded for both the dorsalis pedis (DP) and the posterior tibial (PT) arteries, and the higher of the two is used as the ankle pressure. This procedure is repeated for the opposite ankle. The brachial artery systolic blood pressure is measured in a similar fashion in both arms. For the measurement of ABI, measuring the limb pressures in the following order is recommended: first

TABLE 44. Discriminating Claudication from Pseudoclaudication

Characteristic	Claudication	Pseudoclaudication
Nature of discomfort	Cramping, tightness, aching, fatigue	Same as claudication plus tingling, burning, numbness, weakness
Location of discomfort	Buttock, hip, thigh, calf, foot	Same as claudication; most often bilateral
Exercise-induced	Yes	Variable
Walking distance at onset of symptoms	Consistent	Variable
Discomfort occurs with standing still	No	Yes
Action for relief	Stand or sit	Sit, flexion at the waist
Time to relief	<5 minutes	≤30 minutes

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TABLE 45. Clinical Examination of Patients for Peripheral Arterial Disease
Measure blood pressure in both arms (systolic blood pressure difference >15 mm Hg is suggestive of subclavian stenosis)
Auscultate for presence of arterial bruits (e.g., femoral artery)
Palpate for presence of an abdominal aortic aneurysm
Palpate and record pulses (radial, brachial, carotid, femoral, popliteal, posterior tibial, dorsalis pedis)
Evaluate for elevation pallor and dependent rubor
Inspect feet for ulcers, fissures, calluses, tinea, and tendinous xanthoma; evaluate overall skin care

arm, first PT artery, first DP artery, other PT artery, other DP artery, and other arm. If the systolic blood pressure of the first arm exceeds the systolic blood pressure of the other arm by more than 10 mm Hg, measurement of the blood pressure of the first arm should be repeated (to temper the "white coat effect" of the first measurement), and the first measurement of the first arm should be disregarded. For each leg, the ABI is calculated by dividing the ankle pressure by the higher of the two brachial pressures. In healthy persons, the ankle and arm systolic pressures are approximately the same or slightly higher in the ankle. Thus, a normal resting ABI is between 1.00 and 1.40 (**Table 46**). However, if a fixed obstruction of the arterial lumen supplying the lower extremity is present, a pressure gradient occurs, resulting in a reduced downstream pressure and concomitant reduction in the ABI (ABI <0.90). ABI values between 0.91 and 0.99 are considered borderline, and while equivocal for PAD, these patients are at increased risk for adverse cardiovascular events. An ABI greater than 1.40 is associated with calcification of the arterial wall and may occur in patients with medial calcinosis, diabetes mellitus, or end-stage kidney disease. This finding is uninterpretable, and therefore a toe-brachial index may be useful for diagnosing PAD in patients who are at risk for PAD and have an ABI above 1.40. A toe-brachial index below 0.70 is considered diagnostic of PAD. This test is typically performed in a vascular laboratory.

The sensitivity of the ABI is increased when it is measured after exercise. A common exercise protocol involves walking on a treadmill at 2 mph at a 12% incline for 5 minutes or until the patient is forced to stop because of leg pain. Alternatively, repetitive active pedal plantar flexion ("toe ups") while standing has been proposed for an office-based assessment of postexercise ABI. In patients with even mild PAD, the ankle pressure decreases more during treadmill exercise compared with healthy patients, and the recovery time to the pre-exercise value after exercise cessation is prolonged, proportional to the severity of PAD. A decrease of the ABI by 20% after exercise suggests significant PAD.

TABLE 46. Interpretation of the Ankle-Brachial Index	
Ankle-Brachial Index	**Interpretation**
>1.40	Noncompressible (calcified) vessel (uninterpretable result)
1.00-1.40	Normal
0.91-0.99	Borderline
0.41-0.90	Mild to moderate PAD
0.00-0.40	Severe PAD

PAD = peripheral arterial disease.

A common procedure in many vascular laboratories is measurement of multiple or segmental pressures in the lower extremities along with pulse volume recordings, which measure the magnitude and contour of the blood pulse volume. Once a patient is placed in a supine position for 5 to 10 minutes, blood pressures are obtained at successive levels of the extremity, localizing the level of disease fairly accurately.

Noninvasive angiography may be performed for anatomic delineation of PAD in patients requiring surgical or endovascular intervention. CT angiography (CTA) is rapid and easily available but requires the administration of intravenous contrast dye. The risk of dye-induced nephropathy must be considered in patients with chronic kidney disease, especially if an endovascular repair is being contemplated, because this would entail repeat administration of iodinated contrast dye. Magnetic resonance angiography (MRA) requires intravenous gadolinium for PAD definition; gadolinium has been associated with nephrogenic systemic fibrosis in patients with severe kidney disease. Additionally, MRA may be contraindicated in patients with implanted pacemakers or cardioverter-defibrillators. Both CTA and MRA compare favorably with digital subtraction (invasive) angiography for the detection of occlusive arterial disease. CTA has additional benefits of demonstrating vascular calcification, has higher spatial resolution than MRA, and allows visualization of adjacent soft tissues and of endovascular stent grafts. Invasive angiography, in most instances, is used only as part of an interventional procedure.

KEY POINTS

- An ankle-brachial index of 0.90 or below is diagnostic for peripheral arterial disease.
- An ankle-brachial index greater than 1.40 is uninterpretable, and a toe-brachial index should be obtained for diagnosing peripheral arterial disease.
- An exercise ankle-brachial index (ABI) may help establish the diagnosis of peripheral arterial disease (PAD) in patients in whom the resting ABI is equivocal; a decrease of the ABI by 20% after exercise suggests significant PAD.

Medical Therapy

The treatment of PAD has evolved over the past decade to include a broad approach, focusing on the reduction of adverse cardiovascular events, improving symptoms in claudication, and preventing tissue loss in critical limb ischemia.

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Cardiovascular Risk Reduction

Cigarette smoking is the strongest risk factor for PAD and for subsequent complications, and smoking cessation is imperative for patients with PAD. Smokers with PAD who quit have lower risks for myocardial infarction and stroke and an improved long-term survival versus those who continue to smoke. Cessation of cigarette smoking is also associated with a lower amputation rate, lower incidence of rest ischemia, improvement in maximal treadmill walking distance, and improved bypass graft patency rates.

A moderate- or high-intensity statin is indicated in all patients with PAD. Although no prospective statin trials have focused singularly on PAD, the Heart Protection Study (HPS) studied 6748 patients with PAD. Use of simvastatin was associated with relative reduction in overall mortality by 12%, vascular mortality by 17%, and cardiovascular events by 24% at a mean follow-up of 5 years.

Antihypertensive therapy is effective at reducing cardiovascular events in patients with PAD. Current guidelines recommend a brachial blood pressure goal of less than 140/90 mm Hg for patients with PAD. Whereas cardiovascular groups have advocated a lower target of 130/80 mm Hg for patients with PAD and diabetes or kidney disease, the recently released report of the Eighth Joint National Committee (JNC 8) suggests a therapeutic target of 140/90 mm Hg with or without diabetes or kidney disease. Data are insufficient to recommend use of one class of antihypertensive agents over another. Concern has been raised regarding the use of β-blockers in the treatment of hypertension in the setting of intermittent claudication; however, data have not supported this concern. Thus, β-blockers are not contraindicated in patients with PAD and should be used when appropriate. Nonetheless, thiazide diuretics, ACE inhibitors or angiotensin receptor blockers, and calcium channel blockers remain first-line therapy in patients with hypertension. In the Heart Outcomes Prevention Evaluation (HOPE) trial, ramipril (5 to 10 mg/d) decreased cardiovascular events in subjects with PAD with or without hypertension. The use of an ACE inhibitor is reasonable in patients with lower-extremity PAD to reduce the risk of adverse cardiovascular events.

Current guidelines recommend antiplatelet therapy in patients with PAD. Because most patients with PAD have concomitant coronary artery disease or cerebrovascular disease, aspirin is an acceptable antiplatelet agent in this setting despite the lack of good-quality evidence supporting improved outcomes in PAD. In addition to aspirin, clopidogrel (as monotherapy, not with aspirin) is a reasonable alternative strategy, and some data suggest clopidogrel may be particularly effective in patients with PAD.

Oral anticoagulation with warfarin has not been established to reduce cardiovascular events in patients with PAD because it is no more effective than antiplatelet therapy and confers a higher risk of bleeding. There are no data to suggest using newer anticoagulants in patients with PAD for the reduction of cardiovascular events.

Diabetes is one of the strongest risk factors for PAD. Although intensive diabetic control (hemoglobin A_{1c} ≤7%) can be effective to reduce microvascular complications, no prospective studies have demonstrated that this strategy reduces macrovascular complications, including PAD. In general, diabetes treatment of patients with PAD should follow current national treatment guidelines, with meticulous attention paid to foot care.

Symptom Relief

Exercise rehabilitation is a class I, level of evidence A, recommendation for the treatment of claudication in patients with PAD. Either treadmill exercise or resistance training improves functional performance, but treadmill exercise has shown greater increases in the 6-minute walk distance and in the maximum treadmill walking time compared with resistance training. Although supervised exercise therapy has statistically significant benefit on treadmill walking distance compared with non-supervised regimens, a randomized trial found benefit in both a supervised exercise and a home-based exercise program in patients with claudication. The National Institutes of Health–funded CLEVER trial evaluated the relative efficacy, safety, and health economic impact of noninvasive and endovascular treatment strategies for patients with aortoiliac PAD and claudication. Whereas supervised exercise provided a superior improvement in walking outcomes, patients undergoing endovascular repair had greater improvements in self-reported physical function.

Cilostazol is a phosphodiesterase inhibitor with antiplatelet activity and vasodilatory properties. A meta-analysis of eight randomized trials that included 2702 patients with PAD with claudication found that cilostazol improved maximum and pain-free treadmill walking distance and quality-of-life measures. Cilostazol may have an additional benefit of reducing restenosis and repeat revascularization following endovascular therapy. Because milrinone, another phosphodiesterase inhibitor, increased mortality in patients with heart failure, cilostazol should not be used in this population. In the absence of heart failure, a therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication.

Pentoxifylline is a xanthine derivative that affects platelet adhesiveness and whole-blood viscosity. A meta-analysis demonstrated a modestly improved walking distance with pentoxifylline, but it was substantially less effective than either cilostazol or a supervised exercise program.

Some data have shown that therapy with statins and ACE inhibitors leads to substantial improvements in pain-free walking time and maximal walking time.

KEY POINTS

- Smoking cessation, lipid control, antiplatelet medications, and antihypertensive therapy are important components of cardiovascular risk reduction in patients with peripheral arterial disease.
- Exercise therapy and cilostazol are effective treatments for claudication.

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Interventional Therapy

Endovascular or surgical revascularization is indicated for patients with significant disability due to claudication who have had an inadequate response to exercise or pharmacologic therapy, provided the benefits outweigh the risks. Revascularization should be considered in the following settings:

- The patient is significantly disabled by claudication, resulting in an inability to perform normal work or other activities that are important to the patient.
- The patient has not had an adequate response in symptom alleviation to exercise rehabilitation and pharmacologic therapy.
- The patient is able to benefit from an improvement in claudication; that is, exercise is not limited by another cause, such as angina, heart failure, lung disease, or orthopedic problems.

In addition, the characteristics of the lesion should permit appropriate intervention at low risk with a high likelihood of initial and long-term success. Inflow (aortoiliac artery) and outflow (infrapopliteal artery) should always be assessed before revascularization. Inflow lesions should be revascularized first followed by outflow lesions if bothersome symptoms persist.

Endovascular options are minimally invasive and confer a lower risk of perioperative adverse events than open surgery. The most common endovascular options include balloon angioplasty with or without stenting; other options include drug-coated balloons, lasers, atherectomy devices, and thermal devices. Endovascular treatment has become the revascularization modality of choice for aortoiliac disease in all but the most complex lesions. Endovascular procedures have high rates of procedural success, low restenosis rates, and decreased morbidity and mortality compared with open surgical repair. In patients with aortoiliac disease, primary stenting is associated with a 43% reduction in long-term failure compared with angioplasty alone. Infrainguinal (femoral, popliteal, and infrapopliteal arteries) revascularization offers less robust clinical benefit than aortoiliac revascularization. As a general rule, excellent long-term results can be achieved with intervention for short focal lesions, whereas longer lesions are associated with less durable primary patency rates following intervention. In patients with infrainguinal disease, balloon angioplasty is usually performed without stenting, as the latter procedure has significant reocclusion and restenosis rates and does not appear to improve outcomes after intervention. Recent trials suggest that use of drug-coated balloons may be an effective endovascular approach; however, long-term data are needed. Lesions with complex anatomy (for example, long-segment stenosis, multifocal stenosis, eccentric/calcified stenosis, or long-segment occlusions) may be better treated surgically.

Patients with critical limb ischemia (ABI <0.40, a flat waveform on pulse volume recording, and low or absent pedal flow on duplex ultrasonography) should be considered for immediate revascularization, either surgical or endovascular.

KEY POINTS

- Endovascular or surgical revascularization is indicated for patients with significant disability due to claudication who have had an inadequate response to exercise or pharmacologic therapy.
- Patients with critical limb ischemia should be considered for immediate revascularization, either surgical or endovascular.

Acute Limb Ischemia

Acute limb ischemia is an uncommon manifestation of PAD that carries significant risk of morbidity and mortality. Physical findings are characterized by the "6Ps"—Paresthesia, Pain, Pallor, Pulselessness, Poikilothermia (coolness), and Paralysis. Acute limb ischemia is caused by acute thrombosis of a limb artery or bypass graft, embolism, dissection, or trauma. Limb viability is determined by clinical findings and by the viability of tissues at the time of potential revascularization (**Table 47**). The onset of acute limb ischemia represents a true emergency. Complication rates of acute limb ischemia are high; despite urgent revascularization, amputation occurs in 10% to 15% of patients during hospitalization. Approximately 15% to 20% of patients die within 1 year after presentation.

Anticoagulation should be started as soon as the diagnosis has been made. Early consultation with a vascular specialist is appropriate. Patients with acute limb ischemia and a salvageable extremity should undergo emergent angiography to define the anatomic level of occlusion and assess treatment options. Treatment consists of surgical or percutaneous revascularization or, in selected patients, thrombolytic therapy. Catheter-directed thrombolysis is an adjunctive approach that may be useful in patients with a viable or marginally threatened limb, recent occlusion (no more than 2 weeks' duration), thrombosis of a synthetic graft or an occluded stent, and at least one identifiable distal runoff vessel. Although many patients will require revascularization following thrombolysis, the procedure is frequently less complex than if thrombolysis was not performed.

Following limb reperfusion, close monitoring is required for limb edema and tissue swelling that may cause a compartment syndrome. Symptoms and signs include severe pain, hypoesthesia, and weakness of the affected limb; myoglobinuria and increased serum creatine kinase levels often occur. If the compartment syndrome occurs, surgical fasciotomy is indicated to prevent irreversible neurologic and soft-tissue damage.

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TABLE 47. Categories and Prognosis of Acute Limb Ischemia

Category	Sensory Loss	Muscle Weakness	Arterial Doppler Signals	Prognosis
Viable	None	None	Audible	Not immediately threatened
Marginally threatened	None to minimal (toes)	None	Inaudible	Salvageable with prompt treatment
Immediately threatened	More than toes	Mild to moderate	Inaudible	Salvageable only with immediate revascularization
Irreversible	Profound anesthesia	Profound/paralysis	Inaudible	Not viable; major tissue loss inevitable

Adapted from Hirsch AT, Haskal ZJ, Hertzer NR, etal; American Association for Vascular Surgery; Society for Vascular Surgery; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiology; ACC/AHA Task Force on Practice Guidelines Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease; American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; Vascular Disease Foundation. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006 Mar 21;113(11):e488. [PMID: 16549646]

KEY POINTS

- Physical findings of acute limb ischemia are characterized by the "6Ps"—Paresthesia, Pain, Pallor, Pulselessness, Poikilothermia (coolness), and Paralysis.
- Patients with acute limb ischemia should receive immediate anticoagulation therapy; those with a salvageable extremity should undergo an emergent evaluation that defines the anatomic level of occlusion and leads to prompt endovascular or surgical revascularization.
- Following limb reperfusion in patients with acute limb ischemia, close monitoring is required for limb edema and tissue swelling that may cause a compartment syndrome.

Cardiovascular Disease in Cancer Survivors

Cardiotoxicity of Radiation Therapy to the Thorax

Chest radiation therapy is associated with significant cardiotoxicity, which can manifest as a complex, life-threatening disorder. Radiation-induced toxicity can affect nearly every component of the cardiovascular system, with manifestations such as pericarditis (acute or chronic), cardiomyopathy, aortitis, conduction system disease, valvulopathy, and coronary artery disease (**Table 48**). These pathologic alterations are likely caused by the generation of reactive oxygen species from irradiation, which leads to blood vessel injury and a cascade of inflammation, ischemia with loss of capillary density, and fibrosis of the cardiovascular structures.

Although pericarditis may occur acutely with chest radiation, manifestations of radiation-induced cardiotoxicity frequently develop after a long indolent period (5 to 20 years or later) owing to the chronic nature of the pathology and therefore require a high index of suspicion in at-risk patients. The clinical manifestations are related to the affected portion of the cardiovascular system. Myocardial fibrosis leads to a restrictive cardiomyopathy, resulting in poor chamber compliance and diastolic heart failure (see Myocardial Disease). Signs of restrictive cardiomyopathy have been reported in 15% to 50% of patients with previously treated Hodgkin lymphoma and are more evident in those who have received therapy with cardiotoxic drugs. Constrictive pericarditis also frequently is present. The potential for coexistent constrictive pericarditis and restrictive cardiomyopathy presents significant challenges in the management of these patients, as the clinical manifestations frequently overlap while the treatments for these two disorders vary considerably (that is, pericardiectomy versus cardiac transplantation). Pericardial effusion is particularly common in patients treated for esophageal cancer (approximately 25%), with a median presentation time of 5 months after therapy in one report. Any cardiac valve can be affected by radiation injury (5%-40% of patients), although left-sided lesions predominate and frequently occur with mixed stenosis and regurgitation. Coronary artery disease typically is ostial or proximal in location; microvasculopathy (disease involving vessels that are not epicardial in location) also can occur.

Recognition of the potential for cardiotoxicity has led to reductions in radiation exposure in the treatment of chest malignancy. Most contemporary studies have demonstrated significant decreases in cardiac mortality in comparison with historical studies. However, the increased risk of cardiotoxicity and death due to vascular complications attributable to radiation therapy remains. Thus, lifetime clinical monitoring for

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TABLE 48. Cardiotoxicity of Radiation Therapy to the Thorax

Manifestations	Clinical Onset After Radiation Therapy	Comments
Acute pericarditis or pericardial effusion	As early as 2 months, but 5 months on average	A common cardiac complication historically (25%), less common now (2%) owing to methods minimizing mediastinal irradiation
Pericardial fibrosis and constriction	As early as 1.5 years, but often 10 to 15 years or more	Risk persists for >25 years RV more extensively involved, leading to marked findings of RV failure
Accelerated coronary atherosclerosis	Average onset 7 years	Predilection for involvement of ostia or proximal segments of coronary arteries Patients with traditional risk factors for CAD are at higher risk May manifest as myocardial infarction Sudden death may occur rarely
Valvular fibrosis and regurgitation	10 to 25 years or more	Frequency greater in left- vs. right-sided valves Clinically significant aortic regurgitation may occur in ≥25% of long-term survivors Slowly progressive and requires lifelong monitoring Concomitant anthracycline use increases risk
Myocardial fibrosis, diastolic dysfunction, and restrictive cardiomyopathy	Years	Concomitant anthracycline use increases risk for heart failure
Fibrosis of conduction pathways leading to bradycardia, dysrhythmias, or heart block	Years or decades	

CAD = coronary artery disease; RV = right ventricle.

radiation-induced cardiotoxicity is warranted owing to the chronic, lethal nature of this complication. Propensity for radiation-induced injury is related to younger age at treatment, female sex, radiation exposure (total dose, dose per fraction, and cardiac chamber affected), the use of concomitant cardiotoxic drugs (such as anthracyclines), and the presence of cardiac risk factors (hypertension, smoking, hyperlipidemia). There is no clearly defined threshold of radiation exposure for cardiotoxicity risk. In all patients with a history of significant chest radiation, aggressive management of risk factors for atherosclerosis is warranted owing to the heightened risk of ischemic heart disease in these patients.

Although contemporary studies have shown a lower incidence of radiation-induced cardiotoxicity, the follow-up in these studies has been relatively short (frequently 5 to 10 years) and thus may be inadequate to ascertain the indolent effects of radiation-induced cardiotoxicity. Recent analyses frequently have focused on mortality rates without detailed examinations of other complications, such as myopathy, valvular disease, and constrictive pericarditis. The timing and clinical methods for serial monitoring have not been defined, but cardiotoxicity should be considered in any patient with symptoms or signs of cardiovascular disease and a history of chest radiation.

Owing to the frequent multiple cardiac pathologies in these patients, management of radiation-induced heart disease can be challenging. Treatment is directed primarily toward the predominant pathology, although it is recognized that concomitant abnormalities increase the surgical procedural risk. For example, patients undergoing pericardiectomy will be at significant operative risk owing to the propensity for increased surgical bleeding and myopathy in these patients. Thus, a high degree of individualization of the treatment plan for patients with radiation-induced heart disease is recommended.

KEY POINTS

- In all patients with a history of significant chest radiation, aggressive management of risk factors for atherosclerosis is warranted owing to the heightened risk of ischemic heart disease in these patients.
- Cardiotoxicity should be considered in any patient with a history of chest radiation who develops symptoms or signs of cardiovascular disease.

Cardiotoxicity of Chemotherapy

Cardiotoxicity from chemotherapy can result from traditional cytotoxic chemotherapy agents, such as anthracyclines (doxorubicin, daunorubicin, mitoxantrone), as well as from newer agents, such as monoclonal antibodies (trastuzumab) and tyrosine kinase inhibitors. Cardiotoxicity can occur in patients with normal hearts but is more common in patients with

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preexisting cardiac disease. Cardiotoxicity from these agents can manifest as dilated cardiomyopathy, myocardial ischemia from coronary vasospasm, or arrhythmias (**Table 49**).

The cardiotoxic effects of chemotherapy can be short-term, intermediate, or long-term. 5-Fluorouracil is associated with a high incidence of acute chest pain and electrocardiographic changes (70% within 72 hours of the first treatment cycle), resulting in death in 2% to 8% of patients affected by 5-fluorouracil toxicity.

Early manifestations of anthracycline toxicity are relatively uncommon (3%) and include high-grade heart block, supraventricular and ventricular arrhythmias, heart failure, myocarditis, and pericarditis, with resolution in many patients occurring within 1 week after presentation. Chronic cardiotoxicity due to anthracyclines, which begins with a subclinical decline in systolic and diastolic function, manifests with symptoms usually within months after completion of chemotherapy. However, cardiotoxicity from anthracyclines can have long latency periods (10 years or more).

The strongest risk factor for cardiotoxicity related to anthracycline agents is cumulative dose. The incidence of cardiotoxicity for doxorubicin or daunorubicin has been reported to be less than 1% for cumulative dose of less than 400 mg/m^2, but 26% for cumulative doses of 550 mg/m^2 or more. It is generally accepted that maximum cumulative doses for these drugs should be limited to 450 to 500 mg/m^2, but the doses

TABLE 49. Late-Onset Cardiotoxicity of Chemotherapeutic Agents[a]

Drug	Cardiotoxicity
Anthracyclines	Synergistic toxicity when administered with nonanthracycline agents
Doxorubicin	Heart failure (1.6%-5%)
	Higher in elderly women
	Typically irreversible
	Improved by aggressive treatment (resynchronization therapy)
	Left ventricular dysfunction (progression slowed by standard treatment)
	Dilated cardiomyopathy (odds ratio: 6.25[b])
	Cardiac death (odds ratio: 4.94[b])
Daunorubicin	Presumably similar to doxorubicin
Epirubicin	Heart failure (<5% with appropriate dosing)
Mitoxantrone	Heart failure
	Incidence significantly increased with dose >160 mg/m^2
	Survival improved by standard heart failure treatment
	Left ventricular dysfunction
Alkylating agents	
Cyclophosphamide	Heart failure (dose dependent)
	Left ventricular dysfunction (3%-5% with dose >100 mg/kg)
Cisplatin	Heart failure
Mitomycin	Cardiomyopathy
5-Fluorouracil	Vasospasm (common) and heart failure (rare) from myocardial infarction occurring during treatment
Paclitaxel	Heart failure (if given with doxorubicin)
Trastuzumab	Heart failure
	0.6% (NYHA class III or IV)
	1.5% (NYHA class II at 2 y)
	Left ventricular dysfunction (3%; asymptomatic and reversible)
	Not dose dependent
Interleukin-2	Heart failure from previous cardiomyopathy, myocarditis, or myocardial infarction occurring during treatment (rare)
Interferon-α	Heart failure from previous myocardial infarction during treatment (rare)

NYHA = New York Heart Association.

[a]Cardiotoxicity emerging 1 year or more after chemotherapy.

[b]When an anthracycline is added to chemotherapy regimen.

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that lead to toxic responses vary considerably among individual patients. Other risk factors for cardiotoxicity include age at treatment, concomitant therapy with other cardiotoxic agents, chest radiation, and preexisting cardiac disease. The toxic responses to anthracyclines can be modified by liposome encapsulation of the molecule, infusional rather than bolus administration, use of structural analogues (epirubicin and mitoxantrone), and adjunctive cardioprotective agents. Dexrazoxane is an EDTA chelator that reduces the risk of chronic cardiotoxicity associated with doxorubicin and epirubicin and may be considered in patients being treated with high anthracycline doses (>300 mg/m^2).

Cardiotoxicity due to trastuzumab typically causes a chronic, asymptomatic decline in ventricular function with a low frequency of overt heart failure (3%-7%). Older patients (age >50 years) and those with prior or concomitant exposure to anthracyclines are at increased risk of trastuzumab-induced cardiotoxicity. In most patients, cardiotoxicity due to trastuzumab is related to changes in contractility and is reversible. Unlike anthracyclines, trastuzumab-related cardiotoxicity is not dose related and patients can be successfully rechallenged after recovery of ventricular function.

Kinase inhibitors, such as tyrosine kinase inhibitors, are a relatively new approach to tumor receptor–targeted therapy. Hypertension is a potential adverse effect that may require dose adjustment or, in patients with severe hypertension, discontinuation of the kinase inhibitor.

In adult patients being considered for chemotherapy with anthracyclines, baseline evaluation of left ventricular function should be considered before initiation of therapy, although the need for this assessment is controversial in patients with no symptoms or signs of abnormal left ventricular function and in whom the cumulative dose is expected to be low (<300 mg/m^2). For patients who receive treatment with trastuzumab, a baseline evaluation of left ventricular function should be performed, particularly if there is a history of anthracycline use. Routine surveillance of cardiac function using echocardiography should be performed in all patients with assessment of left ventricular ejection fraction as well as indices of diastolic function. The timing intervals for these assessments are individualized based on the patient's baseline function, chemotherapeutic regimen, risk profile, and evidence of change in function in serial evaluations.

In adults undergoing doxorubicin therapy, the drug should be discontinued if there is evidence of heart failure, a 10% or greater decline in left ventricular ejection fraction to below the lower limit of normal, an absolute left ventricular ejection fraction of less than 45%, or a 20% decline in left ventricular ejection fraction to any level. Owing to the reversible nature of cardiotoxicity related to trastuzumab, this therapy can be resumed after recovery of left ventricular function in selected patients.

Although other echocardiographic indices (such as strain imaging or volume measurements) and serum markers (cardiac troponin, B-type natriuretic peptide) have been proposed for serial monitoring of patients who have undergone chemotherapy, the thresholds for these markers as well as the appropriate timing for their measurement remain uncertain. Patients who have left ventricular dysfunction should receive appropriate therapy with β-blockers, vasodilators, and diuretics as in patients with heart failure disorders not related to chemotherapy toxicity.

KEY POINTS

- Hypertension is a potential adverse effect of kinase inhibitors that may require dose adjustment or, in patients with severe hypertension, discontinuation of the kinase inhibitor.
- Cardiotoxicity related to trastuzumab is not dose related and is reversible.
- Chronic cardiotoxicity with anthracyclines is dose related and is not reversible.
- In patients who have undergone chemotherapy, baseline evaluation and routine surveillance of cardiac function using echocardiography should be performed with assessment of left ventricular ejection fraction as well as indices of diastolic function.

Pregnancy and Cardiovascular Disease

Cardiovascular Changes During Pregnancy

Understanding the normal physiologic changes of pregnancy is important in the interpretation of signs and symptoms in the pregnant patient (**Table 50**). During a normal pregnancy, there is an increase in plasma volume and a lesser increase in erythrocyte mass, resulting in increased total blood volume and relative anemia. The systemic vascular resistance decreases during pregnancy, but the heart rate and cardiac output rise; as a result, there is generally a slight reduction in mean arterial pressure. Maternal cardiac output peaks at approximately 40% above the prepregnancy level by the 32nd week of pregnancy and then plateaus until delivery. During delivery, heart rate and blood pressure increase, leading to a rise in cardiac output to as much as 80% above the prepregnancy level.

Prepregnancy Evaluation

Prepregnancy evaluation is recommended for all women with cardiovascular disease who are anticipating pregnancy. Patients with congenital heart disease should consult with a cardiologist specializing in congenital conditions and a high-risk obstetrician to discuss the need for genetic counseling, evaluate the risks of future pregnancy, and develop a plan for management during labor and the postpartum period.

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TABLE 50. Normal Versus Abnormal Cardiac Symptoms and Signs in Pregnancy

Symptom or Sign	Normal	Pathologic
Shortness of breath	Mild, with exertion	Orthopnea, PND, cough
Palpitations	Atrial and ventricular premature beats	Atrial fibrillation or flutter; ventricular tachycardia
Chest pain	No	Chest pressure, heaviness, or pain
Murmur	Basal systolic murmur grade 1/6 or 2/6 present in 80% of pregnant women	Systolic murmur grade ≥3/6; any diastolic murmur
Tachycardia	Heart rate increased by 20%-30%	Heart rate >100/min
Low blood pressure	Blood pressure typically is modestly decreased (~10 mm Hg)	Low blood pressure associated with symptoms
Edema	Mild peripheral	Pulmonary edema
Gallop	S_3	S_4

PND = paroxysmal nocturnal dyspnea.

The CARPREG index is used to estimate risk for cardiovascular complications during pregnancy in women with cardiovascular disease (**Table 51**). Women with severe pulmonary hypertension (pulmonary artery pressure ≥ two-thirds systemic pressure) are at high risk during pregnancy, with an estimated maternal mortality rate between 30% and 50%. Systolic ventricular dysfunction (ejection fraction <40%) with New York Heart Association (NYHA) functional class III or IV heart failure confers a high risk of maternal and fetal complications and is considered a contraindication to pregnancy.

Patients with severe obstructive cardiac disease, such as mitral or aortic valve stenosis, are generally considered for intervention before pregnancy, even if asymptomatic.

KEY POINTS

- Women with severe pulmonary hypertension are at high risk for pregnancy-related death.
- Systolic ventricular dysfunction (ejection fraction <40%) with New York Heart Association (NYHA) functional class III or IV heart failure is considered a contraindication to pregnancy.

Management of Cardiovascular Disease During Pregnancy

Because pregnancy involves an increase in blood volume and cardiac output, women with severe obstructive cardiac lesions

TABLE 51. Predictors of Maternal Cardiac Events in Women with Congenital or Acquired Cardiac Disease (CARPREG Index)

Risk Factor (Predictor)	Operational Definition
Previous cardiac event or arrhythmia	Heart failure, transient ischemic attack, stroke, arrhythmia
Baseline NYHA functional class III or IV or cyanosis	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity
Left-sided heart obstruction	Mitral valve area <2 cm^2; aortic valve area <1.5 cm^2 or resting peak left ventricular outflow tract gradient >30 mm Hg
Reduced systemic ventricular systolic function	Ejection fraction <40%

Estimated Risk for Cardiac Events[a]

No. of Predictors	Estimated Risk (%)	Recommendation
0	4	Consider preconception cardiac intervention for specific lesions; increase frequency of follow-up; delivery at community hospital
1	31	Consider preconception cardiac intervention for specific lesions; refer to regional center for ongoing care
>1	69	Consider preconception cardiac intervention for specific lesions; refer to regional center for ongoing care

NYHA = New York Heart Association.

[a]Pulmonary edema, tachyarrhythmia, embolic stroke, cardiac death.

Data and recommendations from Siu SC, Sermer M, Colman JM, et al. Cardiac Disease in Pregnancy (CARPREG) Investigators. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001;104(5):515-521. [PMID: 11479246]

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generally develop symptoms during pregnancy, whereas women with regurgitant valve lesions tolerate pregnancy reasonably well.

Vaginal delivery is generally preferred for patients with cardiovascular disease because it results in a shorter and less marked hemodynamic derangement than cesarean delivery. To reduce the risk of fetal intracranial hemorrhage, cesarean delivery is recommended in women receiving warfarin anticoagulation therapy. Cesarean delivery is also recommended for obstetric reasons and in select patients with severe pulmonary hypertension or a markedly dilated aorta.

Peripartum Cardiomyopathy

Left ventricular systolic dysfunction identified toward the end of pregnancy or in the months following delivery in the absence of another identifiable cause is known as peripartum cardiomyopathy. This occurs with increased frequency in women who are multiparous, older (age >30 years), and black; in those with multifetal pregnancy, gestational hypertension, or preeclampsia; and in those treated with tocolytic agents.

The leading cause of pregnancy-related maternal death in North America is peripartum cardiomyopathy. Death in women with peripartum cardiomyopathy results from heart failure, thromboembolic events, and arrhythmias. Half of women who develop peripartum cardiomyopathy show improvement in left ventricular function within 6 months of delivery, and 20% to 40% have normalization of ventricular function.

Prompt initiation of medical therapy is recommended for women with peripartum cardiomyopathy and includes β-blockers, digoxin, hydralazine, nitrates, and diuretics. ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists should be avoided until after delivery owing to teratogenicity. Anticoagulation with warfarin is recommended for women with peripartum cardiomyopathy with left ventricular ejection fraction below 35%, owing to the increased risk of thromboembolism related to this disorder; the duration of anticoagulation is individualized, and anticoagulation is discontinued when the ejection fraction improves.

In women with acute severe peripartum cardiomyopathy, bromocriptine, which blocks prolactin secretion, has been shown to improve left ventricular ejection fraction and clinical outcomes when added to peripartum-related heart failure therapy. Bromocriptine inhibits lactation and may increase risk of thromboembolism; therefore, anticoagulation is suggested in conjunction with bromocriptine. For these reasons, discussion with the patient is an important precursor to initiating therapy. Referral for ventricular assist device or heart transplantation should be considered for women with refractory severe heart failure related to peripartum cardiomyopathy.

Women with peripartum cardiomyopathy with persistent left ventricular dysfunction should be counseled to avoid subsequent pregnancy since another pregnancy is often associated with recurrent or further reduction of left ventricular function, which can result in clinical deterioration or even death.

Other Cardiovascular Disorders

Women with Marfan syndrome have been reported to have an increased risk of aortic dissection during pregnancy. Women with Marfan syndrome and an ascending aortic diameter of 4.5 cm or greater are recommended to have aortic repair surgery before considering pregnancy to reduce this risk. Some women with Marfan syndrome and aortic diameter less than 4.5 cm are at high risk for dissection during pregnancy and are counseled to have aortic valve replacement before pregnancy; these include patients with rapid dilatation of the ascending aorta or a family history of aortic dissection.

Spontaneous coronary artery dissections in women without risk factors for coronary artery disease may occur in the peripartum setting. Spontaneous healing may occur with conservative medical therapy, but revascularization, either percutaneous or bypass surgery, has been utilized as well.

Cardiovascular Medication Use During Pregnancy

Limited data are available on the safety of cardiovascular medications administered during pregnancy. The FDA categorizes drugs by their fetal effects during pregnancy (see MKSAP 17 General Internal Medicine, Women's Health). Most cardiovascular drugs are not FDA-approved for use during pregnancy. General guidelines for the use of several cardiovascular drugs during pregnancy are provided in **Table 52**. Cardiovascular medications should be used only when needed and at the lowest possible dose, and the desired therapeutic effect should outweigh the risk.

When β-blockers are used during pregnancy or lactation, periodic fetal and newborn heart rate monitoring and initial newborn blood glucose assessment are indicated because β-blockers cross the placenta and are present in human breast milk. Atenolol is usually avoided during pregnancy because it has been reported to cause small fetal gestational size, early delivery, and low birth weight. Patients taking atenolol are usually transitioned to a different β-blocker.

The treatment of choice for acute symptomatic supraventricular tachycardia during pregnancy is adenosine. Recurrent tachycardia symptoms are often treated with β-blockers and digoxin; sotalol and flecainide have also been safely used. Amiodarone is rarely used owing to toxicity concerns.

Spironolactone is considered compatible with breastfeeding; although spironolactone and its active metabolite, canrenone, appear in breast milk, the concentrations are pharmacologically insignificant. ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists are teratogenic and should be avoided during pregnancy. Some ACE inhibitors are safe to use while breastfeeding. Angiotensin receptor blockers are generally avoided during lactation because data are inconclusive regarding infant risk when used during breastfeeding.

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TABLE 52. Drugs for Cardiac Disorders in Pregnan y

Drug	Use in Pregnancy	Compatibility with Breastfeeding	Comments
ACE inhibitors			
Captopril, enalapril	No	Yes	Teratogenic in first trimester; cause fetal/neonatal kidney failure with second or third trimester exposure; scleroderma renal crisis is only indication
Lisinopril	No	?	Same as above
ARBs	No	?	Teratogenic in first trimester; cause fetal/neonatal kidney failure with second or third trimester exposure
Adenosine	Yes	?	No change in fetal heart rate when used for supraventricular tachycardia
Amiodarone	No	No	Fetal hypothyroidism, prematurity
Antiplatelet agents			
Dipyridamole, clopidogrel	Yes	?	Second-line agent; no evidence of harm in animal clopidogrel studies; no human data
Aspirin(≤81 mg)	Yes	Yes	
β-Blockers			
Atenolol	Yes	No	Second-line agent; low birth weight, intrauterine growth restriction
Esmolol	Yes	?	Second-line agent; more pronounced bradycardia
Labetalol	Yes	Yes	Preferred drug in class
Metoprolol	Yes	Yes	Shortened half-life
Propranolol	Yes	Yes	Second-line agent; intrauterine growth restriction
Sotalol	Yes	?	Second-line agent; insufficient data; reserve use for arrhythmia not responding to alternative agent
Calcium channel blockers			
Diltiazem, verapamil	Yes	Yes	Second-line agent; maternal hypotension with rapid intravenous infusion; used for fetal supraventricular tachycardia
Digoxin	Yes	Yes	Second-line agent; shortened half-life
Disopyramide	Yes	Yes	Second-line agent; case reports of preterm labor
Diuretics	Yes	Yes	Second-line agent; use when needed for maternal volume overload only
Flecainide	Yes	?	Second-line agent; inadequate data but used for fetal arrhythmia; case report of fetal hyperbilirubinemia
Hydralazine	Yes	Yes	Vasodilator of choice
Lidocaine	Yes	Yes	Treatment of choice for ventricular arrhythmias
Sodium nitroprusside	No	No	Potential fetal thiocyanate toxicity
Organic nitrates	Yes	?	No apparent increased risk
Phenytoin	No	Yes	Known teratogenicity and bleeding risk; last resort for arrhythmia
Procainamide	Yes	Yes	Used for fetal arrhythmia
Propafenone	Yes	?	Second-line agent; used for fetal arrhythmia
Quinidine	Yes	Yes	Preferred drug in class; increases digoxin levels

ARB = angiotensin receptor blocker; ? = unknown.

Adapted from Rosene-Montella K, Keely EJ, Lee RV, Barbour LA. Medical Care of the Pregnant Patient. 2nd Edition. Philadelphia, PA: American College of Physicians; 2008. p 356-357. Copyright 2008, American College of Physicians.

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Anticoagulation Therapy During Pregnancy

Pregnancy is a hypercoagulable state, and anticoagulation is often indicated during pregnancy; regimens and levels of anticoagulation depend on the specific indication (**Table 53**). Prepregnancy counseling is recommended for all women receiving chronic warfarin anticoagulation to help them understand maternal and fetal risk and to make an informed decision regarding which anticoagulation regimen to use during their pregnancy.

Unfractionated heparin, low-molecular-weight heparin (LMWH), and warfarin can all be used for anticoagulation during pregnancy. Meticulous monitoring and dose adjustment are recommended for all anticoagulation regimens. Warfarin is stopped before delivery owing to the risk of fetal intracranial hemorrhage if spontaneous labor occurs while the mother, and thus the fetus, is anticoagulated with warfarin.

Women with mechanical valve prostheses represent a high-risk subset of patients during pregnancy, with excess risk of valve thrombosis, bleeding, and fetal morbidity and mortality. The optimal anticoagulation regimen for this patient group has not been established. Warfarin anticoagulation during pregnancy may be the safest agent for prevention of maternal prosthetic valve thrombosis; however, warfarin poses an

TABLE 53. Anticoagulation Regimens During Pregnancy

Weeks of Gestation	Recommended Regimen
	Venous Thromboembolism
Weeks 6-12	Warfarin (if dose to attain INR 2-3 is ≤5 mg)
	UFH (IV or SQ; aPTT 2 × control)
	Weight-based LMWH
Weeks 13-37	UFH (SQ; aPTT 2 × control)
	Weight-based LMWH
	Warfarin (INR 2-3)
Weeks 37 to term	UFH (IV; aPTT 2 × control)
	Atrial Fibrillation
Weeks 6-12	Warfarin (if dose to attain INR 2-3 is ≤5 mg)
	UFH (IV or SQ; aPTT 2 × control)
	Weight-based LMWH
Weeks 13-37	UFH (SQ; aPTT 2 × control)
	Weight-based LMWH
	Warfarin (INR 2-3)
Weeks 37 to term	UFH (IV; aPTT 2 × control)
	Mechanical Valve Prosthesis
Weeks 6-12	Warfarin dose ≤5 mg for therapeutic INR
	Continue warfarin (class IIa)
	UFH: IV; aPTT 2 × control (class IIb)
	Anti-factor Xa adjusted LMWH (class IIb)
	Warfarin dose >5 mg for therapeutic INR
	UFH: IV; aPTT 2 × control (class IIa)
	Anti-factor Xa adjusted LMWH (class IIa)
Weeks 13-37	Warfarin (therapeutic INR)
Weeks 37 to term	UFH (IV; aPTT 2 × control)

aPTT = activated partial thromboplastin time; IV= intravenous; LMWH = low-molecular-weight heparin; SQ = subcutaneous; UFH = unfractionated heparin.

Recommendations from Nishimura RA, Otto CM, Bonow RO, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):2438-88. Erratum in: J Am Coll Cardiol. 2014 Jun 10;63(22):2489. [PMID: 24603192] *and* Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO; American College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis (9th edition): American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e691S-736S. [PMID: 22315276] *and* Furie KL, Kasner SE, Adams RJ, et al; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011 Jan;42(1):227-276. [PMID: 20966421]

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increased fetal risk, with possible teratogenicity, miscarriage, and fetal loss due to intracranial hemorrhage. Data suggest that LMWH and unfractionated heparin are safer for the fetus than warfarin, but these therapies appear to increase the risk of maternal prosthetic valve thrombosis.

Guidelines from the American College of Cardiology/American Heart Association on the management of anticoagulation during pregnancy conclude that intravenous unfractionated heparin, LMWH, or warfarin may be used for anticoagulation of pregnant women with mechanical heart valves. Intravenous unfractionated heparin is the drug of choice for patients with mechanical valve prostheses around the time of delivery.

KEY POINTS

- Women with Marfan syndrome and an ascending aortic diameter of 4.5 cm or greater are recommended to have aortic repair surgery before considering pregnancy to reduce the risk of aortic dissection.
- ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists are teratogenic and should be avoided during pregnancy.
- Unfractionated heparin, low-molecular-weight heparin, or warfarin may be used for anticoagulation of pregnant women with mechanical heart valves; unfractionated heparin is the drug of choice for patients with mechanical valve prostheses around the time of delivery.

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 33-year-old woman is evaluated as an outpatient following an episode of atrial fibrillation. The episode resolved shortly after arriving at the emergency department. She has a history of tetralogy of Fallot with repair performed at the age of 4 years.

On physical examination, blood pressure is 110/70 mm Hg, pulse rate is 62/min and regular, and respiration rate is 18/min. BMI is 28. The estimated central venous pressure is normal. The apical impulse is normal; there is a parasternal impulse at the left sternal border. S_1 is normal. The S_2 is single, and there is a soft early systolic murmur at the second left intercostal space. A grade 2/6 decrescendo diastolic murmur that increases with inspiration is noted at the left sternal border. The remainder of the physical examination is normal.

Which of the following is the most likely diagnosis?

(A) Aortic valve regurgitation
(B) Pulmonary valve regurgitation
(C) Recurrent ventricular septal defect
(D) Tricuspid valve regurgitation

Item 2

A 58-year-old man is evaluated during a routine appointment and asks for advice on cardiac risk assessment. He does not have any current cardiac symptoms, exercises 4 days per week, and has never smoked. He has no chronic health issues and takes no medications. He has no known drug allergies. Results of the physical examination are normal.

Cardiovascular risk calculation using the Pooled Cohort Equations predicts a 6% risk of a myocardial infarction or coronary death in the next 10 years.

Which of the following tests should be performed next?

(A) Adenosine cardiac magnetic resonance (CMR) imaging
(B) Cardiac CT angiography
(C) Fractionated lipoprotein profile
(D) High-sensitivity C-reactive protein assay
(E) Stress echocardiography

Item 3

A 64-year-old woman is evaluated during a routine examination. She has no symptoms. Medical history is significant for hypertension and type 2 diabetes mellitus. Medications are amlodipine, losartan, atorvastatin, and metformin.

On physical examination, she is afebrile, blood pressure is 154/77 mm Hg and equal on both sides, pulse rate is 82/min, and respiration rate is 16/min. BMI is 28. Cardiac examination shows a grade 1/6 decrescendo diastolic murmur heard best over the apex. There are no changes with a Valsalva maneuver or change in position. Peripheral pulses are normal.

Electrocardiogram shows sinus rhythm with nonspecific ST changes.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Chest CT
(B) Exercise echocardiography stress testing
(C) Transthoracic echocardiography
(D) No further testing

Item 4

A 58-year-old woman is evaluated during a routine physical examination. She has a history of atrial fibrillation and had an atrial fibrillation ablation procedure 6 months ago. Before her ablation, she had persistent atrial fibrillation with palpitations and dyspnea. Since her ablation, she has been asymptomatic with no palpitations. Ambulatory electrocardiographic monitoring at 3 and 6 months after the ablation demonstrated no atrial fibrillation. Medical history is also significant for a transient ischemic attack, hypertension, and hyperlipidemia. Her medications are warfarin, metoprolol, candesartan, and simvastatin.

On physical examination, the patient is afebrile, blood pressure is 130/80 mm Hg, pulse rate is 64/min, and respiration rate is 16/min. BMI is 30. Heart rate and rhythm are regular.

An electrocardiogram shows normal sinus rhythm.

Which of the following is the most appropriate management?

(A) Continue warfarin
(B) Continue warfarin and add aspirin
(C) Discontinue warfarin
(D) Discontinue warfarin and start aspirin
(E) Discontinue warfarin and start aspirin and clopidogrel

Item 5

A 52-year-old woman is seen in follow-up for dyspnea. Over the past 6 months, she has noticed increasing shortness of breath during her daily run, which she has had to decrease from 2 miles to 1 mile. She is able to complete other aerobic exercises, such as biking and tennis, with minimal limitation. She has experienced no chest pain or syncope. Medical history is significant for hypertension, diagnosed 10 years ago. Her only medication is hydrochlorothiazide.

On physical examination, blood pressure is 122/70 mm Hg and pulse rate is 66/min. Lungs are clear to auscultation. Cardiac examination reveals a rapid carotid upstroke and a grade 3/6 holosystolic murmur heard best at the left lower sternal border. The murmur increases during both end-expiration and squat-to-stand maneuvers.

Transthoracic echocardiogram shows left ventricular hypertrophy and dynamic left ventricular outflow tract obstruction consistent with a diagnosis of hypertrophic cardiomyopathy.

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Which of the following is the most appropriate next step in treatment?

(A) Discontinue hydrochlorothiazide
(B) Dual-chamber pacemaker
(C) Initiate lisinopril
(D) Surgical myectomy

Item 6

A 71-year-old man is evaluated in the emergency department for severe pain in the chest and back that was abrupt in onset and has persisted for 3 hours. He has no abdominal pain, leg pain, or neurologic symptoms. His medical history is notable for hypertension. Medications are amlodipine and lisinopril.

On physical examination, the patient is afebrile, blood pressure is 180/100 mm Hg in both arms, pulse rate is 98/min, and respiration rate is 18/min. Oxygen saturation is 96% on ambient air. Cardiac auscultation discloses an S_4 gallop but no murmur. Pulmonary examination is normal. Pulses are symmetric and equal in all extremities.

Laboratory studies show a D-dimer level of 1.2 µg/mL (1.2 mg/L) and a serum creatinine level of 1.0 mg/dL (88.4 µmol/L). Initial serum cardiac troponin I level is not elevated.

Electrocardiogram shows left ventricular hypertrophy with repolarization abnormalities. Chest radiograph shows an enlarged cardiac silhouette. Chest CT scan with intravenous contrast demonstrates a focal penetrating ulcer in the thoracic descending aorta (shown).



Which of the following is the most appropriate immediate next step in management?

(A) Heparin followed by warfarin
(B) Endovascular stenting
(C) Intravenous β-blockade followed by intravenous sodium nitroprusside
(D) Open surgical repair

Item 7

A 52-year-old woman is evaluated for fatigue and lower extremity swelling. One year ago, she had acute idiopathic pericarditis treated with anti-inflammatory medications and colchicine. Symptoms initially improved and her medications were discontinued. However, for the past 3 months, she has had worsening symptoms of exertional fatigue and edema in both legs. She currently takes no medications.

On physical examination, she is afebrile, blood pressure is 130/78 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. Pulsus paradoxus of 15 mm Hg is present. The estimated central venous pressure is 10 cm H_2O, and the jugular venous pulse contour shows diminished *y* descents. The lungs are clear to auscultation. Heart sounds are normal, with no rubs or gallops. Hepatomegaly is present, and peripheral edema is noted in both lower extremities up to the knees.

A 12-lead electrocardiogram is normal. Echocardiogram shows the cardiac chambers to be normal in size and function with a moderate circumferential pericardial effusion. A CT of the heart shows normal pericardial thickness.

A pericardiocentesis fails to resolve the elevated right atrial pressure documented on right heart catheterization.

Which of the following is the most likely diagnosis?

(A) Cor pulmonale
(B) Effusive constrictive pericarditis
(C) Heart failure
(D) Recurrent acute pericarditis

Item 8

A 58-year-old man is evaluated during a routine appointment. He is asymptomatic. He was diagnosed with type 2 diabetes mellitus 4 years ago and has hypertension, dyslipidemia, and obesity. His medications are enteric-coated low-dose aspirin, lisinopril, fluvastatin (20 mg/d), and metformin.

His calculated 10-year risk of atherosclerotic cardiovascular disease (ASCVD) using the Pooled Cohort Equations is 10%.

On physical examination, blood pressure is 126/78 mm Hg and pulse rate is 72/min. The remainder of the examination is normal.

Laboratory studies:

Total cholesterol	186 mg/dL (4.82 mmol/L)
LDL cholesterol	123 mg/dL (3.19 mmol/L)
HDL cholesterol	44 mg/dL (1.14 mmol/L)
Triglycerides	109 mg/dL (1.23 mmol/L)

Which of the following is the most appropriate statin management?

(A) Increase fluvastatin to 40 mg/d
(B) Switch to atorvastatin, 40 mg/d
(C) Switch to lovastatin, 20 mg/d
(D) Switch to pravastatin, 20 mg/d
(E) Switch to simvastatin, 10 mg/d

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Item 9

A 34-year-old woman with idiopathic heart failure diagnosed 9 months ago is evaluated for a 3-month history of nonproductive cough. She sleeps on one pillow and has no paroxysmal nocturnal dyspnea. Medical history is otherwise unremarkable, and she has never smoked. Medications are lisinopril, carvedilol, and furosemide.

On physical examination, the patient is afebrile, blood pressure is 102/70 mm Hg, pulse rate is 64/min, and respiration rate is 16/min. Oxygen saturation on ambient air is 98%. The remainder of the examination, including heart and lung examinations, is unremarkable.

Her most recent left ventricular ejection fraction is 40%. Chest radiograph is unremarkable.

Which of the following is the most appropriate management?

(A) Discontinue lisinopril and start valsartan
(B) Echocardiography
(C) Obtain B-type natriuretic peptide level
(D) Pulmonary function testing

Item 10

A 48-year-old man with newly diagnosed hypertension is referred for an echocardiogram to assess findings of left ventricular hypertrophy noted on the electrocardiogram. He is asymptomatic, and his medical history is unremarkable other than hypertension. His only medication is chlorthalidone.

On physical examination, blood pressure is 128/70 mm Hg, pulse rate is 60/min and regular, and respiration rate is 18/min. BMI is 24. The cardiac examination is normal other than the presence of an S_4.

The transthoracic echocardiogram demonstrates normal left ventricular size, function, and mass index. An atrial septal aneurysm with a small left-to-right shunt indicative of a patent foramen ovale is noted by color-flow Doppler imaging. The right ventricular chamber size, systolic function, and estimated pressures are normal.

Which of the following is the most appropriate management based on this patient's echocardiographic findings?

(A) Anticoagulation therapy
(B) Closure of the defect
(C) Transesophageal echocardiography
(D) No further evaluation or treatment

Item 11

A 69-year-old man is evaluated for exertional chest pain that began 2 months ago. The patient describes the chest pain as tightness in the left side of his chest that occurs after walking approximately a half-mile. This chest tightness improves with rest. Two years ago, he had a myocardial infarction. The patient's medications are low-dose aspirin, metoprolol, lisinopril, and rosuvastatin.

On physical examination, blood pressure is 124/72 mm Hg and pulse rate is 52/min. The remainder of the examination is normal.

Resting electrocardiogram (ECG) shows no evidence of left ventricular hypertrophy and no ST- or T-wave changes.

Exercise ECG is performed. The patient is able to exercise on the Bruce protocol for 10 minutes and 20 seconds; blood pressure rises appropriately, but he develops chest tightness and stops because of breathlessness. There are no ECG changes.

Which of the following is the most appropriate management?

(A) Add diltiazem
(B) Add isosorbide mononitrate
(C) Coronary angiography
(D) Pharmacologic nuclear stress test

Item 12

A 32-year-old man is evaluated during an initial office visit. He has no symptoms and no significant medical history. He takes no medications.

On physical examination, blood pressure is 120/70 mm Hg in both arms, pulse rate is 64/min, and respiration rate is 12/min. Cardiac examination reveals a grade 1/6 decrescendo diastolic murmur heard best at the left lower sternal border. Femoral pulses are equal.

Which of the following is the most likely cause of the patient's murmur?

(A) Aortic coarctation
(B) Atrial septal defect
(C) Bicuspid aortic valve
(D) Mitral stenosis

Item 13

A 69-year-old woman is evaluated for follow-up 3 months after a non-ST-elevation myocardial infarction. She was assessed to be at low risk, and she was treated medically. Since the acute event, the patient has done well. She has no chest discomfort or shortness of breath. She has hypercholesterolemia and hypertension. Medications are lisinopril, metoprolol, atorvastatin, aspirin, and clopidogrel. She has modified her diet and has begun performing physical activity 5 days a week.

On physical examination, the patient is afebrile, blood pressure is 125/80 mm Hg, pulse rate is 60/min, and respiration rate is 12/min. BMI is 26. A normal carotid upstroke without carotid bruits is noted, jugular venous pulsations are normal, and normal S_1 and S_2 heart sounds are heard without murmurs. Lung fields are clear, distal pulses are normal, and no peripheral edema is present.

Laboratory studies show adherence to her lipid therapy and are otherwise normal.

Which of the following will offer this patient the greatest reduction in her risk of future cardiovascular events?

(A) Colchicine
(B) Folic acid
(C) Influenza vaccine
(D) Vitamin E

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Item 14

A 51-year-old woman is admitted to the hospital with community-acquired pneumonia after outpatient therapy was unsuccessful. She presented 5 days ago with cough, fever, and dyspnea, and she was found to have right lower lobe crackles on examination and a corresponding infiltrate on chest radiography. She was started on oral moxifloxacin. However, she has remained febrile with worsening shortness of breath and is now admitted to the hospital for further treatment. Medical history is significant for hypertension and depression, for which she takes carvedilol and amitriptyline. Her current medications are moxifloxacin, carvedilol, and amitriptyline.

On physical examination, temperature is 38.4 °C (101.1 °F), blood pressure is 140/90 mm Hg, pulse rate is 88/min, and respiration rate is 18/min. Oxygen saturation breathing ambient air is 89%. BMI is 25. Chest examination is consistent with right lower lobe consolidation. The remainder of the physical examination is unremarkable.

An electrocardiogram (ECG) at the time of hospital admission is shown.

Which of the following medications should be discontinued based on this patient's ECG findings?

(A) Amitriptyline
(B) Amitriptyline and carvedilol
(C) Amitriptyline and moxifloxacin
(D) Moxifloxacin

Item 15

A 74-year-old man is evaluated in the emergency department for a 7-day history of progressive exertional dyspnea associated with a dry cough, increasing orthopnea (from two to four pillows), and inability to buckle his belt. He has a 20-year history of hypertension treated with diltiazem.

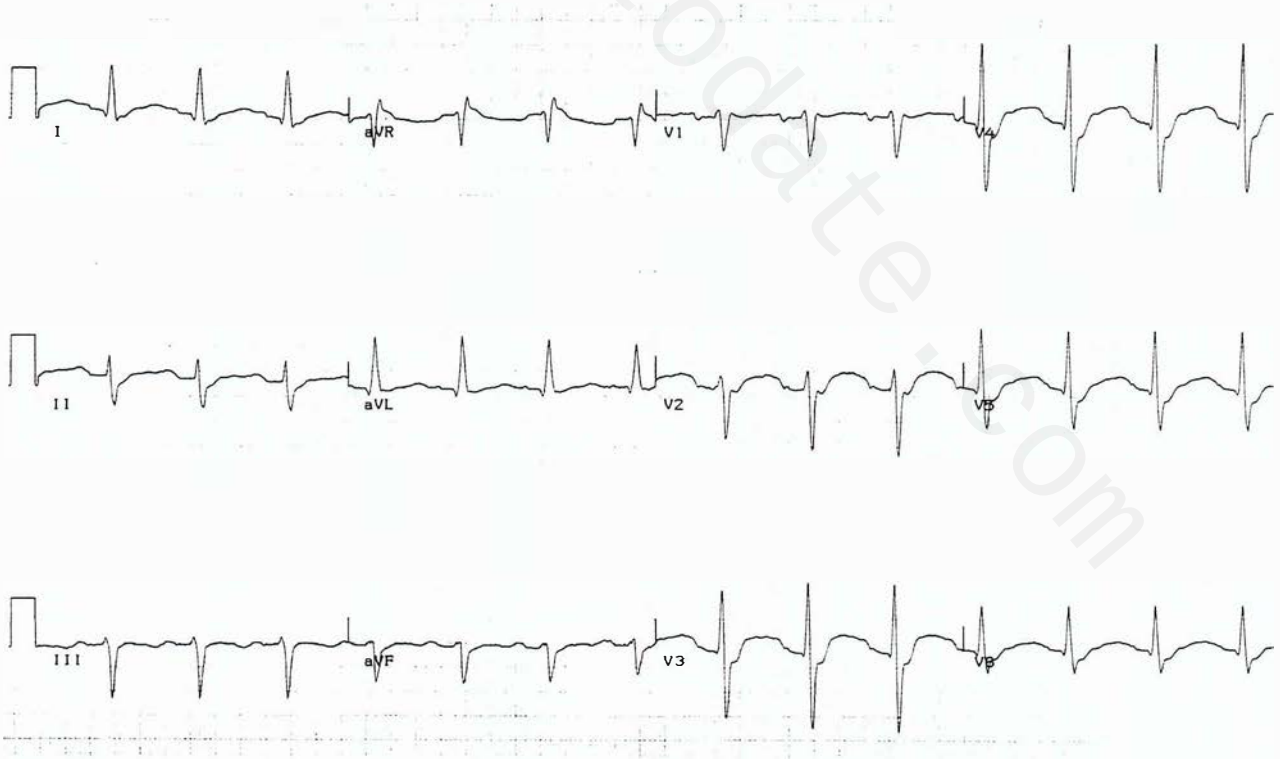
On physical examination, blood pressure is 162/86 mm Hg, pulse rate is irregularly irregular at 84/min, and respiration rate is 18/min. Estimated central venous pressure is 14 cm H_2O. Cardiac examination reveals an irregularly irregular rhythm and an S_1. Bibasilar crackles are heard on auscultation of the lungs. His liver is enlarged 2 cm below the costal margin. His extremity examination reveals bilateral pitting edema.

Serum electrolyte levels and kidney function tests are normal. Serum B-type natriuretic peptide level is 2472 pg/mL (2472 ng/L).

Electrocardiogram shows atrial fibrillation. Echocardiogram shows a left ventricular ejection fraction of 60%, septal wall thickness of 1.5 cm, and posterior wall thickness of 1.4 cm. Chest radiograph shows hazy bilateral infiltrates.

Which of the following is the most appropriate next step in management?

(A) β-Blocker
(B) Cardioversion
(C) Furosemide
(D) Spironolactone



ITEM 14

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Item 16

A 58-year-old man is evaluated in the hospital for weakness, fatigue, and hypotension. The patient reports a 3-week history of anorexia and 2-year history of non-small cell lung cancer with metastatic involvement in the liver treated with combination cytotoxic chemotherapy.

On physical examination, the patient appears cachectic. Blood pressure is 70/52 mm Hg and pulse rate is 110/min. The lungs are clear to auscultation. The jugular venous pulse contour is flat. Carotid upstrokes are brisk. S_1 and S_2 are distant. No rubs, gallops, or murmurs are present. No peripheral edema is noted. The remainder of the physical examination is unremarkable.

Echocardiogram shows a small left ventricular cavity with hyperdynamic function (ejection fraction, 75%). A moderately sized circumferential pericardial effusion is evident. Diastolic inversion of the right atrium and significant respiratory variation in the mitral inflow pattern are present.

The blood pressure does not change after administration of a 1-L bolus of intravenous fluid.

In addition to continued intravenous fluid, which of the following is the most appropriate next step in treatment?

(A) Intra-aortic balloon pump
(B) Pericardiocentesis
(C) Phenylephrine
(D) Window pericardiectomy

Item 17

A 54-year-old man is evaluated during a routine appointment. He has hypertension, dyslipidemia, obesity, and erectile dysfunction. He currently drinks three alcoholic beverages daily. His mother had a nonfatal myocardial infarction (MI) at age 55 years, and he is concerned about his risk of MI. Medications are hydrochlorothiazide, atorvastatin, and sildenafil as needed.

Which of the following components of this patient's medical history is associated with the greatest risk for future myocardial infarction?

(A) Alcohol consumption
(B) Dyslipidemia
(C) Hypertension
(D) Obesity

Item 18

A 63-year-old man is evaluated for follow-up of coronary artery disease that was diagnosed by exercise stress testing 3 weeks ago. For his exertional chest pain, he was started on a β-blocker and nitrate in addition to his baseline medications. He reports that his symptoms have improved, although he remains limited in his activities because of exertional chest pain. Medical history is significant for hypertension, type 2 diabetes mellitus, and hyperlipidemia. His current medications are aspirin, lisinopril, simvastatin, insulin, metoprolol, isosorbide mononitrate, and as-needed sublingual nitroglycerin.

On physical examination, he is afebrile, blood pressure is 112/72 mm Hg, pulse rate is 62/min, and respiration rate is 12/min. Cardiac examination shows a normal S_1 and S_2 without S_3, S_4, murmurs, or rubs. Lung examination is normal. He has no lower extremity edema. The remainder of the examination is normal.

Diagnostic coronary angiography reveals a 90% stenosis in the proximal left anterior descending artery; the left circumflex artery has a diffuse 70% stenosis, and the right coronary artery has a 70% ostial stenosis. Left ventriculography shows a left ventricular ejection fraction of 50% with mild anterior wall hypokinesis.

Which of the following is the most appropriate management?

(A) Change metoprolol to amlodipine
(B) Coronary artery bypass graft surgery
(C) Multivessel percutaneous coronary intervention
(D) Myocardial viability nuclear perfusion scan

Item 19

A 74-year-old woman is evaluated for a 3-week history of left shoulder pain and dyspnea on exertion. Medical history is significant for COPD, hypertension, and coronary artery disease; she underwent stenting of the mid-left anterior descending coronary artery 3 years ago. Because of her lung disease, she has limited exercise ability. Medications are lisinopril, hydrochlorothiazide, atorvastatin, aspirin, fluticasone, albuterol, and ipratropium.

On physical examination, the patient is afebrile, blood pressure is 142/88 mm Hg, pulse rate is 82/min, and respiration rate is 18/min. BMI is 29. Estimated central venous pressure is 8 cm H_2O. Cardiac examination reveals a grade 2/6 midsystolic murmur heard best at the cardiac base and late expiratory wheezing bilaterally.

Electrocardiogram shows left ventricular hypertrophy and repolarization abnormalities.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Adenosine single-photon emission CT myocardial perfusion imaging
(B) Coronary catheterization
(C) Dobutamine stress echocardiogram
(D) Exercise stress echocardiogram

Item 20

A 68-year-old man is evaluated for a newly diagnosed cardiac murmur. He is active and swims and jogs regularly. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, he is afebrile, blood pressure is 140/70 mm Hg, pulse rate is 82/min, and respiration rate is 16/min. Cardiac examination reveals a late-peaking systolic murmur located at the right upper sternal border with an audible S_2.

Transthoracic echocardiogram shows normal left ventricular systolic function. Aortic valve area is 0.8 cm^2. The mean gradient is 44 mm Hg, with a peak gradient of 53 mm Hg.

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Which of the following is the most appropriate management?

(A) Balloon aortic valvuloplasty
(B) Follow-up echocardiography in 6 to 12 months
(C) Surgical aortic valve replacement
(D) Transcatheter aortic valve replacement

Item 21

A 66-year-old woman is evaluated at the hospital for 6 hours of chest pressure and shortness of breath. Earlier this day, the patient's husband was diagnosed with lung cancer. Medical history is otherwise unremarkable.

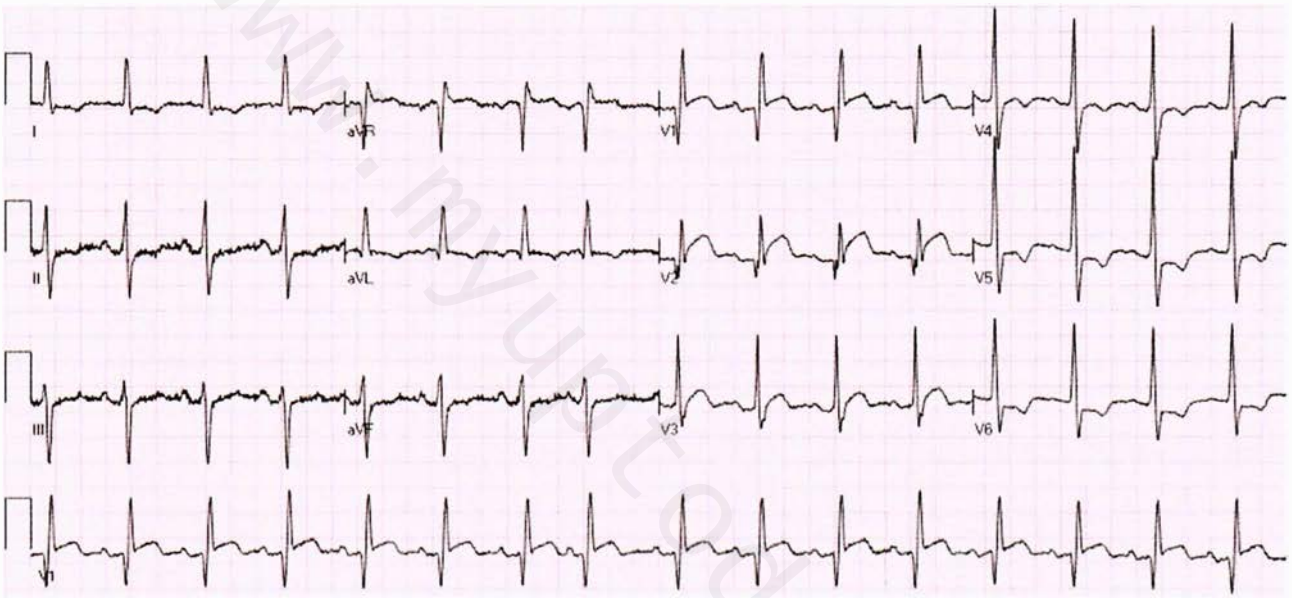
On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 110/62 mm Hg, and pulse rate is 98/min. BMI is 25. Cardiac examination shows a normal S_1 and S_2 without S_3, S_4, murmur, or rub. Lung examination is normal. Serum troponin T level is 2.0 ng/mL (2.0 µg/L).

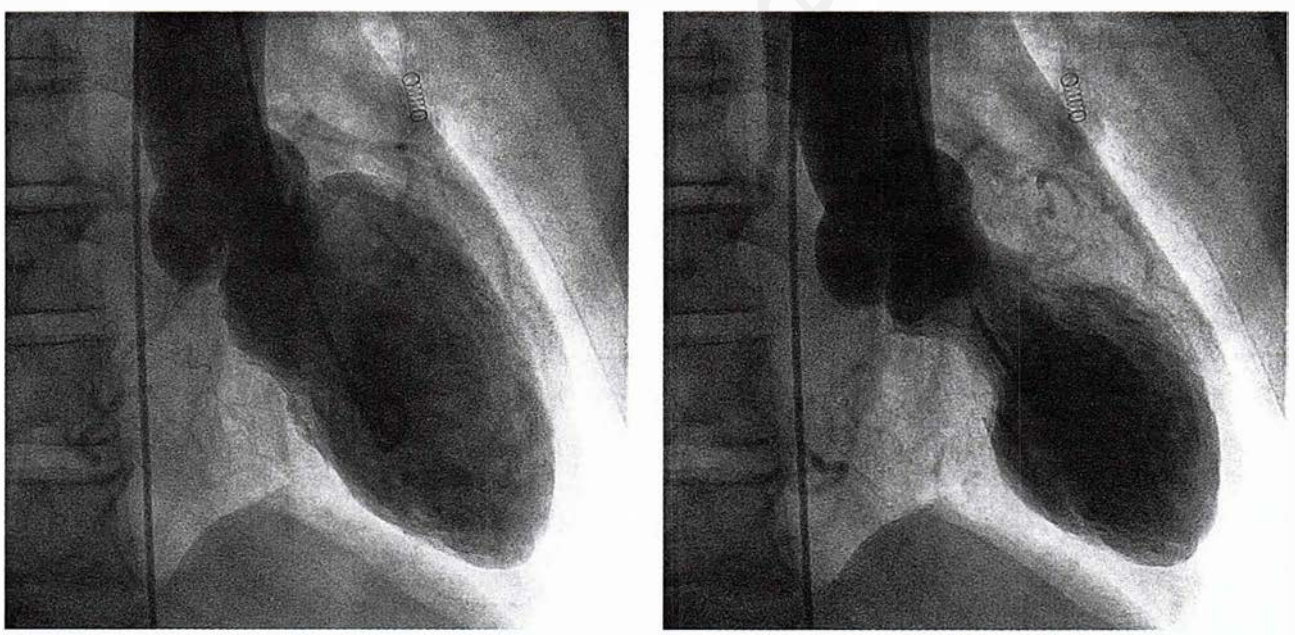
Electrocardiogram is shown.

The patient is administered aspirin, clopidogrel, and unfractionated heparin. Emergency coronary angiography shows normal coronary anatomy. Diastolic (*left panel*) and systolic (*right panel*) images from left ventriculography are shown.

Which of the following is the most appropriate management?

(A) Endomyocardial biopsy
(B) Intra-aortic balloon pump





ITEM 21

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CONT.

(C) Metoprolol and captopril
(D) Thrombolytic therapy

Item 22

A 56-year-old woman is evaluated during a n appointment to establish care. She has a developmental delay, and she is known to have pulmonary hypertension due to a congenital cardiac condition. There is no history of cardiac surgery. She is on low-dose aspirin and thyroid replacement therapy.

On physical examination, blood pressure is 110/70 mm Hg, pulse rate is 68/min and regular, and respiration rate is 18/min. BMI is 32. The central venous pressure is elevated with a prominent *a* wave. The apical impulse is normal. There is a prominent parasternal impulse at the left sternal border. The S_1 is normal; the S_2 is loud. There is a grade 1/6 holosystolic murmur at the left lower sternal border. The toes demonstrate cyanosis and digital clubbing; her hands appear normal. The remainder of the physical examination is unremarkable.

Which of the following is the most likely cause of this patient's pulmonary hypertension?

(A) Atrial septal defect
(B) Patent ductus arteriosus
(C) Tetralogy of Fallot
(D) Ventricular septal defect

Item 23

A 56-year-old man with heart failure is admitted to the hospital with a 2-week history of increasing exertional dyspnea and fatigue. He also has type 2 diabetes mellitus. Medications are metformin, lisinopril, carvedilol, furosemide, metolazone, and digoxin.

On physical examination, blood pressure is 88/60 mm Hg, pulse rate is 95/min, and respiration rate is 20/min. He is somewhat confused and inattentive. Jugular venous distention is present to the angle of the jaw while sitting. Cardiac examination reveals an S_3. There are bibasilar crackles on pulmonary examination. He has edema to the midthighs. Extremities appear mottled and are cool to the touch.

Serum creatinine level is 3.1 mg/dL (274 µmol/L); baseline value was 1.1 mg/dL (97.2 µmol/L). Serum sodium level is 133 mEq/L (133 mmol/L). Electrocardiogram shows no evidence of ischemia. Chest radiograph shows cardiomegaly and vascular congestion.

In addition to intravenous diuresis, which of the following is the most appropriate management?

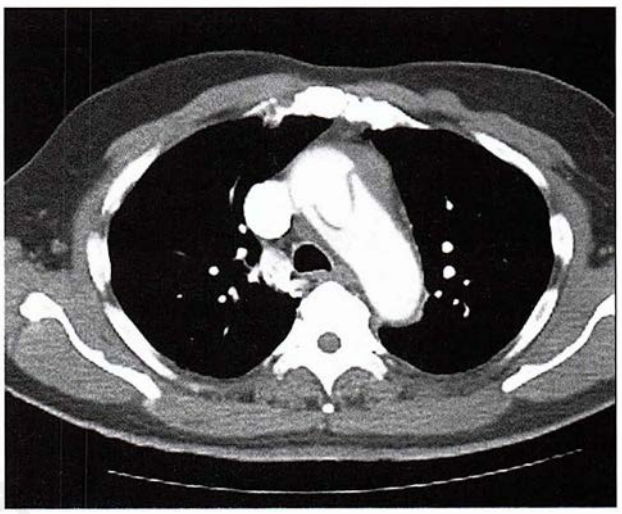
(A) Dobutamine
(B) Intra-aortic balloon pump
(C) Milrinone
(D) Right heart catheterization

Item 24

A 46-year-old man is evaluated in the emergency department for severe pain in the chest and upper back that began acutely about 1 hour ago. The pain is described as "deep" and constant. He has no other associated symptoms. Medical history is significant for hypertension, and his medications are chlorthalidone and valsartan.

On physical examination, the patient is in significant pain. He is afebrile, blood pressure is 118/70 mm Hg in both upper extremities, pulse rate is 122/min, and respiration rate is 22/min. The estimated central venous pressure is 10 cm H_2O. The lungs are clear. The heart examination is notable for an early diastolic decrescendo murmur heard loudest at the right upper sternal border. The dorsalis pedis and posterior tibialis pulses are palpable and equal bilaterally.

Serum cardiac troponin T level is 0.4 ng/mL (0.4 µg/L). Electrocardiogram shows sinus tachycardia but is otherwise normal. Chest radiograph is normal. Chest CT with intravenous contrast is shown.



An intravenous β-blocker is started.

Which of the following is the most appropriate next step in management?

(A) Continued medical therapy alone
(B) Emergency surgical intervention
(C) Endovascular stenting
(D) Heparin

Item 25

A 46-year-old man is evaluated in the hospital prior to undergoing an elective hernia repair. Medical history is significant for a bicuspid aortic valve and a mechanical aortic valve replacement 3 years ago for severe aortic stenosis. His only medication is warfarin.

On physical examination, blood pressure is 130/75 mm Hg, pulse rate is 82/min, and respiration rate is 14/min. Cardiac examination reveals a grade 1/6 midsystolic murmur at the right upper sternal border.

Which of the following is the most appropriate management option for endocarditis prophylaxis?

(A) Amoxicillin
(B) Ceftriaxone
(C) Clindamycin
(D) No antibiotic prophylaxis

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Item 26

A 48-year-old man is evaluated for tightness in his calves. His symptoms are exacerbated with walking and resolve with rest. His medical history is significant for hypertension, type 2 diabetes mellitus, and chronic kidney injury. Medications are hydrochlorothiazide, lisinopril, metformin, glyburide, and atorvastatin. He was a cigarette smoker with a 30-pack-year tobacco use history but quit 6 months ago.

On physical examination, blood pressure is 138/74 mm Hg, pulse rate is 68/min and regular, and respiration rate is 16/min. BMI is 32. No abdominal or femoral bruit is present. No skin changes are noted in the lower extremities. The remainder of the physical examination is unremarkable.

Laboratory studies are significant for a serum creatinine level of 1.9 mg/dL (168 µmol/L), normal electrolyte levels, and a hemoglobin A_{1c} value of 6.4%.

Ankle-brachial index testing:

Right systolic brachial pressure	140 mm Hg
Left systolic brachial pressure	132 mm Hg
Right posterior tibialis pressure	200 mm Hg
Left posterior tibialis pressure	130 mm Hg
Right dorsalis pedis pressure	Not detected
Left dorsalis pedis pressure	140 mm Hg

Which of the following is the most appropriate diagnostic test to perform next?

(A) Exercise ankle-brachial index
(B) Lower extremity CT angiography
(C) Lower extremity magnetic resonance angiography
(D) Toe-brachial index

Item 27

An 81-year-old man is evaluated in the office 3 days following a percutaneous coronary intervention with placement of a bare metal stent in the left anterior descending artery for angina refractory to maximal medical therapy. He indicates that he feels well except for palpitations that were not present before the procedure. Medical history is significant for hypertension and type 2 diabetes mellitus. He has no risk factors for or history of significant bleeding. Medications are aspirin, clopidogrel, lisinopril, atorvastatin, and metformin.

On physical examination, the patient is afebrile, blood pressure is 110/60 mm Hg, pulse rate is 65/min, and respiration rate is 12/min. BMI is 32. Estimated central venous pressure is not elevated. The heart has an irregularly irregular rhythm. Lungs are clear without crackles.

An electrocardiogram shows atrial fibrillation with a heart rate of 65/min and no acute ischemic changes. An echocardiogram demonstrates a left ventricular ejection fraction of 30%.

Which of the following is the most appropriate therapeutic regimen for this patient?

(A) Aspirin and clopidogrel
(B) Aspirin and dabigatran
(C) Aspirin and warfarin
(D) Aspirin, clopidogrel, and warfarin

Item 28

A 37-year-old woman is evaluated for exertional dyspnea. She noticed mild shortness of breath with significant exercise several years ago. Although she is still active, she has had to progressively decrease the amount of exercise she is able to do because of her symptoms. She has no other health problems, takes no medications, and has no known drug allergies.

On physical examination, she is afebrile, blood pressure is 120/70 mm Hg, pulse rate is 67/min, and respiration rate is 14/min. Cardiac examination demonstrates a grade 3/6 crescendo-decrescendo systolic murmur located at the right upper sternal border with delayed carotid upstrokes.

Transthoracic echocardiography demonstrates normal systolic function with a left ventricular ejection fraction of 60%, mild concentric left ventricular hypertrophy, and a bicuspid aortic valve. The aortic valve has a mean gradient of 42 mm Hg and valve area of 0.9 cm^2.

Which of the following is the most appropriate management?

(A) Balloon aortic valvuloplasty
(B) Start an ACE inhibitor
(C) Surgical aortic valve replacement
(D) Transcatheter aortic valve replacement

Item 29

A 28-year-old woman is evaluated after a 4-hour self-limited episode of palpitations. The symptoms occurred while at work yesterday. She has no history of cardiovascular disease and has no other cardiovascular symptoms. She is active without limitations. She is on no medications.

On physical examination, blood pressure is 110/70 mm Hg, pulse rate is 60/min and regular, and respiration rate is 15/min. BMI is 23. The estimated central venous pressure is elevated. The apical impulse is normal; there is a parasternal impulse present at the left sternal border, and a soft midsystolic murmur is heard at the second left intercostal space. Fixed splitting of the S_2 is noted throughout the cardiac cycle. The remainder of the physical examination is normal.

Electrocardiogram is shown (see top of next page).

Which of the following is the most likely diagnosis?

(A) Atrial septal defect
(B) Bicuspid aortic valve with aortic stenosis
(C) Congenital pulmonary valve stenosis
(D) Mitral valve prolapse with mitral regurgitation

Item 30

A 32-year-old woman is evaluated for a prepregnancy assessment. She has a heart murmur but is asymptomatic. She has no history of atrial fibrillation. Her only medication is prenatal vitamins.

On physical examination, blood pressure is 102/60 mm Hg and pulse rate is 70/min and regular. The estimated central venous pressure is elevated. The apical impulse is tapping, and there is a parasternal impulse at the left sternal border. The S_1 and S_2 are loud, and a grade

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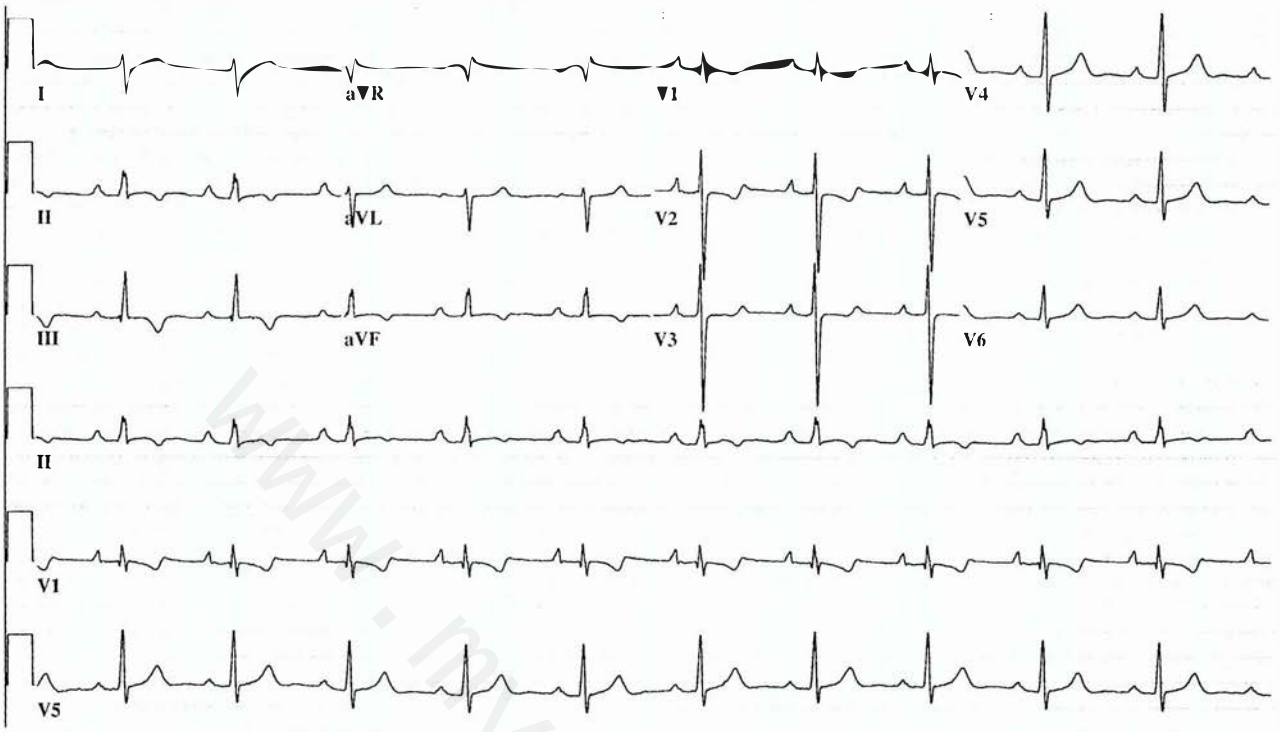

ITEM 29

2/6 diastolic decrescendo murmur is heard at the apex. No opening snap is appreciated. The lungs are clear, and there is no edema.

A transthoracic echocardiogram demonstrates normal left ventricular size and function. The mitral valve is thickened with diastolic doming. The mitral valve mean gradient is 12 mm Hg; the calculated mitral valve area is 0.9 cm^2. There is no mitral valve regurgitation. The estimated pulmonary artery systolic pressure is 55 mm Hg.

Which of the following is the most appropriate management at this time?

(A) Initiate an ACE inhibitor and dabigatran
(B) Obtain cardiac magnetic resonance imaging
(C) Proceed with mitral valve intervention
(D) Proceed with pregnancy without interventions or testing

Item 31

A 52-year-old woman is evaluated in the office during a routine visit. Her medical history is significant for type 2 diabetes mellitus and hypertension. Medications are aspirin, lisinopril, amlodipine, insulin glargine, insulin aspart, and rosuvastatin.

On physical examination, the patient is afebrile, blood pressure is 128/80 mm Hg, pulse rate is 73/min, and respiration rate is 18/min. BMI is 24. The lungs are clear to auscultation, and no cardiac murmurs are heard. Abdominal examination reveals a pulsatile mass in the epigastrium.

An infrarenal abdominal aortic aneurysm with maximum diameter of 5.7 cm is noted on abdominal ultrasound.

Which of the following is the most appropriate management of this patient's abdominal aortic aneurysm?

(A) Refer for aneurysm repair
(B) Repeat abdominal ultrasonography in 6 months
(C) Repeat abdominal ultrasonography in 12 months
(D) Switch amlodipine to propranolol

Item 32

A 74-year-old man is evaluated 4 months after undergoing uncomplicated bioprosthetic surgical aortic valve replacement. Within the past 2 weeks, he has developed exertional dyspnea, fatigue, and lower extremity edema. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. The estimated central venous pressure is 12 cm H_2O, and the jugular venous pulse shows prominent *y* descents. A pericardial knock is present. Peripheral edema is noted.

An echocardiogram reveals no evidence of pericardial effusion. The aortic and mitral valves are functioning normally. The inferior vena cava is markedly enlarged. A Doppler ultrasound shows expiratory flow reversals in the hepatic veins consistent with constrictive pericarditis.

Which of the following is the most appropriate next step in management?

(A) Ibuprofen
(B) Invasive cardiac hemodynamic evaluation
(C) Pericardiectomy
(D) Transesophageal echocardiography

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Item 33

A 52-year-old man is evaluated during a follow-up visit. He was initially evaluated for severe palpitations 4 months ago. Evaluation at that time included 48-hour ambulatory electrocardiographic monitoring that was significant for frequent premature ventricular contractions (PVCs) and ventricular bigeminy. A stress echocardiogram showed no evidence of ischemia and normal left ventricular function. Cardiac magnetic resonance (CMR) imaging demonstrated no evidence of myocardial scarring. He was started on a β-blocker for treatment of PVCs at that time. He now reports continued significant palpitations despite therapy but does not have presyncope, syncope, or chest pain. He has no family history of sudden cardiac death or heart failure. His only medication is metoprolol.

On physical examination, the patient is afebrile, blood pressure is 110/60 mm Hg, pulse rate is 82/min and irregular, and respiration rate is 12/min. BMI is 34. B-type natriuretic peptide level is mildly elevated.

Electrocardiogram shows frequent monomorphic PVCs but is otherwise normal; the QRS interval on conducted sinus beats is 110 ms. Ambulatory 24-hour electrocardiographic monitoring shows frequent monomorphic PVCs (21% of all beats) and continued frequent ventricular bigeminy. An echocardiogram is significant for mild to moderate global decreased left ventricular function but without regional wall motion abnormalities; ejection fraction is estimated at 40%.

Which of the following is the most appropriate management?

(A) Amiodarone
(B) Cardiac resynchronization therapy
(C) Catheter ablation of premature ventricular contractions
(D) Implantable cardioverter-defibrillator

Item 34

A 66-year-old woman is evaluated prior to discharge. She has ischemic cardiomyopathy and was admitted to the hospital 5 days ago for worsening symptoms of heart failure. She skipped taking her diuretics during a recent business trip. Today, she feels well and is able to walk around the ward twice without any symptoms.

This was her first hospitalization in 3 years, although she has skipped her diuretics during other business trips during this time without apparent ill effect. She had an implantable cardioverter-defibrillator placed 3 years ago. An echocardiogram 1 month ago showed a left ventricular ejection fraction of 15% (stable for the past 6 years). Medications are captopril, metoprolol succinate, digoxin, furosemide, and spironolactone.

On physical examination, blood pressure is 110/72 mm Hg, pulse rate is 56/min, and respiration rate is 14/min. She has no jugular venous distention and no S_4. Lungs are clear, and she has no edema.

Electrocardiogram shows sinus rhythm, a QRS interval of 90 ms, and Q waves in V_1 through V_4. There are no changes compared with the admission electrocardiogram recorded 3 years ago.

Which of the following is the most appropriate management?

(A) Discharge and schedule follow-up within 7 days
(B) Measure B-type natriuretic peptide
(C) Obtain echocardiography prior to discharge
(D) Upgrade to biventricular implantable cardioverter-defibrillator

Item 35

A 20-year-old man is evaluated for newly noted hypertension. He is asymptomatic and his medical history is unremarkable. He takes no medications and has no family history of hypertension.

On physical examination, blood pressure is 180/80 mm Hg in both upper extremities, pulse rate is 60/min and regular, and respiration rate is 18/min. BMI is 20. The estimated central venous pressure is normal. The apical impulse is displaced and sustained. The S_1 and S_2 are normal. An S_4 is noted at the apex. A soft systolic murmur is noted over the left posterior chest. An abdominal bruit is audible. The femoral pulses are difficult to palpate, and there is a radial artery–to–femoral artery pulse delay.

The electrocardiogram is consistent with left ventricular hypertrophy.

Which of the following is the most likely diagnosis?

(A) Aortic coarctation
(B) Essential hypertension
(C) Hypertrophic cardiomyopathy
(D) Renovascular hypertension

Item 36

A 29-year-old woman who is 10 weeks pregnant is evaluated for hypertension; this is her first pregnancy. She has no symptoms and no prior cardiovascular disease. She is taking no medications. She has a family history of hypertension, and she does not recall when she last had her blood pressure checked.

On physical examination, blood pressure is 156/96 mm Hg and pulse rate is 80/min. BMI is 31. There is an apical S_4, but no murmurs are detected. Pulses are normal throughout. The remainder of the examination is unremarkable.

Serum creatinine level, plasma glucose level, and urinalysis all are normal. An ambulatory blood pressure monitor demonstrates an average blood pressure of 155/92 mm Hg.

Which of the following is the most appropriate treatment?

(A) Start labetalol
(B) Start lisinopril
(C) Start losartan
(D) No intervention is necessary

Item 37

A 28-year-old pregnant woman is evaluated for a cardiac murmur identified on examination by her obstetrician. She

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is asymptomatic. She is in her 24th week of pregnancy. Medical history is unremarkable, and there is no family history of heart disease. She takes prenatal vitamins and no other medications.

On physical examination, she is afebrile, blood pressure is 120/70 mm Hg, pulse rate is 86/min, and respiration rate is 18/min. Cardiac examination reveals a midsystolic ejection click followed by a grade 3/6 early peaking, crescendo-decrescendo murmur at the right upper sternal border. The murmur radiates toward the apex and decreases slightly with the Valsalva maneuver. No diastolic murmur is heard.

Which of the following is the most likely diagnosis?

(A) Bicuspid aortic valve
(B) Hypertrophic obstructive cardiomyopathy
(C) Mammary souffle
(D) Mitral valve prolapse
(E) Physiologic murmur of pregnancy

Item 38

A 64-year-old man is evaluated for chest discomfort that he has had over the past year. It does not always occur with exercise. There is no associated nausea or diaphoresis. Medical history is significant for hypertension and hyperlipidemia. Medications are metoprolol, hydrochlorothiazide, and lisinopril.

On physical examination, vital signs are normal, as is the remainder of the physical examination. Electrocardiogram is normal.

The patient is scheduled for exercise stress testing.

Which of the following should be done prior to the stress test?

(A) Stop hydrochlorothiazide
(B) Stop lisinopril
(C) Stop metoprolol
(D) Stop all medications

Item 39

A 43-year-old woman is evaluated for a 1-month history of chest discomfort. She states that she experiences a vague pressure-like sensation in her chest that occurs intermittently, with each episode lasting less than 5 minutes. She has had approximately two episodes each week, and several have seemed to be associated with exertion but also appear to have resolved after taking antacids. Her medical history is significant for hypertension. Her only medication is lisinopril. She is a current smoker with a 15-pack-year history. Family history is negative for coronary artery disease.

On physical examination, the patient is afebrile, blood pressure is 132/78 mm Hg, pulse rate is 85/min, and respiration rate is 12/min. BMI is 32. Cardiopulmonary examination is unremarkable, as is the remainder of her physical examination.

An electrocardiogram shows sinus rhythm, normal PR and QRS intervals, and no ST-segment or T-wave abnormalities or Q waves.

An exercise electrocardiographic treadmill test is performed. The patient is able to exercise for 4 minutes to a heart rate of 82% of the maximum predicted and energy expenditure of 4 metabolic equivalents until the study is discontinued because of fatigue. Testing did not reproduce her symptoms, and there were no significant electrocardiographic changes with exercise.

Which of the following is the most appropriate next step in management?

(A) Cardiac catheterization
(B) Pharmacologic stress testing
(C) Switch lisinopril to metoprolol
(D) Clinical observation

Item 40

A 72-year-old woman is evaluated for sharp chest pain that occurs randomly. She walks 3 to 4 miles daily, and her symptoms have never occurred with exertion. She has never smoked. Medical history is significant for hypertension, type 2 diabetes mellitus, and hyperlipidemia. Medications are low-dose aspirin, metformin, lisinopril, and simvastatin (10 mg/d). She has no known drug allergies.

On physical examination, blood pressure is 122/76 mm Hg, pulse rate is 76/min, and respiration rate is 12/min. Cardiac examination shows a normal S_1 and S_2; there is no S_3, S_4, murmur, or rub. The remainder of the examination is normal.

Laboratory findings include a serum total cholesterol level of 200 mg/dL (5.18 mmol/L), LDL cholesterol level of 126 mg/dL (3.26 mmol/L), and HDL cholesterol level of 50 mg/dL (1.30 mmol/L).

An exercise treadmill test is administered for 8 minutes, 40 seconds. There are no electrocardiogram changes at rest or with exercise. She does not have chest pain during exercise or recovery.

Which of the following is the most appropriate management?

(A) Increase simvastatin to 80 mg/d
(B) Continue current therapy
(C) Start atorvastatin, discontinue simvastatin
(D) Start clopidogrel

Item 41

A 57-year-old man is evaluated in follow-up 1 month after being diagnosed with peripheral arterial disease. He initially presented with left calf pain and was diagnosed by an abnormal ankle-brachial index. An exercise rehabilitation program was completed, but he continues to feel lower extremity discomfort in his left leg that limits his walking ability. He is a former smoker who quit 1 year ago. His medical history is otherwise notable for hypertension and dyslipidemia. Medications are enalapril, amlodipine, rosuvastatin, and aspirin.

On physical examination, blood pressure is 124/72 mm Hg, pulse rate is 78/min and regular, and respiration rate is 16/min. Peripheral examination reveals a left femoral bruit.

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The left lower extremity is warm and without tenderness or skin changes. The remainder of the examination is unremarkable.

Which of the following is the most appropriate addition to his current therapy?

(A) β-Blocker
(B) Cilostazol
(C) Clopidogrel
(D) Warfarin

Item 42

A 75-year-old woman is evaluated in the hospital 4 hours after onset of chest pain with findings of an ST-elevation myocardial infarction. She was taken emergently to the catheterization laboratory and underwent emergency percutaneous coronary intervention for a totally occluded vessel. Her post-intervention ventriculogram demonstrated a left ventricular ejection fraction of 30%. One hour after the procedure, she developed an acute arrhythmia. Medications are aspirin, metoprolol, atorvastatin, and clopidogrel.

On physical examination, the patient is afebrile, blood pressure is 100/60 mm Hg, pulse rate is 92/min, and respiration rate is 12/min. BMI is 25. Neck examination demonstrates cannon *a* waves. Cardiac examination demonstrates regular rhythm with a variable S_1. Lungs are clear to auscultation.

Electrocardiogram is shown.

Which of the following is the most appropriate management?

(A) Amiodarone
(B) Cardioversion
(C) Implantable cardioverter-defibrillator
(D) Lidocaine
(E) No intervention

Item 43

A 68-year-old man is evaluated in the emergency department for a 24-hour history of persistent chest pain. He had a non-ST-elevation myocardial infarction 1 week ago that was managed medically with complete symptom recovery. Yesterday, he developed recurrent chest pain that differs from his previous angina pain. The pain is constant but exacerbated when leaning forward and not associated with other symptoms. Medications are low-dose aspirin, clopidogrel, metoprolol, and atorvastatin.

On physical examination, vital signs are normal. There is no jugular venous distention. The lungs are clear to auscultation. S_1 and S_2 are normal, and there is no S_3 or S_4. A two-component friction rub is present at the left lower sternal border, and a grade 2/6 holosystolic murmur is heard at the apex. The remainder of the physical examination is unremarkable.

Electrocardiogram shows diffuse, concave upward ST-segment elevations and PR-segment depression most prominent in leads V_1 through V_6.

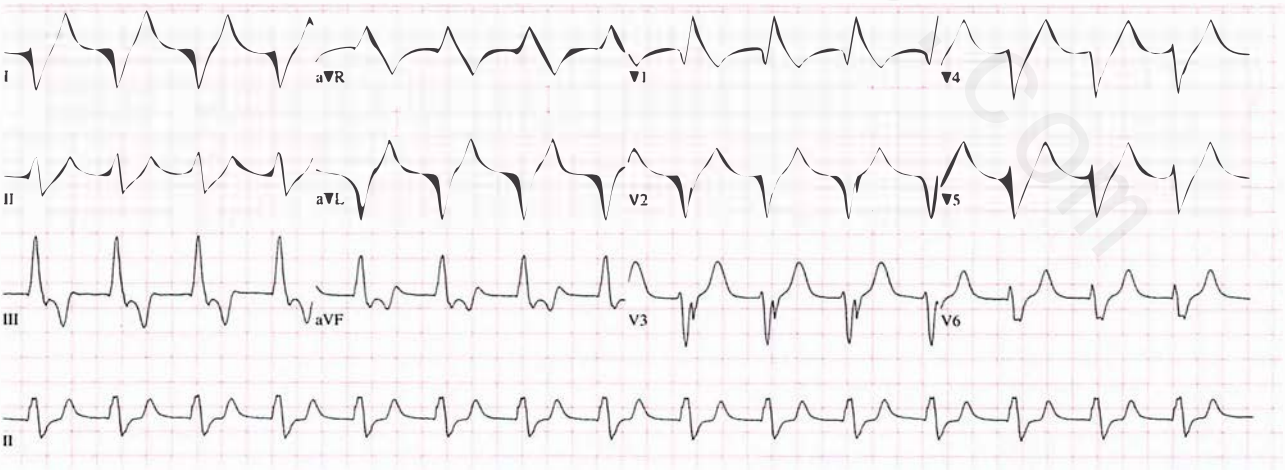
Which of the following is the most appropriate primary treatment?

(A) High-dose aspirin
(B) Ibuprofen
(C) Nitroglycerin
(D) Prednisone

Item 44

A 56-year-old man is admitted to the coronary care unit with recent-onset substernal chest discomfort and dyspnea. Upon admission, he was given aspirin, ticagrelor, metoprolol, and enoxaparin. He has hyperlipidemia. Regular medications are low-dose aspirin and simvastatin.

On physical examination, temperature is 36.5 °C (97.7 °F), blood pressure is 134/82 mm Hg, and pulse rate is 82/min. Cardiac and pulmonary examinations are normal, as is the remainder of the examination.



ITEM 42

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CONT.

Serum troponin level is elevated. Electrocardiogram shows normal sinus rhythm and heart rate of 80/min. There are nonspecific ST-T wave abnormalities but no ST-segment elevation or depression.

Cardiac catheterization is significant for preserved left ventricular systolic function and two-vessel coronary artery disease. Percutaneous coronary intervention of the mid left anterior descending artery and proximal right coronary artery is performed with placement of drug-eluting stents.

In addition to continuing aspirin, which of the following is the most appropriate management of this patient's antiplatelet regimen?

(A) Continue ticagrelor for 30 days
(B) Continue ticagrelor for 1 year
(C) Continue ticagrelor indefinitely
(D) Stop ticagrelor, start clopidogrel

Item 45

A 42-year-old woman is evaluated for a routine outpatient medical assessment. She was diagnosed with a ventricular septal defect at age 6 months. Evaluation was performed early in life and observation was recommended. She has no symptoms and is taking no medications.

On physical examination, blood pressure is 100/60 mm Hg, pulse rate is 70/min and regular, and respiration rate is 15/min. BMI is 28. The estimated central venous pressure is normal. The apical impulse is normal. There is no parasternal impulse. S_1 and S_2 are masked by a loud holosystolic murmur noted at the left lower sternal border. The rest of the examination is unremarkable.

An electrocardiogram is normal. The heart size is normal on the chest radiograph. An echocardiogram demonstrates normal left ventricular size and function with an ejection fraction of 60%. A membranous ventricular septal defect is noted with a small left-to-right shunt. The right heart chambers and valve function are normal. The estimated pulmonary artery pressure is normal.

Which of the following is the most appropriate management?

(A) Cardiac catheterization
(B) Cardiac magnetic resonance (CMR) imaging
(C) Endocarditis prophylaxis
(D) Follow-up in 3 to 5 years
(E) Stress testing to determine exercise capacity

Item 46

A 72-year-old woman is evaluated in the hospital for a 3-month history of increasing shortness of breath. Although she had previously been physically active, her ambulation is now limited to about 50 feet because of shortness of breath. Medical history is significant for rheumatic fever as a child, diverticulosis with gastrointestinal bleeding that required blood transfusions, hypertension, and hyperlipidemia. Medications are chlorthalidone and atorvastatin.

On physical examination, the patient is afebrile, blood pressure is 140/70 mm Hg, pulse rate is 83/min, and respiratory rate is 16/min. Oxygen saturation breathing ambient air is 98%. There is no jugular venous distention. Lungs are clear. Cardiac examination reveals a regular rate and a grade 3/6 apical holosystolic murmur that radiates to the axilla. There is no lower extremity edema.

Electrocardiogram shows normal sinus rhythm and evidence of left atrial enlargement. Echocardiogram shows severe eccentric mitral regurgitation with marked calcification of the valve leaflets; left ventricular systolic function is normal.

Which of the following is the most appropriate treatment?

(A) Bioprosthetic mitral valve replacement
(B) Mechanical mitral valve replacement
(C) Oral vasodilator therapy
(D) Percutaneous mitral valvuloplasty

Item 47

A 75-year-old woman is evaluated for a 3-month history of progressive exertional dyspnea and decreased exercise tolerance. She does not have chest pain. She has a history of hypertension and COPD. She has a 55-pack-year tobacco use history but quit 3 years ago. She has no history of alcohol use. Medications are lisinopril, tiotropium, and as-needed albuterol.

On physical examination, blood pressure is 136/78 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. The central venous pressure is estimated at 9 cm H_2O. There are decreased breath sounds throughout both lung fields, but no crackles are detected. An S_4 is heard on cardiac examination. There is trace bilateral lower extremity edema.

Laboratory studies, including thyroid function studies, are normal. Electrocardiogram is shown (see top of next page). A chest radiograph shows changes consistent with COPD, mild vascular congestion, and blunting of the costophrenic angles bilaterally. Echocardiogram shows a left ventricular ejection fraction of 30% and an akinetic anterior wall.

The patient is started on furosemide.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Cardiac magnetic resonance (CMR) imaging
(B) Coronary artery calcium scoring
(C) Myocardial perfusion imaging stress test
(D) Endomyocardial biopsy

Item 48

A 59-year-old woman is evaluated for continued substernal chest pain. She presented with exertional chest pain 6 months ago that occurred with minimal ambulation. She was evaluated with a stress nuclear medicine myocardial perfusion study that showed no ST-segment changes but a small area of inducible ischemia in the lateral area of the left ventricle and an ejection fraction of 45%. She was initially treated medically but has continued to have chest pain with exertion despite the addition of multiple antianginal agents. Medical history is significant for hypertension, hypercholesterolemia, and type 2 diabetes mellitus. She has a 30-pack-year smoking history but quit 1 year ago.

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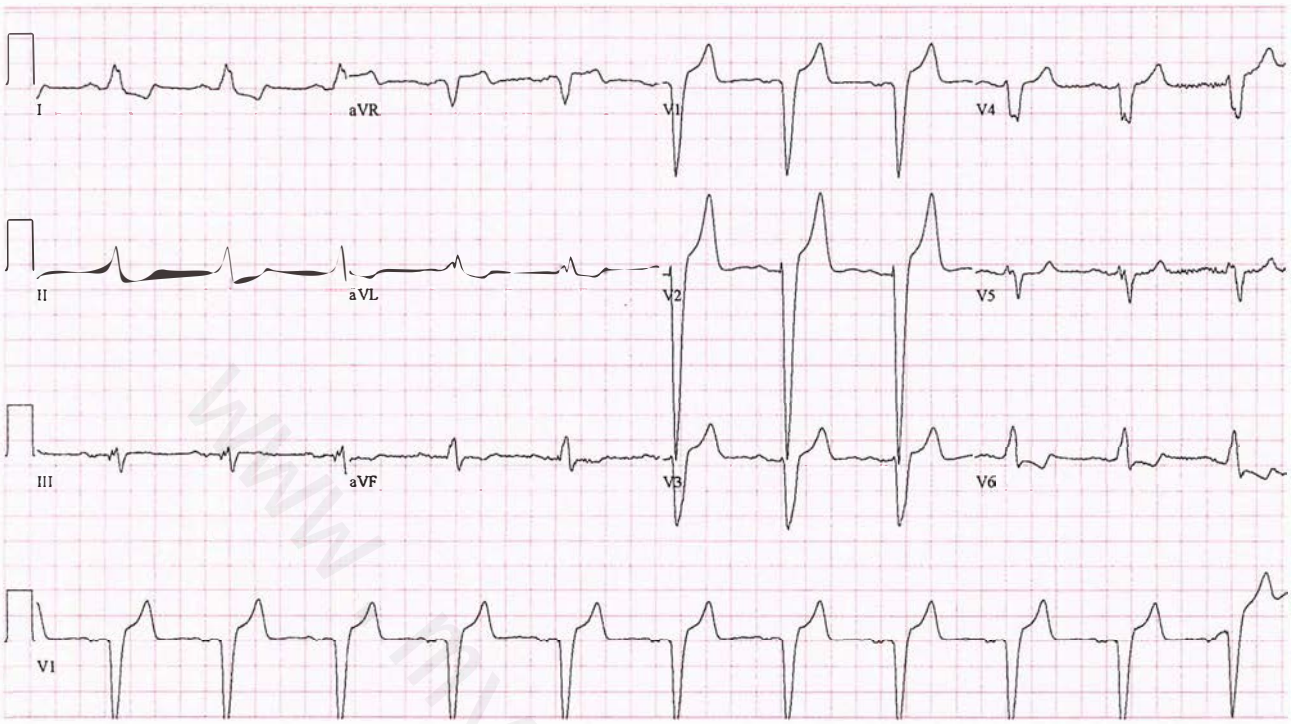

ITEM 47

Medications are aspirin, lisinopril, simvastatin, metformin, metoprolol, and long-acting nitroglycerin.

On physical examination, the patient is afebrile, blood pressure is 132/72 mm Hg, pulse rate is 68/min, and respiration rate is 16/min. BMI is 28. The remainder of her physical examination is normal.

Electrocardiogram is unchanged from the time of her stress test.

Which of the following is the most appropriate next step in management?

(A) Cardiac catheterization
(B) CT angiography
(C) Dobutamine stress echocardiography
(D) Continued medical therapy

Item 49

A 26-year-old woman is evaluated during a visit to establish care. She has noted shortness of breath for the past 18 months that is progressively worsening. She has no significant medical history. She is active and exercises regularly. She takes no medications.

On physical examination, blood pressure is 115/70 mm Hg and pulse rate is 62/min. BMI is 45. Cardiac examination reveals a midsystolic click with a grade 3/6 late systolic murmur heard over the apex and radiating toward the axilla.

Transthoracic echocardiogram (TTE) shows moderate to severe mitral regurgitation with marked prolapse of the anterior leaflet, normal left ventricular systolic function with an ejection fraction of 55%, and normal chamber sizes; the regurgitant jet is not well visualized.

Which of the following is the most appropriate management?

(A) Mitral valve repair
(B) Repeat TTE in 6 months
(C) Start lisinopril
(D) Transesophageal echocardiography

Item 50

A 35-year-old man is evaluated for a 6-month history of intermittent palpitations. His symptoms occur about once a week with no consistent pattern. He occasionally becomes lightheaded with the palpitations but has no syncope. He exercises three times weekly and does not notice symptoms during exercise. He has a history of migraine, for which he takes naproxen and sumatriptan as needed. He has no family history of sudden cardiac death.

On physical examination, the patient is afebrile, blood pressure is 138/68 mm Hg, pulse rate is 75/min, and respiration rate is 16/min. BMI is 24. Cardiac examination and the remainder of the examination are unremarkable.

Electrocardiogram is normal.

Which of the following is the most appropriate testing option?

(A) 30-Day event recorder
(B) Echocardiogram
(C) Exercise stress test
(D) 24-Hour continuous ambulatory electrocardiographic monitor

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Item 51

A 76-year-old man is admitted to the hospital for recurrent palpitations and dyspnea that began 4 days ago. He has hypertension and coronary artery disease, which was treated with percutaneous intervention 8 years ago. Medications are aspirin, atorvastatin, and lisinopril.

On physical examination, temperature is 36.8 °C (98.2 °F), and blood pressure is 115/62 mm Hg. The resting heart rate is 110/min with intermittent irregularity. The estimated central venous pressure is not elevated. S_1 and S_2 are unremarkable. The lung fields are clear, and the extremities are without edema.

An electrocardiogram obtained after the physical examination is shown.

Which of the following is the most appropriate next step in treatment?

(A) Emergent cardioversion
(B) Initiate β-blocker therapy
(C) Intravenous amiodarone
(D) Intravenous procainamide

Item 52

A 74-year-old woman is evaluated during a routine examination. Her medical history is significant for hypertension and obesity. She is a former smoker, stopping 5 years ago. Medications are amlodipine, lisinopril, and aspirin.

On physical examination, she is afebrile, blood pressure is 136/78 mm Hg, pulse rate is 68/min, and respiration rate is 15/min. BMI is 32. The lungs are clear to auscultation, and no murmurs are noted. A bruit is heard over the left femoral artery.

The right ankle-brachial index is 1.2 and the left is 0.81.

Which of the following is the most appropriate management?

(A) Initiate atorvastatin
(B) Initiate cilostazol
(C) Initiate warfarin
(D) Obtain CT angiography
(E) Obtain segmental limb pressures

Item 53

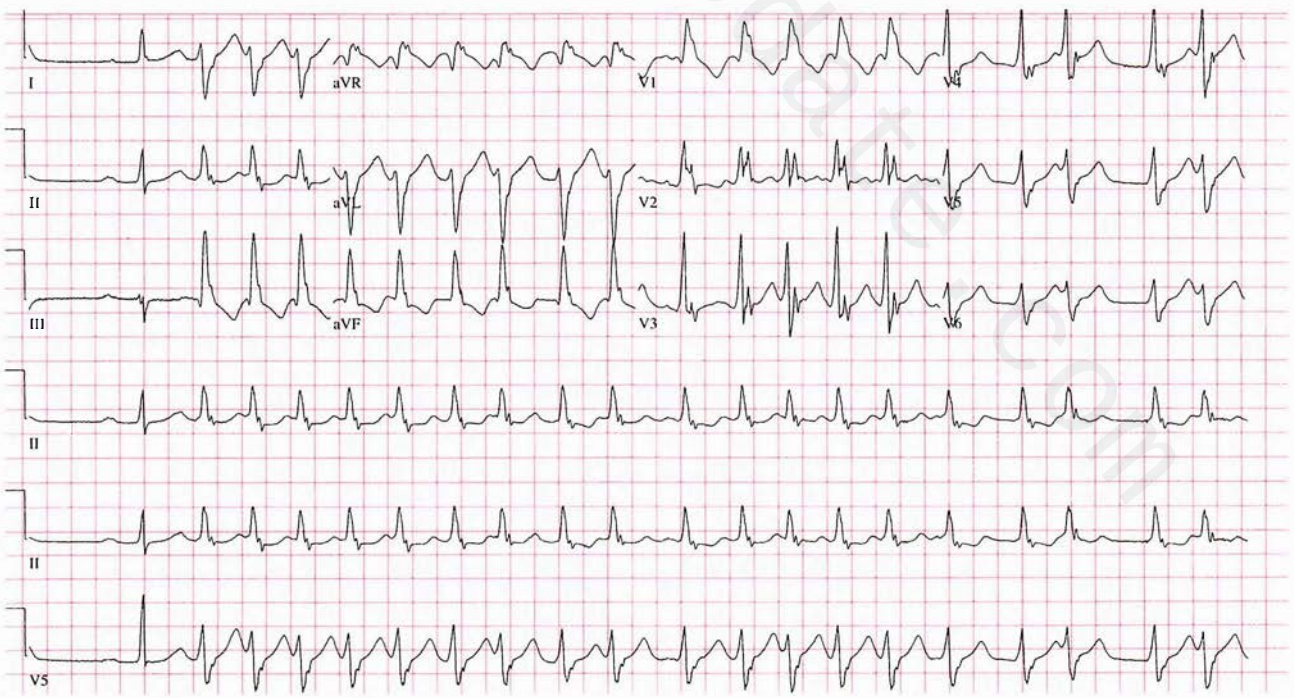
A 58-year-old man is ready for hospital discharge following a non-ST-elevation myocardial infarction. He was treated with ticagrelor and underwent percutaneous coronary intervention with drug-eluting stent implantation. He has remained free of chest pain since admission to the hospital.

The patient's medical history is significant for hypertension and hyperlipidemia. Medications are low-dose aspirin, ticagrelor, metoprolol, lisinopril, atorvastatin, and sublingual nitroglycerin as needed.

On physical examination, blood pressure is 124/78 mm Hg and pulse rate is 54/min. BMI is 26. Lungs are clear to auscultation. Cardiac examination shows a normal S_1 and S_2; there is no S_3, S_4, murmur, or rub. The remainder of the examination is normal. His left ventricular systolic function is normal, as measured on transthoracic echocardiography on the day after hospital admission.

Which of the following is the most appropriate adjustment to his discharge medications?

(A) Add diltiazem
(B) Discontinue ticagrelor, start clopidogrel
(C) Increase dose of metoprolol
(D) Start eplerenone
(E) Make no changes to his medications



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Item 54

A 54-year-old man is evaluated after a recent diagnosis of systolic heart failure. He initially presented with a 4-month history of exertional dyspnea. He has not had prior regular medical care and had no known medical problems. His blood pressure was 164/96 mm Hg at the time of diagnosis. Echocardiography showed evidence of hypertensive cardiomyopathy with no regional wall motion abnormalities and a left ventricular ejection fraction of 30%. Cardiac stress testing showed no evidence of ischemia, and he exercised for 7 minutes and 10 seconds to a peak heart rate of 142/min. He was started on lisinopril and is now able to walk 6 blocks before experiencing dyspnea.

On physical examination, blood pressure is 110/72 mm Hg, pulse rate is 84/min, and respiration rate is 14/min. Estimated central venous pressure is 6 cm H_2O. The lungs are clear. Cardiac examination shows the point of maximal impulse is shifted to the left anterior axillary line. There is no lower extremity edema.

Laboratory studies, including electrolytes and kidney function, are normal.

Which of the following medications is the most appropriate addition to this patient's treatment regimen?

(A) Amlodipine
(B) Carvedilol
(C) Furosemide
(D) Spironolactone
(E) No added therapy

Item 55

A 63-year-old man is hospitalized following a recent inferior myocardial infarction. Percutaneous coronary intervention was not successful. An echocardiogram obtained following the attempted coronary intervention demonstrated a left ventricular ejection fraction of 55% with inferior wall akinesis and a dilated and dysfunctional right ventricle. On the third day after admission, the patient develops progressive oxygen desaturation and dyspnea despite oxygen therapy while upright that improves when supine.

On physical examination, his blood pressure is 90/70 mm Hg, pulse rate is 86/min and regular, and respiration rate is 25/min. Estimated central venous pressure is markedly elevated. The apical impulse is normal; there is a parasternal impulse at the left sternal border. The heart sounds are distant. There is a soft holosystolic murmur at the left sternal border that increases with inspiration. The oxygen saturation is 90% on oxygen administered by mask while the patient is sitting and improves to 94% on return to his bed. The remainder of the physical examination is normal.

Which of the following is the most likely diagnosis?

(A) Patent foramen ovale with right-to-left shunt
(B) Mitral regurgitation
(C) Severe left ventricular systolic dysfunction
(D) Ventricular septal defect

Item 56

A 77-year-old man with a 5-year history of idiopathic cardiomyopathy is evaluated for progressive exertional fatigue and dyspnea. He has recently stopped carrying groceries in from the car because of his exertional dyspnea. He had an implantable cardioverter-defibrillator placed 3 years ago. Medical history is also significant for hypertension. Medications are lisinopril, 40 mg/d; metoprolol succinate, 25 mg/d; furosemide, 40 mg/d; and spironolactone, 25 mg/d.

On physical examination, blood pressure is 94/60 mm Hg and pulse rate is 70/min. Estimated central venous pressure is 5 cm H_2O. There is no edema.

Serum electrolyte levels and kidney function are normal. Electrocardiogram shows normal sinus rhythm, a PR interval of 210 ms, QRS duration of 160 ms, and a new left bundle branch block. His left ventricular ejection fraction 3 months ago was 25%.

Which of the following is the most appropriate next step in management?

(A) Cardiac resynchronization therapy
(B) Dobutamine therapy
(C) Increase furosemide dose
(D) Left ventricular assist device placement

Item 57

A 53-year-old man is evaluated for a 6-week history of epigastric and chest discomfort. The onset of the pain has a variable relationship to stress and exercise and spicy food. The discomfort is relieved at times with antacids and with rest. He has hypertension and is a former smoker (quit 2 years ago). Medications are lisinopril and hydrochlorothiazide.

On physical examination, he is afebrile, blood pressure is 140/92 mm Hg, pulse rate is 78/min, and respiration rate is 12/min. BMI is 29. Funduscopic examination is normal. Results of the cardiac examination are normal, with no S_3 or S_4.

Electrocardiogram is shown (see top of next page).

Which of the following is the most appropriate diagnostic test to perform next?

(A) Adenosine myocardial perfusion study
(B) Cardiac magnetic resonance (CMR) imaging
(C) CT angiography
(D) Dobutamine stress echocardiography
(E) Exercise stress test

Item 58

A 58-year-old man is evaluated for a 2-week history of malaise and subjective fever. Medical history is significant for well-controlled type 2 diabetes mellitus and sinus node dysfunction. A dual-chamber pacemaker was implanted 5 years ago. He does not have dyspnea or weight loss. None of his family members have had a recent viral or febrile illness.

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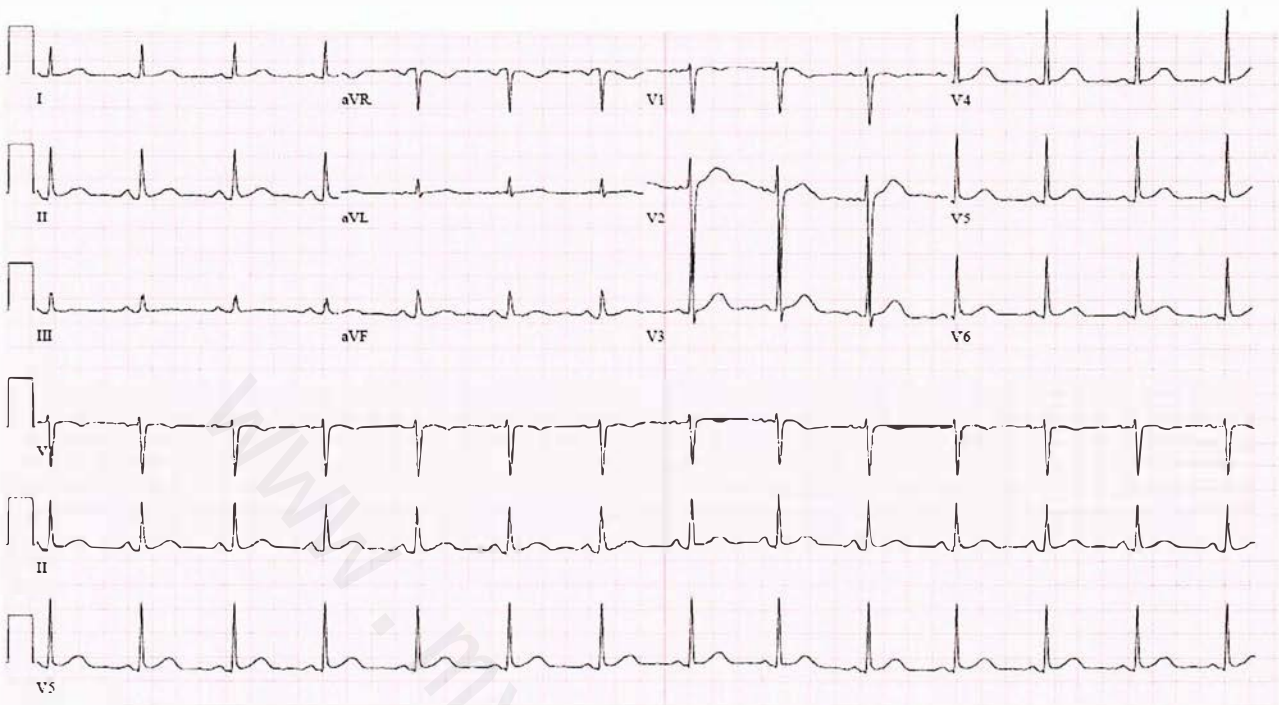

ITEM 57

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On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 132/75 mm Hg, pulse rate is 62/min, and respiration rate is 16/min. BMI is 32. His conjunctivae, oropharynx, and tympanic membranes are normal in appearance. There is no head, neck, axillary, or inguinal lymphadenopathy. The skin overlying the patient's pacemaker pocket is mildly erythematous and warm. There is no fluctuance, but there is mild tenderness to palpation. The precordial cadence is regular, and there is no evidence of cardiopulmonary congestion. Results of a complete blood count with differential and an erythrocyte sedimentation rate are pending.

Which of the following is the most appropriate management?

(A) Blood cultures
(B) Pacemaker pocket aspiration
(C) Ultrasonography of the pacemaker pocket
(D) Repeat evaluation in 1 week

Item 59

A 47-year-old man is evaluated during a routine examination. He has no symptoms. Medical history is significant for a bicuspid aortic valve. He is not taking any medications.

On physical examination, he is afebrile, blood pressure is 130/70 mm Hg, pulse rate is 56/min, and respiration rate is 15/min. Cardiac examination reveals a grade 1/6 diastolic murmur at the left lower sternal border.

Echocardiogram shows a bicuspid aortic valve with moderate aortic regurgitation, normal left ventricular systolic function, and normal left ventricular chamber size.

Which of the following is the most appropriate management?

(A) Aortic valve replacement
(B) Clinical reassessment in 1 year
(C) Endocarditis prophylaxis
(D) Start an ACE inhibitor
(E) Start a calcium channel blocker

Item 60

A 26-year-old woman with a mechanical mitral valve prosthesis visits to discuss anticoagulation management during pregnancy. Her last menstrual period was 6 weeks ago and her pregnancy was confirmed by laboratory testing in the office. Her mitral valve was replaced 5 years ago. Her medications are low-dose aspirin, metoprolol, and warfarin (4 mg/d).

On physical examination, vital signs are normal. Cardiac auscultation demonstrates a normal mechanical S_1. There are no murmurs or added sounds. Her INR is 2.6.

Which of the following anticoagulation regimens will provide the greatest protection against thromboembolism during her pregnancy?

(A) Continue warfarin and aspirin
(B) Stop warfarin and start dabigatran
(C) Stop warfarin and start subcutaneous fixed-dose unfractionated heparin
(D) Stop warfarin and start weight-based low-molecular-weight heparin

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Item 61

A 72-year-old woman is evaluated in the emergency department for progressive chest pain that began 2 hours ago. She has not had recent surgery or stroke. She takes amlodipine for hypertension.

On physical examination, blood pressure is 154/88 mm Hg, and pulse rate is 88/min. Cardiac and pulmonary examinations are normal.

Initial electrocardiogram shows 2-mm ST-segment elevation in leads V_1 through V_5 with reciprocal ST-segment depression in leads II, III, and aVF. Chest radiograph shows no cardiomegaly and no evidence of pulmonary edema.

The patient is given aspirin, clopidogrel, unfractionated heparin, and a β-blocker. Because the nearest hospital with primary percutaneous coronary intervention capabilities is more than 120 minutes away, she is also given a bolus dose of tenecteplase.

Thirty minutes later, the patient's blood pressure has dropped to 85/58 mm Hg. Her chest pain persists, and she rates the pain as 8 out of 10. Pulmonary crackles are auscultated to the scapulae. Electrocardiogram shows 3-mm ST-segment elevation in leads V_1 through V_5 with reciprocal ST-segment depression in leads II, III, and aVF.

Which of the following is the most appropriate management?

(A) Continued medical therapy
(B) Glycoprotein IIb/IIIa inhibitor
(C) Repeat tenecteplase
(D) Transfer for emergency percutaneous coronary intervention

Item 62

A 56-year-old man is being evaluated after his 18-year-old son had a syncopal episode during a high school basketball game and was diagnosed with hypertrophic cardiomyopathy (HCM). The patient has had no symptoms, including with physical activity such as golfing or playing tennis. Medical history is unremarkable, and a review of family history is negative for other relatives with HCM, sudden cardiac death, or tachyarrhythmias. He takes no medications.

Findings of a comprehensive physical examination are unremarkable.

An electrocardiogram and echocardiogram are normal, with no evidence of HCM.

When should this patient next be screened for HCM?

(A) In 6 months
(B) In 1 to 2 years
(C) In 5 years
(D) No further screening is necessary

Item 63

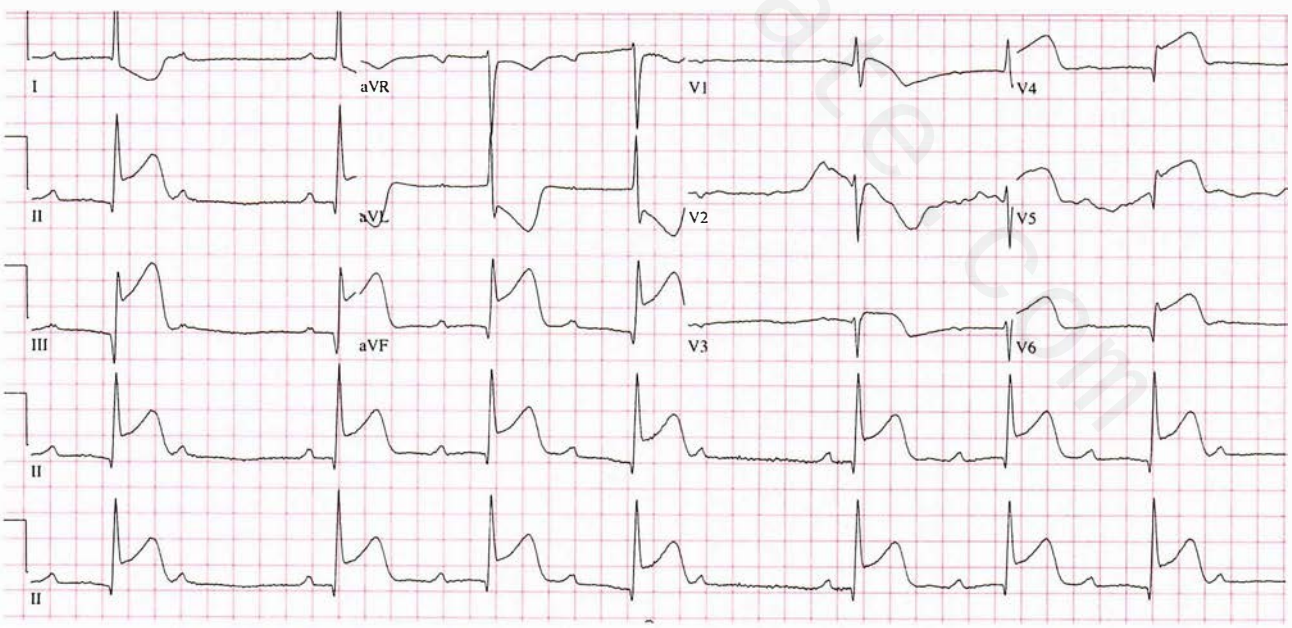
A 73-year-old man is evaluated in the emergency department for chest pain of 2 hours' duration. He is bradycardic. He does not have dyspnea, lightheadedness, or loss of consciousness. Medical history is significant for type 2 diabetes mellitus, hypertension, and hyperlipidemia. Medications are aspirin, metformin, lisinopril, and hydrochlorothiazide.

On physical examination, the patient is afebrile, blood pressure is 120/60 mm Hg, pulse rate is 47/min, and respiration rate is 12/min. BMI is 34. He is warm and well-perfused. Trace bibasilar crackles are heard in the lungs.

The electrocardiogram is shown.

Which of the following is the most appropriate treatment?

(A) Aminophylline
(B) Low-dose dopamine
(C) Percutaneous coronary intervention
(D) Temporary pacing



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Item 64

A 53-year-old woman with Eisenmenger syndrome related to a ventricular septal defect is evaluated in the emergency department for fever and chills over the past 12 hours. She has dysuria and urinary frequency. Her only outpatient medication is bosentan.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 110/70 mm Hg, pulse rate is 86/min and regular, and respiration rate is 20/min. Oxygen saturation on ambient air is 85%. BMI is 24. Digital clubbing and cyanosis are evident. The estimated central venous pressure is elevated with a prominent *a* wave. The apical impulse is normal. A prominent parasternal impulse is present at the left sternal border. The S_1 is normal; the S_2 is loud. A soft holosystolic murmur is heard at the left lower sternal border. Mild right flank tenderness is noted.

A urinary Gram stain is positive; urine and blood culture results are pending. The hemoglobin level is 18 g/dL (180 g/L), hematocrit is 55%, and the leukocyte count is 20,000/μL (20×10^9/L).

In addition to intravenous antibiotic administration, which of the following is the most appropriate management?

(A) Air filters on intravenous lines
(B) Oxygen by close-fitting mask
(C) Phlebotomy
(D) Transthoracic echocardiogram

Item 65

A 62-year-old man is evaluated during a routine visit. He is asymptomatic and walks 1 mile most days of the week. Medical history is significant for aortic stenosis, type 2 diabetes mellitus, hypertension, and hyperlipidemia. Medications are aspirin, metformin, lisinopril, metoprolol, and rosuvastatin.

On physical examination, the patient is afebrile, blood pressure is 130/66 mm Hg, pulse rate is 68/min, and respiration rate is 14/min. BMI is 29. Cardiac examination reveals a grade 2/6 early-peaking systolic murmur at the cardiac base. Carotid upstrokes are normal. The remainder of the examination is unremarkable.

Laboratory studies demonstrate a total serum cholesterol level of 150 mg/dL (3.89 mmol/L). Electrocardiogram is within normal limits. Echocardiogram from 1 year ago shows a peak velocity of 2.0 m/s, mean transaortic gradient of 13 mm Hg, aortic valve area of 1.5 cm^2, and preserved ejection fraction.

Which of the following is the most appropriate management?

(A) Echocardiogram
(B) Exercise perfusion study
(C) Exercise stress test
(D) No additional testing

Item 66

A 78-year-old man is evaluated in the emergency department because of a painful right foot. He has a 1-year history of right-sided claudication. Three days ago he developed severe rest pain in the right foot that is starting to subside. He has hypertension and a 10-year history of type 2 diabetes mellitus. He has a 55-pack-year history of cigarette smoking but stopped 2 years ago. Medications are aspirin, metformin, losartan, and amlodipine.

On physical examination, vital signs are stable. The right foot is cool and pale with slow capillary refill in the nail beds. The dorsalis pedis and posterior tibialis pulses are not palpable. Arterial Doppler ultrasound signal over the dorsalis pedis is present but markedly diminished. Sensation of light touch is present but decreased over the dorsum of the right foot.

Laboratory studies are significant for normal complete blood count, electrolytes, and kidney function. Electrocardiogram demonstrates sinus rhythm.

A continuous heparin infusion is started.

Which of the following is the most appropriate next step in management?

(A) Catheter-directed thrombolytic therapy
(B) Emergent surgical amputation
(C) Initiation of warfarin
(D) Urgent angiography

Item 67

A 72-year-old man is evaluated during a routine examination. He has no symptoms or significant medical history. He is active and exercises regularly. He does not take any medications.

On physical examination, blood pressure is 135/70 mm Hg, pulse rate is 82/min, and respiration rate is 17/min. Cardiac examination reveals a grade 3/6 apical holosystolic murmur.

Echocardiogram shows severe mitral regurgitation and a left ventricular ejection fraction of 45% without evidence of regional wall motion abnormalities.

Which of the following is the most appropriate management?

(A) Vasodilator therapy
(B) Percutaneous mitral balloon valvuloplasty
(C) Repeat echocardiogram in 6 months
(D) Surgical mitral valve repair

Item 68

A 40-year-old man is evaluated in the emergency department for syncope. He was attending a baseball game when he experienced a witnessed, abrupt episode of syncope while seated. He did not experience any prodromal symptoms. He sustained some facial trauma when he struck the railing in front of him. He has experienced near-syncope on several occasions in the past. His father died suddenly at age 50 years. The patient takes no medications and has no drug allergies.

On physical examination, the patient is afebrile, blood pressure is 125/64 mm Hg, pulse rate is 64/min, and respiration rate is 16/min. BMI is 26. Estimated central venous pressure is normal. Cardiac examination shows a regular

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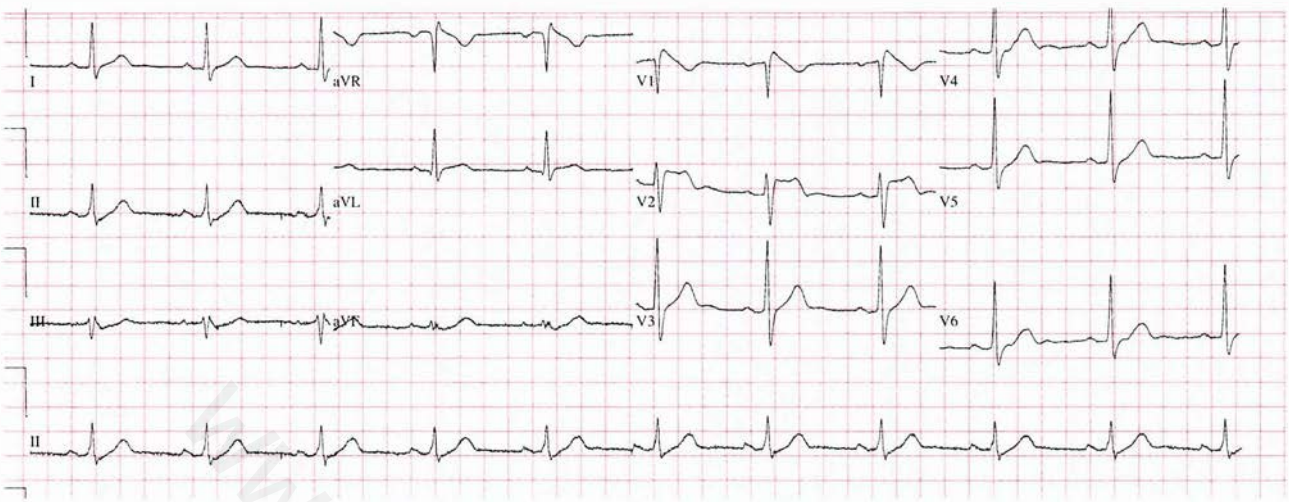

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rate with normal heart sounds and no murmurs. He has no peripheral edema.

Pertinent laboratory findings include a negative troponin test, a normal metabolic profile, and normal kidney function studies.

Electrocardiogram is shown. Echocardiogram demonstrates no structural heart disease and shows normal left ventricular function.

Which of the following is the most appropriate management?

(A) Cardiac magnetic resonance (CMR) imaging
(B) Exercise treadmill stress test
(C) Implantable cardioverter-defibrillator placement
(D) Tilt-table test

Item 69

A 68-year-old man is evaluated at a follow-up appointment. He has a 7-year history of heart failure secondary to ischemic cardiomyopathy. Over the past 6 months, he has had three hospitalizations for exacerbations of his heart failure. He currently has exertional dyspnea while getting dressed, and his maximal activity level is limited to riding to the store with his wife but staying in the car. Medical history is significant for disseminated prostate cancer treated with androgen deprivation therapy. Medications are aspirin, lisinopril, carvedilol, furosemide, digoxin, spironolactone, rosuvastatin, and leuprolide. He is stable on his current medications.

On physical examination, blood pressure is 92/60 mm Hg and pulse rate is 80/min. There is no jugular venous distention. An S_3 is heard on cardiac examination. The legs are cool to the touch; there is no edema.

Laboratory studies are significant for a serum sodium level of 132 mEq/L (132 mmol/L) and serum creatinine level of 1.8 mg/dL (159 µmol/L).

Which of the following is the most appropriate management?

(A) Add metolazone
(B) Cardiac transplantation evaluation
(C) Evaluation for left ventricular assist device placement
(D) Home inotropic therapy

Item 70

A 75-year-old woman is evaluated during a follow-up visit for recently diagnosed atrial fibrillation that is adequately rate controlled on medication. Medical history is significant for hypertension and end-stage kidney disease; she is on hemodialysis. Medications are metoprolol, digoxin, lisinopril, and amlodipine. She has not yet been started on stroke prevention therapy.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 120/65 mm Hg, pulse rate is 72/min, and respiration rate is 16/min. BMI is 29. The precordial cadence is irregularly irregular. There is no evidence of pulmonary or peripheral congestion.

Which of the following is the most appropriate treatment?

(A) Apixaban
(B) Aspirin and clopidogrel
(C) Dabigatran
(D) Dose-adjusted warfarin
(E) Rivaroxaban

Item 71

A 62-year-old woman is evaluated in the emergency department for sudden onset of severe chest, upper abdominal, and back pain of 2 hours' duration. She has not had similar symptoms previously and notes no other symptoms. Medical history is significant for hypertension. She is a current smoker with a 55-pack-year history. Her medications are amlodipine and benazepril.

On physical examination, she is afebrile, blood pressure is 165/100 mm Hg in both arms, pulse rate is 102/min, and respiration rate is 20/min. Oxygen saturation is 98% on ambient air. Cardiac auscultation reveals an S_4 gallop but no murmurs. Pulmonary examination is normal. Pulses are

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symmetric and equal in all extremities. The remainder of the physical examination is unremarkable.

Laboratory studies reveal a D-dimer level of 0.8 µg/mL (0.8 mg/L) and a serum creatinine level of 2.4 mg/dL (212 µmol/L) (baseline is <1 mg/dL [88.4 µmol/L]). Initial cardiac troponin T level is 0.4 ng/mL (0.4 µg/L).

Electrocardiogram shows left ventricular hypertrophy with repolarization abnormalities. Chest radiograph demonstrates an enlarged cardiac silhouette. A magnetic resonance angiography study demonstrates aortic dissection originating distal to the left subclavian artery extending to the aortoiliac bifurcation (maximum diameter 63 mm). Bilateral renal arteries arise from the false lumen.

Treatment with analgesics, a β-blocker, and sodium nitroprusside is started.

Which of the following is the most appropriate next step in management?

(A) Aortic repair
(B) Coronary angiography
(C) Continue current medical therapy
(D) Intravenous heparin

Item 72

An 18-year-old woman with Noonan syndrome is evaluated for a heart murmur noted on a sports physical examination. She is asymptomatic and her medical history is unremarkable. She takes no medications.

On physical examination, blood pressure is 120/70 mm Hg, pulse rate is 70/min and regular, and respiration rate is 18/min. BMI is 18. The patient is of short stature and has hypertelorism, neck webbing, and a low hairline. The central venous pressure is elevated with a prominent *a* wave. The apical impulse is normal. There is a prominent parasternal impulse at the left sternal border. The S_1 is normal; the S_2 is soft. A grade 4/6 late-peaking systolic murmur is heard at the left sternal border and second left intercostal space. An ejection click is not audible.

An echocardiogram demonstrates a dysplastic pulmonary valve with a peak instantaneous systolic gradient of 62 mm Hg and mean systolic gradient of 45 mm Hg. There is moderate pulmonary valve regurgitation. The right ventricular size and function are normal, but there is right ventricular hypertrophy. The left heart size and function are normal.

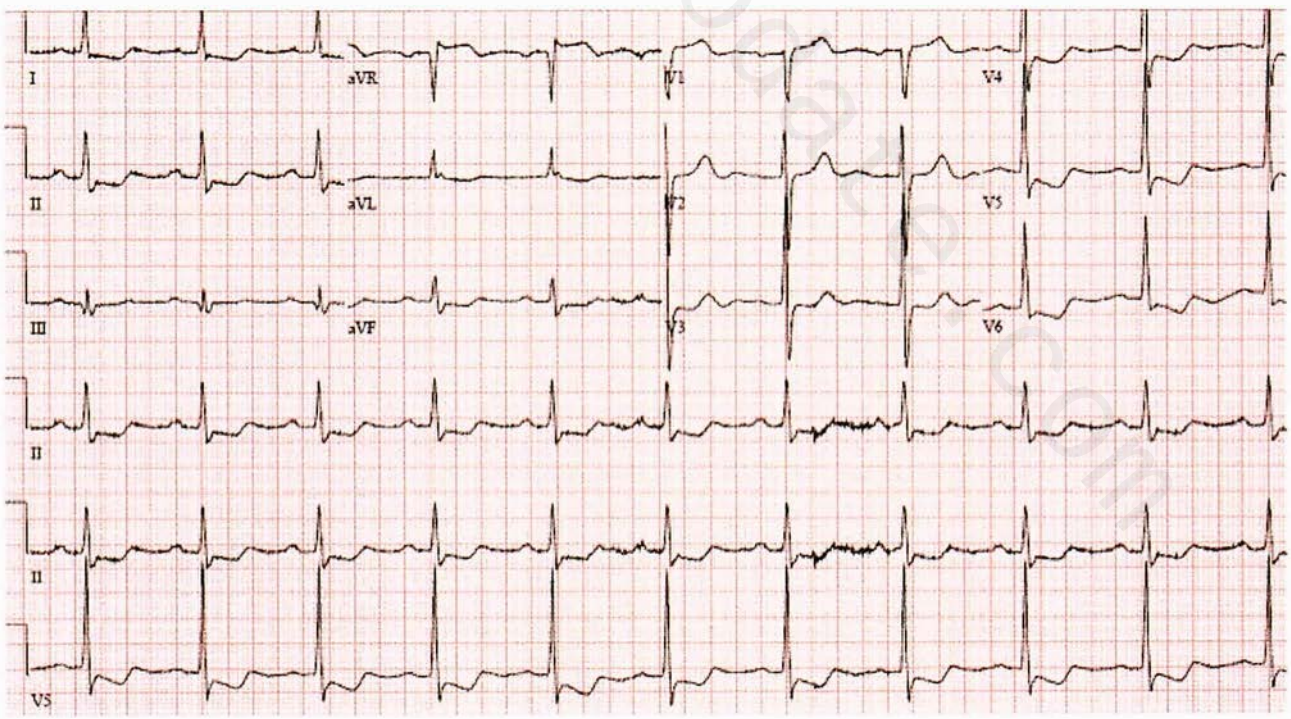
Which of the following is the most appropriate management for this patient?

(A) Endocarditis prophylaxis
(B) Exercise testing
(C) Pulmonary valve replacement
(D) Observation

Item 73

A 62-year-old man is evaluated in the emergency department (ED) for a 3-hour history of dull, substernal chest discomfort. He has type 2 diabetes mellitus, hypertension, and dyslipidemia. He does not smoke cigarettes. Medications are low-dose aspirin, lisinopril, and pravastatin. His younger sister was diagnosed with coronary artery disease at the age of 50 years.

Electrocardiogram obtained upon his arrival to the ED is shown. He is administered aspirin and sublingual nitroglycerin. His chest discomfort is relieved within 15 minutes of arrival.



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On physical examination, blood pressure is 148/86 mm Hg, pulse rate is 62/min and regular, and oxygen saturation is 94% on ambient air. BMI is 28. Cardiac examination is significant only for the presence of a grade 1/6 holosystolic murmur at the left lower sternal border. The murmur does not radiate. Lungs are clear. The reminder of the examination is normal.

Initial serum troponin I concentration is 0.94 ng/ml. (0.94 μg/L).

Portable chest radiograph demonstrates a normal cardiac silhouette and no evidence of pulmonary edema.

Which of the following is the most appropriate initial management?

(A) Administer clopidogrel and enoxaparin
(B) Emergent coronary angiography
(C) Exercise stress testing
(D) Monitor in the emergency department until a second set of cardiac enzyme markers is available

Item 74

A 55-year-old woman is evaluated for a 3-week history of progressive shortness of breath. She now has difficulty walking up two flights of stairs. Medical history is significant for asthma and mitral valve prolapse with moderate mitral regurgitation. Her last echocardiogram was 4 months ago and showed mild left atrial enlargement and normal left ventricular size and thickness, with an ejection fraction of 65%. Her only medication is an albuterol inhaler as needed.

On physical examination, the patient is afebrile, blood pressure is 132/56 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. BMI is 27. Cardiac examination reveals a grade 3/6 holosystolic murmur radiating to the axilla. Lungs are clear to auscultation.

Electrocardiogram shows normal sinus rhythm.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Exercise stress testing
(B) 24-Hour continuous ambulatory electrocardiographic monitoring
(C) Spirometry
(D) Transesophageal echocardiogram
(E) Transthoracic echocardiogram

Item 75

A 38-year-old man is evaluated for an insurance physical examination. He has a history of aortic coarctation with an end-to-end anastomosis performed at the age of 3 years. He is asymptomatic, works full time, and performs regular exercise without limitation. He takes chlorthalidone once daily for blood pressure control.

On physical examination, blood pressure is 120/80 mm Hg, pulse rate is 78/min and regular, and respiration rate is 18/min. BMI is 24. The estimated central venous pressure is normal. The apical impulse is normal. The S_1 and S_2 are normal. An ejection click is noted at the left lower sternal border. A grade 3/6 midpeaking systolic murmur is noted at the second right intercostal space. The femoral pulses are easily palpated, and there is no radial artery–to–femoral artery pulse delay.

Which of the following is the most likely cause of the systolic murmur?

(A) Aortic valve stenosis
(B) Ascending aortic aneurysm
(C) Mitral valve regurgitation
(D) Recurrent aortic coarctation

Item 76

A 55-year-old man with a 6-month history of heart failure is evaluated during a follow-up appointment. At diagnosis, his left ventricular ejection fraction was 15%, and he had moderate mitral and tricuspid regurgitation. Cardiac catheterization at that time revealed normal coronary arteries. He was started on the appropriate medications and is now back to working at a desk job. He has dyspnea walking up a flight of stairs. Medical history is also significant for hypertension. Medications are enalapril, carvedilol (25 mg twice daily), furosemide, and spironolactone.

On physical examination, blood pressure is 100/65 mm Hg, and pulse rate is 56/min. Weight is 72 kg (159 lb). On cardiovascular examination, there is a grade 3/6 holosystolic murmur at the apex radiating to axilla and no S_3 gallop. The remainder of the examination is normal.

Serum electrolyte levels and kidney function tests are normal. Recent echocardiogram shows a left ventricular ejection fraction of 20% and moderate mitral regurgitation. Electrocardiogram demonstrates normal sinus rhythm with a QRS width of 100 ms.

Which of the following is the most appropriate management?

(A) Add an angiotensin receptor blocker
(B) Implantable cardioverter-defibrillator placement
(C) Increase carvedilol to 37.5 mg twice daily
(D) Mitral valve replacement

Item 77

H

A 45-year-old woman is evaluated in the emergency department for a 1-week history of dyspnea and fatigue. The patient is being treated with systemic chemotherapy for a diagnosis of breast cancer. She has received two cycles of adjuvant chemotherapy with doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2); her first treatment occurred 3 months ago and her most recent treatment occurred 2 weeks ago. She has had no chest pain, and medical history is otherwise unremarkable. She takes no other medications.

On physical examination, blood pressure is 120/72 mm Hg and pulse rate is 88/min; BMI is 25. Carotid upstrokes are normal. The estimated central venous pressure is 10 cm H_2O. Crackles are present in both lung fields. S_1 is normal, the pulmonic component of S_2 is increased, an S_3 is present, and there is no S_4. A soft holosystolic murmur at the left lower sternal border is audible. Lower extremity edema to the midshins is present. The mastectomy site is healing well.

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CONT.

A chest radiograph shows infiltrates in both lung fields with a normal cardiac silhouette. Echocardiogram shows a left ventricular ejection fraction of 30%. The estimated pulmonary artery systolic pressure is 50 mm Hg. No other significant echocardiographic findings are present.

The patient is started on lisinopril and furosemide.

Which of the following is the most appropriate next step in the management of her doxorubicin chemotherapy?

(A) Continue doxorubicin
(B) Discontinue doxorubicin
(C) Reduce the dose of doxorubicin
(D) Substitute daunorubicin

Item 78

A 60-year-old man is evaluated for increasing shortness of breath. He noticed progressive exertional intolerance 1 month ago. His symptoms have worsened, and he is now short of breath with walking mild inclines. He does not have chest pain, orthopnea, paroxysmal nocturnal dyspnea, cough, wheezing, or lower extremity edema. He has a history of atrial fibrillation but remains in sinus rhythm after his second catheter ablation procedure for atrial fibrillation 1 year ago. Medical history also includes hypertension and hyperlipidemia but is negative for heart failure or left ventricular dysfunction. Medications are warfarin, metoprolol, ramipril, and atorvastatin.

On physical examination, the patient is afebrile, blood pressure is 132/78 mm Hg, pulse rate is 70/min, and respiration rate is 18/min. Pulse oximetry demonstrates 98% oxygen saturation on ambient air. BMI is 30. Cardiac rate and rhythm are regular. He has bilateral breath sounds but no wheezes, crackles, or rhonchi. There is no prolongation of the expiratory phase.

The electrocardiogram shows normal sinus rhythm. A plain chest radiograph is normal, and pulmonary function tests demonstrate no obstruction. An echocardiogram demonstrates normal left ventricular function with a left ventricular ejection fraction above 55% and evidence of mild diastolic dysfunction.

Which of the following is the most likely cause of this patient's dyspnea?

(A) Chronic thromboembolic disease
(B) Intracardiac shunting
(C) Phrenic nerve injury
(D) Pulmonary vein stenosis

Item 79

A 41-year-old man comes to the office to discuss management of hypertrophic cardiomyopathy (HCM), which was diagnosed 2 weeks ago after a murmur was detected incidentally on examination for another medical condition. HCM has since been diagnosed in his father and brother during family screening. There is no family history of sudden cardiac death. He is asymptomatic.

On physical examination, vital signs are normal. A soft holosystolic murmur is heard, which decreases during both handgrip and stand-to-squat maneuvers.

Transthoracic echocardiogram shows myocardial hypertrophy (maximal septal wall thickness, 32 mm) and mild left ventricular outflow tract obstruction at rest (gradient, 31 mm Hg). On a 24-hour ambulatory electrocardiography study, a four-beat run of nonsustained ventricular tachycardia is present.

Which of the following is the most appropriate next step in treatment?

(A) Alcohol septal ablation
(B) β-Blocker therapy
(C) Implantable cardioverter-defibrillator
(D) Surgical myectomy

Item 80

A 65-year-old man is evaluated for a routine examination. He is asymptomatic and is active, walking 2 miles on a treadmill three times a week. He has hypertension and dyslipidemia. He has a 15-pack-year smoking history but has not smoked since age 30 years. Current medications are hydrochlorothiazide, atorvastatin, and aspirin.

On physical examination, his blood pressure is 134/76 mm Hg in the right upper extremity and 146/80 mm Hg in the left. His pulse rate is 72/min. BMI is 23. He has a grade 2/6 midsystolic murmur heard loudest at his left sternal border. Abdominal examination reveals a pulsatile mass in the epigastrium.

An abdominal ultrasound reveals an aneurysm with a maximum diameter of 4.7 cm not involving the renal arteries.

Which of the following is the most appropriate management of this patient's abdominal aortic aneurysm?

(A) Refer for aneurysm repair
(B) Repeat abdominal ultrasonography in 6 to 12 months
(C) Repeat abdominal ultrasonography in 24 to 36 months
(D) No follow-up management is needed

Item 81

A 54-year-old man is evaluated in the emergency department for an episode of crushing substernal chest pain and discomfort that began 30 minutes ago. He is obese and currently smokes 1 to 2 packs of cigarettes daily. He has dyslipidemia. The patient's medications are enteric-coated low-dose aspirin and simvastatin.

On physical examination, he is afebrile, blood pressure is 146/88 mm Hg, pulse rate is 88/min and symmetric bilaterally, and respiration rate is 18/min. BMI is 32. Cardiac examination reveals a normal S_1 and S_2 and no S_3; there is an S_4. There are no murmurs or rubs. The remainder of the examination is normal.

Serum troponin levels are elevated. Hematocrit is 42% and platelet count is 220,000/μL (220×10^9/L). Electrocardiogram shows changes consistent with an inferior ST-elevation myocardial infarction. Portable chest radiograph shows a normal cardiac silhouette and no infiltrate.

The patient is treated with enteric-coated aspirin, nitrates, and a β-blocker. The hospital does not have capabilities to

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H CONT. perform primary percutaneous coronary intervention (PCI), and the nearest primary PCI center is more than 2 hours away. The patient is administered intravenous tenecteplase.

Which of the following is the most appropriate treatment?

(A) Abciximab
(B) Clopidogrel
(C) Prasugrel
(D) Ticagrelor

Item 82

A 56-year-old man with Eisenmenger syndrome related to a ventricular septal defect is evaluated for recent fatigue and dyspnea. He had an elective cholecystectomy for symptomatic cholelithiasis 4 weeks ago and has had persistent fatigue and exertional dyspnea since his operation. He has no other symptoms. His current medications are sildenafil and bosentan.

On physical examination, vital signs are normal. BMI is 25. The estimated central venous pressure is elevated with a prominent *a* wave. The apical impulse is normal. There is a prominent parasternal impulse at the left sternal border. The S_1 is normal; the S_2 is loud. No murmur is appreciated. Digital clubbing and central cyanosis are noted. The abdominal wound is healing well with no evidence of infection.

Laboratory testing reveals a hemoglobin level of 11.8 g/dL (118 g/L) and hematocrit of 45%. A review of the patient's recent laboratory results shows a hemoglobin level of 18.6 g/dL (186 g/L) and hematocrit of 56% before the cholecystectomy, and a hemoglobin level of 12 g/dL (120 g/L) and hematocrit of 47% at the time of hospital discharge.

Which of the following is the most appropriate management?

(A) Erythrocyte transfusion
(B) Erythropoietin
(C) Initiate intravenous epoprostenol
(D) Initiate short-course iron therapy
(E) Refer for heart-lung transplantation

Item 83

A 55-year-old man is evaluated for cardiovascular risk assessment. He has osteoarthritis and hypertension. He is a construction worker. His brother had a myocardial infarction at the age of 53 years. The patient's medications are lisinopril and naproxen. He is a nonsmoker.

On physical examination, the patient is afebrile, blood pressure is 138/70 mm Hg, pulse rate is 78/min, and respiration rate is 14/min. BMI is 25. The remainder of the examination is unremarkable.

Laboratory studies are significant for a serum LDL cholesterol level of 135 mg/dL (3.50 mmol/L) and an HDL cholesterol level of 38 mg/dL (0.98 mmol/L).

His American College of Cardiology/American Heart Association 10-year atherosclerotic cardiovascular disease risk based on the Pooled Cohort Equations is 6%.

Which of the following is the most appropriate management?

(A) Coronary artery calcium scoring
(B) Exercise stress testing
(C) Increase dose of lisinopril
(D) Recommend antioxidant vitamin therapy

Item 84

A 61-year-old man is evaluated for a 3-month history of progressive aching pain in the left lower extremity; the pain is present during walking and is absent with rest. He has a 30-pack-year history of smoking and quit 1 year ago. His medical history is significant for New York Heart Association functional class II heart failure, hypercholesterolemia, and type 2 diabetes mellitus. Medications are aspirin, lisinopril, simvastatin, metformin, and metoprolol.

On physical examination, vital signs are stable. BMI is 25. Femoral, popliteal, and foot pulses are diminished. There is no distal ulceration or skin breakdown. The ankle-brachial index is 0.70 on the left and 0.85 on the right.

Which of the following is the most appropriate management?

(A) Initiate cilostazol
(B) Refer for endovascular repair
(C) Refer for vascular surgery
(D) Start a supervised exercise program

Item 85

A 19-year-old woman is evaluated during a routine examination. She has no symptoms or significant medical history. She takes no medications.

On physical examination, blood pressure is 130/70 mm Hg and pulse rate is 72/min. Cardiac examination reveals a grade 1/6 diastolic murmur at the base of the heart. Pulses are equal in the upper and lower extremities.

Transthoracic echocardiogram shows a bicuspid aortic valve with mild aortic regurgitation. The aortic dimension is 4.2 cm at the sinuses of Valsalva. Chest CT scan with contrast confirms the aortic root measurements, and no other pathology is noted.

Which of the following is the most appropriate management?

(A) Annual cardiac magnetic resonance (CMR) imaging
(B) Annual multidetector CT
(C) Annual transesophageal echocardiography
(D) Annual transthoracic echocardiography
(E) Reassurance and clinical observation

Item 86

A 66-year-old woman is evaluated for a 3-week history of worsening dyspnea on exertion. Medical history is significant for type 2 diabetes mellitus and hypertension.

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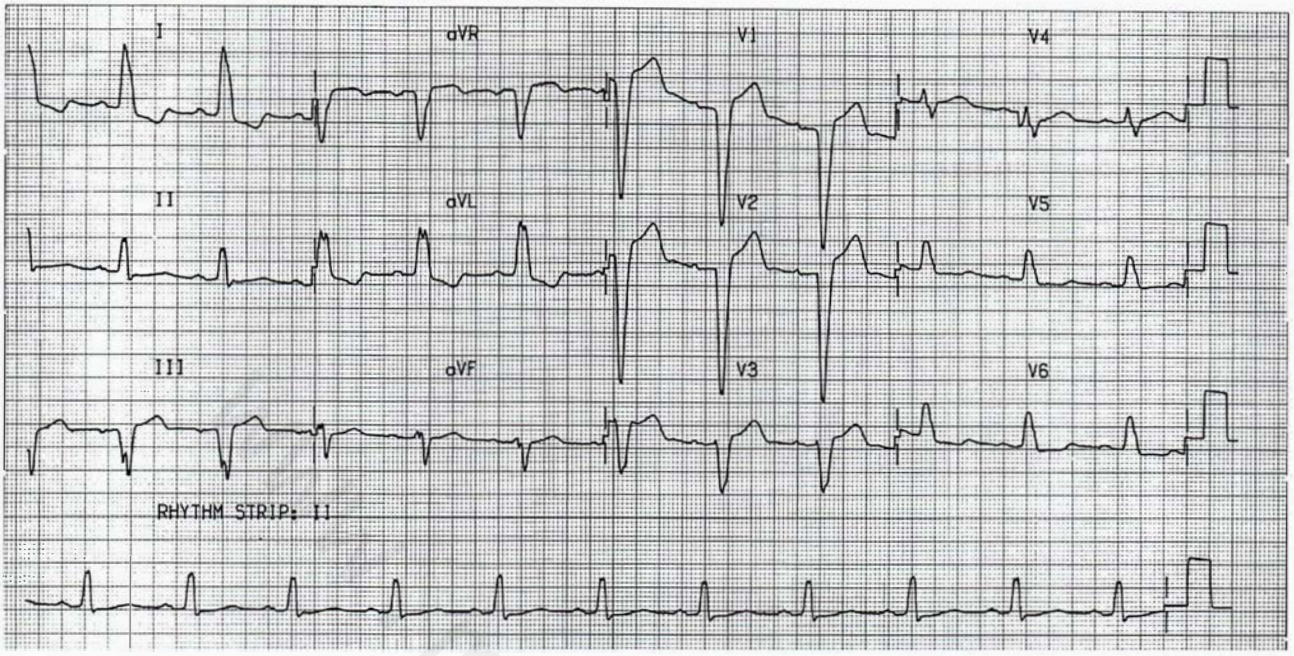

ITEM 86

Medications are metformin, lisinopril, and hydrochlorothiazide.

On physical examination, the patient is afebrile, blood pressure is 132/78 mm Hg, pulse rate is 78/min, and respiration rate is 14/min. BMI is 28. The remainder of the examination is unremarkable.

Electrocardiogram is shown.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Coronary artery calcium scoring
(B) Exercise nuclear perfusion imaging
(C) Exercise treadmill stress testing
(D) Vasodilator nuclear perfusion imaging

Item 87

A 49-year-old woman is evaluated for intermittent sharp, nonradiating, substernal chest pain for the past 2 weeks. The pain occurs more frequently in the morning and is not associated with meals or exertion but may be initiated with emotional stress. The pain does not include any pleuritic or positional components, and she states that there are no aggravating factors. The pain often lasts for 10 minutes and subsides spontaneously. She has hyperlipidemia treated with pravastatin. Her mother had a myocardial infarction and heart failure starting at the age of 52 years.

On physical examination, blood pressure is 132/82 mm Hg and pulse rate is 78/min. BMI is 28. Lungs are clear to auscultation. Cardiac examination shows a normal S_1 and S_2; there is no S_3, S_4, murmurs, rubs, or gallops. She has no lower extremity edema. The remainder of the examination is normal.

Electrocardiogram shows a heart rate of 80/min. The QRS axis is normal, and there are no ST-T wave changes.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Diagnostic coronary angiography
(B) Exercise electrocardiography
(C) Exercise nuclear perfusion study
(D) Pharmacologic nuclear perfusion study

Item 88

A 48-year-old woman is evaluated during a follow-up visit. She has a 5-year history of type 2 diabetes mellitus. She has no other significant medical history. Medications are atorvastatin, metformin, and a multivitamin. She works as a mail carrier and has a walking route that takes 3 hours each day. She consumes a diet high in fruits and vegetables and does not smoke.

On physical examination, the patient is afebrile, blood pressure is 128/80 mm Hg, pulse rate is 70/min, and respiration rate is 12/min. BMI is 26. The remainder of the examination is unremarkable.

Laboratory studies are significant for a serum LDL cholesterol level of 135 mg/dL (3.50 mmol/L) and serum HDL cholesterol level of 37 mg/dL (0.96 mmol/L). Urinalysis is negative for albuminuria.

Her estimated 10-year cardiovascular risk by the Pooled Cohort Equations is 2.7%.

Which of the following is the most appropriate cardiovascular disease risk management?

(A) Aspirin
(B) Coronary artery calcium scoring
(C) Exercise stress testing
(D) Folic acid supplementation
(E) No further testing or therapy

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Item 89

A 57-year-old woman is evaluated in the hospital for chronic systolic heart failure. She was admitted with progressive dyspnea of 2 weeks' duration. After 3 days of aggressive diuretic therapy with weight loss of 5 kg (11 lb), she remained very dyspneic, and right heart catheterization was performed. Medications are lisinopril, digoxin, spironolactone, and intermittent furosemide intravenously.

On physical examination, blood pressure is 96/74 mm Hg, pulse rate is 118/min, and respiration rate is 20/min. The internal jugular vein is not visible when the patient is in an upright position. Lungs are clear. An S_3 is heard on cardiac examination. There is bilateral edema to the knees. Her serum creatinine level is 1.7 mg/dL (150.3 µmol/L).

Hemodynamic measurements:

Right atrium pressure	4 mm Hg
Pulmonary capillary wedge pressure	16 mm Hg
Cardiac output	3.1 L/min (normal, 4.0-8.0 L/min)
Cardiac index	1.8 L/min/m^2
Systemic vascular resistance	2050 dyne/s/cm^2 (normal, 800-1200 dyne/s/cm^2)

Which of the following is the most appropriate change in this patient's therapy?

(A) Continuous intravenous furosemide
(B) Dopamine infusion
(C) Esmolol drip
(D) Nitroprusside

Item 90

A 47-year-old man is evaluated for a 3-month history of fatigue, abdominal fullness, and lower extremity edema. Ten years ago, the patient had acute pericarditis with cardiac tamponade; the tamponade was treated successfully with pericardiocentesis, and the pericarditis resolved following a course of an anti-inflammatory medication. He has no history of significant alcohol consumption, hepatitis, or autoimmune disease, and takes no medications.

On physical examination, the patient is icteric. Vital signs are normal; BMI is 30. The estimated central venous pressure is 12 cm H_2O, and the jugular venous pulse shows a prominent *y* descent. S_1 and S_2 are normal, and no murmurs, rubs, or gallops are heard. There is dullness to percussion at the right lung base. The remainder of the pulmonary examination is normal. Both ascites and lower extremity edema are present.

Transthoracic echocardiography is technically challenging, and limited information is obtained. Fluid obtained from abdominal paracentesis is transudative.

Which of the following is the most appropriate next step in management?

(A) Hemodynamic cardiac catheterization
(B) Liver biopsy
(C) Measurement of B-type natriuretic peptide
(D) Vigorous diuresis

Item 91

A 64-year-old woman is evaluated for a 3-month history of sharp chest discomfort that she experiences during gardening. Medical history is significant for hypertension and hyperlipidemia. The patient's father had a coronary artery bypass graft at the age of 68 years. Medications are losartan, hydrochlorothiazide, and atorvastatin, and she recently started taking low-dose aspirin daily.

On physical examination, the patient is afebrile, blood pressure is 136/84 mm Hg, pulse rate is 78/min, and respiration rate is 16/min. BMI is 26. The remainder of the physical examination is unremarkable.

Baseline electrocardiogram shows left ventricular hypertrophy with ST-segment depressions less than 0.5 mm in the lateral leads. During exercise stress testing, the patient develops 1-mm ST-segment depressions in leads II, III, and aVF. She exercised 5 minutes and 30 seconds of a Bruce protocol; her peak heart rate was 129/min (85% predicted maximum), and blood pressure was 186/76 mm Hg.

Which of the following is the most appropriate next step in the management of this patient?

(A) Add a β-blocker
(B) Cardiac catheterization
(C) Cardiac magnetic resonance (CMR) imaging
(D) Stress echocardiography

Item 92

A 66-year-old man is evaluated in the emergency department for 45 minutes of substernal chest pain that radiates to the left shoulder. The patient's medical history is significant for hypertension, type 2 diabetes mellitus, and hyperlipidemia. He has never had abnormal bleeding. Medications are low-dose aspirin, glimepiride, lisinopril, and simvastatin. He has no known drug allergies.

On physical examination, blood pressure is 174/92 mm Hg and pulse rate is 82/min. Cardiac examination shows a normal S_1 and S_2; there is no S_3, S_4, murmur, or rubs. The remainder of the physical examination is normal.

Hemoglobin concentration is 13.4 g/dL (134 g/L) and serum creatinine level is 1.0 mg/dL (88.4 µmol/L). Results of serum troponin levels are pending. Electrocardiogram is shown (see top of next page).

The patient is given aspirin, clopidogrel, unfractionated heparin, and a β-blocker. Transport to the nearest hospital with primary percutaneous coronary intervention (PCI) capabilities would take approximately 135 minutes.

Which of the following is the most appropriate management?

(A) Administer tenecteplase and transfer to a PCI-capable center
(B) Admit to the hospital and await cardiac biomarker results
(C) Initiate abciximab and transfer for urgent coronary angiography
(D) Transfer for primary percutaneous coronary intervention

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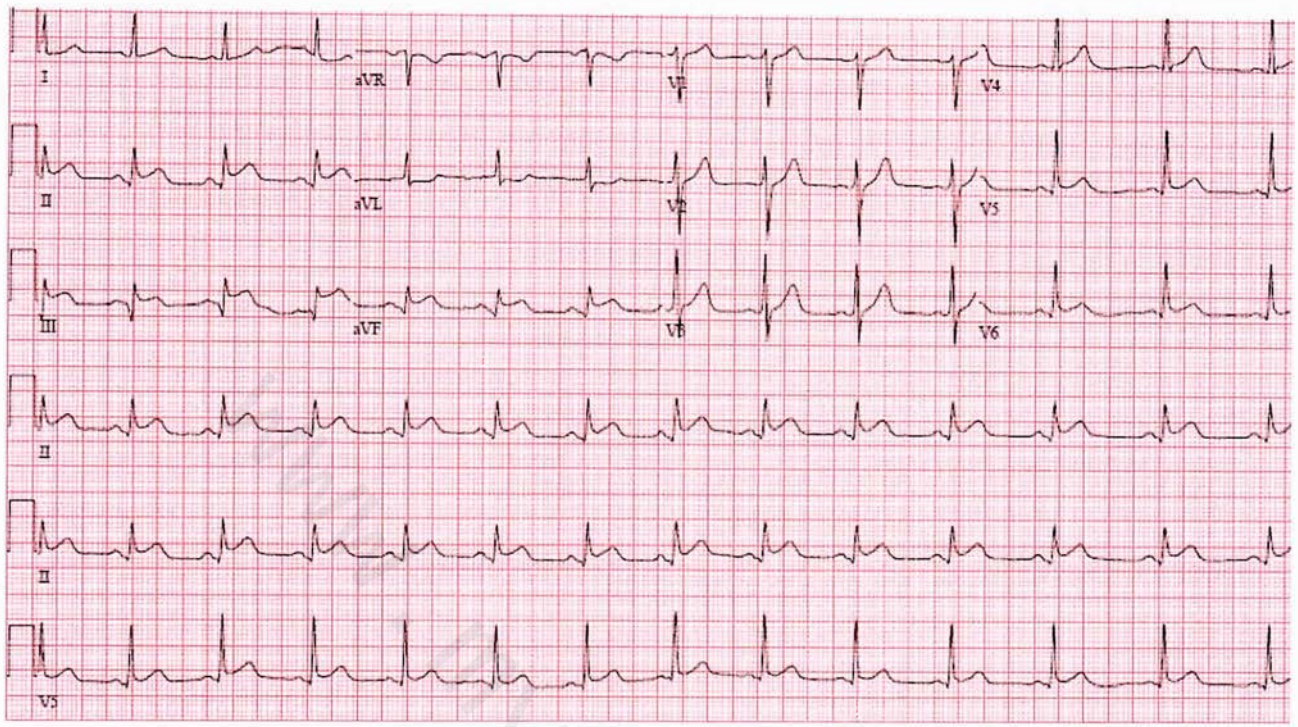

ITEM 92

Item 93

A 60-year-old man is evaluated for a murmur that was noted on a routine examination. He reports exertional dyspnea when walking up stairs. He has hypertension and takes lisinopril.

On physical examination, the patient is afebrile, blood pressure is 160/60 mm Hg, pulse rate is 90/min, and respiration rate is 16/min. Cardiac examination reveals a laterally displaced cardiac apex, soft S_1, and absent S_2. There is a grade 2/6 high-pitched blowing diastolic murmur at the left third intercostal space and a grade 1/6 rumbling mid-diastolic murmur at the apex.

Which of the following is the most likely diagnosis?

(A) Aortic regurgitation
(B) Mitral stenosis
(C) Patent ductus arteriosus
(D) Ruptured sinus of Valsalva aneurysm

Item 94

A 72-year-old woman is evaluated for cramping pain in the buttocks and thighs with standing and walking. Symptoms are exacerbated after standing at work for several hours and are relieved by sitting. Her symptoms have been present for 6 to 8 months and have been stable. Her medical history is significant for hypertension. She has a history of smoking but quit 12 years ago. Her medications are amlodipine and lisinopril.

On physical examination, vital signs are normal. BMI is 22. Deep tendon reflexes are decreased at the ankles but normal at the knees. Lower extremity muscle strength is normal. No abdominal or femoral bruit is present. No skin changes are noted in the lower extremities. Distal pulses are palpable bilaterally. The resting ankle-brachial index is 1.1 on both sides.

Which of the following is most likely to confirm the diagnosis?

(A) Exercise ankle-brachial index
(B) MRI of the lumbosacral spine
(C) Segmental limb plethysmography
(D) Toe-brachial index

Item 95

A 35-year-old woman with recently diagnosed nonischemic systolic heart failure and a left ventricular ejection fraction of 30% presents 1 week after hospital discharge with a new cough, increased exertional dyspnea, and peripheral edema. Medications are lisinopril (5 mg/d) and furosemide (40 mg/d).

On physical examination, blood pressure is 100/70 mm Hg, pulse rate is 98/min and regular, respiration rate is 13/min, and oxygen saturation on ambient air is 96%. Estimated central venous pressure is 15 cm H_2O. Her weight has increased by 2.3 kg (5 lb). Cardiac examination reveals a grade 2/6 holosystolic murmur at the apex and an S_3. Extremity examination reveals bilateral peripheral pitting edema.

Her electrocardiogram shows sinus rhythm and is unchanged from baseline. Serum electrolyte levels and kidney function tests are normal.

In addition to a low-sodium diet, which of the following is the most appropriate management?

(A) Increase furosemide
(B) Increase lisinopril
(C) Start carvedilol
(D) Start spironolactone

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Item 96

A 46-year-old man is evaluated in the emergency department for an episode of left facial and left upper extremity numbness and weakness that began just over 1 hour ago. The motor symptoms have resolved fully, but some numbness persists. He has no other medical problems and takes no medications.

On physical examination, vital signs are normal. BMI is 35. There are no carotid bruits or heart murmurs. The neurologic examination is now normal, with the exception of facial numbness.

Laboratory testing and electrocardiogram are normal. Carotid ultrasonography is normal. Magnetic resonance angiography demonstrates a small right-sided ischemic stroke but no other lesions. Ultrasonography of the lower extremities is normal.

A transesophageal echocardiogram is unremarkable with the exception of a patent foramen ovale with right-to-left shunt noted with cough and Valsalva release.

Which of the following is the most appropriate treatment?

(A) Aspirin
(B) Patent foramen ovale device closure
(C) Warfarin
(D) No therapy

Item 97

A 46-year-old man is evaluated in follow-up for a bicuspid aortic valve. He exercises regularly without any activity-limiting symptoms and feels well. His medical history is otherwise negative and he takes no medications.

On physical examination, blood pressure is 138/85 mm Hg. BMI is 28. A systolic ejection click followed by a crescendo-decrescendo murmur are noted at the left sternal border. No diastolic murmur is appreciated. The lower extremity pulses are normal. The remainder of the examination is unremarkable.

Transthoracic echocardiogram shows a bicuspid aortic valve with systolic doming of the aortic valve and a valve area of 1.7 cm^2. The mean gradient across the aortic valve is 22 mm Hg. The ascending aorta is dilated at 4.5 cm; the descending thoracic aorta is incompletely visualized. Chest CT demonstrates a 4.6-cm aneurysm of the ascending aorta with no evidence of coarctation and no enlargement of the descending aorta.

Which of the following is the most appropriate next step in management?

(A) Aortic valve replacement
(B) Aortic valve replacement and ascending aortic repair
(C) Ascending aortic repair
(D) Repeat echocardiogram in 1 year

Item 98

A 42-year-old woman is evaluated for episodes of palpitations that last several seconds in duration. They occur once or twice a month and are accompanied by lightheadedness and mild dyspnea. She has not experienced loss of consciousness. The episodes are not precipitated by any particular activity, including exercise. She takes no medications.

On physical examination, the patient is afebrile, blood pressure is 110/68 mm Hg, pulse rate is 72/min, and respiration rate is 16/min. BMI is 29. Cardiac examination reveals physiologic splitting of S_2, regular rate and rhythm, and no gallop. Estimated central venous pressure is normal. She has no edema. Serum thyroid-stimulating hormone level is normal.

A 12-lead electrocardiogram shows normal sinus rhythm.

Which of the following is the most appropriate diagnostic testing option?

(A) 30-Day wearable loop recorder
(B) Echocardiogram
(C) Exercise treadmill stress test
(D) 48-Hour ambulatory electrocardiographic monitor
(E) Implantable loop recorder

Item 99

A 56-year-old man is evaluated in the hospital for a 2-week history of fevers and malaise. Medical history is significant for a bicuspid aortic valve. The patient takes no medications.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 140/50 mm Hg, pulse rate is 98/min, and respiration rate is 16/min. There is no jugular venous distention. The lungs are clear. Cardiac examination reveals a grade 1/6 diastolic murmur. There are no signs of peripheral embolic disease. No lower extremity edema is present.

Electrocardiogram shows normal sinus rhythm, a PR interval of 230 ms, and nonspecific T-wave changes. Except for the increased PR interval, there are no changes compared with a prior tracing. A transthoracic echocardiogram shows a 6-mm vegetation on the aortic valve with mild to moderate aortic regurgitation. A transesophageal echocardiogram confirms the valve findings and suggests the presence of an area of fluid around the aortic annulus posterior to the vegetation, indicative of an aortic root abscess.

Blood cultures are positive for *Staphylococcus aureus* sensitive to methicillin. Appropriate antibiotics are started.

Which of the following is the most appropriate treatment?

(A) Antibiotic therapy for 6 weeks and then reassess
(B) Antibiotic therapy for 3 months and then reassess
(C) Aortic valve replacement after 6 weeks of antibiotic therapy
(D) Urgent aortic valve replacement

Item 100

A 26-year-old woman is evaluated in the emergency department for palpitations and pounding in her neck. She often gets these episodes and they typically last several minutes; however, this episode has been going on for 30 minutes. She can usually stop the episodes by bearing down, but on this occasion this has not worked. She reports feeling a little

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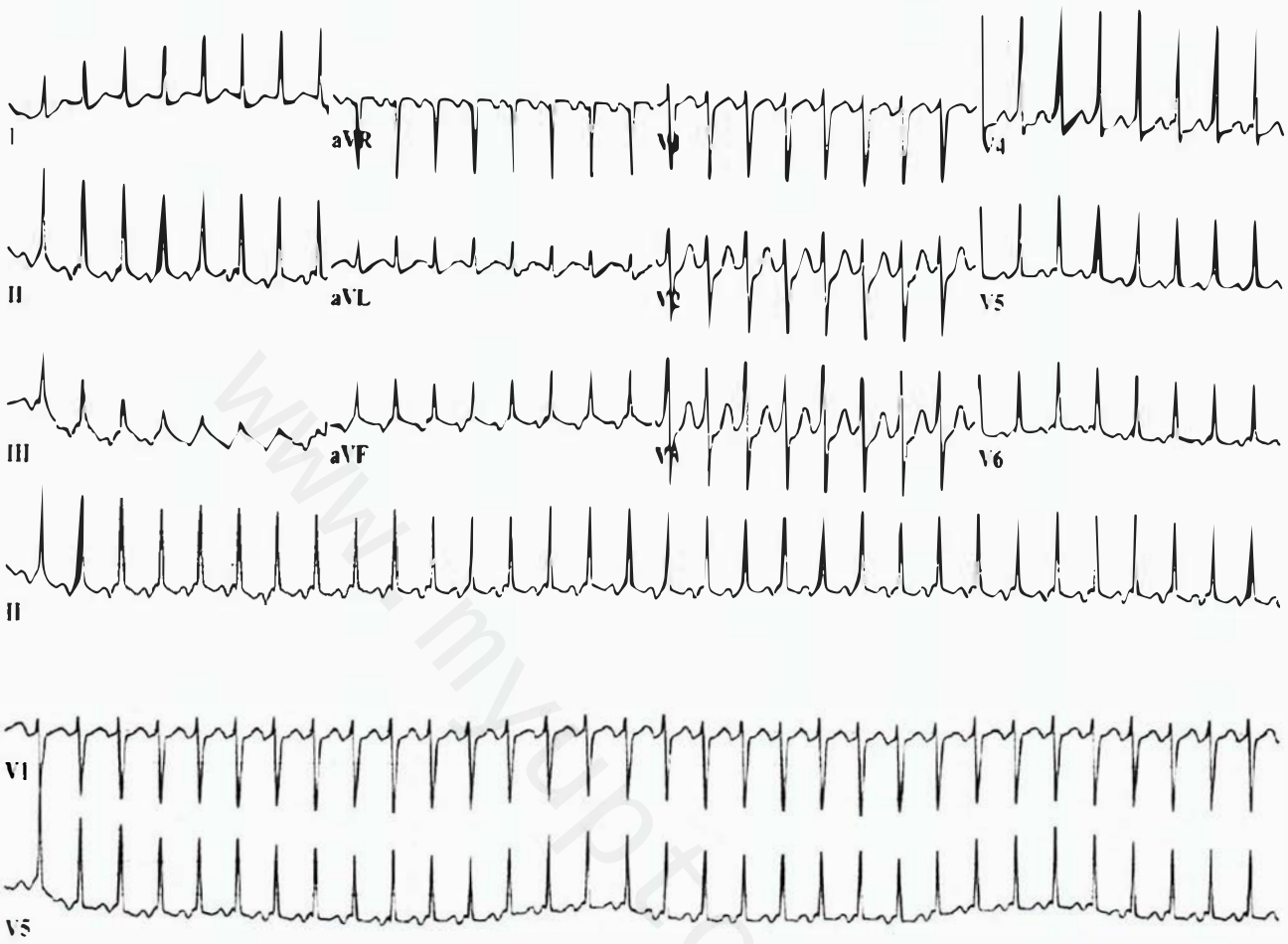

ITEM 100

CONT. short of breath, but she does not have chest pain or loss of consciousness. She has no other significant medical history, and her only medication is an oral contraceptive.

On physical examination, the patient is afebrile, blood pressure is 120/80 mm Hg, pulse rate is 145/min, and respiration rate is 18/min. BMI is 25. Cardiac examination shows tachycardia but regular rhythm. Lungs are clear to auscultation.

The electrocardiogram is shown.

Which of the following is the most appropriate treatment?

(A) Adenosine
(B) Amiodarone
(C) Cardioversion
(D) Ibutilide

Item 101

A 64-year-old man is evaluated before discharge from the hospital following a non-ST-elevation myocardial infarction treated with placement of a bare metal stent. He is currently pain free and tolerating his medications well. He notes no new symptoms. Medications prior to admission were aspirin, lisinopril, and atorvastatin; upon admission to the hospital, he began receiving metoprolol, clopidogrel, and intravenous heparin.

Vital signs are normal, and his physical examination is unremarkable.

In addition to continuing aspirin indefinitely, how long should this patient's clopidogrel therapy be continued?

(A) 2 weeks
(B) 1 month
(C) 1 year
(D) Lifelong

Item 102

A 68-year-old man is evaluated for progressive shortness of breath. He underwent heart transplantation 10 years ago for ischemic cardiomyopathy and has had no limitations of his activities since then until developing dyspnea with exertion over the past 3 weeks. Medical history is otherwise significant for hypertension, hyperlipidemia, and a 45-pack-year smoking history; he stopped smoking before his transplant. Medications are aspirin, lisinopril, atorvastatin, and tacrolimus.

On physical examination, blood pressure is 140/78 mm Hg, pulse rate is 102/min, and respiration rate is 16/min.

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CONT.

There is no jugular venous distention. The lungs are clear, and the heart examination is unremarkable. The remainder of the examination is normal.

Electrocardiogram demonstrates sinus tachycardia, right bundle branch block, and no Q waves. Echocardiogram shows a left ventricular ejection fraction of 55%, evidence of mild diastolic dysfunction, septal wall thickness of 0.9 cm, posterior wall thickness of 1.0 cm, and moderate tricuspid regurgitation.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Coronary angiography
(B) Endomyocardial biopsy
(C) Pulmonary function test
(D) Ventilation-perfusion lung scan

Item 103

A 69-year-old woman scheduled to undergo shoulder surgery is evaluated in the hospital for perioperative management of her cardiac device. She was diagnosed with heart failure 1 year ago, and a dual-chamber implantable cardioverter-defibrillator was placed. Her last device check was 3 months ago. Medical history is significant for previous myocardial infarction, coronary artery bypass graft surgery 1 year ago, ventricular tachycardia, and complete heart block. Medications are aspirin, metoprolol, lisinopril, furosemide, and spironolactone.

On physical examination, the patient is afebrile, blood pressure is 95/50 mm Hg, pulse rate is 64/min, and respiration rate is 16/min. BMI is 32. Estimated central venous pressure is normal. There is no carotid bruit. Cardiac auscultation reveals a normal rate and a fixed split S_2. Lungs are clear to auscultation. She has no edema.

An electrocardiogram shows sequential atrioventricular pacing.

Which of the following is the most appropriate preoperative device management?

(A) Disable shocking function
(B) Proceed with surgery and interrogate the device postoperatively
(C) Reprogram to asynchronous pacing and disable shocking function
(D) Advise against surgery

Item 104

A 38-year-old man is evaluated for gradually progressive exertional dyspnea. He had one episode of atrial fibrillation 1 year ago but converted spontaneously in the emergency department. No additional testing was performed at that time, and no medical therapy was initiated. He is otherwise healthy and has been active. His medical history is otherwise unremarkable. He takes no medications and has no allergies.

On physical examination, blood pressure is 120/70 mm Hg, pulse rate is 68/min and regular, and respiration rate is 16/min. BMI is 26. The estimated central venous pressure is elevated. There is a parasternal impulse at the left sternal border. Persistent splitting of the S_2 is noted. There is a soft midsystolic murmur at the second left intercostal space and a separate holosystolic murmur at the apex. The rest of the examination is normal.

The electrocardiogram is shown.

Which of the following is the most likely diagnosis?

(A) Coronary sinus atrial septal defect (ASD)
(B) Ostium primum ASD
(C) Ostium secundum ASD
(D) Patent foramen ovale
(E) Sinus venosus ASD



ITEM 104

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Item 105

An 82-year-old man was admitted to the coronary care unit (CCU) 48 hours ago after a late presentation with anterior ST-elevation myocardial infarction. The patient underwent coronary angiography and was found to have an occluded proximal left anterior descending coronary artery but did not undergo an attempt at revascularization at the time of coronary angiography because of his late presentation and symptomatic improvement. Today, he felt faint and lost consciousness while visiting with his family in the CCU. Medications are aspirin, ticagrelor, metoprolol, lisinopril, and atorvastatin.

On physical examination, blood pressure is 72/54 mm Hg and pulse rate is 108/min. Cardiac examination shows tachycardia with a normal S_1 and S_2, new holosystolic murmur heard best at the left lower sternal border that radiates to the apex, and a right ventricular heave. Crackles are heard at the bases of both lungs, one third of the way up. He has no lower extremity edema. The remainder of the examination is normal.

Electrocardiogram shows persistent ST-segment elevation and Q waves in leads V_1 through V_4. Heart rate is 110/min. Emergency transthoracic echocardiogram shows a left ventricular ejection fraction of 35% with severe anterior-apical akinesis, a small pericardial effusion, and a color flow jet across the ventricular septum, suggestive of left-to-right flow.

Which of the following is the most appropriate management?

(A) Emergency cardiac surgery
(B) Emergency pericardiocentesis
(C) Percutaneous coronary intervention to left anterior descending artery
(D) Right heart catheterization and dopamine infusion

Item 106

A 72-year-old woman is evaluated for progressive heart failure symptoms. She has a 10-year history of nonischemic heart failure. She currently experiences exertional dyspnea with climbing one flight of stairs, which she was able to do without shortness of breath 3 months ago. Medical history is significant for hypertension, and her medications are lisinopril, carvedilol, furosemide, digoxin, and spironolactone. The patient is black.

On physical examination, blood pressure is 134/72 mm Hg and pulse rate is 66/min. BMI is 35. She has no jugular venous distention. Cardiac examination reveals a grade 1/6 holosystolic murmur but is otherwise normal. There is no lower extremity edema. The remainder of her examination is unremarkable.

Laboratory studies are significant for normal electrolyte levels and a serum creatinine level of 1.5 mg/dL (133 µmol/L).

Electrocardiogram shows normal sinus rhythm, a QRS duration of 110 ms, and nonspecific ST-T wave changes. Echocardiogram shows a left ventricular ejection fraction of 38% and trace mitral regurgitation.

Which of the following is the most appropriate treatment?

(A) Add hydralazine and isosorbide dinitrate
(B) Add losartan
(C) Add warfarin
(D) Cardiac resynchronization therapy

Item 107

A 45-year-old man being treated for infective endocarditis is seen for a follow-up examination. He was diagnosed with endocarditis 1 week ago after presenting with fatigue and fever. Initial transthoracic echocardiogram showed a bicuspid aortic valve with a small vegetation but was otherwise normal. Blood cultures were positive for methicillin-sensitive *Staphylococcus aureus*, and intravenous nafcillin was initiated. Blood cultures obtained 48 hours and 72 hours after starting antibiotic therapy showed no growth.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 128/78 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. BMI is 25. Physical examination reveals no cutaneous or ocular stigmata of bacterial endocarditis. Cardiac examination reveals a grade 2/6 early systolic murmur at the base of the heart, unchanged from previous examinations. The remainder of the physical examination is normal.

Electrocardiogram is unchanged from the time of diagnosis except for an increase in the PR interval from 120 to 210 ms.

Which of the following is the most appropriate next step in management?

(A) Cardiac CT
(B) Continued antibiotic therapy without additional testing
(C) Repeat transthoracic echocardiogram
(D) Transesophageal echocardiogram

Item 108

A 58-year-old man is evaluated for a 3-month history of left upper extremity symptoms and dizziness. He is left-handed and works as a carpenter. He describes an aching sensation and feeling of fatigue in his arm and occasional dizziness that occur within 2 to 3 minutes of using a hand saw; these symptoms resolve several minutes after stopping activity. He is otherwise asymptomatic. Medical history is significant for hypertension, hyperlipidemia, and type 2 diabetes mellitus. He has a 40-pack-year smoking history but quit 1 year ago. Medications are lisinopril, atorvastatin, and metformin.

On physical examination, he is afebrile, left arm blood pressure is 135/76 mm Hg, pulse rate is 68/min, and respiration rate is 16/min. BMI is 29. The carotid upstrokes are normal. The chest is clear and the cardiac examination is normal. Examination of the left upper extremity is unremarkable, with palpable distal pulses and no evidence of distal ulceration or skin breakdown. The remainder of his physical and neurologic examination is unremarkable.

Which of the following elements of the physical examination would be most helpful in establishing the diagnosis?

(A) Ankle-brachial index
(B) Bilateral blood pressure measurement
(C) Evaluation for pulsus paradoxus
(D) Thoracic outlet maneuvers

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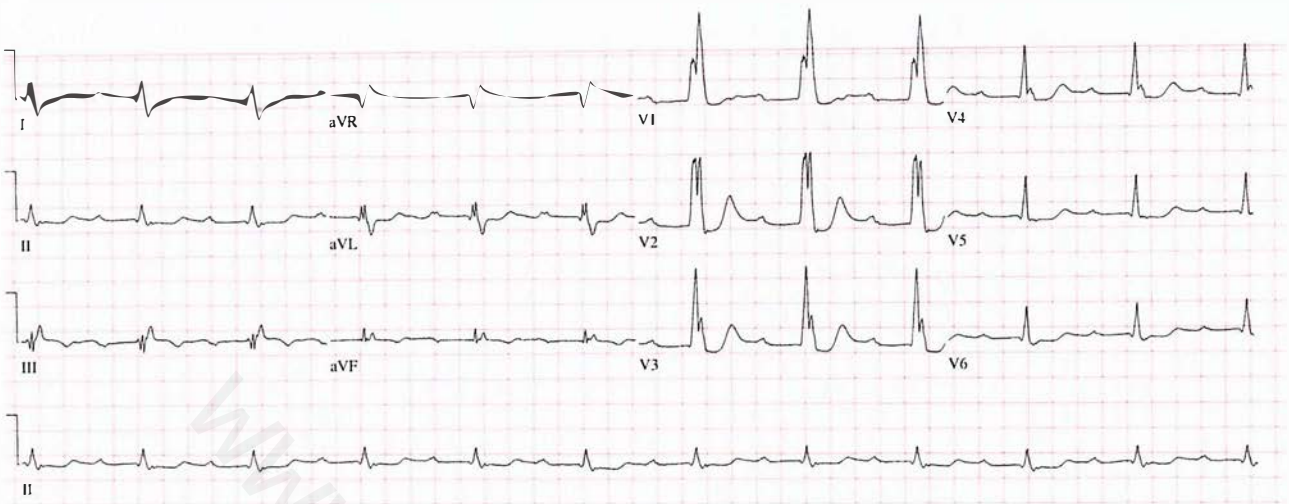

ITEM 109

Item 109

An 86-year-old man is evaluated in the emergency department after a fall. He reports tripping over a rug. He did not experience presyncope or other symptoms. He otherwise feels well and is active. Medical history is significant for hypertension. Family history is notable for pacemaker implantation in his sister. His only medication is lisinopril. A perfusion stress test 1 year ago obtained because of chest discomfort demonstrated normal left ventricular wall motion and ejection fraction.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 135/80 mm Hg, pulse rate is 67/min, and respiration rate is 12/min. BMI is 24. His neck veins are flat. The point of maximal impulse is in the mid-clavicular line without heave or lift. There is mild bruising over his left hip. He has no lower extremity edema.

Plain radiographs of the left hip are negative for fracture. Laboratory evaluation demonstrates a normal metabolic profile and preserved kidney function. His 12-lead electrocardiogram is shown.

Which of the following is the most appropriate management?

(A) Adenosine nuclear stress test
(B) Dual-chamber pacemaker
(C) Single-chamber pacemaker
(D) No intervention is indicated

Item 110

A 58-year-old woman is evaluated during a routine examination. She is asymptomatic. She had a myocardial infarction 4 years ago and has hypertension and dyslipidemia. She is a former smoker and consumes one alcoholic beverage daily. She has no limitations with physical activity and is able to exercise periodically. Medications are low-dose aspirin, hydrochlorothiazide, metoprolol, and high-dose atorvastatin.

On physical examination, blood pressure is 146/94 mm, and pulse rate is 52/min. BMI is 28. The remainder of the examination is normal.

Laboratory studies:

Total cholesterol	152 mg/dL (3.94 mmol/L)
LDL cholesterol	72 mg/dL (1.86 mmol/L) (pre-treatment baseline: 150 mg/dL [3.89 mmol/L])
HDL cholesterol	46 mg/dL (1.19 mmol/L)
Triglycerides	84 mg/dL (0.95 mmol/L)

One year ago, she underwent transthoracic echocardiography that was significant for normal left ventricular systolic function and no valvular abnormalities.

Which of the following interventions offers the greatest cardiovascular risk reduction to this patient?

(A) Add fish oil
(B) Add niacin
(C) Reduce alcohol consumption
(D) Start an ACE inhibitor

Item 111

A 52-year-old man is evaluated in the hospital for progressive chest pressure over the past 3 weeks. He has a 35-pack-year history of cigarette smoking. Medical history is significant for hypertension and hyperlipidemia treated with aspirin, hydrochlorothiazide, lisinopril, and pravastatin. His brother had a myocardial infarction at age 48 years.

On physical examination, he is afebrile, blood pressure is 148/82 mm Hg, and pulse rate is 98/min. Cardiac and lung examinations are normal.

Cardiac biomarkers are elevated. Initial electrocardiogram shows 2-mm ST-segment depression in leads I, aVL, and V_1 through V_6.

He is admitted to the coronary care unit and given aspirin, metoprolol, nitroglycerin paste, and enoxaparin. Over the course of the first 12 hours, his chest pressure worsens, requiring intravenous nitroglycerin infusion. Subsequently,

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CONT.

his chest pressure improves and he undergoes coronary angiography.

Coronary angiography is significant for a 70% left main coronary artery stenosis, 80% mid left anterior descending stenosis, and 90% proximal right coronary artery stenosis. Left ventricular ejection fraction is 45% with mild anterior hypokinesis. Mild mitral regurgitation is noted.

He is cu ently hemodynamically stable and pain free.

Which of the following is the most appropriate management?

(A) Coronary artery bypass graft surgery
(B) Intra-aortic balloon pump placement
(C) Percutaneous coronary intervention
(D) Continue current therapy

Item 112

A 60-year-old woman is evaluated in the hospital for a 3-week history of worsening dyspnea and chest pain. Medical history is significant for hypertension, hyperlipidemia, and previous coronary artery bypass graft surgery. Medications are aspirin, furosemide, metoprolol, and atorvastatin.

On physical examination, she is afebrile, blood pressure is 110/70 mm Hg, pulse rate is 92/min, and respiration rate is 16/min. Estimated central venous pressure is elevated. Examination at the cardiac base demonstrates a grade 3/6 late-peaking systolic murmur and a grade 1/6 diastolic murmur. An S_2 is not heard.

Echocardiogram shows a markedly calcified bicuspid aortic valve with severe aortic stenosis and moderate aortic regurgitation.

Which of the following is the most appropriate treatment?

(A) Aortic valve repair
(B) Balloon aortic valvuloplasty
(C) Surgical aortic valve replacement
(D) Transcatheter aortic valve replacement

Item 113

A 56-year-old woman is evaluated for a 1-year history of exertional dyspnea. She also occasionally experiences lightheadedness during intense aerobic activity, such as running. Symptoms are not associated with chest pain and have been relatively stable since onset. She also reports a 6.8-kg (15-lb) weight loss and intermittent fevers over the past 4 months. She had a colonoscopy and mammography 6 months ago with normal results. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, blood pressure is 120/72 mm Hg, and pulse rate is 62/min; BMI is 18. The jugular venous pulse, carotid upstroke, and lung examination findings are all normal. The precordium is quiet, and S_1 and S_2 are normal. A soft grade 2/6 diastolic rumble is heard at the apex and is preceded by an early diastolic filling sound. The remainder of the examination is unremarkable.

Echocardiogram shows a 2.5 × 2.2 cm mass in the left atrium; the mass is moderately mobile with a pedunculated stalk adherent to the fossa ovalis. Left ventricular function and the myocardium both appear normal. No pericardial effusion or significant disease involving the cardiac valves is present.

Which of the following tumors is the most likely cause of the patient's symptoms and clinical findings?

(A) Adenocarcinoma
(B) Angiosarcoma
(C) Lipoma
(D) Myxoma
(E) Papillary fibroelastoma

Item 114

A 38-year-old woman is evaluated for a 1-week history of substernal chest pain. Symptoms are aggravated by lying in the supine position or taking a deep breath. The patient is otherwise healthy and takes no medications.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 112/70 mm Hg, and pulse rate is 84/min. Systolic pressure variation with respiration is 5 mm Hg. The lungs are clear to auscultation. A loud, three-component cardiac rub is heard at the apex. S_1 and S_2 are normal. The remainder of the physical examination is unremarkable.

Laboratory studies are significant for a leukocyte count of 7000/μL (7.0×10^9/L). Echocardiogram shows normal left and right ventricles. A moderately sized circumferential pericardial effusion is noted. The inferior vena cava is normal in size. A Doppler ultrasound shows minimal change in mitral inflow with respiration.

High-dose ibuprofen, a proton pump inhibitor, and colchicine are started.

Which of the following is the most appropriate next step in management?

(A) Cardiac CT
(B) Clinical follow-up
(C) Glucocorticoid administration
(D) Inpatient monitoring
(E) Pericardiocentesis

Item 115

A 31-year-old man is evaluated for follow-up 2 days after an emergency department visit for palpitations. He reports intermittent palpitations and occasional episodes of shortness of breath. These episodes have increased in frequency and are often accompanied by light-headedness. He experienced loss of consciousness on one occasion. He does not have chest discomfort or jaw pain. His medical history is unremarkable except for a previous emergency department visit several years ago for palpitations. He has no significant family history.

On physical examination, the patient is afebrile, blood pressure is 105/68 mm Hg, pulse rate is 67/min, and respiration rate is 12/min. BMI is 24. His neck veins are flat, and the point of maximal impulse is in the midclavicular line without heave or lift. He has no lower extremity edema.

Serum thyroid-stimulating hormone level is normal.

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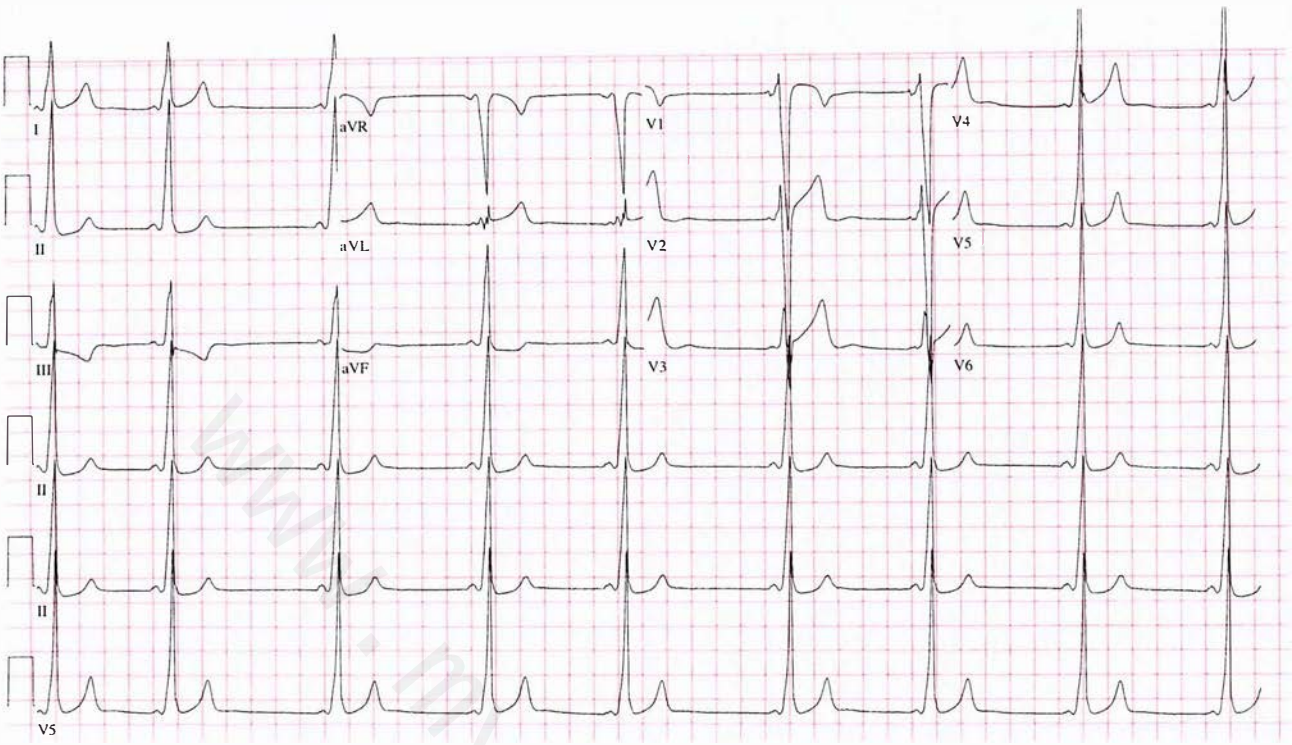

ITEM 115

Electrocardiogram is shown. Transthoracic echocardiogram shows no structural abnormalities.

Which of the following is the most appropriate next step in management?

(A) Antiarrhythmic drug therapy
(B) Diltiazem
(C) Electrophysiology study
(D) Metoprolol

Item 116

A 48-year-old woman is evaluated for a 3-week history of progressive dyspnea, palpitations, and peripheral edema. She has loose stools and a recent 2.3-kg (5-lb) weight loss. Medical history is unremarkable, and she does not use injection drugs. She does not take any medications and has no known drug allergies.

On physical examination, temperature is 37.3 °C (99.2 °F), blood pressure is 92/60 mm Hg, pulse rate is 118/min, and respiration rate is 22/min. BMI is 23. Jugular venous distention extends to the jaw. The thyroid is palpable but without identifiable nodules. The precordium is hyperdynamic, and an S_3 is heard on cardiac examination. She has severe bilateral lower extremity edema extending to the midcalf. Examination of the joints is normal, and there is no skin rash.

Leukocyte count is 6000/μL (6.0×10^9/L) with a normal differential. Results of complete blood count are normal. Electrocardiogram shows sinus tachycardia, no Q waves or T-wave abnormalities, and no signs of left ventricular hypertrophy. Echocardiogram shows a left ventricular ejection fraction of 10% and no valvular regurgitation.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Antinuclear antibody level
(B) Endomyocardial biopsy
(C) Thyroid studies
(D) Viral titers

Item 117

A 31-year-old woman is evaluated during a follow-up examination. Marfan syndrome was diagnosed 6 months ago and was confirmed by significant family history and the presence of ectopia lentis. She has been in good health and physically active. She does not report any chest discomfort, shortness of breath, syncope, or presyncope.

On physical examination, the patient is tall and slender. Blood pressure is 100/62 mm Hg and equal in both arms. Significant findings include a high arched palate, pectus excavatum, and arachnodactyly. The jugular and carotid examinations are normal. There is a grade 1/6 blowing diastolic murmur best heard at the left sternal border. The remainder of the examination is unremarkable.

Except for pectus excavatum, a chest radiograph is unremarkable. Transthoracic echocardiography shows enlargement of the aortic root, measuring 3.9 cm with mild aortic regurgitation, unchanged from previous imaging studies. The remainder of the echocardiographic examination is unremarkable.

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How frequently should this patient undergo surveillance imaging?

(A) Every 6 months
(B) Every 12 months
(C) Every 24 months
(D) Every 3 to 5 years

Item 118

A 59-year-old man is evaluated for a 3-month history of intermittent exertional chest discomfort. He has hypertension treated with lisinopril and amlodipine.

On physical examination, the patient is afebrile, blood pressure is 138/92 mm Hg, pulse rate is 82/min, and respiration rate is 14/min. BMI is 27. The remainder of the examination is unremarkable.

Exercise electrocardiographic stress testing shows 1.5-mm ST-segment depressions in leads II, III, and aVF; in addition, the patient developed chest pressure during this test. He exercised 4 minutes and stopped because of chest discomfort. Heart rate and blood pressure increased appropriately. Duke treadmill score is -11.5.

Which of the following is the most appropriate next step in management?

(A) Begin aspirin, β-blocker, and statin and re-evaluate in 2 weeks
(B) Cardiac catheterization
(C) Dobutamine stress echocardiography
(D) Exercise myocardial perfusion imaging

Item 119

A 26-year-old woman is evaluated in the emergency department for progressive dyspnea. She is 2 weeks postpartum. The pregnancy was complicated by preeclampsia but resulted in a normal delivery. The infant is healthy. She has no history of cardiovascular disease. Her only medication is prenatal vitamins.

On physical examination, the patient is afebrile. Blood pressure is 100/70 mm Hg in both arms, pulse rate is 105/min and regular, and respiration rate is 25/min. BMI is 29. The oxygen saturation on ambient air is 96%. The estimated central venous pressure is elevated. The apical impulse is diffuse. The S_1 and S_2 are soft. An S_4 and S_1 are present. A soft holosystolic murmur is heard at the apex. Crackles are heard over both lung fields. Pitting edema is noted to the knees.

An electrocardiogram is shown. An echocardiogram reveals a global reduction in contractility and left ventricular enlargement without hypertrophy.

Which of the following is the most likely diagnosis?

(A) Acute pulmonary embolism
(B) Ischemic cardiomyopathy
(C) Peripartum cardiomyopathy
(D) Stress-induced cardiomyopathy

Item 120

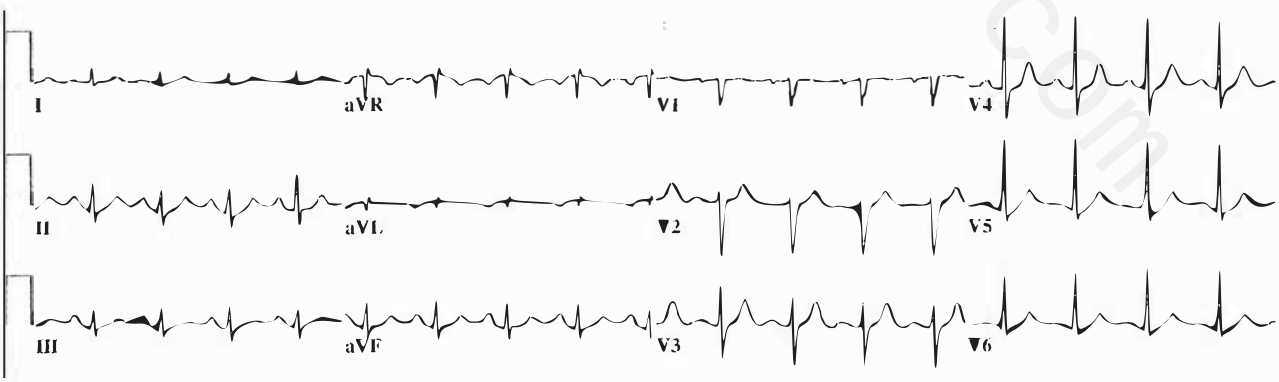
A 37-year-old man is evaluated for a 6-month history of exercise intolerance and shortness of breath when walking up stairs. He has no significant medical history and takes no medications.

On physical examination, blood pressure is 140/70 mm Hg, pulse rate is 62/min, and respiration rate is 16/min. Cardiac examination reveals an irregularly irregular rhythm. An opening snap is heard after S_2, followed by a grade 1/6 diastolic rumble at the apex.

Electrocardiogram shows atrial fibrillation. Transthoracic echocardiographic findings are consistent with rheumatic valve disease, showing a mildly thickened mitral valve with minimal calcification and mild restriction in leaflet motion. The subchordal apparatus is mildly thickened, and there is mild mitral regurgitation and marked left atrial enlargement. Mean gradient across the mitral valve is 13 mm Hg. Mitral valve area is 1.2 cm^2. Transesophageal echocardiogram shows no left atrial appendage thrombus and confirms transthoracic echocardiographic findings.

In addition to anticoagulation therapy, which of the following is the most appropriate management?

(A) Medical management; repeat echocardiogram in 6 months
(B) Mitral valve replacement
(C) Percutaneous mitral balloon valvuloplasty
(D) Surgical mitral valve repair



ITEM 119

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Answers and Critiques

Item 1 Answer: B

Educational Objective: Diagnose pulmonary valve regurgitation as a late consequence of tetralogy of Fallot repair.

The most likely diagnosis is pulmonary valve regurgitation. Tetralogy of Fallot comprises a large subaortic ventricular septal defect, infundibular or valvular pulmonary stenosis, aortic override, and right ventricular hypertrophy. Pulmonary regurgitation is the most common structural disorder that occurs following tetralogy of Fallot repair. The clinical findings include features of right heart volume overload with a parasternal (right ventricular) lift and a soft systolic pulmonary outflow murmur. There is a single S_2 because the function of the pulmonary valve is sacrificed during repair. The diastolic murmur heard at the left sternal border that increases in intensity with inspiration is caused by pulmonary valve regurgitation.

Aortic valve regurgitation can occur late in patients following tetralogy of Fallot repair owing to progressive aortic enlargement. The aortic diastolic murmur is generally heard at the left sternal border, but it decreases in intensity with inspiration. A right ventricular prominence would not be expected in a patient with aortic regurgitation.

Recurrent ventricular septal defect also can occur in patients following tetralogy of Fallot repair. However, the physical examination findings would include a systolic murmur heard at the left sternal border, which often obliterates the S_1 and S_2. A right ventricular prominence would not be expected in a patient with a recurrent ventricular septal defect.

Tricuspid valve regurgitation may occur late in patients following tetralogy of Fallot repair owing to progressive right ventricular and annular dilatation from long-standing severe pulmonary valve regurgitation. The physical examination findings include a holosystolic murmur located at the lower left sternal border that increases with inspiration. The systolic murmur in the patient presented here is soft and heard over the pulmonary valve region.

KEY POINT

- Pulmonary regurgitation is the most common structural disorder that occurs following tetralogy of Fallot repair.

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Item 2 Answer: D

Educational Objective: Use high-sensitivity C-reactive protein level to guide treatment and cardiac risk stratification in a patient at intermediate risk of cardiovascular disease.

The most appropriate management of this patient is to obtain high-sensitivity C-reactive protein (hsCRP) levels. He has an intermediate risk of myocardial infarction and coronary death (5% to below 7.5% as defined by the Pooled Cohort Equations). The measurement of hsCRP has been proved to be useful for guiding primary prevention strategies in intermediate-risk patients, with as many as 30% of patients being reclassified as either low risk or high risk based on hsCRP measurement.

When used for this purpose, the CRP assay should be able to detect levels to at least 0.03 mg/L (high sensitivity); a single test is appropriate in patients with levels below 1.0 mg/L, but testing should be repeated in 2 weeks for values of 1.0 mg/L or higher to assess for persistent elevation. Patients with hsCRP measurement below 1.0 mg/L are considered at a low relative risk for coronary heart disease and those with levels of 3.0 mg/L or higher are considered at a high relative risk. A meta-analysis from the Emerging Risk Factors Collaboration in 2010 found that hsCRP levels have a strong linear association with both ischemic stroke and vascular mortality. Although evidence is not strong that modification of risk can occur with treatment after hsCRP measurement, the JUPITER study randomized patients with serum LDL cholesterol levels below 130 mg/dL (3.37 mmol/L) and hsCRP levels greater than or equal to 2.0 mg/L to rosuvastatin or placebo. Patients were followed for the occurrence of death, myocardial infarction, stroke, or a composite of first major cardiovascular event for 5 years. In addition to lowering serum LDL cholesterol levels from 108 to 55 mg/dL (2.80 to 1.42 mmol/L) and hsCRP from 4.2 to 2.2 mg/L, rosuvastatin significantly reduced the incidence of major cardiovascular events.

Because this patient is asymptomatic, adenosine cardiac magnetic resonance (CMR) imaging, cardiac CT angiography, and stress echocardiography are not indicated and have not been associated with reduction in cardiovascular events.

There is currently no role for the evaluation of lipid particle size and number (fractionated lipoprotein profiling). No studies to date have shown that treatment targeted to lipoprotein particle size and number affects outcomes, and the use of these tests is not addressed in current cholesterol management guidelines.

KEY POINT

- In patients with an intermediate risk of cardiovascular disease, the measurement of high-sensitivity C-reactive protein (hsCRP) has been proved to be useful for guiding primary prevention strategies, with as many as 30% of patients being reclassified as either low risk or high risk based on the hsCRP measurement.

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Item 3 Answer: C

Educational Objective: Evaluate a patient with a diastolic murmur.

This asymptomatic patient has a diastolic murmur and should undergo transthoracic echocardiography (TTE). TTE is indicated for asymptomatic patients with a systolic murmur that is grade 3/6 or higher, a late or holosystolic murmur, or a diastolic or continuous murmur; TTE is also indicated for patients with a murmur and accompanying symptoms.

Chest CT may be helpful in the further evaluation of patients with documented aortic valve pathology (such as identification of a bicuspid valve or screening for concomitant aortopathy in a patient with a bicuspid aortic valve), but it would not be the first step in identifying the cause of this patient's murmur and would expose the patient to unnecessary radiation.

Exercise echocardiography stress testing is most commonly used to evaluate for coronary heart disease in those ineligible for electrocardiographic stress testing, although in selected patients it may be helpful in evaluating the hemodynamic significance of valvular disease. Diastolic murmurs tend not to vary with exercise; therefore, exercise echocardiography stress testing would not be an appropriate initial test to help clarify the cause of the murmur.

Although there are multiple benign causes of systolic murmurs, diastolic murmurs are virtually always considered abnormal. Therefore, further evaluation of this patient's cardiac findings is needed.

KEY POINT

- Transthoracic echocardiography is indicated for asymptomatic patients with a systolic murmur that is grade 3/6 or higher, a late or holosystolic murmur, or a diastolic or continuous murmur and for patients with a murmur and accompanying symptoms.

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Item 4 Answer: A

Educational Objective: Manage thromboembolic risk following atrial fibrillation ablation.

This patient should continue taking warfarin. She has a history of symptomatic atrial fibrillation and is now symptom-free without evidence of recurrent atrial fibrillation after catheter ablation. However, patients with successful ablation and elimination of symptoms may have transient asymptomatic atrial fibrillation with continued risk for atrial fibrillation–associated thromboembolic disease. Therefore, current consensus recommendations counsel that stroke prevention therapy following atrial fibrillation ablation be based on risk factors and not rhythm status, with the preferred risk stratification tool being the CHA_2DS_2-VASc risk score, which has improved predictive ability relative to the $CHADS_2$ score. The patient is a 58-year-old woman with a prior transient ischemic attack (TIA) and hypertension. Accordingly, her CHA_2DS_2-VASc risk score is 4 (2 points for TIA, 1 point for hypertension, and 1 point for female sex). Current guidelines advocate oral anticoagulation for any patient with nonvalvular atrial fibrillation and a CHA_2DS_2-VASc score greater than 1. She has a history of a central nervous system event, and her annual risk of stroke is high (greater than 5% annually). Therefore, she should be continued on anticoagulation with warfarin.

Concomitant aspirin therapy with warfarin is reserved for patients with active coronary artery disease. This patient has risk factors for atherosclerosis, but she does not have a history of coronary artery disease or acute coronary syndromes. The addition of aspirin to warfarin significantly increases the risk of bleeding.

Discontinuation of warfarin and substitution with aspirin or dual antiplatelet therapy is not correct. Aspirin is insufficient therapy for a patient at high risk of stroke. The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) trial compared warfarin with therapy with aspirin and clopidogrel and found that aspirin with clopidogrel was inferior to warfarin for stroke prevention with no statistically significant difference in bleeding.

Anticoagulation with a novel oral anticoagulant (such as dabigatran, rivaroxaban, or apixaban) could be considered; however, these agents have been associated with increased gastrointestinal bleeding compared with warfarin.

KEY POINT

- Stroke prevention therapy after catheter ablation of atrial fibrillation should be based upon risk stratification, not heart rhythm status.

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Item 5 Answer: A

Educational Objective: Treat a patient with hypertrophic cardiomyopathy.

Hydrochlorothiazide should be discontinued in this patient. She has mild symptoms of obstructive hypertrophic cardiomyopathy (HCM). Dynamic left ventricular outflow tract (LVOT) obstruction affects 70% of patients with HCM and is exacerbated by decreases in preload (for example, from diuretic

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use or squat-to-stand maneuvers) and afterload (for example, from expiration or vasodilator therapy) and by increases in myocardial contractility (for example, from digoxin therapy). For patients with symptoms of HCM, the initial treatment is medical therapy that addresses the factors that predispose toward LVOT obstruction. Use of hydrochlorothiazide and other diuretics, particularly in high doses, will exacerbate the propensity towards dynamic LVOT obstruction and, therefore, should be avoided in patients with HCM. Similarly, vasodilator therapy also should not be used. Negative inotropic agents, such as β-receptor antagonists, calcium channel blockers, and disopyramide, are the cornerstone of medical therapy in these patients. This patient was previously stable on hydrochlorothiazide; however, HCM and its associated pathophysiology can manifest at any age and result in symptoms of heart failure.

Dual-chamber pacemaker implantation previously was considered to be a therapeutic option but was found to be relatively ineffective in randomized clinical trials of patients with HCM. These trials showed a significant placebo effect (40%-50%) from dual-chamber pacing without clear clinical benefit.

ACE inhibitors, such as lisinopril, reduce afterload and can exacerbate LVOT obstruction, and therefore they should be avoided in patients with HCM.

For patients with drug-refractory, severely symptomatic obstructive HCM, septal reduction therapy with surgical myectomy or alcohol septal ablation may be considered. Neither myectomy nor alcohol ablation is recommended for patients with the minimal symptoms that this patient has or for those without an adequate trial of appropriate pharmacotherapy.

KEY POINT

- Diuretics, particularly in high doses, will exacerbate the propensity towards dynamic left ventricular outflow tract obstruction and, therefore, should be avoided in patients with hypertrophic cardiomyopathy.

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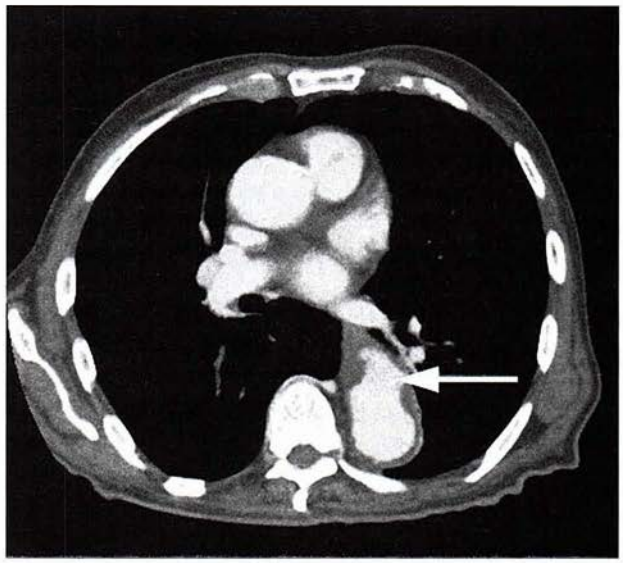
Item 6 Answer: C

Educational Objective: Treat a penetrating atherosclerotic ulcer in the descending aorta.

The most appropriate management for this patient is intravenous β-blockade followed by intravenous sodium nitroprusside. The CT scan (shown, see top of next column) reveals a focal penetrating atherosclerotic ulcer (PAU) in the proximal descending aorta (*arrow*), a type B acute aortic syndrome. PAU is a focal defect or lesion occurring at the site of an intimal atherosclerotic plaque. Patients tend to be older and with greater cardiovascular comorbidity. PAU occurs most



commonly in the descending aorta, which may reflect a greater burden of atheromatous disease at this site. Elevation of the D-dimer level frequently accompanies acute aortic syndromes. Uncomplicated type B acute aortic injury is best treated medically, initially with β-blockade to decrease the heart rate to below 60/min followed by a parenteral arterial vasodilator as needed to control blood pressure.

Chest pain is a common presenting symptom in the emergency department, and three potentially lethal causes must be rapidly excluded: acute myocardial infarction, pulmonary embolism, and an acute aortic syndrome. Anticoagulation therapy would be considered standard of care if an acute coronary syndrome were suspected. In this patient, although a non–ST-elevation myocardial infarction cannot be excluded based on the electrocardiogram, it is less likely given his normal troponin I level; the troponin level would likely be elevated after 3 hours of ongoing cardiac ischemia. The patient also has a low pretest probability of pulmonary embolism by Wells scoring. Given his clinical and radiographic presentation, neither alternative diagnosis to an acute aortic syndrome is likely, and anticoagulation is not indicated in acute aortic syndrome.

Malperfusion syndromes are uncommon with an aortic penetrating atherosclerotic ulcer but could occur with transformation to classic dissection. In such cases, emergency endovascular stenting with or without fenestration may be necessary. This patient shows no evidence of lower limb or visceral malperfusion, and catheterization with endovascular repair is not indicated. Emergency open surgery is rarely indicated in this setting with the advent of endovascular therapies.

KEY POINT

- Uncomplicated type B acute aortic injury is best treated medically, initially with β-blockade followed by a parenteral arterial vasodilator to control blood pressure.

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Item 7 Answer: B

Educational Objective: Diagnose effusive constrictive pericarditis.

The most likely diagnosis in this patient is effusive constrictive pericarditis. Effusive constrictive pericarditis is a clinical entity in which patients who have a pericardial effusion, with or without cardiac tamponade, experience persistent symptoms and hemodynamic derangements after treatment and relief of the pericardial effusion. In some patients with constrictive pericarditis, pericardial inflammation results in an effusion, which is placed under pressure by the inelastic pericardium. Symptoms of low cardiac output, systemic congestion, and an elevated jugular venous pulse are seen, as in constrictive pericarditis; however, in patients with effusive constrictive pericarditis, a pericardial knock is absent and the *y* descent of the jugular venous pulse may be less prominent. Additionally, pulsus paradoxus may be present, which is not a typical finding of constrictive pericarditis. This disorder is caused by pericarditis involving the visceral layer of the pericardium. Thickening of the visceral layer of the pericardium can be difficult to detect with CT and other noninvasive imaging, and a high index of clinical suspicion is necessary to establish the diagnosis. In this patient, effusive constrictive pericarditis is suggested by the persistently elevated right atrial pressure following pericardiocentesis.

Similar findings in the jugular venous pulse can occur in patients with cor pulmonale or heart failure. With cor pulmonale, however, evidence of right ventricular dysfunction or chamber enlargement is usually seen on imaging. The clear lungs on auscultation do not support the presence of heart failure.

The presence of a normal electrocardiogram and the absence of the typical symptom of chest pain argue against recurrent acute pericarditis as a diagnosis. Additionally, acute pericarditis cannot explain this patient's pulsus paradoxus and elevated jugular venous pulse.

KEY POINT

- Effusive constrictive pericarditis is a clinical entity in which patients who have a pericardial effusion experience persistent symptoms and hemodynamic derangements after relief of the pericardial effusion.

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Item 8 Answer: B

Educational Objective: Manage high LDL cholesterol level in a patient with diabetes mellitus and an elevated risk for coronary artery disease.

The most appropriate management in this patient with a coronary heart disease (CHD) risk equivalent is to switch to atorvastatin, 40 mg/d. Current guidelines recommend that statin therapy be initiated in patients at high risk for CHD. The intensity of the statin therapy should be tailored to the CHD risk. Candidates for high-intensity statin therapy include:

- Patients with known atherosclerotic disease (clinical CHD, cerebrovascular disease, or peripheral arterial disease)
- Patients with an LDL cholesterol level 190 mg/dL (4.92 mmol/L) or greater
- Patients with diabetes mellitus, an LDL cholesterol level below 190 mg/dL (4.92 mmol/L), and calculated 10-year CHD risk of 7.5% or higher
- Some patients without diabetes with an LDL cholesterol level below 190 mg/dL (4.92 mmol/L) and calculated 10-year CHD risk of 7.5% or higher

Moderate-intensity statin therapy can be considered for:

- Patients with diabetes who are not receiving high-intensity therapy
- Most patients without diabetes with an LDL cholesterol level below 190 mg/dL (4.92 mmol/L) and calculated 10-year CHD risk of 7.5% or higher
- Some patients without diabetes with an LDL cholesterol level below 190 mg/dL (4.92 mmol/L) and calculated 10-year CHD risk of 5% or higher but lower than 7.5%

This patient has diabetes, an LDL cholesterol level less than 190 mg/dL (4.92 mmol/L), and a calculated 10-year CHD of 10%, and, therefore, should be considered for high-intensity statin therapy. Drugs and doses that constitute high-intensity statin therapy include atorvastatin, 40 to 80 mg/d; rosuvastatin, 20 to 40 mg/d; and simvastatin, 80 mg/d. (The FDA has issued a warning regarding the incidence of muscle injury with products that contain 80 mg of simvastatin and recommends that patients be switched to a different statin rather than increasing the dosage of simvastatin to 80 mg/d.)

Fluvastatin, 40 mg/d; lovastatin, 20 mg/d; pravastatin, 10 mg/d; and simvastatin, 10 mg/d, are all classified as low-intensity dosing and are inadequate to reduce this patient's CHD risk.

KEY POINT

- Patients with diabetes mellitus should receive moderate- or high-intensity statin therapy to reduce their risk of coronary heart disease.

Bibliography

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Item 9 Answer: A

Educational Objective: Manage ACE inhibitor side effects in a patient with heart failure.

The most appropriate treatment for this patient is to switch from her ACE inhibitor (lisinopril) to an angiotensin receptor blocker (ARB), such as valsartan, and observe her closely for several weeks to see if her cough resolves. For patients with heart failure, the two most common causes of a nonproductive cough are volume overload and ACE inhibitors. An ACE inhibitor–induced cough may occur at any time after an ACE inhibitor has been initiated, and it would not be surprising that she could develop an ACE inhibitor cough after 9 months of therapy. The most appropriate course of therapy, therefore, would be to switch to an ARB. Although data regarding mortality outcomes in patients with heart failure taking ARBs are limited, results thus far demonstrate equivalent mortality outcomes and fewer medication-related adverse events in this setting.

An echocardiogram evaluates left ventricular function and valvular abnormalities. It would not be helpful in a patient with diagnosed heart failure to assess for volume overload. Indications for repeating echocardiograms in patients with heart failure include a decline in functional status and to reassess function after uptitrating medications. Additionally, in patients followed over time, repeating an echocardiogram every 2 to 3 years is indicated to assess for further left ventricular dilation and evaluate left ventricular ejection fraction for further decline. It is unlikely to be helpful in this patient, who has no evidence of volume overload on examination and no pulmonary edema on chest radiograph.

B-type natriuretic peptide (BNP) level is useful for the assessment of acute dyspnea. Studies have shown that levels of BNP are elevated in patients with heart failure. Additionally, higher levels are associated with an increase in mortality. BNP has not been demonstrated to be useful to guide diuresis in patients with heart failure. In a patient with a history of heart failure, a random BNP level would not help in the assessment of fluid overload being the cause of a cough.

Pulmonary function testing is useful primarily in the evaluation of dyspnea or to assess for the presence of underlying lung disease that might contribute to cough, such as cough-variant asthma. However, this patient has no clinical history or increased risk for lung disease, is a never-smoker, and has a normal lung examination. Therefore, pulmonary function testing would not be appropriate prior to a trial of medication adjustment.

KEY POINT

- An ACE inhibitor–induced cough may occur at any time after an ACE inhibitor has been initiated; the best course of therapy is to switch to an angiotensin receptor blocker.

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Item 10 Answer: D

Educational Objective: Manage incidental finding of atrial septal aneurysm with patent foramen ovale.

No further evaluation or treatment is the appropriate management approach for this patient with an incidentally discovered atrial septal aneurysm. Atrial septal aneurysm is redundant atrial septal tissue that is often associated with a patent foramen ovale. When atrial septal aneurysm is identified incidentally, no medical treatment or intervention is needed. Antiplatelet therapy is recommended for patients with cryptogenic stroke and an isolated atrial septal aneurysm.

In patients with an atrial septal aneurysm and recurrent stroke while taking antiplatelet therapy, anticoagulant therapy is recommended if no other cause of stroke is identified.

Rarely, surgical excision of an atrial septal aneurysm and defect closure is considered in patients in whom antiplatelet or warfarin therapy fails to prevent stroke recurrence or in patients with a large left-to-right shunt causing right heart enlargement. Percutaneous device closure is rarely performed in patients with atrial septal aneurysms, because a large device is required to plicate the atrial septal aneurysm and close multiple fenestrations.

Atrial septal aneurysms are most commonly detected by transesophageal echocardiogram. However, when an incidental atrial septal aneurysm is well visualized by transthoracic echocardiogram, additional imaging with a transesophageal echocardiogram is not needed.

KEY POINT

- When an atrial septal aneurysm is identified incidentally, no further evaluation, medical treatment, or intervention is needed.

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Item 11 Answer: B

Educational Objective: Manage a patient with stable angina pectoris and a low-risk stress test result.

In this patient with ongoing stable angina pectoris and a low-risk exercise stress test result (that is, a Duke treadmill score of +6), initiation of a long-acting nitrate such as isosorbide mononitrate is recommended by current guidelines. β-Blockers and nitrates improve functional capacity, delay onset of exercise-induced myocardial ischemia, and decrease the frequency and severity of anginal episodes. Most patients with stable angina will require combination therapy with these two classes of drugs to achieve effective control of

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anginal symptoms. Although this patient is at low risk, initiation of medical therapy is also appropriate in patients who are at intermediate risk and high risk based on clinical risk factors, symptom burden, and/or stress testing results. Those patients with intermediate-risk stress test findings (Duke treadmill score of -10 to +4) and high-risk stress testing findings (Duke treadmill score of less than -11) have a 1% to 3% cardiovascular mortality per year and a 3% or higher cardiovascular mortality rate per year, respectively.

Calcium channel blockers, such as diltiazem, are second-line therapy in patients with stable angina pectoris who are intolerant of β-blockers or who have continued symptoms on β-blockers and nitrates. This patient is tolerating his β-blocker well and is not yet taking a nitrate for his angina. Therefore, diltiazem is not indicated at this time.

Because of the invasive nature of coronary angiography and the inherent risks of vascular complications, it should be reserved for patients with lifestyle-limiting angina despite optimal medical therapy or high-risk criteria on noninvasive stress testing such as significant ST-segment depression at a low work load, ST-segment elevation, or hypotension.

Pharmacologic nuclear stress testing is not indicated in this patient owing to the presence of stable symptoms, lack of optimal medical therapy, and low-risk findings on exercise stress testing.

KEY POINT

- First-line antianginal therapy for patients with stable angina pectoris is β-blockers and nitrates.

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Item 12 Answer: C

Educational Objective: Diagnose bicuspid aortic valve.

This patient most likely has a bicuspid aortic valve. Bicuspid aortic valve is the most common congenital heart lesion, occurring in approximately 0.5% to 2% of the general population. It is the second most common cause of aortic stenosis after calcific degeneration of a tricuspid aortic valve and the second most common cause of aortic regurgitation after aortic root dilation. Many patients with a bicuspid aortic valve are asymptomatic, with the diagnosis being suggested based on incidentally noted auscultatory findings. The presenting murmur depends on the degree of valve dysfunction, with a systolic ejection murmur that varies in intensity, ranging from minimal flow disturbance to findings consistent with the murmur of aortic stenosis as the degree of outflow obstruction increases. A diastolic murmur may occur if aortic valve incompetence with regurgitation is present, as in this patient. Bicuspid aortic valve has an increased prevalence associated with congenital lesions such as aortic coarctation, interrupted aortic arch, and Turner syndrome. More than 70% of patients with a bicuspid aortic valve will require surgical intervention for a stenotic or regurgitant valve or aortic pathology over the course of a lifetime. The presence of a bicuspid aortic valve increases the risk for aortic stenosis or regurgitation, and stenosis proceeds at a faster rate when the aortic valve is bicuspid. The risk for infective endocarditis also is increased in these patients. In addition, bicuspid aortic valve is associated with aortopathy and a predisposition to aneurysm formation and thoracic aortic dissection.

Adults with previously undiagnosed aortic coarctation may present with hypertension or a murmur. Palpation of reduced femoral pulses and measurement of discrepant blood pressures during routine examination are helpful in raising suspicion for the diagnosis. The murmur associated with coarctation may be nonspecific but is usually a systolic murmur in the left infraclavicular area and under the left scapula.

The murmur associated with an atrial septal defect is a midsystolic flow murmur caused by the ejection of increased right-sided volume, owing to the left-to-right shunt that occurs initially with this defect. This murmur is best heard over the pulmonic area of the chest and may radiate toward the back, as with the murmur of pulmonary stenosis. The most characteristic finding on auscultation in patients with an atrial septal defect is a fixed split S_2.

The murmur of mitral stenosis is a diastolic low-pitched decrescendo murmur heard best in the left lateral decubitus position. With mitral stenosis, S_1 has increased intensity and S_2 is normal. The opening snap, which is due to forceful opening of the mitral valve, occurs when the pressure in the left atrium is greater than the pressure in the left ventricle. As the severity of the mitral stenosis increases, the pressure in the left atrium increases, and the mitral valve opens earlier in ventricular diastole.

KEY POINT

- A bicuspid aortic valve is often discovered incidentally; the murmur depends on the degree of valve dysfunction, with a systolic ejection murmur that may range from a minimal flow disturbance to findings consistent with the murmur of aortic stenosis as the degree of outflow obstruction increases.

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Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol. 2010 Jun 22;55(25):2789-800. [PMID: 20579534]

Item 13 Answer: C

Educational Objective: Recommend influenza vaccination for the secondary prevention of ischemic heart disease.

Providing this patient with an annual influenza vaccination would significantly reduce her risk of future cardiovascular events. A meta-analysis of randomized trials demonstrated that use of the influenza vaccine was associated with a 36%

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lower risk of major adverse cardiovascular events compared with nonimmunized patients. Based on these data, the American Heart Association and American College of Cardiology recommend influenza vaccination for the secondary prevention of ischemic heart disease. In addition to influenza vaccination as a preventive measure for cardiovascular disease, this patient also qualifies for influenza vaccination according to Advisory Committee on Immunization Practices (ACIP) guidelines that recommend all persons aged 6 months or older receive the influenza vaccination.

Colchicine has anti-inflammatory properties, and observational studies of patients taking colchicine for gout or familial Mediterranean fever suggest a decreased risk of cardiovascular disease associated with treatment. However, its use for secondary prevention of cardiovascular disease has not been established.

Folic acid lowers homocysteine levels, which have been associated with increased cardiovascular disease in observational studies. However, clinical trials examining the effectiveness of lowering homocysteine levels by folic acid supplementation have failed to show a reduction in adverse cardiovascular events. Folic acid supplementation for this purpose is therefore not recommended as secondary prevention.

Because inflammation and oxidative stress are involved in atherosclerosis, the use of antioxidant agents, including vitamins E and C and β-carotene, has been proposed as both a primary and secondary preventive intervention for cardiovascular disease. Although supported by some basic science and observational data, several large, randomized controlled trials have failed to document benefit of antioxidant therapy for either purpose. Therefore, the use of vitamin E supplementation would not be appropriate in this patient.

KEY POINT

- Influenza vaccine should be administered to patients with established cardiovascular disease to reduce the risk of future cardiovascular events.

Bibliography

Udell JA, Zawi R, Bhatt DL, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. JAMA. 2013 Oct 23;310(16):1711-20. [PMID: 24150467]

Item 14 Answer: C

Educational Objective: Treat acquired QT-interval prolongation.

Both amitriptyline and moxifloxacin should be discontinued in this patient. Her electrocardiogram (ECG) demonstrates QT-interval prolongation. Many medications may prolong the QT interval, including amitriptyline and moxifloxacin; QT prolongation may be markedly increased in patients taking more than one medication with this effect.

The corrected QT interval (QTc) is most often determined using the Bazett formula (QT interval / $\sqrt{\text{R-R interval}}$). This patient's ECG at the time of admission shows a QTc interval of 630 ms; a normal QTc is defined as 460 ms or less in women and 440 ms or less in men. A QTc greater than 500 ms is associated with increased risk of torsades de pointes.

The cause of this patient's QT prolongation is likely her pharmacotherapy. Many drugs have been implicated in QT-interval prolongation, including antiarrhythmic agents, antibiotics (including some macrolides and fluoroquinolones), antipsychotic drugs, and antidepressants. A list of QT-prolonging drugs is available at http://crediblemeds.org/. The large degree of QTc prolongation in this patient may be caused by either the presence of two QT-prolonging medications or an underlying ion channel variant that is only evident in the setting of a QT-prolonging medication.

Although both medications may lead to her ECG findings, discontinuing either the moxifloxacin or amitriptyline in isolation is insufficient treatment given the significant degree of QT prolongation on this patient's ECG.

Carvedilol does not prolong the QT interval directly, although it may increase the risk of bradycardia-related arrhythmias in patients with acquired QT-interval prolongation by slowing the heart rate. However, the most important intervention in this patient is to reduce the risk of torsades de pointes by discontinuing the offending QT-prolonging agents.

KEY POINT

- A corrected QT interval greater than 500 ms is associated with increased risk of torsades de pointes; patients with this degree of QT-interval prolongation should discontinue any potentially QT-interval prolonging drugs.

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Item 15 Answer: C

Educational Objective: Manage heart failure with preserved ejection fraction with diuretics.

This patient should be admitted to the hospital and given intravenous furosemide. His presentation is characteristic for heart failure with preserved ejection fraction (HFpEF). He has volume overload manifested by increasing abdominal girth, increased exertional dyspnea, and progressive orthopnea. His left ventricular ejection fraction is normal, but he has mild left ventricular hypertrophy and a long history of hypertension. Additionally, he has a markedly elevated B-type natriuretic peptide level. The etiology of his acute exacerbation into heart failure is most likely acute atrial fibrillation, but because he is already on diltiazem and has a normal heart rate, he may have been in atrial fibrillation for some time and not noticed it.

In contrast to patients with a reduced ejection fraction, no drugs have been shown to reduce mortality rates in patients with HFpEF. Instead, guidelines emphasize controlling blood pressure and volume. Patients with HFpEF are

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CONT.

often volume sensitive, and careful use of diuretics to maintain euvolemia is important. This patient is not already taking a diuretic, and starting with a low dose of furosemide is a reasonable approach. If the patient were already on an oral diuretic, giving at least the equivalent dose intravenously would be suggested. Patients with HFpEF should be encouraged to monitor their weight closely, as small differences in volume can quickly cause volume overload and subsequent hospital admissions.

β-Blocker therapy is relatively contraindicated in this patient with acute decompensated heart failure as it may exacerbate his heart failure. Once his heart failure is successfully treated with diuretics, this patient may benefit from β-blocker therapy to help manage his heart rate and blood pressure, but this should be avoided in the setting of acute volume overload, whenever possible.

Despite the fact that the patient is currently in atrial fibrillation, cardioversion at this point is incorrect. Because he is hemodynamically stable with good rate control, there is no indication for immediate cardioversion. In addition, because it is unclear how long he has been in atrial fibrillation, cardioversion without a transesophageal echocardiogram to rule out thrombus or initiation of prophylactic anticoagulation would place the patient at risk for embolization at the time of the procedure.

Several small trials have suggested that aldosterone antagonists may improve diastolic function in patients with HFpEF. However, a recent trial comparing spironolactone with placebo showed a reduction in heart failure hospitalizations but no difference in mortality rates or all-cause hospitalizations in patients with HFpEF, and spironolactone was associated with significant increases in serum creatinine and potassium levels. Given this minimal benefit but substantial increase in risk of adverse effects, the addition of spironolactone for his current symptoms is not appropriate in this patient with HFpEF.

KEY POINT

- Patients with heart failure with preserved ejection fraction are often volume sensitive, and careful use of diuretics to maintain euvolemia is important.

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Heart Failure Society of America; Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail. 2010 Jun;16(6):e1-e194. [PMID: 20610207]

Item 16 Answer: B

Educational Objective: Treat low-pressure cardiac tamponade.

This patient should undergo pericardiocentesis. He has low-pressure cardiac tamponade, which is tamponade occurring in the setting of clinical dehydration. Evidence of cardiac tamponade on echocardiography includes diastolic inversion of the right-sided chambers and respiratory variation in the mitral inflow pattern; a ventricular septal shift and plethora of the inferior vena cava also may be present. However, because of volume contraction, the intracardiac filling pressures are low, and tamponade does not result in an elevation of estimated central venous pressure. Therefore, several physical examination findings usually associated with pericardial tamponade, such as jugular venous distention and pulsus paradoxus, may not be evident in many patients. Low-pressure cardiac tamponade may be caused by malignancy, tuberculosis, or other severe chronic illnesses that result in both dehydration and pericardial effusions, with metastatic involvement of the pericardium likely present in this patient with known disseminated cancer.

In cardiac tamponade, the pericardial effusion causes intrapericardial pressure to exceed ventricular diastolic pressures, which leads to impairment in ventricular filling and stroke volume. Sinus tachycardia, as evident in this patient, is a compensatory response to maintain forward cardiac output. Treatment should consist of acute intravenous hydration to augment ventricular preload and stroke volume and, most importantly, procedures to relieve the tamponade, specifically pericardiocentesis.

An intra-aortic balloon pump is used in patients with hemodynamic instability, usually as a bridging device until definitive treatment can be undertaken. Because removal of pericardial fluid in this patient would be expected to markedly improve his hemodynamic status, pericardiocentesis is indicated prior to pursuing additional supportive therapy.

Phenylephrine is a potent vasoconstrictor. Although phenylephrine may improve this patient's blood pressure by increasing his systemic vascular resistance, the increase in resistance will reduce stroke volume, which is already significantly impaired by tamponade and hypovolemia. Phenylephrine, therefore, would not be an appropriate intervention prior to treating the tamponade and ensuring adequate volume expansion.

A window pericardiectomy procedure is performed in the operating room either as an open procedure or using video-assisted thoracoscopy by cardiac surgery and would be indicated only if this patient's tamponade was unresponsive to pericardiocentesis, a less invasive bedside procedure.

KEY POINT

- Treatment of low-pressure cardiac tamponade should include acute intravenous hydration to augment ventricular preload and stroke volume and pericardiocentesis to relieve the tamponade.

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Item 17 Answer: B

Educational Objective: Identify the importance of individual risk factors in the risk of myocardial infarction.

The presence of dyslipidemia places this patient at highest risk for future myocardial infarction (MI), accounting for

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approximately 50% of the risk of developing acute MI. The INTERHEART study assessed the prevalence of nine potentially modifiable risk factors in more than 15,000 patients with first acute MI and almost 15,000 asymptomatic age- and sex-matched controls. Nine risk factors were strongly associated with acute MI in the 52 countries included in the trial. In descending order, these are: dyslipidemia, smoking, psychosocial stressors, diabetes mellitus, hypertension, obesity, alcohol consumption, physical inactivity, and diet low in fruits and vegetables. Results of the INTERHEART study suggest that these modifiable risk factors account for more than 90% of the risk for acute MI.

KEY POINT

- Nine modifiable risk factors account for more than 90% of the risk for acute myocardial infarction; in descending order, these are: dyslipidemia, smoking, psychosocial stressors, diabetes mellitus, hypertension, obesity, alcohol consumption, physical inactivity, and diet low in fruits and vegetables.

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Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART Study): case-control study. Lancet. 2004 Sep 11-17;364(9438):937-52. [PMID: 15364185]

Item 18 Answer: B

Educational Objective: Manage a patient with diabetes mellitus and three-vessel coronary artery disease.

The appropriate management of this patient is coronary artery bypass grafting (CABG). He has type 2 diabetes mellitus and multivessel coronary artery disease (CAD) with moderate to severe symptoms despite optimal medical therapy. In multiple observational studies and randomized controlled trials, performing CABG compared with percutaneous coronary intervention (PCI) as the initial revascularization strategy in patients with a clear indication was associated with improved outcomes, including reduced rates of death, myocardial infarction (MI), and stroke. The FREEDOM trial evaluating management of multivessel CAD in patients with diabetes showed that the composite endpoint of death, MI, and stroke was significantly lower in patients treated with CABG versus PCI. This difference was driven by a statistically significant reduction in the occurrence of death and MI in CABG patients, although stroke rates were higher in the CABG group than the PCI group. CABG is recommended for patients who remain symptomatic despite optimal medical therapy and have specific angiographic findings (either left main disease or multivessel disease with involvement of the proximal left anterior descending artery), concomitant reduced systolic function, or diabetes mellitus.

β-Blockers are first-line antianginal agents because of their ability to reduce heart rate, myocardial contractility, and blood pressure, resulting in reduced myocardial oxygen demand. Calcium channel blockers are reasonable second-line therapy in patients who are intolerant of β-blockers or who have continued symptoms on β-blockers and nitrates. However, it would not be appropriate to switch to a calcium channel blocker, such as amlodipine, in this patient who currently tolerates an effective dose of a β-blocker.

Myocardial viability testing is performed with a radionuclide radiotracer that is taken up by viable myocardial tissue. Viability testing may demonstrate hypoperfused regions of the heart that might show functional improvement if revascularization is performed. However, information from a substudy of the Surgical Treatment of Ischemic Heart Failure (STICH) trial demonstrated no relationship between the results of viability imaging and the effectiveness of bypass surgery. Therefore, in this patient who remains symptomatic despite optimal medical therapy and is a reasonable surgical candidate, revascularization is indicated, and myocardial perfusion testing would not contribute significant information regarding medical decision making. Myocardial perfusion testing is typically limited to use in patients at high risk for revascularization surgery in whom assessing the degree of viable myocardium present may influence the risk-benefit ratio of surgical treatment.

KEY POINT

- Coronary artery bypass grafting is recommended for patients who remain symptomatic with optimal medical therapy and have specific angiographic findings (either left main disease or multivessel disease with involvement of the proximal left anterior descending artery), concomitant reduced systolic function, or diabetes mellitus.

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Item 19 Answer: C

Educational Objective: Evaluate coronary artery disease in a patient with COPD.

This patient should undergo dobutamine stress echocardiography. She has a history of coronary artery disease (CAD) with new atypical, but exertional, symptoms suggestive of cardiac ischemia. Because she has baseline electrocardiogram abnormalities (left ventricular hypertrophy with repolarization abnormalities) that will make interpretation of ST-segment changes difficult, she should undergo stress testing with imaging, with either stress echocardiography with dobutamine or myocardial perfusion imaging with a vasodilator.

With stress echocardiography, regional myocardial function is assessed in real time. Stress images are obtained at peak or immediately after stress, before cardiac function returns to baseline. Wall motion abnormalities indicate either infarction (seen on stress and rest images) or ischemia (seen on stress images only). For patients who cannot

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exercise, such as this patient, pharmacologic stressors such as dobutamine in combination with imaging can be used in place of exercise and imaging.

Because of her COPD with active wheezing on examination, pharmacologic testing with vasodilators should be avoided. Pharmacologic vasodilators, such as dipyridamole, adenosine, and regadenoson, can cause bronchospasm and are therefore contraindicated in a patient who is actively wheezing. These agents can be used with caution in a patient with a history of bronchospastic airways disease, but the presence of active wheezing in this patient precludes the use of a vasodilator. Therefore, stress testing with dobutamine is the correct choice.

This patient has no symptoms to indicate an acute coronary syndrome that would prompt cardiac catheterization as the initial diagnostic test. Evaluation of the extent and severity of disease would be the first step in deciding management in this patient. If she has a small perfusion defect, she could be treated medically with more intensive antianginal therapies.

KEY POINT

- Pharmacologic vasodilators, such as dipyridamole, adenosine, and regadenoson, can cause bronchospasm during cardiac stress testing; these agents can be used with caution in a patient with a history of COPD but are contraindicated in a patient who is actively wheezing.

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Item 20 Answer: B

Educational Objective: Manage asymptomatic severe aortic stenosis.

Although this patient has severe aortic stenosis based on quantitative echocardiographic findings, he is asymptomatic with normal left ventricular (LV) systolic function; therefore, follow-up echocardiography in 6 to 12 months is the most appropriate management. Appropriate follow-up in patients with asymptomatic severe aortic stenosis includes a clinical evaluation and echocardiography every 6 to 12 months. Patients should also be educated to identify and report possible aortic stenosis–related symptoms, such as dyspnea, reduced exercise tolerance, exertional chest pain, lightheadedness, and syncope, before scheduled follow-up.

Balloon valvuloplasty, although important in the treatment of the pediatric patient with severe aortic stenosis, has a more limited role in adults owing primarily to its limited efficacy and the high rate of complications associated with the procedure. Additionally, this patient is asymptomatic, so there is no indication for intervention at present.

Surgical aortic valve replacement is indicated for symptomatic patients with severe aortic stenosis, asymptomatic patients with severe aortic stenosis and LV systolic dysfunction (LV ejection fraction <50%), and patients with severe aortic stenosis who are undergoing coronary artery bypass graft or surgery on the aorta or other heart valves. This patient is asymptomatic with normal LV systolic function, and he does not have any other cardiac procedures planned.

Transcatheter aortic valve replacement (TAVR) is indicated for patients with symptomatic severe aortic stenosis who are considered unsuitable for conventional surgery because of severe comorbidities. Currently, TAVR should not be performed in patients with intermediate or low surgical risk, and no therapeutic intervention is currently indicated in this asymptomatic patient.

KEY POINT

- In patients with asymptomatic severe aortic stenosis, close clinical follow-up with echocardiography every 6 to 12 months is appropriate.

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Item 21 Answer: C

Educational Objective: Diagnose stress cardiomyopathy (takotsubo cardiomyopathy).

This patient's clinical history and presentation are consistent with stress cardiomyopathy (takotsubo cardiomyopathy). The absence of coronary artery stenosis and the presence of hypokinesis of the mid and apical left ventricle on ventriculography confirm this diagnosis. This patient with takotsubo cardiomyopathy without evidence of cardiogenic shock should be administered metoprolol and captopril. The treatment of stress cardiomyopathy is supportive, including the use of β-blockers and ACE inhibitors, and most patients have resolution of symptoms and recovery of left ventricular function within 7 days.

Takotsubo cardiomyopathy often mimics non–ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI). Patients present with chest pain or shortness of breath, electrocardiographic changes consistent with anterior and/or lateral ST-segment elevation, and elevated cardiac biomarkers. Although not required for diagnosis, many patients develop symptoms following a stressful or emotional event. The diagnosis of stress cardiomyopathy requires (1) ST-segment elevation on electrocardiography, (2) transient wall motion abnormalities of the mid and apical left ventricle, (3) the absence of significant obstructive coronary artery disease, and (4) the absence of other causes of transient left ventricular dysfunction, such as myocarditis.

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Endomyocardial biopsy is generally not indicated for the initial evaluation of heart failure unless a specific diagnosis that would influence management or prognosis is suspected based on clinical data or noninvasive testing. This patient's presentation, with acute onset following a stressful event, ST-segment elevation, and hypokinesis of the cardiac apex, is characteristic of takotsubo cardiomyopathy, and an endomyocardial biopsy is not indicated as an initial diagnostic test. Myocarditis has a variable presentation, but focal ST-segment changes and apical hypokinesis are not typical.

More than 95% of patients with stress cardiomyopathy recover ventricular function with conservative supportive care (β-blockers and ACE inhibitors). This patient does not have evidence of hemodynamic compromise, and intra-aortic balloon pump implantation is not indicated.

In this patient, the lack of coronary artery obstructive disease in the presence of ST-segment elevation and elevated cardiac biomarkers eliminates STEMI or NSTEMI as possible etiologies for this presentation. Therefore, thrombolytic therapy is not indicated.

KEY POINT

- Stress cardiomyopathy presents similarly to myocardial infarction, with ST-segment elevation and, often, elevated cardiac biomarkers; however, coronary angiography demonstrates an absence of significant obstructive coronary artery disease.

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Item 22 Answer: B

Educational Objective: Diagnose Eisenmenger syndrome due to a patent ductus arteriosus.

The patient has a patent ductus arteriosus (PDA) with secondary pulmonary hypertension (Eisenmenger syndrome). Clinical features of an Eisenmenger PDA include clubbing and oxygen desaturation affecting the lower body. This differential cyanosis and clubbing are caused by desaturated blood reaching the lower part of the body preferentially.

Pulmonary hypertension occurs infrequently in patients with unrepaired atrial septal defects owing to the relatively small shunt size. Clinical features of unrepaired atrial septal defect with pulmonary hypertension include cyanosis and clubbing that affects the hands and feet equally. The clinical findings are otherwise similar to findings in patients with idiopathic pulmonary arterial hypertension, with a parasternal lift and increased S_2.

Unrepaired tetralogy of Fallot consists of right ventricular outflow tract obstruction and a large ventricular septal defect with secondary features of right ventricular hypertrophy and aortic override. Clinical features include cyanosis and clubbing that affect the hands and feet equally and a loud early systolic murmur heard at the left sternal border related to the right ventricular outflow tract obstruction. The pulmonic component of the S_2 is generally soft or absent depending on the degree of pulmonary valve stenosis. Right ventricular hypertension but not pulmonary hypertension is present; the pulmonary vasculature is protected by the presence of pulmonary valve stenosis.

A ventricular septal defect can cause pulmonary hypertension if it remains open beyond age 2 years. Clinical features include cyanosis and clubbing that affect the hands and feet equally, a parasternal lift, and increased S_2. Differential clubbing and cyanosis would not occur in a patient with pulmonary hypertension related to a ventricular septal defect.

KEY POINT

- A patent ductus arteriosus with Eisenmenger syndrome is characterized by differential cyanosis and clubbing affecting the lower body.

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Srinivas SK, Manjunath CN. Differential clubbing and cyanosis: classic signs of patent ductus arteriosus with Eisenmenger syndrome. Mayo Clin Proc. 2013 Sep;88(9):e105-6. [PMID: 24001503]

Item 23 Answer: A

Educational Objective: Treat a patient with acute decompensated heart failure and evidence of low cardiac output.

This patient should be started on dobutamine for probable cardiogenic shock. Cardiogenic shock is present when there is systemic hypotension and evidence for end-organ hypoperfusion, primarily due to inadequate cardiac output. Cardiogenic shock usually requires treatment with intravenous vasoactive medications and, in severe cases, device-based hemodynamic support. Manifestations of end-organ hypoperfusion may include acute kidney failure, elevated serum aminotransferase levels or hyperbilirubinemia, cool extremities, and decreased mental status. In this patient, initiating inotropic therapy is reasonable. Both dobutamine and milrinone are used to increase cardiac output; however, in the setting of kidney dysfunction, dobutamine would be the appropriate choice because milrinone is metabolized by the kidneys. Also, milrinone is a vasodilator, which could exacerbate his hypotension.

Mechanical therapy for cardiogenic shock should be considered in patients with end-organ dysfunction that does not rapidly show signs of improvement (within the first 12-24 hours) with intravenous vasoactive medications and correction of volume overload. Options for mechanical therapy include placement of an intra-aortic balloon pump and percutaneous or surgically implanted ventricular assist devices (VADs). An intra-aortic balloon pump is timed to inflate during diastole, augmenting coronary and systemic perfusion, and deflate during

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systole, reducing left ventricular afterload. It is premature to consider mechanical therapy for this patient.

Right heart catheterization can be helpful to guide therapy if volume status or cardiac output is uncertain. However, it has not been shown to improve outcomes in patients hospitalized with heart failure. This patient has clinical evidence of volume overload, including jugular venous distention, pulmonary crackles, edema to the mid thighs, pulmonary edema on chest radiography, and an S_3. Additionally, he has evidence of low cardiac output (narrow pulse pressure, hypotension, acute kidney injury, mottled and cool extremities). Placement of a right heart catheter is not necessary prior to initiating inotropic therapy.

KEY POINT

- Cardiogenic shock usually requires treatment with intravenous vasoactive medications and, in severe cases, device-based hemodynamic support.

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Item 24 Answer: B

Educational Objective: Manage type A aortic dissection.

The most appropriate management for this patient with an acute type A aortic dissection is emergency surgical intervention. The abrupt onset of severe chest and back pain is typical of an acute aortic syndrome. A diastolic murmur consistent with aortic valvular insufficiency increases the clinical suspicion for a proximal (type A) aortic dissection that has disrupted normal valve leaflet coaptation. Acute aortic dissection is the most common life-threatening disorder affecting the aorta. In the Stanford classification, type A dissections involve the ascending aorta, and type B dissections are those that do not involve the ascending aorta. Type A dissections require emergency surgical repair, whereas medical therapy, consisting of a β-blocker to decrease the heart rate to below 60/min plus additional medications as needed to control hypertension, is usually the initial strategy for acute type B dissections. Therefore, pursuing medical management alone would not be appropriate in this patient. The immediate mortality rate in aortic dissection is as high as 1% per hour over the first several hours, making early diagnosis and treatment critical for survival.

Although most patients with dissection have underlying hypertension, only a tiny fraction of all persons with hypertension ever have a dissection. Syncope occurs in approximately 10% of patients with an acute aortic dissection and is more commonly associated with proximal dissection. Pulse deficits occur in less than 20% of type A dissections. Abnormal aortic contour or widening of the aortic silhouette may be an important clue to the diagnosis of aortic dissection. However, a normal chest radiograph is seen in nearly 15% of patients with acute aortic dissection. The 10-year survival rate of patients with acute dissection who survive initial hospitalization is reported to be 30% to 60%.

Endovascular treatment of dissection is used as an alternative to open surgery primarily in complicated type B dissections. Although endovascular procedures for type A dissections have shown some promise, they are not routinely used, particularly in patients with valve dysfunction requiring surgical repair.

Although heparin is commonly used in the initial treatment of acute coronary syndromes and pulmonary embolism, heparin is not indicated in the setting of an acute type A aortic dissection. The use of heparin in this setting can be complicated by major bleeding and cardiac tamponade. Moreover, heparin can increase the risk of life-threatening major bleeding when used in patients with very elevated blood pressures (commonly seen during a dissection).

KEY POINT

- A dissection involving the ascending aorta (Stanford type A) is a surgical emergency.

Bibliography

Braverman AC. Aortic dissection: prompt diagnosis and emergency treatment are critical. Cleve Clin J Med. 2011 Oct;78(10):685-96. [PMID: 21968475]

Item 25 Answer: D

Educational Objective: Manage antibiotic prophylaxis in a patient with a mechanical aortic valve prosthesis.

For this patient with a mechanical valve preparing for hernia repair surgery, antibiotic prophylaxis to prevent bacterial endocarditis is not indicated. Prophylaxis to prevent bacterial endocarditis is appropriate before certain dental procedures for patients with specific indications placing them at high risk for an adverse outcome from infective endocarditis (class IIa recommendation). These indications include previous endocarditis, a history of cardiac transplantation, a prosthetic valve, and specific forms of complex congenital heart disease. However, prophylaxis is not recommended for nondental procedures, including transesophageal echocardiography and genitourinary or gastrointestinal procedures (such as upper endoscopy, colonoscopy, or hernia repair), in the absence of active infection (class III recommendation). Dental procedures for which antibiotic prophylaxis is reasonable include those that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. Prophylaxis is not recommended for routine dental procedures, including radiographs and orthodontics.

When antibiotic prophylaxis is indicated, it should be given as a single dose 30 to 60 minutes before the dental procedure. If the prophylactic medication is inadvertently not administered, it may be given up to 2 hours after the procedure. Options include amoxicillin, 2 g orally, or ampicillin, 2 g intravenously. For patients allergic to penicillin or amoxicillin, alternatives include clindamycin, 600 mg orally;

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CONT. azithromycin, 500 mg orally; or cefazolin/ceftriaxone, 1 g intramuscularly or intravenously.

KEY POINT

- Antibiotic prophylaxis to prevent bacterial endocarditis is not recommended for nondental procedures, including transesophageal echocardiography and genitourinary or gastrointestinal procedures, in the absence of active infection.

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Bonow RO, Carabello BA, Chatterjee K, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008 Sep 23;52(13):e1-142. [PMID: 18848134]

Item 26 Answer: D

Educational Objective: Diagnose peripheral arterial disease in a patient with uninterpretable ankle-brachial index testing.

The most appropriate diagnostic test to perform next in this patient is a toe-brachial index. The ankle-brachial index (ABI) is obtained by measuring the systolic pressures in the dorsalis pedis and posterior tibialis arteries on both sides. The ABI for each leg is the highest ankle pressure for that side divided by the highest brachial pressure (regardless of side). An ABI of 0.90 or lower establishes a diagnosis of peripheral arterial disease (PAD). In this patient, the right ABI is greater than 1.40. An ABI above 1.40 suggests noncompressible vessels, which may reflect medial calcification but is not diagnostic of flow-limiting atherosclerotic disease. An ABI greater than 1.40 is associated with worse cardiovascular outcomes than a normal ABI. In such patients, an appropriate next step is to either measure great toe pressure or calculate a toe-brachial index (systolic great toe pressure divided by systolic brachial pressure). Vessels within the great toe rarely become noncompressible, and a great toe systolic pressure below 40 mm Hg or a toe-brachial index of less than 0.70 is consistent with PAD.

An ABI obtained immediately following symptom-limited exercise is useful when a high clinical suspicion for PAD remains despite a normal (1.00-1.40) or borderline resting ABI. A decrease of the ABI by 20% compared with the resting ABI is consistent with significant PAD. This patient's resting ABI is above the normal range; therefore, exercise ABI would not help to establish the diagnosis.

In patients with an established diagnosis of PAD and indications for revascularization, further vascular anatomic data can be obtained noninvasively using gadolinium-enhanced magnetic resonance angiography or contrast-enhanced multi-detector CT angiography. However, these tests should be reserved for planning intervention in patients who have not benefited from medical therapy; they should not be used for the diagnosis of PAD. Moreover, this patient has chronic kidney injury, and use of contrast for either study should be avoided if possible.

KEY POINT

- In a patient with suspected peripheral arterial disease, an ankle-brachial index above 1.40 is uninterpretable; measurement of the great toe systolic pressure can establish the diagnosis.

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Item 27 Answer: D

Educational Objective: Manage atrial fibrillation in a patient following percutaneous coronary intervention for treatment of refractory angina.

This patient should be treated with aspirin, clopidogrel, and warfarin ("triple therapy"). He has new-onset atrial fibrillation in the setting of recent bare metal stent placement for medically refractory angina. Patients with a bare metal stent should be treated with dual antiplatelet therapy for at least 1 month to allow endothelialization of the stent; with drug-eluting stents, the requirement for dual antiplatelet therapy is longer and depends upon the type of stent implanted. This patient is also at high risk of thromboembolic disease associated with atrial fibrillation. He has a CHA_2DS_2-VASc score of 5 (2 points for age >75 years, 1 point each for diabetes mellitus, hypertension, and vascular disease). Therefore, oral anticoagulant therapy is also indicated. Although triple therapy with two antiplatelet agents and systemic anticoagulation is associated with a significant increase in bleeding risk, this regimen is appropriate treatment in this patient for at least 1 month until stent endothelialization can be assured, at which time he can be transitioned to only aspirin and an oral anticoagulant to decrease bleeding risk but provide adequate thromboembolic prophylaxis. If warfarin is used as an anticoagulant during triple therapy, careful maintenance of the INR within the recommended range of 2.0 to 2.5 in patients without mechanical valves may reduce the overall bleeding risk.

Aspirin and clopidogrel are inferior to oral anticoagulation for the prevention of stroke in patients with an indication for anticoagulation for thromboembolism prophylaxis in atrial fibrillation.

Treatment with aspirin and dabigatran is not optimal for two reasons. First, in the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial, there was a numeric excess of myocardial infarctions observed with dabigatran. More importantly, no data are available regarding the efficacy of aspirin and dabigatran for the prevention of stent thrombosis following an acute coronary syndrome.

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Treatment with dual antiplatelet therapy is indicated in all patients with a coronary stent, with the recommended duration based on the underlying condition and type of stent placed. Therefore, treatment with aspirin and warfarin does not optimally prevent acute stent occlusion in a patient with stent placement.

KEY POINT

- Patients with atrial fibrillation and recent stent placement should be treated with appropriate systemic anticoagulation and antiplatelet therapy as determined by risk scoring and the type of stent placed.

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Item 28 Answer: C

Educational Objective: Manage symptomatic severe aortic stenosis.

The patient should be referred for surgical aortic valve replacement. She has symptomatic severe aortic stenosis, a class I indication for valve replacement. Surgical aortic valve replacement is the treatment of choice for most patients with symptomatic severe aortic stenosis and is associated with low mortality rates (1%-3%) in patients younger than 70 years.

Balloon valvuloplasty of the aortic valve has an extremely limited role in treating aortic stenosis owing to the high risk of complications associated with the procedure (10%-20%), a short-lived clinical benefit, and poor long-term outcomes. It would not be an appropriate treatment option in this patient.

Medical therapy for aortic stenosis is limited. Multiple agents have been evaluated for treatment of aortic stenosis, including ACE inhibitors, angiotensin receptor blockers, digoxin, diuretics, and statins. None have been shown to alter the progression of disease and valve replacement remains the indicated therapy. These agents are appropriate if there are other indications for their use, none of which are present in this patient.

Transcatheter aortic valve replacement (TAVR) is an option for patients with an indication for aortic valve replacement but who are not operative candidates or are at high risk for death or major morbidity with open aortic valve replacement. However, TAVR is not currently approved in patients with a bicuspid aortic valve, and given this patient's age and significant lack of comorbidities, she would appear to be a good candidate for surgical replacement.

KEY POINT

- Surgical aortic valve replacement is the treatment of choice for most patients with symptomatic severe aortic stenosis.

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Item 29 Answer: A

Educational Objective: Diagnose atrial septal defect.

This patient has features of an ostium secundum atrial septal defect. Adults with atrial septal defects often present with atrial arrhythmias. The characteristic physical examination findings in atrial septal defect are fixed splitting of the S_2 and a right ventricular heave. A pulmonary midsystolic flow murmur and a tricuspid diastolic flow rumble caused by increased flow through the right-sided valves from a large left-to-right shunt may be heard. In ostium secundum atrial septal defect, the electrocardiogram (ECG) demonstrates right axis deviation and incomplete right bundle branch block. Ostium primum atrial septal defects are nearly always associated with anomalies of the atrioventricular valves, particularly a cleft in the anterior mitral valve leaflet or defects of the ventricular septum. The ECG in ostium primum atrial septal defect characteristically demonstrates first-degree atrioventricular block, left axis deviation, and right bundle branch block.

Bicuspid aortic valve with aortic stenosis causes a systolic murmur at the second right intercostal space. The central venous pressure is normal in aortic stenosis, and a right ventricular impulse would not be expected. Fixed splitting of the S_2 is not heard in patients with bicuspid aortic valve with aortic stenosis. The ECG typically demonstrates a normal axis and features of left ventricular hypertrophy.

Patients with pulmonary valve stenosis may demonstrate jugular venous pressure elevation with prominence of the *a* wave and a parasternal impulse from increased right ventricular pressure. The ejection murmur of pulmonary valve stenosis is heard at the second left intercostal space, and the timing of the peak of the murmur is related to stenosis severity. An ejection click is often heard; the proximity of the click to the S_2 varies depending on the severity of stenosis. Splitting of the S_2 results from prolonged ejection delay in the pulmonary valve component and may become fixed in severe pulmonary valve stenosis. The ECG typically demonstrates right axis deviation and features of right ventricular hypertrophy.

Mitral valve prolapse with mitral regurgitation may cause symptoms of palpitations. The murmur of mitral regurgitation is generally heard best at the apex. The central venous pressure is generally normal, and a right ventricular impulse would not be expected. Fixed splitting of the S_2 is not heard in patients with mitral valve prolapse. The ECG is typically normal.

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KEY POINT

- Fixed splitting of the S_2 throughout the cardiac cycle and a right ventricular heave are characteristic clinical features of atrial septal defect.

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Item 30 Answer: C

Educational Objective: Manage a patient with mitral valve stenosis considering pregnancy.

This patient has clinical and echocardiographic features of severe mitral valve stenosis as indicated by mitral valve mean gradient, valve area, and pulmonary artery systolic pressure greater than 50 mm Hg. Planned pregnancy is a class I indication for intervention in patients with severe mitral stenosis despite the absence of baseline symptoms. Most young patients will be candidates for mitral balloon valvuloplasty.

In severe mitral valve stenosis, negative chronotropic drugs such as β-blockers allow increased diastolic filling time of the left ventricle and may improve symptoms. If atrial fibrillation develops (even if paroxysmal), chronic anticoagulation therapy with warfarin is indicated to reduce the risk of thromboembolism, which is much higher than in nonvalvular atrial fibrillation. ACE inhibitors provide no particular benefit to patients with mitral stenosis and are contraindicated in pregnant patients. Dabigatran is approved for prevention of systemic embolism in adults with nonvalvular atrial fibrillation; however, its effectiveness in preventing embolism in patients with valvular heart disease is unknown, and it is not recommended in this setting.

Cardiac magnetic resonance imaging will not add incremental information to determine therapeutic strategy for this patient with rheumatic mitral stenosis considering pregnancy.

Pregnancy is associated with a marked increase in blood volume and cardiac output. Patients with severe mitral stenosis and moderate pulmonary hypertension often develop symptoms during pregnancy and should receive intervention prior to pregnancy.

KEY POINT

- Planned pregnancy is a class I indication for mitral valve intervention in patients with severe mitral valve stenosis despite the absence of baseline symptoms.

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Item 31 Answer: A

Educational Objective: Manage abdominal aortic aneurysm with referral for repair.

The most appropriate management is to refer this patient for abdominal aortic aneurysm (AAA) repair. AAA is a common and potentially life-threatening condition, and management of detected aneurysms is based on size or rate of expansion. Elective repair to prevent rupture in asymptomatic patients is optimal management in those meeting criteria for intervention. Once an aneurysm reaches 5.5 cm in men and 5.0 cm in women, repair is generally warranted. Repair may be performed by an open approach or an endovascular approach, if the anatomy of the aneurysm is amenable; the mode of therapy should be decided by the surgeon, the internist, and the patient after a comprehensive discussion of risks and long-term benefits. Randomized trials show that endovascular aneurysm repair (EVAR) is associated with lower perioperative morbidity and mortality compared with open AAA repair, but EVAR does not completely eliminate the future risk of AAA rupture. Open repair is associated with higher perioperative morbidity and mortality than EVAR, but it provides a more definitive repair.

The optimal surveillance schedule for patients once an AAA has been identified has not been clearly defined. Annual surveillance is recommended, but larger aneurysms expand faster than small ones and may require more frequent surveillance. Aneurysm diameter is the most important factor predisposing to rupture, with risk increasing markedly at aneurysm diameters greater than 5.5 cm. For asymptomatic patients, the risk of AAA rupture generally exceeds the risk associated with elective AAA repair when aneurysm diameter exceeds 5.0 cm in a woman and 5.5 cm in a man. This patient's AAA is 5.7 cm in diameter; therefore, she should be referred for repair, rather than continuing surveillance.

Although controlling risk factors for cardiovascular disease is essential in patients with AAA, there is little compelling evidence for treating hypertension in these patients with a specific agent, including β-blockers, to prevent aneurysm expansion. As this patient's blood pressure is well controlled, no change in antihypertensive therapy is indicated.

KEY POINT

- An abdominal aortic aneurysm larger than 5.5 cm in men and 5.0 cm in women is an indication for referral for repair.

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Item 32 Answer: A

Educational Objective: Treat a patient with potentially transient constrictive pericarditis.

This patient has evidence of constrictive pericarditis and should be treated with an anti-inflammatory medication, such as a high-dose NSAID or prednisone. Supportive findings are symptoms and signs of right heart failure and congestion, with hemodynamic evidence of constriction on echocardiography. In some patients with constrictive pericarditis, the constriction can be transient and either spontaneously resolve or respond to medical therapy. This subtype of constrictive pericarditis more frequently has idiopathic, viral, or postsurgical causes. Although a minority of patients will have this transient constrictive pericarditis, a trial of medical therapy with an anti-inflammatory medication is reasonable. If medical therapy is successful, then surgical pericardiectomy can be avoided. Anti-inflammatory medication regimens for potentially transient constrictive pericarditis are similar to those for acute pericarditis, with relatively high doses of NSAIDs used (for example, ibuprofen, 800 mg three times daily; indomethacin, 50 mg three times daily; aspirin, 650 mg three times daily), with a slow taper over 2 to 3 weeks.

Cardiac catheterization for hemodynamic assessment of possible constriction is only indicated when diagnostic information cannot be obtained with echocardiography, which is not the case in this patient.

Pericardiectomy is inappropriate before a 2- to 3-month trial of anti-inflammatory medication in this patient. Although pericardiectomy is the definitive treatment for relief of heart failure in patients with constrictive pericarditis, it is a complex, invasive procedure that should not be used in patients with transient constriction.

Transesophageal echocardiography is only indicated when data from other noninvasive imaging studies (such as transthoracic echocardiography) are inconclusive.

KEY POINT

- In some patients with constrictive pericarditis, the constriction may be transient and either spontaneously resolve or respond to medical therapy, which obviates the need for surgical pericardiectomy.

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Haley JH, Tajik AJ, Danielson GK, Schaff HV, Mulvagh SL, Oh JK. Transient constrictive pericarditis: causes and natural history. J Am Coll Cardiol. 2004 Jan 21;43(2):271-5. [PMID: 14736448]

Item 33 Answer: C

Educational Objective: Manage symptomatic premature ventricular contractions.

This patient has frequent, symptomatic premature ventricular contractions (PVCs) with decline in his left ventricular function despite treatment with β-blocker therapy. As there is no clear underlying myocardial process, it is likely that his PVCs may represent a reversible cause of his cardiomyopathy. He should be referred to a cardiac electrophysiologist for catheter ablation of his PVCs.

PVCs are common and are usually benign. However, symptomatic or frequent PVCs (>10,000 PVCs/24 hours or >10% of all beats) require treatment. Up to one third of patients with frequent PVCs develop PVC-induced cardiomyopathy and progressive left ventricular dysfunction. First-line therapy for symptomatic or frequent PVCs is β-blocker or calcium channel blocker therapy. Patients with medically refractory frequent PVCs or who develop left ventricular dysfunction should undergo catheter ablation of the PVCs. Catheter ablation leads to resolution of PVC-induced cardiomyopathy in most patients.

Amiodarone could be used for PVC suppression; however, it has many long-term risks, including thyroid, liver, pulmonary, and neurologic toxicity. Given this patient's relatively young age, amiodarone would not be the most appropriate therapy, particularly if long-term control is needed.

Cardiac resynchronization therapy involves the simultaneous pacing of both ventricles in patients with advanced heart failure and evidence of intraventricular conduction delay (QRS interval ≥150 ms) to reduce dyssynchrony to improve pump performance. This patient does not have severe heart failure or evidence of dyssynchrony. As his symptoms are related more to his ventricular ectopy, cardiac resynchronization therapy would not be appropriate.

An implantable cardioverter-defibrillator (ICD) is indicated in patients at risk for ventricular tachycardia or ventricular fibrillation to prevent sudden cardiac death. Although this patient has very frequent PVCs, including bigeminy, he does not have sustained tachyarrhythmias of potential hemodynamic significance. Therefore, ICD placement would not be appropriate in this patient.

KEY POINT

- Patients with frequent premature ventricular contractions and subsequent cardiomyopathy should be treated with catheter ablation.

Bibliography

Yokokawa M, Good E, Crawford T, et al. Recovery from left ventricular dysfunction after ablation of frequent premature ventricular complexes. Heart Rhythm. 2013 Feb;10(2):172-5. [PMID: 23099051]

Item 34 Answer: A

Educational Objective: Manage discharge of a patient with heart failure to prevent readmission.

This patient should be discharged home, with a follow-up appointment scheduled within 7 days. She has had one heart failure hospitalization in the past 3 years and her nonadherence with her diuretic medication was the most likely cause of the admission. With any heart failure hospitalization, it is important to reassess several factors before discharge. First, patients must be adequately diuresed prior to discharge. It is important to know that measuring a serum B-type natriuretic peptide level will not help with that assessment. Patients

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should be examined for flat neck veins, resolution of peripheral or abdominal edema (if possible), and resolution of the signs and symptoms of acute heart failure (S_3, exertional dyspnea and fatigue, orthopnea, paroxysmal nocturnal dyspnea). Second, patients should be on appropriate medical therapy for their stage of heart failure. For this patient, appropriate medications include an ACE inhibitor or angiotensin receptor blocker, β-blocker, aldosterone antagonist, and an adequate dosage of diuretic to prevent readmission. Third, it has been demonstrated that a patient being seen within 1 week after discharge is associated with a reduction of future heart failure hospitalizations. This patient is adequately diuresed and is on appropriate medications. Reducing her risk of readmission requires a follow-up visit within 7 days of discharge and appropriate patient education.

An echocardiogram performed 1 month ago demonstrated that the patient's left ventricular function is stable. There is no suggestion of ischemia or change in valvular function as a precipitant of this hospitalization. If this patient had not had an echocardiogram in at least 6 months, it would be reasonable to repeat the echocardiogram during the hospitalization; otherwise unless there is a suspicion of a change, there is no reason to do so.

Patients are candidates for a biventricular pacemaker if they have all of the following indications: on guideline-directed medical therapy, a reduced ejection fraction (≤35%), a wide QRS interval (≥150 ms) or a left bundle branch block, and New York Heart Association functional class III or IV symptoms. This patient has a narrow QRS interval and therefore would not be a candidate for upgrading to a biventricular implantable cardioverter-defibrillator.

KEY POINT

- Patients hospitalized for heart failure who are scheduled for a follow-up appointment within 1 week after discharge have a reduced risk of future heart failure hospitalization.

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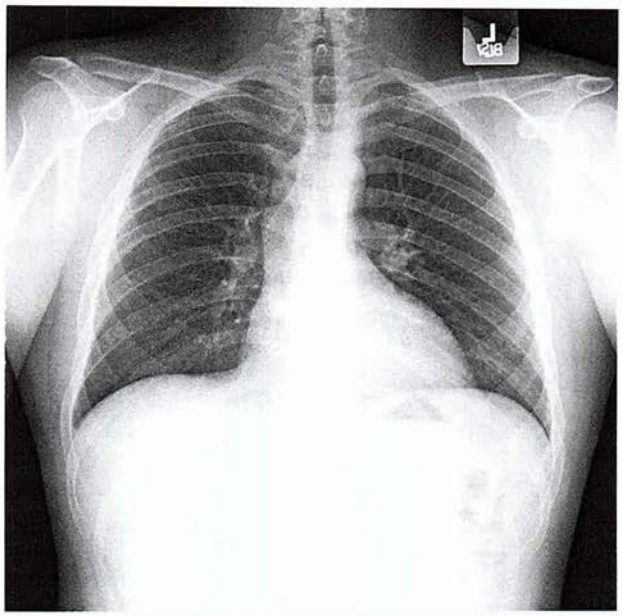
Item 35 Answer: A

Educational Objective: Diagnose aortic coarctation in an adult.

This patient presents with newly diagnosed hypertension and clinical features of aortic coarctation, which include upper extremity hypertension and a radial artery-to-femoral artery pulse delay suggesting a mechanical obstruction between the radial and femoral arteries; lower extremity blood pressure determinations may be low or difficult to obtain. A systolic murmur over the left posterior chest is common in patients with severe aortic coarctation; these murmurs can arise from the obstruction or the collateral blood flow. The chest radiograph (shown) demonstrates "rib notching" affecting several of the posterior ribs; rib notching results from exaggerated collateral blood flow diverting blood around the area of obstruction. Also present on the chest radiograph is the "figure 3 sign" caused by dilatation of the aorta above and below the area of coarctation.



Essential hypertension is the most common cause of hypertension in adults. A family history of hypertension is common. The physical examination in a patient with severe essential hypertension often includes an S_4, but a pulse and blood pressure differential between the upper and lower extremities is not expected.

Patients with hypertrophic cardiomyopathy do not usually present with hypertension. The systolic murmurs in hypertrophic cardiomyopathy characteristically include an ejection quality murmur at the left sternal border related to outflow obstruction and a late systolic murmur at the apex related to mitral valve regurgitation.

Renovascular hypertension is a common cause of hypertension occurring primarily in patients with diffuse atherosclerosis. An epigastric bruit may be audible. The rest of the physical examination in a patient with renovascular hypertension is usually normal. A pulse and blood pressure differential between an upper and a lower extremity is not expected.

KEY POINT

- Aortic coarctation is characterized clinically by upper extremity hypertension and a radial artery–to–femoral artery pulse delay.

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Item 36 Answer: A

Educational Objective: Treat hypertension during pregnancy.

The most appropriate treatment for this patient is labetalol. When hypertension is noted before the 20th week of gestation, it is most consistent with a new diagnosis of chronic hypertension. There is no evidence that tight control of hypertension during pregnancy will prevent preeclampsia; instead, antihypertensive therapy is warranted only to limit maternal end-organ damage in those with severe hypertension. Hypertension of the magnitude demonstrated by this patient (systolic blood pressure >150 mm Hg) is a class I indication for pharmacologic treatment during pregnancy.

If treatment is necessary, it is important to note that all antihypertensive agents cross the placenta. Methyldopa and labetalol appear to be the safest choices, whereas ACE inhibitors, angiotensin receptor blockers (ARBs), and likely renin inhibitors are not safe.

ACE inhibitors (such as lisinopril), ARBs (such as losartan), and direct renin inhibitors (aliskiren) are contraindicated during pregnancy owing to fetal toxicity. Fetal exposure to these agents during the first trimester can cause central nervous system and cardiovascular malformations, and exposure during the second trimester can cause urogenital and renal developmental malformations.

Diet and weight loss should be used in conjunction with pharmacologic therapy in this patient, but nonpharmacologic strategies alone are not sufficient in a patient with this magnitude of hypertension.

Not treating this patient's chronic hypertension may result in maternal end-organ damage and is not an acceptable option.

KEY POINT

- Labetalol has been demonstrated to be safe and effective for the treatment of hypertension during pregnancy and is the preferred β-blocker for use during pregnancy.

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Item 37 Answer: A

Educational Objective: Diagnose a murmur heard in a pregnant woman.

The most likely cause of this woman's murmur is a bicuspid aortic valve, the most common congenital heart abnormality. The characteristic finding of a bicuspid aortic valve is an aortic ejection sound associated with either a systolic or diastolic murmur. While the murmur associated with aortic stenosis usually radiates to the carotid arteries, the murmur of a nonstenotic bicuspid aortic valve may radiate to the apex. Fetal echocardiography is indicated if there is maternal cardiac structural disease because of the increased risk of fetal cardiac abnormalities, which is estimated to be in the range of 3% to 7%.

The altered hemodynamics of pregnancy may bring out murmurs not previously heard or may bring the pregnant patient to medical attention for the first time owing to the increase in systemic blood volume and cardiac output. Systolic murmurs are common during pregnancy. Most often these are ejection murmurs caused by increased flow through the right and left ventricular outflow tracts. The murmurs tend to be grade 1/6 or 2/6 midsystolic murmurs that do not radiate. Diastolic murmurs are not common.

The systolic murmur associated with hypertrophic obstructive cardiomyopathy generally increases with maneuvers that decrease preload, such as the Valsalva maneuver or change in position from squatting to standing.

A mammary souffle is a continuous murmur with a soft, humming quality. It is typically heard over the breast during late pregnancy and lactation and is thought to result from increased blood flow to the breast.

While the murmur of mitral valve prolapse is often late systolic and can be associated with a click, this click would not be described as an ejection click. The click associated with mitral valve prolapse is mid- to late systolic and is related to tensing of the chordae tendineae or valve leaflets. The click is responsive to changes in ventricular volume induced by posture or pharmacologic agents.

Functional murmurs, or physiologic murmurs, can occur in the absence of valvular pathology. An increase in cardiac output, as occurs in pregnancy, can result in physiologic ejection murmurs.

Given the findings on examination, it would be appropriate to obtain transthoracic echocardiography for this patient to identify the etiology of the murmur and the potential need for adjuvant screening to evaluate for associated aortopathy.

KEY POINT

- The characteristic finding of a bicuspid aortic valve is an aortic ejection sound associated with either a systolic or diastolic murmur.

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Franklin WJ, Gandhi M. Congenital heart disease in pregnancy. Cardiol Clin. 2012 Aug;30(3):383-94. [PMID: 22813364]

Item 38 Answer: C

Educational Objective: Manage medication use prior to stress testing.

This patient's metoprolol should be withheld for 48 hours before stress testing. In this intermediate-probability patient with a normal electrocardiogram, exercise stress testing is appropriate. Exercise stress is preferred to pharmacologic stressors because it provides a gauge of functional capacity and a contextual understanding of symptoms, and it records hemodynamic response to exercise. The sensitivity of the

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study to detect obstructive coronary artery disease (CAD) is lowered, however, if patients are taking certain medications. β-Blockers and nondihydropyridine calcium channel blockers can blunt the maximal heart rate that can be achieved with exercise and may limit a patient's ability to reach 85% of the maximal predicted heart rate. However, dihydropyridine calcium channel blockers do not need to be withheld prior to testing. Similarly, digoxin can limit the maximal heart rate and should be withheld. Nitrates are effective antianginal agents but may minimize the ischemic response on stress testing; therefore, they should also be withheld. If, however, a patient has known CAD and the goal of testing is to determine whether symptoms are related to ischemia or to assess adequacy of antianginal therapy, there is no need to stop any of the medications.

There is no evidence that ACE inhibitors, such as lisinopril, or angiotensin receptor blockers alter the sensitivity of exercise stress testing in the diagnosis of CAD, and these agents do not need to be discontinued before testing. For this patient on several medications for hypertension, an appropriate strategy would be to continue hydrochlorothiazide and lisinopril and discontinue metoprolol.

KEY POINT

- In patients undergoing stress testing to diagnose coronary artery disease, β-blockers should be withheld for 24 to 48 hours before testing.

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Item 39 Answer: B

Educational Objective: Manage a patient with new-onset exertional angina pectoris.

This patient with an intermediate risk of ischemic heart disease and an inadequate exercise electrocardiographic (ECG) stress test should undergo pharmacologic stress testing. Although exercise ECG stress testing is the preferred diagnostic study in patients with an indication for testing who have an interpretable resting ECG and are able to exercise, in patients who are unable to meet the minimal criteria for adequacy on this study (achievement of at least 85% of the age-predicted maximal heart rate and maximal metabolic demand), additional testing is indicated to appropriately evaluate for ischemic heart disease. Dobutamine stress echocardiography or a vasodilator nuclear medicine stress test would be appropriate studies in this clinical setting and would allow for further stratification of this patient's risk for ischemic heart disease.

Proceeding directly to cardiac catheterization may be appropriate in patients at very high risk for ischemic heart disease in whom noninvasive testing would not be expected to significantly change the pretest probability of disease. However, in this patient with an intermediate risk of disease, adequate noninvasive testing would be helpful in evaluating for the presence of ischemic heart disease, and coronary angiography would not be indicated as a next diagnostic test.

Switching the patient's antihypertensive medication to an agent with antianginal properties would not be indicated without establishing the presence of ischemic heart disease, particularly with adequate control of her blood pressure on her current regimen.

Because an inadequate exercise ECG exercise test is unable to assess for the presence of ischemic heart disease in this patient at intermediate risk, clinical observation without further evaluation would not be appropriate.

KEY POINT

- Exercise stress testing is recommended as the initial test of choice for patients with intermediate risk of ischemic heart disease who are capable of exercising and have a normal resting electrocardiogram, although advanced imaging is indicated if the exercise stress test is inadequate or indeterminate.

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Item 40 Answer: C

Educational Objective: Manage cardiovascular risk in an older woman with diabetes mellitus.

This patient should start atorvastatin, discontinue simvastatin, and continue her other medications. The most recent cholesterol guidelines recommend a moderate- or high-intensity statin, such as atorvastatin, in patients aged 40 to 75 years with diabetes mellitus who have a 10-year cardiovascular risk greater than or equal to 7.5%. This patient's 10-year cardiovascular risk is above 10%. A cardiovascular risk calculator based on the Pooled Cohort Equations for the purpose of managing cholesterol levels is available at http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp. In patients with diabetes in this age group with a 10-year risk below 7.5%, a moderate-intensity statin (such as simvastatin 20-40 mg/d) would be recommended. While there are multiple options for a

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high-intensity statin, the fact that atorvastatin has a generic alternative makes it a more attractive choice.

Increasing simvastatin from 10 mg/d to 80 mg/d is incorrect, as the FDA issued a black box warning against the use of simvastatin 80 mg/d because of a heightened risk of muscle adverse effects.

Continuing the patient's current medications is incorrect because this patient's cardiovascular risk warrants change to a moderate- or high-intensity statin.

The addition of clopidogrel to this patient's drug regimen is incorrect because dual antiplatelet therapy (such as aspirin plus clopidogrel) increases the risk of bleeding and is not routinely recommended for patients for primary prevention of cardiovascular events.

Despite a negative exercise stress test, aspirin therapy would be recommended in this woman who has several risk factors for cardiovascular events and stroke, including hypertension, type 2 diabetes mellitus, hyperlipidemia, and her age. In the Women's Health Study of 40,000 healthy women, 100 mg/d of aspirin decreased the risk of stroke, myocardial infarction, and cardiovascular death in patients older than 65 years.

KEY POINT

- A moderate- or high-intensity statin is recommended for patients aged 40 to 75 years with diabetes mellitus who have a 10-year cardiovascular risk greater than or equal to 7.5%.

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Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934. Erratum in: J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):3024-3025. [PMID: 24239923]

Item 41 Answer: B

Educational Objective: Manage claudication with pharmacologic therapy in a patient with peripheral arterial disease.

The most appropriate treatment is the addition of cilostazol. Cilostazol is an oral phosphodiesterase-3 inhibitor that has demonstrated increases in pain-free walking and overall walking distance in patients with claudication in randomized clinical trials. Cilostazol is contraindicated in patients with heart failure or a left ventricular ejection fraction below 40%. This contraindication exists because cilostazol has a similar pharmacologic action to the inotropic drugs milrinone and amrinone, which demonstrated increased mortality rates with long-term use in patients with heart failure. In the absence of heart failure, a therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication.

Antihypertensive therapy is recommended for reduction of cardiovascular events in patients with peripheral arterial disease (PAD). Although concern has been raised in the past regarding use of β-blockers for treatment of hypertension in patients with PAD because of the possibility of loss of β-receptor–mediated vasodilation causing worsening claudication, this has not been supported by study data. Therefore, β-blockers may be used in patients with PAD for blood pressure control. However, this patient's hypertension is well controlled, and β-blockade is not indicated as therapy for claudication symptoms.

Clopidogrel or another thienopyridine should be added to aspirin therapy in all patients following an acute coronary syndrome and in those undergoing coronary stent placement. However, there is no benefit in adding clopidogrel to aspirin in patients with PAD for treatment of the vascular occlusion or reducing the risk of cardiovascular events.

In the Warfarin Antiplatelet Vascular Evaluation (WAVE) trial among patients with PAD, the combination of an oral anticoagulant and antiplatelet therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications and was associated with an increase in life-threatening bleeding.

KEY POINT

- Cilostazol has been shown to be effective at improving pain-free walking and overall walking distance in patients with claudication.

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Item 42 Answer: E

Educational Objective: Manage an accelerated idioventricular rhythm following myocardial infarction.

This patient requires no further intervention at this time. She developed a wide complex rhythm shortly after percutaneous coronary intervention and reperfusion of her infarct-related artery. The electrocardiogram (ECG) shows a regular wide complex rhythm at 92/min with no clearly discernible atrial activity, findings consistent with accelerated idioventricular rhythm (AIVR). AIVR is postulated to result from abnormal automaticity in the subendocardial Purkinje fibers. It is observed in up to 15% of patients who undergo reperfusion of an infarct-related artery. The rate is almost always less than 120/min and usually less than 100/min. Most studies have shown that it is a benign rhythm when it occurs within 24 hours of reperfusion. This patient is tolerating the rhythm well and is already on a β-blocker for post–myocardial infarction care; therefore, no intervention is required.

Neither amiodarone nor lidocaine is indicated because AIVR is a benign ventricular arrhythmia and usually does not recur. Studies of prophylactic lidocaine after acute coronary syndromes have demonstrated potential harm, and amiodarone has been associated with decreased survival after myocardial infarction.

Cardioversion is not indicated because AIVR is a transient rhythm and, in this patient, it is well-tolerated.

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AIVR usually indicates successful (or at least partial) reperfusion and is considered a reversible arrhythmia. Implantable cardioverter-defibrillator (ICD) placement is not indicated at this time given the patient's recent revascularization and nature of the arrhythmia. If the left ventricular ejection fraction remains low despite medical therapy, ICD placement might be indicated in the future.

KEY POINT

- Accelerated idioventricular rhythm is a common complication following coronary reperfusion and does not require intervention when it occurs within 24 hours of reperfusion.

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Item 43 Answer: A

Educational Objective: Treat a patient with acute pericarditis with high-dose aspirin.

This patient should receive high-dose aspirin. He has acute pericarditis in the setting of a recent myocardial infarction. The typical chest pain, physical examination findings, and abnormal electrocardiogram (ECG) are all consistent with this diagnosis, especially the findings of concave upward ST-segment elevation and PR-segment depression in all leads, except aVR, on the ECG. Anti-inflammatory therapy with aspirin or other NSAIDs, such as ibuprofen, is indicated in patients with acute pericarditis. In those whose pericarditis is associated with myocardial infarction, such as this patient, only aspirin should be used because ibuprofen and other NSAIDs can impair myocardial healing and increase the risk of mechanical complications. The anti-inflammatory medication should be given in relatively high doses to achieve an anti-inflammatory effect and then tapered slowly over 2 to 4 weeks to reduce the risk of recurrent pericarditis. Colchicine (0.5-1.2 mg/d) also has been shown to be effective as adjunctive therapy to anti-inflammatory agents in patients with acute pericarditis, further reducing the risk of recurrent pericarditis and treatment failure. Colchicine is not recommended for patients with post-infarction pericarditis. Colchicine may be associated with gastrointestinal side effects, liver toxicity, and bone marrow suppression but is generally well tolerated.

Nitroglycerin is an effective therapy for chest pain caused by myocardial ischemia but is not effective for symptoms caused by pericarditis.

Glucocorticoids, such as prednisone, are reserved for patients with contraindications to NSAIDs or those with refractory acute pericarditis, primarily because there is evidence that their use is associated with an increased risk of recurrent pericarditis. As this patient has no apparent contraindication to aspirin use, treatment with glucocorticoids is not indicated.

KEY POINT

- Anti-inflammatory therapy with aspirin or other NSAIDs, such as ibuprofen, is indicated in patients with acute pericarditis; when the pericarditis is associated with myocardial infarction, only aspirin should be used because other NSAIDs can impair myocardial healing and increase the risk of mechanical complications.

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Item 44 Answer: B

Educational Objective: Manage dual antiplatelet therapy after drug-eluting stent placement following non-ST-elevation myocardial infarction.

This patient, who has undergone drug-eluting stent placement following a non-ST-elevation myocardial infarction, should continue taking ticagrelor for 1 year. He also should continue taking aspirin indefinitely. The American College of Cardiology/American Heart Association percutaneous coronary intervention (PCI) guidelines recommend at least 1 year of dual antiplatelet therapy for patients undergoing PCI with a drug-eluting stent (DES).

Antiplatelet drugs indicated for patients who have received a drug-eluting stent following an acute coronary syndrome are clopidogrel, ticagrelor, and prasugrel. In the PLATelet inhibition and patient Outcomes (PLATO) trial, ticagrelor was found to be superior to clopidogrel in reducing the incidence of cardiovascular death, myocardial infarction, and stroke following an acute coronary syndrome.

Dual antiplatelet therapy for patients who have undergone placement of a bare metal stent following an acute coronary syndrome is indicated for at least 4 weeks and up to 1 year. Following placement of a DES, however, a 30-day duration of ticagrelor is insufficient.

Despite numerous studies about the risk of very late stent thrombosis, defined as the occurrence of stent thrombosis greater than 1 year after placement, there is no recommendation for lifelong dual antiplatelet therapy in current treatment guidelines.

Stopping ticagrelor and starting clopidogrel is incorrect because there is no indication to stop ticagrelor, an agent that appears to be superior to clopidogrel in improving cardiovascular outcomes following an acute coronary syndrome. Cost and adverse events (including bleeding, dyspnea, and bradycardia) are the most common reasons for discontinuation of ticagrelor.

KEY POINT

- At least 1 year of dual antiplatelet therapy is recommended for patients undergoing percutaneous coronary intervention with a drug-eluting stent (DES); therapeutic options for agents to be taken with aspirin are clopidogrel, ticagrelor, and prasugrel.

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Item 45 Answer: D

Educational Objective: Manage a patient with ventricular septal defect.

The most appropriate management for this patient with a small uncomplicated ventricular septal defect (VSD) is follow-up in 3 to 5 years. She has clinical features of a small membranous VSD without associated volume overload of the left heart, pulmonary hypertension, or valve regurgitation.

Cardiac catheterization is not indicated for this patient because the echocardiogram does not demonstrate left heart enlargement or features that suggest pulmonary hypertension.

Cardiac magnetic resonance (CMR) imaging will usually demonstrate a membranous VSD and can quantitate the impact of the VSD on the left heart; however, it is not indicated in this patient because the clinical assessment and echocardiogram suggest that observation is appropriate. CMR imaging would be a reasonable test if the transthoracic echocardiogram images were not diagnostic.

Endocarditis prophylaxis is recommended for patients with congenital heart disease characterized by unrepaired cyanotic congenital heart disease, including palliative shunts and conduits; a completely repaired congenital heart defect with prosthetic material or device during the first 6 months after the procedure; and repaired congenital heart disease with residual defects. Patients with uncomplicated VSDs without a prior history of endocarditis do not require endocarditis prophylaxis.

Functional aerobic capacity measured by stress testing is not used to determine management in patients with small VSDs. A small VSD does not impact exercise capacity and thus assessment of exercise capacity will not change management in this patient.

KEY POINT

- A small membranous ventricular septal defect without left heart enlargement, pulmonary hypertension, recurrent endocarditis, or valve regurgitation can be observed clinically.

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Item 46 Answer: A

Educational Objective: Treat mitral regurgitation with bioprosthetic mitral valve replacement.

The most appropriate treatment for this patient is mitral valve replacement (MVR) with a bioprosthetic valve. She has a history of rheumatic fever and extensive degeneration of the mitral valve with severe mitral regurgitation on echocardiogram, consistent with rheumatic heart disease. Indications for mitral valve surgery include symptomatic severe mitral regurgitation with left ventricular (LV) ejection fraction greater than 30% and asymptomatic severe mitral regurgitation with mild to moderate LV dysfunction (ejection fraction of 30%-60% and/or LV end-systolic diameter ≥40 mm). Although surgical valve repair is generally preferred to valve replacement, it may not be possible with extensive calcification of the valve leaflet or annulus, prolapse of more than one third of the leaflet tissue, or extensive destruction of the chordal apparatus. The choice of valve intervention and prosthetic valve type should be a shared decision-making process. When valve replacement is indicated, as in this patient, a bioprosthesis is preferred in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired. In addition, a bioprosthesis is a reasonable choice for patients older than 70 years. This patient's history of gastrointestinal bleeding and her advanced age make a bioprosthetic valve the more reasonable choice.

Intravenous vasodilator therapy improves forward blood flow and symptoms acutely in patients with severe mitral regurgitation. However, there is little evidence that long-term oral vasodilator therapy is beneficial for symptomatic mitral regurgitation, and it is used primarily in patients unable to undergo surgical correction. Because this patient has no clear contraindication to surgical therapy, medical therapy alone would not be appropriate.

Percutaneous mitral valve repair procedures include percutaneous valvuloplasty or implantation of a clip to reduce regurgitant flow. However, these procedures are either under investigation or their use is limited to a small group of patients.

KEY POINT

- When valve replacement is indicated, a bioprosthesis is preferred in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired.

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Item 47 Answer: C

Educational Objective: Evaluate a patient with new-onset heart failure who has evidence of coronary artery disease.

The most appropriate diagnostic test to perform next in this patient is myocardial perfusion imaging stress testing. This patient has evidence of new-onset heart failure as evidenced by her clinical presentation (decreased exercise tolerance, jugular venous distention, crackles on lung examination, and lower extremity edema). A diagnosis of new-onset heart

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failure should be confirmed by echocardiography, which has both high sensitivity and specificity for heart failure and may be useful in evaluating for specific possible causes of heart failure, such as valve dysfunction. Treatable causes of heart failure include coronary artery disease (CAD), thyroid disease, alcohol abuse, and some valvular diseases (such as aortic stenosis, if repaired early) and should be looked for during the initial evaluation.

As many as two thirds of cases of heart failure are caused by CAD. This patient has several risk factors for cardiovascular disease, including hypertension and a history of smoking. Her electrocardiogram (ECG) demonstrates left bundle branch block and her echocardiogram demonstrates an akinetic left wall, both of which suggest CAD. Patients with heart failure and multiple risk factors or symptoms of CAD should be evaluated by either a stress test or cardiac catheterization. The reason to evaluate for CAD is that revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery may improve her left ventricular ejection fraction and reduce her symptoms of heart failure. Noninvasive exercise testing is often performed initially to provide information about the possible presence of ischemic heart disease but also to assist in risk stratification and prognosis. Cardiac catheterization may be helpful in patients with suggestive findings on noninvasive testing or may be an appropriate initial study in selected patients.

Cardiac magnetic resonance (CMR) imaging is not part of the routine evaluation of new-onset heart failure but may be used if an infiltrative or an inflammatory process is suspected, such as myocarditis, hemochromatosis, Wilson disease, or sarcoidosis. If the patient's evaluation for CAD as a cause of her heart failure is normal and myocarditis is a consideration, CMR imaging may be a reasonable test.

Coronary artery calcium scoring is a method of measuring vascular calcification in the coronary arteries, with increased levels of calcium being associated with an increased burden of atherosclerotic plaque and cardiac events. Its optimal use may be in providing additional information for making therapeutic decisions in asymptomatic patients at intermediate risk for atherosclerotic cardiovascular disease. However, its role in evaluating patients with heart failure believed to be caused by CAD has not been established.

Endomyocardial biopsy is indicated in patients with heart failure that progresses despite medical therapy and those with malignant arrhythmias to evaluate for giant cell myocarditis, as well as in those in whom amyloidosis or hemochromatosis is suspected. Endomyocardial biopsy is not indicated in this patient with evidence of heart failure in whom CAD has not been evaluated.

KEY POINT

- Patients with new-onset heart failure with multiple risk factors or symptoms of coronary artery disease should be evaluated by either a stress test or cardiac catheterization.

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Item 48 Answer: A

Educational Objective: Manage a patient with diabetes mellitus presenting with stable angina pectoris not controlled with optimal medical therapy.

This patient with stable angina pectoris with symptoms that are not adequately controlled on optimal medical therapy should undergo left heart catheterization for further evaluation and potential revascularization. Her myocardial perfusion imaging results are consistent with ischemic coronary artery disease (CAD); however, these findings alone would not be an indication for left heart catheterization. In patients with stable angina pectoris, coronary revascularization has not been shown to improve morbidity or mortality, and thus is not indicated in patients whose symptoms are able to be controlled with optimal medical therapy. However, in patients with coronary ischemia who fail to respond to adequate antianginal therapy, such as this patient, coronary angiography is indicated to evaluate for possible revascularization to control her angina symptoms. Catheterization may allow for percutaneous intervention to address a coronary occlusion leading to her angina symptoms, or assessment for the need for surgical revascularization if extensive or complex CAD is present.

CT angiography is an emerging technology for the noninvasive evaluation of the coronary arteries. Although it may be able to confirm the diagnosis of CAD in this patient, it would not allow the opportunity for percutaneous coronary intervention, if possible. The use of CT angiography to estimate the need or benefit of coronary artery bypass grafting also has not been established. Therefore, this study would not be indicated in this clinical setting.

Dobutamine stress echocardiography is typically used to evaluate for ischemic CAD in patients who are unable to exercise. However, in this patient with documented coronary ischemia established by a nuclear medicine myocardial perfusion study, there would be no benefit to performing this alternative diagnostic study for ischemia.

Because this patient remains symptomatic with restrictions on her quality of life, continuing her current medical therapy without additional intervention would not be appropriate.

KEY POINT

- Patients with stable angina not adequately controlled with optimal medical therapy should undergo coronary angiography to evaluate for possible revascularization.

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Item 49 Answer: D

Educational Objective: Use appropriate imaging to evaluate mitral regurgitation.

Transesophageal echocardiography (TEE) would be the most appropriate next step in management of this patient. Evaluating the degree of mitral regurgitation and assessing the causative valve abnormalities provides essential information for guiding therapy, particularly whether surgical repair is possible or indicated. Although this information is usually obtained with transthoracic echocardiography, in situations in which full evaluation of the valve and degree of mitral regurgitation is not possible, such as in this very obese patient in whom accurate Doppler parameters cannot be obtained, TEE is indicated. Because the transducer in TEE is able to be closely approximated to the left atrium and mitral valve, structural details, including integrity of the valve leaflets and chordae, and the regurgitant jet, are almost always well visualized, allowing assessment of valvular abnormalities and accurate measurement of Doppler parameters. Chest CT angiography and cardiac magnetic resonance imaging may also be useful adjuvants, allowing assessment of coronary anatomy, valve structure, and coexisting structural heart disease. Three-dimensional echocardiography, both transthoracic and transesophageal, can further help identify leaflet and scallop involvement, likelihood of operative repair, and additional quantification of mitral regurgitation severity.

The decision to proceed with mitral valve surgery, including mitral valve repair, would be premature in this patient without adequate knowledge of the severity of mitral regurgitation and better definition of the underlying valvular abnormalities.

Although clinical follow-up with serial echocardiography may be appropriate for this patient, the appropriateness of this management strategy depends upon adequate initial evaluation of her mitral valve disease.

Medical therapy for patients with asymptomatic mitral regurgitation is limited. To date, no studies have shown benefit of ACE inhibitors, angiotensin receptor blockers, or diuretics in the absence of another specific indication, such as hypertension, left ventricular systolic dysfunction, or evidence of volume overload. This patient has none of those features.

KEY POINT

- In patients with mitral regurgitation, transthoracic echocardiography (TTE) is used to evaluate the degree of mitral regurgitation and assess the causative valve abnormalities, thereby providing essential information for guiding therapy; if visualization is inadequate with TTE, transesophageal echocardiography is indicated.

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Solis J, Piro V, Vazquez de Prada JA, Loughlin G. Echocardiographic assessment of mitral regurgitation: general considerations. Cardiol Clin. 2013 May;31(2):165-8. [PMID: 23743069]

Item 50 Answer: A

Educational Objective: Evaluate infrequent palpitations in a patient without syncope.

An event recorder would be appropriate to evaluate this patient's episodic symptoms of palpitations and lightheadedness. The evaluation and identification of arrhythmias can be challenging because of their intermittent nature; the modality used depends on the frequency and nature of the symptoms. In patients with infrequent symptoms, event recorders are the most effective means of obtaining rhythm information around the time of the symptoms. Event recorders record electrocardiographic (ECG) tracings only when activated by the patient and are more useful for infrequent symptoms. Two types of event recorders are used. A patient-triggered recorder is an external device without leads that is held to the chest and triggered by the patient when symptoms occur. The advantage of this device is the lack of electrode leads, making it more comfortable and convenient; however, no preceding rhythm is saved when the device is triggered. When the patient activates a looping event recorder, a permanent recording is created that includes several seconds of the presymptom rhythm, which is useful in patients with syncope.

In patients in whom pathologic structural heart disease is suspected, transthoracic echocardiography provides noninvasive, quantitative evaluation of cardiac size and function, valve morphology and function, pericardial disease, pulmonary artery pressures, and proximal great vessels. Physical examination findings in patients with structural disease include signs of heart failure and abnormal cardiac auscultation. In this patient, there is no evidence of structural heart disease by either history or examination, so an echocardiogram is not warranted.

Exercise ECG stress testing allows diagnosis of exercise-related arrhythmias, as well as assessment of the impact of the arrhythmia on blood pressure. The patient does not describe exercise-related symptoms, and an exercise stress test is not indicated.

Ambulatory ECG monitors record continuous rhythms and can be useful when patients have frequent, usually daily, symptoms. Monitors are usually worn for 24 or 48 hours.

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Patients are encouraged to perform their normal activities while wearing the monitor. Patients keep a symptom diary or trigger a marker on the continuous reading that correlates with symptoms. Ambulatory ECG monitors can also be useful to detect asymptomatic arrhythmias, such as asymptomatic atrial fibrillation. This patient's symptoms occur about once a week, and a 24- or 48-hour ambulatory monitoring period is likely to miss the symptomatic episodes.

KEY POINT

- In patients with infrequent symptoms, cardiac event recorders are the most effective means of obtaining rhythm information around the time of the symptoms.

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Zimetbaum P, Goldman A. Ambulatory arrhythmia monitoring: choosing the right device. Circulation. 2010 Oct 19;122(16):1629-36. [PMID: 20956237]

Item 51 Answer: B

Educational Objective: Treat wide-complex tachycardia due to atrial fibrillation with aberrant conduction.

The most appropriate next step in treatment of this patient is to initiate β-blocker therapy. He has paroxysmal atrial fibrillation with aberrant conduction, resulting in a wide-complex tachycardia. The electrocardiogram demonstrates a normal sinus beat followed by a run of atrial fibrillation with right bundle branch block. Note the irregularly irregular nature of the tachycardia and the QRS morphology consistent with typical right bundle branch block. Given his rapid ventricular response and his symptoms of palpitations and dyspnea, the atrial fibrillation requires treatment. β-Blocker therapy is the preferred atrioventricular nodal blocking agent given the patient's history of coronary artery disease.

Assessment of the need for anticoagulation therapy is also indicated in this patient with atrial fibrillation. Current guidelines recommend the use of the CHA_2DS_2-VASc score for this purpose, replacing the $CHADS_2$ score because of its ability to more clearly discriminate stroke risk. This patient has a CHA_2DS_2-VASc score of 4 (1 point for hypertension, 2 points for age, and 1 point for coronary artery disease), placing him at moderate risk for stroke. Therefore, initiation of oral anticoagulation also is appropriate.

Emergent cardioversion is not necessary because the patient is hemodynamically stable and appears to be having self-terminating paroxysms of tachycardia. If the patient had a sustained arrhythmia accompanied by hemodynamic instability, emergent cardioversion would be indicated regardless of the specific etiology of the arrhythmia (that is, supraventricular versus ventricular).

Intravenous amiodarone would be an appropriate treatment for recurrent ventricular tachycardia. The electrocardiogram appearance is consistent with right bundle branch block. There is an rSR pattern in lead V_1 and a terminal S wave in leads I and V_6. Right axis deviation is present (QRS axis 123 degrees); however, there is also evidence of left posterior fascicular block (small r waves and deep S waves in leads I and aVL; qR complexes in leads II, III, and aVF). Thus, these features are most consistent with aberrant conduction in the setting of atrial fibrillation rather than ventricular tachycardia.

Intravenous procainamide would be the agent of choice if this tachycardia were pre-excited (Wolff-Parkinson-White syndrome). Pre-excitation is evidenced by the presence of a delta wave. This patient's electrocardiogram does not demonstrate pre-excitation in either the sinus beat or the tachycardia.

KEY POINT

- Paroxysms of an irregularly irregular rhythm with a typical right bundle branch block appearance on electrocardiogram most likely represent atrial fibrillation with aberrant conduction.

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Item 52 Answer: A

Educational Objective: Manage cardiovascular risk reduction in a patient with peripheral arterial disease.

The most appropriate management is to start a moderate- or high-intensity statin. Peripheral arterial disease (PAD) is strongly associated with smoking, diabetes mellitus, and aging. PAD is defined noninvasively by calculation of the ankle-brachial index (ABI). An ABI of 0.90 or below is diagnostic of PAD. Most patients with PAD are asymptomatic; approximately 25% have symptoms referable to circulatory compromise. PAD is considered a coronary artery disease risk equivalent and statin therapy has been demonstrated to lower cardiovascular events in patients with PAD.

Exercise and cilostazol are effective therapies for patients with stable symptomatic PAD. Cilostazol significantly increases pain-free walking time and maximal walking time, although the gains with structured exercise are two- to three-fold greater than with cilostazol alone. Since this patient is asymptomatic, cilostazol is not indicated.

Antiplatelet therapy is indicated for all patients with symptomatic PAD, previous lower extremity revascularization, or amputation due to PAD. Antiplatelet therapy is reasonable in patients with asymptomatic PAD, particularly if they have evidence of atherosclerosis elsewhere (coronary or cerebral arteries). Combination treatment with an antiplatelet agent and warfarin, and warfarin monotherapy (adjusted to an INR of 2.0-3.0), is no more effective than antiplatelet therapy alone and carries a higher risk of life-threatening bleeding.

Noninvasive angiography is performed for anatomic delineation of PAD in patients requiring surgical or endovascular

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intervention. CT angiography (CTA) is rapid and easily available but requires the administration of intravenous contrast dye. While CTA compares favorably with digital subtraction (invasive) angiography for the detection of occlusive arterial disease, imaging is not needed at this time because the patient does not require surgical intervention.

Lower extremity segmental pressure measurement can help determine the level and extent of PAD. Using specialized equipment in the vascular laboratory, blood pressures are obtained at successive levels of the extremity, localizing the level of disease. Many vascular laboratories use air plethysmography to measure volume changes within the limb, in conjunction with segmental limb pressure measurement. Lower extremity segmental pressure measurement is not needed at this time because localization of disease is not needed to guide therapy, such as would be required if surgical intervention were being planned.

KEY POINT

- Patients with peripheral arterial disease should be treated with a moderate- or high-intensity statin.

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Item 53 Answer: E

Educational Objective: Choose appropriate antiplatelet agents following acute coronary syndrome and percutaneous coronary intervention.

No changes should be made to this patient's medications at the time of hospital discharge.

Calcium channel blockers, with the exception of nifedipine, can be used in patients with contraindications to β-blockers and in those with continued angina despite optimal doses of β-blockers and nitrates. This patient has no indications for a calcium channel blocker such as diltiazem.

There is no evidence to support a change from ticagrelor to clopidogrel after percutaneous coronary intervention (PCI) for acute coronary syndrome. In the PLATO (PLATelet inhibition and patient Outcomes) trial, the use of ticagrelor was associated with a 1.9% absolute risk reduction in the occurrence of cardiovascular death, myocardial infarction, and stroke when compared with clopidogrel. A $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, ticagrelor) should be continued for at least 1 year for patients undergoing PCI with stent placement.

Oral β-blockers should be given to all patients with acute coronary syndrome without a contraindication (decompensated heart failure, advanced atrioventricular block, or severe reactive airways disease) and continued indefinitely. This patient is already bradycardic, and an increase in the dosage of metoprolol may be associated with symptomatic bradycardia.

In this patient with an acute coronary syndrome and preserved left ventricular function, there is no evidence to support the use of an aldosterone antagonist such as eplerenone. Based on the EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival) trial, the 2007 American College of Cardiology/American Heart Association guidelines recommend the administration of an aldosterone antagonist to all patients following a non-ST-elevation myocardial infarction (NSTEMI) who are receiving an ACE inhibitor, have a left ventricular ejection fraction of 40% or below, and have either heart failure symptoms or diabetes mellitus.

ACE inhibitors inhibit postinfarction remodeling, helping to preserve ventricular function. ACE inhibitors should be continued indefinitely.

KEY POINT

- Long-term therapy following myocardial infarction includes aspirin, a β-blocker, an ACE inhibitor, and a statin; a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, ticagrelor) should be continued for at least 1 year for patients undergoing coronary percutaneous intervention with stent placement.

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Item 54 Answer: B

Educational Objective: Treat heart failure with reduced ejection fraction with a β-blocker.

This patient with a recent diagnosis of heart failure with reduced ejection fraction (HFrEF) should be started on a β-blocker, such as carvedilol. Standard therapy for patients with HFrEF includes an ACE inhibitor and a β-blocker. This patient is already on an ACE inhibitor for treatment of his blood pressure and for afterload reduction for his heart failure. ACE inhibitors are typically started first in patients with heart failure because of their positive hemodynamic effects. An angiotensin receptor blocker (ARB) would be another treatment option, particularly if an ACE inhibitor were not tolerated. A β-blocker should then be started in stable, euvolemic patients with heart failure, either at the time of diagnosis or after acute decompensation is treated. β-Blockers have several beneficial effects and have been shown to prolong overall and event-free survival.

The β-blockers that have been shown to provide benefit in patients with HFrEF are metoprolol succinate, carvedilol, and bisoprolol. The β-blocker dosage should be increased slowly—at 1- to 2-week intervals—to the maximal dose. Like ACE inhibitors, there are data that suggest improved outcomes on higher doses of β-blockers (increased ejection fraction, reduced symptoms, lower mortality rates); therefore, attempting to up-titrate to maximally tolerated doses is important.

Although dihydropyridine calcium channel blockers, such as amlodipine, are effective antihypertensive and antianginal medications, they do not provide the same benefits as ACE inhibitors, ARBs, or β-blockers, and would not

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be appropriate add-on therapy in this patient who is not currently on a β-blocker and has controlled blood pressure without angina.

This patient has clear lungs, no significant jugular venous distention, and no peripheral edema. He has no evidence of volume overload and therefore does not need a diuretic, such as furosemide. Diuretics have no mortality benefit and are only used for symptom relief in the setting of volume overload.

Spironolactone has been demonstrated to decrease mortality rates in patients with New York Heart Association (NYHA) functional class II to IV heart failure (dyspnea with activities of daily living). This patient has good exercise capacity and has NYHA class II heart failure. However, candidates for spironolactone therapy should already be on standard medical therapy, including an ACE inhibitor and a β-blocker.

Making no changes in this patient's treatment regimen would not be appropriate because he is not being treated with medications associated with improved outcomes in patients with systolic heart failure.

KEY POINT

- Initial treatment for patients with heart failure with reduced ejection fraction (HFrEF) includes an ACE inhibitor and a β-blocker; the β-blockers that have been shown to provide benefit in patients with HFrEF are metoprolol succinate, carvedilol, and bisoprolol.

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Item 55 Answer: A

Educational Objective: Diagnose platypnea-orthodeoxia syndrome.

The most likely diagnosis in this patient is a patent foramen ovale with right-to-left shunt. He presents with features of platypnea-orthodeoxia syndrome, characterized by positional symptoms of cyanosis and dyspnea that generally occur when the patient is sitting and resolve in the supine position. Right-to-left shunting across an atrial septal defect or patent foramen ovale may rarely cause cyanosis and dyspnea owing to deformation of the atrial septum and redirection of shunt flow that result from increased right atrial pressure in the upright position. This patient had an inferior and right ventricular myocardial infarction with associated right heart enlargement and dysfunction and clinical features of hypotension. The right heart enlargement causes annular dilatation and tricuspid regurgitation. The foramen ovale stretches and becomes patent. The preferential cyanosis is caused by the hemodynamic alterations and preferential transfer of right atrial blood across the patent foramen in the upright position.

Mitral regurgitation due to papillary muscle injury or rupture is a recognized complication after myocardial infarction; however, the presentation generally is characterized by acute dyspnea and pulmonary edema rather than platypnea-orthodeoxia. Physical examination findings include a systolic murmur at the apex that increases during expiration rather than inspiration.

Severe left ventricular systolic dysfunction generally does not cause arterial oxygen desaturation. In addition, the initial assessment of left ventricular function was normal. The clinical picture in this patient is more compatible with right ventricular dysfunction.

Ventricular septal defect is a recognized complication after transmural myocardial infarction; however, the presentation generally includes acute dyspnea and pulmonary edema rather than oxygen desaturation. The left-to-right shunt associated with the ventricular septal defect causes left heart volume overload, rather than the right heart volume overload caused by right-to-left shunting seen in this patient. Physical examination findings in patients with ventricular septal defect following myocardial infarction include a holosystolic murmur at the left sternal border that does not change with respiration.

KEY POINT

- Right-to-left shunting across an atrial septal defect or patent foramen ovale may rarely cause cyanosis and dyspnea due to deformation of the atrial septum and redirection of shunt flow that result from increased right atrial pressure in the upright position.

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Item 56 Answer: A

Educational Objective: Manage heart failure with cardiac resynchronization therapy.

This patient with symptomatic heart failure and a reduced left ventricular ejection fraction with evidence of significant conduction system disease should undergo placement of a biventricular pacemaker (cardiac resynchronization therapy [CRT]). He has progressive heart failure symptoms while on appropriate medical therapy and has New York Heart Association (NYHA) functional class III symptoms. With his ejection fraction less than 35% and left bundle branch block (LBBB), he is a candidate for a biventricular pacemaker, which has been demonstrated to reduce mortality and symptoms in patients with NYHA functional class III and IV heart failure by improving cardiac hemodynamics. The 2013 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society(ACCF/AHA/HRS) guideline recommends CRT therapy in patients with an ejection fraction of 35% or below, NYHA functional class III to IV symptoms on guideline-directed medical therapy, and LBBB with QRS duration greater than or equal to 150 ms. This patient already has an implantable cardioverter-defibrillator, which is indicated for patients with NYHA functional class II to III heart

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failure and an ejection fraction less than 35%. Now that he has developed a LBBB and an increase in symptoms, it is reasonable to proceed with placement of a biventricular pacemaker as well.

Inotropic therapy, such as dobutamine, is reserved for patients with end-stage heart failure, either as a bridge to transplantation or for palliative care. Patients in this category often have recurrent hospitalizations for heart failure, have evidence of end-organ compromise such as worsening kidney and liver function, and have very poor exercise tolerance. Although this patient has progressive symptoms, he has not reached this stage yet, and has no indication for inotropic therapy.

The patient has no evidence of volume overload on examination and a borderline low blood pressure; therefore, increasing his diuretic dose would not be expected to improve his symptoms and may worsen them by lowering his cardiac filling pressures and cardiac output.

The patient is fairly symptomatic but has not yet had optimal therapy, as he has an indication for CRT and has not yet received it. Left ventricular assist devices (LVADs) are reserved for patients with end-stage refractory heart failure as a bridge to heart transplantation or as destination therapy in selected patients who are not candidates for transplantation. However, prior to being considered for either an LVAD or heart transplantation, a patient must be on optimal medical therapy.

KEY POINT

- Cardiac resynchronization therapy is recommended in patients with an ejection fraction of 35% or below, New York Heart Association functional class III to IV symptoms on guideline-directed medical therapy, and left bundle branch block or QRS duration of 150 ms or greater.

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Item 57 Answer: E

Educational Objective: Evaluate a patient with cardiovascular risk factors and atypical chest pain and a normal resting electrocardiogram.

The most appropriate diagnostic test for this patient is exercise stress testing. He has an intermediate pretest probability of coronary artery disease (CAD) based on his age, sex, and symptoms. He should undergo stress testing to determine if his symptoms are related to obstructive CAD. Exercise electrocardiographic (ECG) testing is the standard stress test for CAD diagnosis in patients with a normal baseline ECG. If abnormalities limiting ST-segment analysis are present (left bundle branch block [LBBB], left ventricular hypertrophy, paced rhythm, Wolff-Parkinson-White pattern), results may be indeterminate. This patient has none of these conditions, and therefore exercise stress testing is a reasonable option. In patients who can exercise, exercise stress is preferred to pharmacologic stress because of the functional and prognostic information exercise stress provides. Persons who can exercise have a better prognosis than those who are unable to exercise and require pharmacologic stress testing.

Among patients with resting ECG abnormalities that limit ST-segment analysis, the addition of imaging aids diagnostic accuracy and provides improvement in localizing the site and extent of ischemia. In patients with LBBB, exercise stress may result in abnormal septal motion due to conduction delay with falsely positive septal abnormalities; this abnormality is lessened with use of vasodilator (such as adenosine) stress imaging. This patient does not have ECG abnormalities that warrant adenosine myocardial imaging study and the added expense and radiation exposure that this procedure would require.

Cardiac magnetic resonance (CMR) imaging can be used to evaluate aortic pathology, pericardial diseases, and myocardial diseases, as well as to evaluate the extent of myocardial fibrosis. CMR imaging may be useful in determining the extent of myocardial infarction and potential viability. This patient is asymptomatic; therefore, CMR imaging is not indicated.

CT angiography allows determination of the presence and extent of coronary artery disease. If this intermediate-risk patient was unable to exercise or the ECG was uninterpretable, CT angiography could be performed. If, however, obstructive disease was found, the patient would then need to undergo coronary angiography to perform a percutaneous intervention, thus performing two procedures that require contrast agents and radiation exposure.

For patients unable to exercise because of physical limitations or physical deconditioning, pharmacologic stressors, such as dobutamine, can be used. These agents, which are recommended if the patient cannot achieve at least five metabolic equivalents, increase myocardial contractility and oxygen demand. This patient can exercise, and dobutamine stress echocardiography is not indicated.

KEY POINT

- Exercise electrocardiographic testing is the standard stress test for the diagnosis of coronary artery disease in the absence of conditions that limit ST-segment analysis.

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Item 58 Answer: A

Educational Objective: Manage infection of an implanted electronic cardiac device.

This patient has signs and symptoms concerning for possible infection of an implanted cardiac electronic device. He should undergo laboratory evaluation including assessment of a complete blood count with differential, two peripheral blood cultures from separate phlebotomy sites, and an erythrocyte sedimentation rate to assess for the possibility of a device-related infection.

Patients with an implanted cardiac device can develop either a localized tissue infection at the implant site (pocket infection) or a systemic infection with bacteremia (for example, endocarditis). These infections can occur after initial implantation, late after implantation, or following a device battery replacement or revision. If left untreated, implanted cardiac device infections will progress to endocarditis and sepsis and ultimately death. The fatality rate for an untreated device infection approaches 75% to 100%. Antibiotic therapy alone is insufficient. Curative therapy requires antibiotic therapy and complete hardware removal.

The most common pathogens are coagulase-negative *Staphylococcus* species and *S. aureus*. Patients may present with fever or malaise; many also have local findings suggestive of infection, such as erythema or warmth at the implant site. These patients should undergo a laboratory evaluation for signs of infection. Elevated erythrocyte sedimentation rate, leukocytosis with a left shift, and anemia are suggestive of infection. All patients with possible device-related infection (with or without fever) should have a minimum of two blood cultures drawn from separate sites. Once there is suspicion for a device infection, referral to the patient's electrophysiologist or an infectious disease specialist is mandatory.

Pacemaker pocket aspiration should never be performed, as it can seed a sterile pocket and lead to infection, especially if there is superficial cellulitis without deeper tissue involvement.

Ultrasonographic examination of a pacemaker or defibrillator pocket may be helpful in patients with suspected implanted cardiac device infections. However, pocket fluid may not always represent infection, and sterile seromas are sometimes encountered. Therefore, pocket ultrasound has limited—if any—diagnostic value.

Even though the presenting symptoms of a device-related infection may be nonspecific and difficult to distinguish from other common, benign infections, delayed diagnosis may allow more significant complications to develop. Therefore, observation in a high-risk patient would not be appropriate.

KEY POINT

- Patients with possible implanted cardiac device infection (with or without fever) should have a minimum of two blood cultures drawn from separate sites.

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Item 59 Answer: B

Educational Objective: Manage asymptomatic moderate aortic regurgitation.

This patient with moderate aortic regurgitation should be reassessed clinically in 1 year. Patients with moderate aortic regurgitation should be evaluated on a yearly basis and echocardiography performed every 1 to 2 years.

Aortic valve replacement is indicated for symptomatic patients with chronic severe aortic regurgitation irrespective of left ventricular (LV) systolic function, asymptomatic patients with chronic severe aortic regurgitation and LV systolic dysfunction (LV ejection fraction ≤50%), and patients with chronic severe aortic regurgitation undergoing coronary artery bypass graft (CABG) or surgery on the aorta or other heart valves. This patient is not a candidate for aortic valve replacement.

Endocarditis prophylaxis is not recommended for patients with bicuspid aortic valves in the absence of another specific indication such as a prior episode of infective endocarditis, previous valve replacement, prior cardiac transplantation with valvulopathy, and certain forms of complex congenital heart disease.

Medical therapy for chronic aortic regurgitation is limited. ACE inhibitors or angiotensin receptor blockers may be used in patients with chronic severe aortic regurgitation and heart failure as well as in patients with aortic regurgitation and concomitant hypertension, but these agents, as well as dihydropyridine calcium channel blockers, have not been shown to delay surgery in asymptomatic patients without hypertension. There is no established benefit in medical therapy for this patient with moderate aortic regurgitation without other specific indications for treatment.

KEY POINT

- Asymptomatic patients with moderate aortic regurgitation should be evaluated on a yearly basis and have echocardiography performed every 1 to 2 years.

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Item 60 Answer: A

Educational Objective: Manage anticoagulation therapy in a pregnant woman with a mechanical valve prosthesis.

The anticoagulation regimen that will provide the greatest protection against thromboembolism in this patient is warfarin therapy. Low-dose aspirin therapy should also be continued. Women with mechanical valve prostheses carry a high risk of valve thrombosis, bleeding, and fetal morbidity and mortality during pregnancy, and the optimal anticoagulation strategy has not been established. Options include warfarin, unfractionated heparin (UFH), and low-molecular-weight heparin (LMWH). Although warfarin poses an increased risk of teratogenicity and fetal loss, it appears to be the most effective option for reducing thromboembolism risk in the mother. The current dose of warfarin (4 mg/d), used to achieve a therapeutic INR, is associated with a low risk of warfarin embryopathy and a low risk of fetal complications.

The novel oral anticoagulants, such as dabigatran, bivalirudin, rivaroxaban, and apixaban, do not adequately protect patients with mechanical valve prostheses against thromboembolism and should not be used in pregnant or nonpregnant patients with mechanical valve prostheses.

Intravenous UFH is the anticoagulant treatment of choice around the time of delivery. Intravenous UFH can also be used during the first trimester. The dose effect must be measured by activated partial thromboplastin time and the dose adjusted to a therapeutic level. Fixed-dose subcutaneous UFH may not provide adequate anticoagulation.

LMWH can be used as an anticoagulant during pregnancy, but for patients with a mechanical valve prosthesis, a weight-based regimen has been demonstrated to be inadequate. The LMWH dose must be adjusted to anti–factor Xa activity in order to provide adequate anticoagulation.

KEY POINT

- Anticoagulation strategies for pregnant women with a mechanical valve prosthesis include warfarin, dose-adjusted unfractionated heparin, and dose-adjusted low-molecular-weight heparin; of these options, warfarin poses a lesser risk of maternal thromboembolism but a greater risk of fetal embryopathy.

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Item 61 Answer: D

Educational Objective: Treat a patient with thrombolytic failure following an ST-elevation myocardial infarction.

This patient with ST-elevation myocardial infarction (STEMI) should be transferred to the nearest hospital with primary percutaneous coronary intervention (PCI) capabilities for emergency PCI. Thrombolytic therapy failure, which occurs in up to 30% of patients, remains difficult to diagnose. Chest pain resolution, ST-segment elevation improvement, and reperfusion arrhythmias (most commonly an accelerated idioventricular rhythm) indicate successful thrombolysis. Although complete ST-segment elevation resolution is associated with coronary patency, it occurs in a minority of patients. Improvement in ST-segment elevation greater than 50% on an electrocardiogram (ECG) obtained 60 minutes after the administration of thrombolytic therapy is the most commonly used criterion to indicate successful reperfusion. Continued chest pain, lack of improvement in ST-segment elevation, hemodynamic instability, and the absence of reperfusion arrhythmias most likely indicate failure of thrombolytic therapy and indicate the need for rescue PCI. This patient has clear evidence of failed reperfusion or reocclusion (worsening of ST-segment elevation, persistence of symptoms) and now has signs of cardiogenic shock (low blood pressure, pulmonary edema). In patients with thrombolytic therapy failure, guidelines recommend immediate transfer for rescue PCI. In multiple trials of thrombolytic therapy failure, patients who underwent rescue PCI had a significant improvement in the rate of reinfarction when compared with those receiving conservative care, but no improvement in mortality.

The use of glycoprotein IIb/IIIa inhibitors has been tested in multiple scenarios in patients with STEMI. Based on these studies, their use has been limited owing to excessive bleeding events. In patients in whom thrombolytic therapy has failed, rescue PCI without the use of a glycoprotein IIb/IIIa inhibitor or additional thrombolytic agents is preferred.

A meta-analysis published in 2007 compared repeat thrombolytic therapy with conservative therapy in patients in whom initial thrombolytic therapy failed. This analysis showed no significant difference in mortality rates or reinfarction between the two groups, and outcomes in these groups were inferior to rescue PCI.

KEY POINT

- Patients with thrombolytic therapy failure following an ST-elevation myocardial infarction should be immediately transferred for rescue percutaneous coronary intervention.

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Item 62 Answer: C

Educational Objective: Screen patients with a family history of hypertrophic cardiomyopathy for the disease at appropriate intervals.

This patient should again be screened for hypertrophic cardiomyopathy (HCM) in 5 years. All first-degree

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relatives of patients with HCM should undergo screening for the disorder with a comprehensive physical examination, electrocardiogram, and echocardiogram. Because HCM can manifest at any age, lifetime screening of first-degree relatives in whom the disorder has not yet been diagnosed is indicated. The recommended HCM screening intervals, which are based on clinical suspicion, patient age, family history, and participation in competitive athletics, are shown.

Recommended Hypertrophic Cardiomyopathy Screening Intervals

Age Group	Recommendation
<12 years	Screening optional except in the following situations: (1) presence of symptoms; (2) family history of malignant ventricular tachyarrhythmias; (3) patient is competitive athlete in an intense training program; or (4) presence of other clinical suspicion of early left ventricular hypertrophy
12 to 18-21 years	Every 12 to 18 months
>18-21 years	At symptom onset or at least every 5 years (more frequently in families with malignant tachyarrhythmias or late onset)

These recommendations are for relatives of patients with HCM in whom genetic testing is negative, inconclusive, or not performed. Genetic testing of probands can be used to identify pathologic mutations, which can then be used to screen family members and, if negative, may obviate the need for continued imaging. The yield of genetic testing, which can be costly, varies according to the phenotypic expression and familial nature of HCM. Thus, referral to a cardiovascular specialist or a genetic counselor is recommended for clinical decision-making based on genetic testing in patients with HCM.

KEY POINT

- All first-degree relatives of patients with hypertrophic cardiomyopathy should undergo screening for the disorder with a comprehensive physical examination, electrocardiogram, and echocardiogram; lifetime screening of those in whom the disorder has not yet been diagnosed is indicated.

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Item 63 Answer: C

Educational Objective: Treat atrioventricular block complicating acute myocardial infarction.

This patient has evidence of an inferior-posterior ST-elevation myocardial infarction and should undergo urgent percutaneous coronary intervention (PCI). He is bradycardic with Mobitz type 1 second-degree heart block, also known as Wenckebach block. This type of atrioventricular block is almost always within the compact atrioventricular node (and not infra-Hisian) and in this patient is likely caused by right coronary artery occlusion. The right coronary artery supplies the atrioventricular nodal artery in 90% of patients. The most important intervention for this patient is urgent PCI and reperfusion of the infarct-related artery. Although the presence of atrioventricular block is usually transient and resolves with reperfusion, it is associated with worse prognosis and in-hospital survival.

Aminophylline increases cyclic adenosine monophosphate (cAMP) and can be used to promote atrioventricular conduction in patients with hemodynamically unstable bradycardia or advanced atrioventricular block (Mobitz type 2 second-degree or third-degree atrioventricular block) due to coronary ischemia. This patient is hemodynamically stable and his atrioventricular block is not advanced; therefore, aminophylline is not indicated.

Because the patient is not experiencing hemodynamic sequelae, low-dose dopamine infusion is not indicated. If the patient develops hemodynamically significant bradycardia, dopamine infusion could be used to stabilize him until coronary reperfusion and temporary pacing could be accomplished.

Advanced atrioventricular block in the setting of an acute coronary syndrome often requires temporary or permanent pacing. In this patient, temporary pacing is not indicated because he is hemodynamically stable and his block is not advanced. Decisions on permanent pacing should be delayed until a patient has been revascularized and stabilized to determine whether the arrhythmia persists.

KEY POINT

- Patients with acute coronary syndrome and related Mobitz type 1 second-degree atrioventricular block should undergo urgent reperfusion therapy as the treatment of choice for this conduction block.

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Item 64 Answer: A

Educational Objective: Manage intravenous lines in a patient with cyanotic congenital heart disease.

In this patient with Eisenmenger syndrome, air filters on intravenous lines are recommended to reduce the risk of paradoxical air embolism. She has clinical features of pyelonephritis, and intravenous antibiotic therapy is warranted. Patients with Eisenmenger syndrome have an intracardiac right-to-left shunt, and therefore are at risk for paradoxical air embolism. These filters can be easily and rapidly applied to any intravenous line prior to administering intravenous therapy and likely reduce the risk of air embolism. Meticulous care of intravenous lines and catheters is very important in patients with Eisenmenger syndrome owing to the potential for paradoxical embolism, which may cause stroke and debility.

There are no data to support improved survival with chronic oxygen therapy for patients with Eisenmenger syndrome and associated cyanosis. Saturation may increase minimally with oxygen therapy, but it generally does not normalize.

The hemoglobin and hematocrit levels in this patient are physiologic for a patient with Eisenmenger syndrome. Phlebotomy is not recommended.

A transthoracic echocardiogram is not recommended at this time because it is unlikely to change management in this patient who has known heart disease. The patient has features of infection, but the data suggest a urinary tract infection rather than endocarditis. If the patient presented with or develops features of endocarditis, such as a new murmur, septic emboli, or persistent bacteremia, a transesophageal echocardiogram would be favored over a transthoracic echocardiogram.

KEY POINT

- In patients with Eisenmenger syndrome, air filters and meticulous care of all intravenous lines should be instituted to prevent paradoxical air embolism.

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Item 65 Answer: D

Educational Objective: Manage coronary artery disease risk in an asymptomatic patient with diabetes mellitus.

This patient should continue his current therapy; no additional testing is indicated at this time. The leading cause of death in patients with diabetes mellitus is cardiovascular disease, but routine testing for coronary artery disease (CAD) in asymptomatic patients with diabetes does not reduce mortality. Aggressive treatment of cardiovascular risk factors, however, does improve outcomes and reduce mortality as seen in the Steno-2 study. In this study, intensive intervention with behavior modification and multiple pharmacologic interventions aimed at achieving hemoglobin A_{1c} levels below 6.5%, blood pressure below 130/80 mm Hg, and serum total cholesterol levels below 175 mg/dL (4.53 mmol/L) resulted in a 53% reduction of cardiovascular disease in a nearly 8-year follow-up. Continued risk factor management in this patient is, therefore, the most appropriate choice.

This patient does not need an echocardiogram. He is asymptomatic, and the murmur described is consistent with mild aortic stenosis as supported by his echocardiogram 1 year ago. He should undergo an annual clinical evaluation and echocardiography every 3 to 5 years. Echocardiography at this time in the absence of a clinical change is unnecessary.

If a screening test were to be performed prior to exercise, an exercise stress test would be the most appropriate test; exercise perfusion imaging provides no additional information. In routine screening of patients with diabetes in the DIAD study, despite 22% of patients having evidence of perfusion defects on single-photon emission CT, most of which were small, mortality rates were not changed compared with patients who did not undergo screening. The event rates were low in both groups, at about 3% over nearly 5 years.

The 2012 U.S. Preventive Services Task Force statement on screening for CAD with electrocardiography (ECG) recommended against screening with resting or exercise ECG for the prediction of CAD events in asymptomatic adults at low risk for CAD events, and stated that the evidence is insufficient to assess the balance of benefits and harms of screening in asymptomatic adults at intermediate or high risk for CAD events. The 2002 American College of Cardiology/American Heart Association (ACC/AHA) guidelines also concluded that there is no evidence to support routine testing in asymptomatic adults but concluded that it is reasonable to screen for CAD in asymptomatic patients with diabetes who plan to begin a vigorous exercise program.

KEY POINT

- Routine screening for coronary artery disease in asymptomatic patients with diabetes mellitus does not reduce mortality.

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Item 66 Answer: D

Educational Objective: Manage acute limb ischemia.

The most appropriate management for this patient with an ischemic but viable extremity (severe acute limb ischemia)

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H CONT. is urgent angiography to define the anatomic level of occlusion and assess appropriate treatment options, which may include surgical or percutaneous revascularization or thrombolytic therapy in selected patients. He has several risk factors for atherosclerotic peripheral arterial disease (PAD), and the claudication that he has experienced for the past year has progressed to severe resting limb pain. The limb is viable as indicated by the presence of pain, slow but present capillary refill, and the presence of Doppler vascular signals. Acute ischemia can be caused by remote embolization but may also result from in-situ thrombosis. Because of this, anticoagulation is crucial once a diagnosis of acute arterial occlusion has been made by history and physical examination. The next step in management is to further evaluate the limb ischemia and plan for treatment. Digital subtraction angiography provides the most helpful information and is the preferred imaging modality for acute limb ischemia; delaying angiography could lead to limb necrosis and loss of limb functioning.

Catheter-directed thrombolytic therapy may be an option in some patients with acute limb ischemia with a viable or marginally threatened limb as an alternative to a surgical approach, particularly if the duration of acute limb ischemia is less than 1 day. However, initiating thrombolytic therapy in this patient before further evaluation of the nature of the occlusion would not be appropriate.

For a nonviable extremity, surgical amputation without angiography is indicated because of the increased risk of tissue necrosis and infection. However, this patient's foot shows evidence of viability, making immediate amputation inappropriate.

Warfarin has not been shown to be an effective therapy for managing stable PAD, and although anticoagulation is indicated in managing acute limb ischemia pending further evaluation, initiation of long-term anticoagulation with warfarin in this patient with a viable but threatened limb without further intervention would not be appropriate.

KEY POINT

- Patients with an ischemic but viable extremity on clinical examination should undergo urgent angiography to plan surgical or percutaneous revascularization.

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Item 67 Answer: D

Educational Objective: Manage asymptomatic severe mitral regurgitation with reduced left ventricular function.

Mitral valve repair is the most appropriate option for this patient with asymptomatic severe mitral regurgitation and moderate left ventricular (LV) dysfunction. Surgery is indicated for patients with symptomatic acute severe mitral regurgitation, those with symptomatic chronic severe mitral regurgitation with LV ejection fraction greater than 30%, and asymptomatic patients with chronic severe mitral regurgitation and mild to moderate LV dysfunction (ejection fraction of 30%-60% and/or LV end-systolic dimension ≥40 mm). Mitral valve repair is the operation of choice when the valve is suitable for repair and appropriate surgical skill is available and is recommended for most patients. Mitral valve replacement, especially with chordal preservation, is appropriate for patients with severe mitral regurgitation in whom the valve is not repairable or a less than optimal result would be obtained. Recently, a percutaneously placed mitral valve clip has been introduced that is placed to better approximate the edges of the anterior and posterior leaflets of the valve and may be a therapeutic option in patients who are at a prohibitive risk for mitral valve surgery.

Vasodilator therapy, such as with ACE inhibitors or angiotensin receptor blockers, has not been shown to improve outcomes in patients with severe mitral regurgitation who are asymptomatic. Additionally, vasodilator therapy may mask the development of more severe left ventricular dysfunction due to regurgitant volume. Therefore, these agents should not be used as a substitute therapy for surgery when the patient is thought to be a surgical candidate.

Mitral balloon valvuloplasty or valvotomy is indicated for patients with severe mitral stenosis in whom there is a reasonable likelihood of success and in whom there are no contraindications (such as moderate to severe mitral regurgitation or left atrial thrombus). This patient has severe mitral regurgitation, and repair, not valvotomy, is indicated.

Serial echocardiography may be helpful in follow-up of the asymptomatic patient in whom worsening of LV systolic function or increase in chamber size may help facilitate decision for surgery. This patient's LV function is compromised and intervention is indicated.

KEY POINT

- Mitral valve repair is the operation of choice for severe mitral regurgitation when the valve is suitable for repair.

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Item 68 Answer: C

Educational Objective: Manage Brugada syndrome.

This patient should undergo placement of an implantable cardioverter-defibrillator (ICD). He had an episode of abrupt syncope that is concerning for a cardiac etiology, specifically an arrhythmia. He has a structurally normal heart on echocardiogram, but his electrocardiogram (ECG) shows right bundle branch block and 2-mm ST-segment elevation in the precordial leads. These findings are consistent with a type 1 Brugada pattern (coved or descendant ST-segment elevation followed by negative T waves) on ECG. The presence of a type

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1 Brugada pattern and symptoms (cardiac syncope) or ventricular arrhythmia is diagnostic for Brugada syndrome. Brugada syndrome can be genetically heterogeneous, but it is often caused by mutations in the SCN5a sodium channel, which are believed to cause alterations in the ventricular refractory period and are responsible for the characteristic ECG findings and predisposition to sudden cardiac death.

Because this patient with Brugada syndrome is at risk for sudden cardiac death, particularly given his recurrent episodes of near-syncope and syncope, an ICD should be implanted. Patients with precordial ST-segment abnormalities should be referred to a cardiologist or electrophysiologist. Once Brugada syndrome is diagnosed, first-degree family members should be referred to an inherited arrhythmia clinic (electrophysiology clinic specializing in genetic disorders) for counseling and screening. Patients who have a Brugada pattern but are asymptomatic often do not require ICD placement. The incidence of Brugada syndrome is higher in patients of Asian ethnicity.

Cardiac magnetic resonance (CMR) imaging would not be helpful given the normal echocardiogram and diagnosis of Brugada syndrome. CMR imaging would be helpful if occult structural heart disease was suspected, such as cardiac sarcoid, amyloidosis, or arrhythmogenic right ventricular dysplasia.

An exercise treadmill stress test can be valuable for identifying an exercise-induced arrhythmia. Brugada syndrome often presents with nocturnal arrhythmias and is usually not adrenergically driven. A stress test would not aid in this patient's diagnosis.

Tilt-table testing should be reserved for patients with recurrent syncope without known heart disease or those with heart disease in whom a cardiac cause of the syncope has been excluded. Tilt-table testing may also be helpful in evaluating patients in whom documenting neurocardiogenic syncope is important (such as in high-risk occupational settings). In this patient, the ECG is diagnostic for Brugada syndrome and tilt-table testing is not needed.

KEY POINT

- The presence of 2-mm or more coved precordial ST-segment elevation (leads V_1 through V_3) on electrocardiogram and symptoms (cardiac syncope) or ventricular arrhythmia indicates the presence of Brugada syndrome.

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Item 69 Answer: C

Educational Objective: Manage end-stage heart failure with a left ventricular assist device.

This patient should be evaluated for placement of a left ventricular assist device (LVAD). He has end-stage heart failure manifested by extreme limitations of activity, multiple hospitalizations, poor kidney function, diuretic dependence to maintain fluid balance, and hypotension. The two possible options for therapy in a patient with this degree of heart failure are placement of an LVAD and heart transplantation. Because of his diagnosis of disseminated prostate cancer, however, the patient is not a candidate for transplantation. LVADs are indicated either as a bridge to heart transplantation or as destination therapy in selected patients who are not candidates for transplantation. Newer LVAD devices are smaller and easier to maintain than earlier versions, making their long-term use as destination therapy possible. Although this patient might otherwise be a candidate for transplantation, his diagnosis of disseminated prostate cancer is an absolute contraindication because of the required long-term post-transplant immunosuppression. However, placement of an LVAD would be an appropriate consideration in this patient if he is expected to survive for longer than 1 year.

Other contraindications to cardiac transplantation include medical problems associated with a reduced life expectancy (rheumatologic disease, severe pulmonary disease, liver failure), fixed severe pulmonary hypertension, diabetes mellitus with end-organ manifestations, age greater than 65 to 70 years, severe peripheral arterial or cerebrovascular disease, and advanced kidney disease. Although several of these factors are also associated with poorer outcomes with LVAD use (such as advanced age and degree of comorbid disease), assist devices are a viable option for treatment in patients who are clearly not candidates for transplantation.

Metolazone inhibits sodium reabsorption in the distal tubule and may be particularly effective in inducing diuresis when used in combination with a loop diuretic in patients with volume overload who have not responded adequately to high doses of a loop diuretic. However, this patient does not have signs of volume overload (no jugular venous distention or edema) and therefore would not be expected to benefit from the addition of metolazone to his current regimen.

Home inotropic therapy is associated with a mortality rate of approximately 90% at 1 year and should be considered as a palliative care option only. Use of this therapy is associated with worsening heart failure, infection, and arrhythmias. In a patient who is a candidate for either LVAD or heart transplantation, this should not be considered as an alternative therapy. Occasionally, patients require supportive inotropic therapy until they receive a transplant. This should be managed by their transplant cardiologist.

KEY POINT

- Placement of a left ventricular assist device is an option for patients with end-stage heart failure who are not candidates for heart transplantation.

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Item 70 Answer: D

Educational Objective: Prevent stroke in a patient with atrial fibrillation and chronic kidney disease.

This patient with atrial fibrillation should be prescribed dose-adjusted warfarin for stroke prevention, with a goal INR of 2 to 3. Patients with atrial fibrillation and kidney disease are at increased risk for stroke and are also at increased risk for bleeding events with oral anticoagulation. In addition to her kidney disease, the patient has three CHA_2DS_2-VASc risk factors for stroke, including her female sex (1 point), age (2 points), and the presence of hypertension (1 point). Based upon her risk profile (CHA_2DS_2-VASc score = 4), her adjusted risk of stroke is 4% per year. The presence of end-stage kidney disease is also associated with an increased risk of stroke. Accordingly, she is at moderate to high risk of stroke and requires oral anticoagulation.

In the past several years, several novel oral anticoagulants have been approved for stroke prevention in patients with nonvalvular atrial fibrillation. Dabigatran is a direct thrombin inhibitor that is dosed twice daily. Rivaroxaban is a factor Xa inhibitor dosed once daily. Apixaban is a factor Xa inhibitor that is dosed twice daily. All three agents exhibit partial clearance in the kidneys and are contraindicated in patients with end-stage kidney disease. None of the randomized controlled trials evaluating these three new agents included patients with creatinine clearance less than 30 mL/min/1.73 m^2.

Aspirin and clopidogrel (dual antiplatelet therapy) can be considered an alternative therapy for patients who cannot tolerate oral anticoagulation; however, they provide inferior stroke prevention with similar rates of bleeding when compared with dose-adjusted warfarin. The best option for stroke prevention therapy in this patient with atrial fibrillation and end-stage kidney disease at high risk for stroke is dose-adjusted warfarin.

KEY POINT

- The best option for stroke prevention therapy in a patient with atrial fibrillation and end-stage kidney disease at high risk for stroke is dose-adjusted warfarin.

Bibliography

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Item 71 Answer: A

Educational Objective: Manage complicated type B aortic dissection.

The most appropriate management for this patient is emergency aortic repair. She has a complicated type B aortic dissection. Type A dissections or intramural hematomas involve the ascending aorta or aortic arch, whereas type B syndromes begin distal to the left subclavian artery. Complicated dissections include occlusion of a major aortic branch leading to end-organ ischemia, persistent severe hypertension or pain, propagation of the dissection (which may be manifested by persistent or recurrent pain), aneurysmal expansion, and rupture. This patient has new acute kidney failure because the dissection occludes the renal arteries. Emergency surgery is recommended for acute type A and complicated type B dissections; initial medical management is recommended for uncomplicated type B dissections. Because this patient has a complicated type B dissection, medical management alone would not be appropriate.

Because patients with aortic dissection have a significant prevalence of coronary artery disease, coronary angiography is sometimes performed prior to surgical intervention to allow for repair prior to or at the time of operation for treatment of the aortic dissection. However, the benefit of this approach has not been established, and the required contrast administration would be potentially harmful in this patient with acute kidney failure caused by her aortic dissection. It would therefore not be an appropriate next step in the treatment of this patient.

Although some variants of aortic dissection are associated with intramural thrombus, antithrombotic or thrombolytic therapy is contraindicated and may be potentially fatal in patients with aortic dissection. This highlights the need to exclude aortic dissection prior to initiating either therapy, which may be indicated in patients with evidence of cardiac ischemia.

KEY POINT

- Complicated type B aortic dissection is an indication for immediate aortic repair.

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Braverman AC. Acute aortic dissection: clinician update. Circulation. 2010 Jul 13;122(2):184-8. [PMID: 20625143]

Item 72 Answer: C

Educational Objective: Treat severe asymptomatic pulmonary valve stenosis.

This patient should undergo replacement of the pulmonary valve. She has Noonan syndrome, which is an autosomal dominant disorder commonly associated with congenital cardiac lesions, one of which is pulmonary valve stenosis. The pulmonary valve is usually dysplastic in patients with Noonan syndrome and thus is not amenable to balloon intervention. This patient has severe pulmonary valve stenosis demonstrated by physical examination; features include a late-peaking palpable systolic ejection murmur located at the second left intercostal space, absence of an ejection click, and features of right ventricular pressure overload. An ejection click may be audible in patients with pulmonary valve stenosis, but as the severity progresses, the click disappears owing to loss of valve pliability. This patient's echocardiogram confirms severe pulmonary valve stenosis with a peak systolic gradient of 62 mm Hg and mean systolic gradient of 45 mm Hg. Intervention is recommended owing to the severity of obstruction

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despite the absence of symptoms. Surgical valve replacement is recommended given the dysplastic valve features and presence of coexisting moderate pulmonary valve regurgitation. Most patients with severe pulmonary valve stenosis are treated with balloon valvuloplasty, but this patient has a dysplastic valve related to Noonan syndrome and moderate pulmonary valve regurgitation; thus, pulmonary valve replacement is recommended.

Patients with pulmonary valve stenosis without a history of endocarditis or pulmonary valve replacement do not require endocarditis prophylaxis.

Exercise testing could help determine whether the patient has exercise limitation related to her pulmonary valve stenosis but would not change the recommendation for intervention; thus, it is not required.

Clinical observation, with continued participation in competitive sports, is not advised in patients with severe pulmonary valve stenosis regardless of symptom status because of the risk of progressive right heart failure.

KEY POINT

- In patients with severe pulmonary valve stenosis, valve intervention is recommended regardless of the presence or absence of symptoms.

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Burch M, Sharland M, Shinebourne E, Smith G, Patton M, McKenna W. Cardiologic abnormalities in Noonan syndrome: phenotypic diagnosis and echocardiographic assessment of 118 patients. J Am Coll Cardiol. 1993 Oct;22(4):1189-92. [PMID: 8409059]

Item 73 Answer: A

Educational Objective: Manage a patient with a non-ST-elevation myocardial infarction with antiplatelet and anticoagulant medications.

This patient should be given a $P2Y_{12}$ inhibitor, such as clopidogrel, and an anticoagulant, such as the low-molecular-weight heparin enoxaparin, and be admitted to the hospital. Once the diagnosis of a non-ST-elevation myocardial infarction (NSTEMI) has been confirmed by the presence of ischemic chest pain, ST-segment depression on the electrocardiogram (ECG), and/or abnormal cardiac biomarkers, the use of antiplatelet and anticoagulant medications, antianginal medications, and cardioprotective medications is imperative. This patient was given aspirin and nitroglycerin prior to the diagnosis of NSTEMI, and he takes daily ACE inhibitor and statin medications. The additional therapies that are warranted in this situation include a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, ticagrelor), an anticoagulant (unfractionated heparin or low-molecular-weight heparin), and a β-blocker. The use of clopidogrel, in addition to aspirin, is the best-studied combination of antiplatelet medications.

In patients with an ST-elevation myocardial infarction (STEMI), reperfusion, preferably via percutaneous coronary intervention, should be performed as quickly as possible from symptom onset. This patient does not have evidence of ST-segment elevation or left bundle branch block on the initial ECG. Although an early invasive strategy (defined as within 24 hours of hospital admission) has been proved to be effective in treatment of NSTEMI, there is no evidence that earlier angiography (<6 hours or at hospital admission) offers incremental benefit to these patients.

In patients with a low TIMI risk score (0–2), indicating a low in-hospital risk of death or recurrent ischemia/infarction, predischarge stress testing may be warranted to further define a large ischemic burden and guide revascularization decisions. This patient has a TIMI risk score of 4 (≥3 traditional cardiovascular risk factors, ST-segment deviation, daily aspirin use, elevated cardiac biomarkers), placing him at intermediate risk. These patients have improved clinical outcomes with an early invasive strategy. Exercise stress testing is not appropriate and may be dangerous.

Clinical decision-making should not be affected by the results of the second set of cardiac biomarkers. The presence of an elevated troponin level drawn in the emergency department is prognostically significant and warrants hospital admission, treatment of NSTEMI, and risk stratification.

KEY POINT

- Initial therapy of non-ST-elevation myocardial infarction is medical, with antiplatelet and anticoagulant medications, antianginal medications, and cardioprotective medications; early angiography (<6 hours or at hospital admission) does not provide incremental benefit but an early invasive strategy (defined as within 24 hours of hospital admission) may improve outcomes.

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Amsterdam EA, Wenger NK, Brindis RG, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Dec 3;130(25):2354-94. [PMID: 25249586]

Item 74 Answer: E

Educational Objective: Evaluate change in clinical status of a patient with mitral regurgitation.

Transthoracic echocardiography (TTE) in a patient with valvular heart disease is appropriate when there is a change in clinical symptoms. This patient has had worsening dyspnea on exertion for the past 3 weeks that may be a result of worsening mitral regurgitation. In patients with myxomatous mitral valve disease, rupture of a primary or secondary chordae may cause an acute change in the degree of mitral regurgitation and change in clinical status; this is the likely cause of this patient's worsening symptoms. Other causes of her progressive shortness of breath could also be evaluated with an echocardiogram. For example, new wall motion abnormalities could signal recent silent myocardial infarction, and changes in overall ejection fraction would prompt evaluation for new cardiomyopathies.

Exercise stress testing may be appropriate if TTE does not reveal a structural cause of her shortness of breath.

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In addition to evaluating for obstructive coronary artery disease, stress echocardiography could be used to evaluate changes in mitral regurgitation and pulmonary pressures with exercise. However, a TTE at rest should be obtained before deciding whether a stress test is warranted.

This patient's mitral regurgitation increases her risk for atrial fibrillation. However, her baseline electrocardiogram demonstrates sinus rhythm, so paroxysmal atrial fibrillation as a cause of her dyspnea is less likely. In addition, she has had progressive dyspnea on exertion that has not waxed and waned, as might be expected if she was in and out of atrial fibrillation. The fact that she presents with worsening symptoms and is in sinus rhythm makes paroxysmal atrial fibrillation less likely. Therefore, 24-hour ambulatory electrocardiographic monitoring would not be the best choice for this patient.

This patient does not appear to have active asthma symptoms or changes in pulmonary status that would indicate a need for spirometry at this time.

Transesophageal echocardiography may be helpful in further defining the anatomy, particularly if surgical intervention is planned, but should not be the first diagnostic study. If the cause of the valvular disorder or degree of regurgitation is unclear from the TTE, then transesophageal echocardiography may be appropriate.

KEY POINT

- Transthoracic echocardiography in a patient with valvular heart disease is appropriate when there is a change in clinical symptoms.

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Matulevicius SA, Rohatgi A, Das SR, et al. Appropriate use and clinical impact of transthoracic echocardiography. JAMA Intern Med. 2013 Sep 23;173(17):1600-7. [PMID: 23877630]

Item 75 Answer: A

Educational Objective: Diagnose aortic valve stenosis in an asymptomatic adult with repaired aortic coarctation.

This patient most likely has aortic valve stenosis. The systolic ejection click at the left sternal border suggests a bicuspid aortic valve. The quality and location of the systolic ejection murmur suggest associated aortic stenosis. A bicuspid aortic valve is present in more than 50% of patients with aortic coarctation, and more than 70% of patients with a bicuspid valve will require surgical intervention for a stenotic or regurgitant valve or aortic pathology over the course of a lifetime.

Ascending aortic aneurysms occur in up to 50% of patients with aortic coarctation. Aneurysms are generally clinically silent and require imaging to confirm their presence. Ascending aortic aneurysm that results in dilation of the annulus will be associated with the murmur of aortic regurgitation (diastolic murmur), not aortic valve stenosis as seen in this patient.

Mitral valve regurgitation is not an expected sequela of coarctation repair. In addition, the clinical features in patients with mitral valve regurgitation include a holosystolic murmur, heard best at the apex, that radiates to the axilla.

Recurrent aortic coarctation occurs in about 20% of patients with previous coarctation repair. Clinical features include hypertension that is difficult to control with medical therapy. This patient has hypertension that is controlled with medical therapy, which occurs in up to 75% of patients with repaired coarctation. Other features of recurrent coarctation not demonstrated in this patient include a radial artery–to-femoral artery pulse delay and a systolic murmur over the left anterior or posterior chest.

KEY POINT

- A bicuspid aortic valve is present in more than 50% of patients with aortic coarctation; more than 70% of patients with a bicuspid aortic valve will require cardiac surgical intervention for valve dysfunction or aortic pathology over the course of a lifetime.

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Tanous D, Benson LN, Horlick EM. Coarctation of the aorta: evaluation and management. Curr Opin Cardiol. 2009 Nov;24(6):509-15. [PMID: 19667980]

Item 76 Answer: B

Educational Objective: Manage risk of sudden cardiac death in a patient with heart failure with placement of an implantable cardioverter-defibrillator.

This patient with heart failure and a low left ventricular ejection fraction should be referred for placement of an implantable cardioverter-defibrillator (ICD). For patients with an ejection fraction less than or equal to 35% and New York Heart Association (NYHA) functional class II or III heart failure on optimal medical therapy, placement of an ICD is a class I indication. Patients with new-onset heart failure should not undergo placement of an ICD because ventricular function often recovers to above 35%. This patient, however, is on appropriate medical therapy, has had heart failure for at least 6 months, and is still symptomatic. For patients with NYHA functional class IV heart failure symptoms, an ICD is not warranted unless the patient is a cardiac transplant candidate.

Cardiac resynchronization therapy (CRT) with a biventricular pacemaker to improve hemodynamic function of the heart may also be considered in patients with persistent heart failure but is reserved for patients with evidence of conduction system disease. The 2013 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) guideline recommends CRT in patients with an ejection fraction of 35% or below, NYHA functional class III to IV symptoms on guideline-directed medical therapy, and left bundle branch block with QRS duration greater than or equal to 150 ms. With a QRS width of 100 ms, this patient is not a candidate for a biventricular pacemaker in addition to an ICD.

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Adding an angiotensin receptor blocker to a heart failure regimen that already includes an ACE inhibitor would not be indicated in this patient as it would not provide additional benefit, and this medication combination has been shown to increase risk of hyperkalemia and kidney injury.

Because this patient's heart rate is 56/min, indicating adequate β-blockade, and his blood pressure is at a desired level, no benefit would be expected by increasing his dose of carvedilol.

Indications for mitral valve replacement, an invasive procedure that carries risks, include the presence of severe mitral regurgitation and NYHA class III or IV symptoms attributed to the valve disease. None of these are present in this patient. This patient's mitral regurgitation is "functional," meaning it is more likely to be a result of his dilated cardiomyopathy and not the underlying cause.

KEY POINT

- Implantable cardioverter-defibrillator placement is indicated for patients with heart failure and a left ventricular ejection fraction less than or equal to 35% and New York Heart Association functional class II or III heart failure while on optimal medical therapy.

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Bardy GH, Lee KL, Mark DB, et al; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005 Jan 20;352(3):225-37. Erratum in: N Engl J Med. 2005 May 19;352(20):2146. [PMID: 15659722]

Item 77 Answer: B

Educational Objective: Treat cardiotoxicity due to chemotherapy with an anthracycline.

The doxorubicin should be discontinued indefinitely in this patient. The efficacy of anthracycline-based chemotherapy regimens for breast adenocarcinoma has been documented by multiple studies. However, doxorubicin, daunorubicin, and other anthracyclines have known cardiotoxicity, which is dependent on dosage, age, concomitant treatment with other cardiotoxic agents, chest radiation, and pre-existing cardiac disease. The incidence of cardiotoxicity for doxorubicin or daunorubicin is less than 1% for cumulative dosages of less than 400 mg/m^2 but 26% for cumulative dosages greater than or equal to 550 mg/m^2. Cardiotoxicity from anthracyclines usually develops within several months after initiation of chemotherapy, manifesting as either systolic or diastolic heart failure, although there can be a long latency period. Once heart failure is present, as in this patient, anthracyclines should be discontinued. In the absence of heart failure, anthracyclines also should be discontinued when new left ventricular dysfunction is detected. Routine surveillance with serial echocardiography is recommended in patients being treated with anthracyclines, with timing intervals based on the patient's baseline function, risk profile, dose, and clinical suspicion for toxicity. The maximum cumulative dose for these drugs is generally limited to 450 to 500 mg/m^2, but there is considerable individual variation in doses that lead to toxic responses.

This patient developed cardiotoxicity despite a low risk (1%). Therefore, neither continuing doxorubicin nor decreasing the dose is an appropriate treatment. Additionally, because cardiotoxicity is associated with this class of agents, substituting another anthracycline for the doxorubicin, such as daunorubicin, would also not be appropriate. In this patient, anthracycline therapy must be discontinued indefinitely to reverse the cardiotoxic effects and prevent them from recurring.

ACE inhibitors are indicated in patients with asymptomatic or symptomatic systolic dysfunction. There are limited data on the use of these agents to help prevent cardiotoxicity related to chemotherapy, but their use for this indication is not routinely recommended.

KEY POINT

- Anthracyclines, such as doxorubicin, can cause cardiotoxicity in patients being treated with chemotherapy.

Bibliography

Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003 Jun 1;97(11):2869-79. [PMID: 12767102]

Item 78 Answer: D

Educational Objective: Evaluate a patient with dyspnea with a history of catheter ablation for atrial fibrillation.

The most likely cause of dyspnea in this patient is pulmonary vein stenosis. He has progressive, unexplained dyspnea and a history of multiple catheter ablation procedures for atrial fibrillation. During catheter ablation of atrial fibrillation, the tissue around each of the pulmonary veins is cauterized to achieve electrical isolation and prevent ectopic foci from triggering recurrent atrial fibrillation. Following this procedure, approximately 1% to 3% of patients can develop symptomatic pulmonary vein stenosis. The risk is higher after multiple procedures, but it can occur after a single procedure. Patients present with progressive dyspnea, but more severe pulmonary vein stenosis can be accompanied by cough, hemoptysis, or chest pain. The image (shown on top of next page) depicts a three-dimensional cardiac magnetic resonance angiogram showing the pulmonary venous return to the left atrium (LA), with stenosis of a pulmonary vein at its ostium where it empties into the LA (*arrow*).

The most important step in the diagnosis of pulmonary vein stenosis is maintaining a high degree of suspicion when encountering a patient with dyspnea and prior atrial fibrillation ablation. Several diagnostic modalities can be used to make the diagnosis noninvasively, including CT angiography, magnetic resonance angiography, and nuclear lung perfusion scanning. Each method has advantages and disadvantages, and the preferred method of diagnosis often differs from institution to institution.

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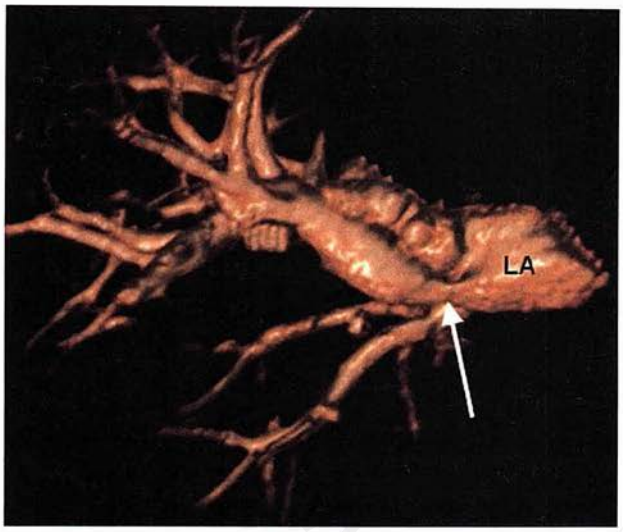

Chronic thromboembolic disease can cause progressive dyspnea, but it would be unlikely in a patient without prior venous thromboembolism and on chronic anticoagulation.

Although intermittent atrial fibrillation could cause symptoms after ablation, it is not likely to cause progressive dyspnea in the setting of sinus rhythm. Intracardiac shunting is rare after an ablation for atrial fibrillation. Although trans-septal catheterization is performed during ablation procedures, the puncture site usually seals off. The normal oxygen saturation in this patient makes the possibility of a symptomatic shunt unlikely.

Phrenic nerve injury can result from delivery of radiofrequency energy in the vicinity of the right superior pulmonary vein with bystander injury of the right phrenic nerve; however, this injury is observed immediately after ablation and is accompanied by an elevated hemi-diaphragm on chest radiograph.

KEY POINT

- Pulmonary vein stenosis is a known complication of catheter ablation of atrial fibrillation and may present with unexplained dyspnea.

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Holmes DR Jr, Monahan KH, Packer D. Pulmonary vein stenosis complicating ablation for atrial fibrillation: clinical spectrum and interventional considerations. JACC Cardiovasc Interv. 2009 Apr;2(4):267-76. [PMID: 19463436]

Item 79 Answer: C

Educational Objective: Identify risk factors for sudden death in a patient with obstructive hypertrophic cardiomyopathy.

The patient should be treated by placement of an implantable cardioverter-defibrillator (ICD). He has asymptomatic mild obstructive hypertrophic cardiomyopathy (HCM). An essential goal in the management of patients with HCM is risk stratification and identification of patients who may benefit from therapy with an ICD. Patients should be considered for ICD therapy if they have any of the following risk factors for sudden cardiac death: (1) massive myocardial hypertrophy (wall thickness ≥30 mm); (2) previous cardiac arrest due to ventricular arrhythmia; (3) blunted blood pressure response or hypotension during exercise; (4) unexplained syncope; (5) nonsustained ventricular tachycardia on ambulatory electrocardiography; and (6) family history of sudden death due to HCM. In patients who have ICD placement for secondary prevention of sudden death (that is, patients with prior cardiac arrest due to ventricular arrhythmia), in whom the indications for implantation are most compelling, the rate of appropriate device discharge is approximately 11% per year. For primary prevention, the annual rate of appropriate ICD discharge is approximately 4%. Although older studies from tertiary referral centers suggested an adverse prognosis for all patients with HCM, multiple contemporary investigations from relatively unselected cohorts have shown that HCM is compatible with normal longevity in most patients, particularly those without risk factors for sudden death, with the overall incidence of death ranging from 0.5% to 0.8% per year.

Septal reduction therapy, with either alcohol septal ablation or surgical myectomy, is indicated only for patients with drug-refractory, severe symptoms and not the mild symptoms that this patient has. Survival has been shown to be favorable among selected patients who undergo septal reduction therapy in experienced centers, but neither ablation nor surgical myectomy is advocated as a means of preventing sudden cardiac death.

β-Blocker therapy is reserved principally for patients with symptoms and has not been associated with reduction in risk of sudden cardiac death.

KEY POINT

- Placement of an implantable cardioverter-defibrillator is an appropriate treatment for patients with hypertrophic cardiomyopathy who have one or more risk factors for sudden cardiac death.

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Gersh BJ, Maron BJ, Bonow RO, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011 Dec 13;58(25):e212-60. [PMID: 22075469]

Item 80 Answer: B

Educational Objective: Manage a small abdominal aortic aneurysm with surveillance.

The most appropriate management for this man with a 4.7-cm abdominal aortic aneurysm (AAA) is surveillance by abdominal ultrasonography every 6 to 12 months. Aneurysm diameter is the most important factor predisposing to rupture, with

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risk increasing with progressive increases in aneurysm size. For aneurysms smaller than 4.0 cm in diameter, the annual rupture risk is below 0.5%, whereas for aneurysms between 5.0 and 5.9 cm in diameter, the annual rupture risk is 3% to 15%. For AAAs with a maximum diameter less than 3.5 cm, repeat surveillance with ultrasonography may be repeated every 3 to 5 years. However, larger aneurysms require more frequent surveillance because of their tendency to expand faster than smaller aneurysms and their increased risk of rupture, with reevaluation on a 6- to 12-month basis recommended. Because this patient's aneurysm is 4.7 cm in diameter, he should undergo surveillance every 6 to 12 months.

Elective repair should be considered for AAAs of 5.5 cm in diameter in men and 5.0 cm in women, for AAAs that increase in diameter by more than 0.5 cm within a 6-month interval, and for those that are symptomatic (tenderness or abdominal or back pain).

AAA rupture has an exceedingly high mortality rate, and the risk of rupture is 0.5% to 5% annually for aneurysms between 4.0 cm and 4.9 cm in diameter. Therefore, no further management would not be appropriate in this patient with a 4.7-cm aneurysm.

KEY POINT

- An abdominal aortic aneurysm smaller than 5.5 cm in men and 5.0 cm in women is managed conservatively, with routine surveillance by abdominal ultrasonography every 6 to 12 months.

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Chaikof EL, Brewster DC, Dalman RL, et al. SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. J Vasc Surg. 2009 Oct;50(4):880-96. [PMID: 19786241]

Item 81 Answer: B

Educational Objective: Treat a patient undergoing thrombolysis for an ST-elevation myocardial infarction with clopidogrel.

This patient who is receiving thrombolytic therapy for an ST-elevation myocardial infarction (STEMI) should be given clopidogrel, 300 mg orally. Clopidogrel is the most widely studied antiplatelet agent in patients undergoing reperfusion for STEMI. Clopidogrel is associated with improved outcomes and no apparent increase in the risk of bleeding when used with concomitant thrombolytic therapy and with primary percutaneous coronary intervention (PCI). In the CLARITY-TIMI 28 study examining clopidogrel as adjunctive therapy in patients undergoing thrombolysis, there was a 6.7% absolute risk reduction in the incidence of occluded infarct-related artery or recurrent myocardial infarction or death in patients assigned to clopidogrel when compared with placebo.

Abciximab is a platelet glycoprotein IIb/IIIa inhibitor that further inhibits platelet aggregation and impairs platelet activation. Glycoprotein IIb/IIIa inhibitors are used in patients undergoing PCI. Owing to the risk of increased bleeding with these agents, their use should be reserved for administration during PCI, rather than "up front" in the emergency department. Large studies have shown no clear mortality benefit and significantly higher rates of major bleeding in patients undergoing fibrinolysis treated with abciximab versus placebo. Use of platelet glycoprotein IIb/IIIa inhibitors in patients undergoing thrombolysis is not currently recommended.

For STEMI patients undergoing primary PCI, both prasugrel and ticagrelor have shown superior efficacy compared with clopidogrel. However, use of these agents in patients treated with thrombolytic therapy has not been well studied, and little evidence exists to recommend the use of either of these agents in patients receiving thrombolytic therapy.

KEY POINT

- Patients with ST-elevation myocardial infarction undergoing thrombolysis should be given adjunctive antiplatelet therapy with clopidogrel.

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Item 82 Answer: D

Educational Objective: Manage iron-deficiency anemia in a patient with cyanotic congenital heart disease.

This patient with Eisenmenger syndrome has symptomatic relative anemia, and short-course iron therapy should be initiated. Most patients with cyanosis have compensated erythrocytosis with stable hemoglobin levels. Iron deficiency and resultant microcytosis in patients with cyanosis are often caused by unnecessary phlebotomy or blood loss. Microcytes are more rigid than normal erythrocytes; thus, microcytosis increases the risk of stroke. The treatment of iron deficiency is challenging. Oral iron often causes a rapid and dramatic increase in erythrocyte mass. Therefore, administration of 1 tablet daily of ferrous sulfate or ferrous gluconate is recommended, with repeat hemoglobin assessment in 7 to 10 days. This patient's usual hemoglobin level would be in the range of 18 g/dL (180 g/L). He developed perioperative anemia that has persisted and caused dyspnea and fatigue. Once the hemoglobin and hematocrit levels begin to increase, iron therapy can be discontinued. Erythrocyte transfusion is considered only for severe symptoms.

Erythropoietin is used in patients with anemia related to kidney disease and some malignancies but is not recommended for patients with heart disease and cyanosis who develop postoperative anemia.

Data are limited regarding the efficacy of epoprostenol in patients with Eisenmenger syndrome and pulmonary hypertension. When used, oral, subcutaneous, and inhaled therapies are preferred. Intravenous epoprostenol is typically avoided because of the risk for paradoxical embolism with continuous intravenous therapy in patients with an intracardiac right-to-left shunt.

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Although heart-lung transplantation is an option for end-stage cardiopulmonary disease in patients with Eisenmenger syndrome, this option is not indicated without further trial of standard medical therapy with iron.

KEY POINT

- Most patients with cyanotic heart disease have compensated erythrocytosis with stable hemoglobin levels.

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Item 83 Answer: A

Educational Objective: Use coronary artery calcium score to clarify cardiovascular risk in an intermediate-risk patient.

The most appropriate option for this patient with intermediate cardiovascular risk is to obtain an additional factor to help clarify risk to guide therapy, such as a coronary artery calcium (CAC) score. Assessment for risk of atherosclerotic cardiovascular disease (ASCVD) is an important component of primary prevention. Several risk assessment tools for ASCVD are available, with the Framingham risk score being the most commonly used. The Pooled Cohort Equations are a new risk assessment instrument developed from multiple community-based cohorts (including the Framingham study) that includes a broader range of variables and endpoints than the Framingham score when evaluating 10-year ASCVD risk. Its use as a primary risk assessment tool was recommended in the 2013 American College of Cardiology/American Heart Association Guideline on the Assessment of Cardiovascular Risk. Using this method, a 10-year risk of ASCVD of below 5% is considered low risk, 5% to below 7.5% is classified as intermediate risk, and 7.5% or above is designated as high risk. For patients with intermediate risk, such as this patient with a risk of 6%, additional factors may be helpful in further refining risk assessment by identifying patients who may benefit from a more aggressive prevention strategy. Factors that can help further define risk include:

- CAC score greater than 300 or greater than 75% for age
- High-sensitivity C-reactive protein level (hsCRP) above 2 mg/L
- Ankle-brachial index below 0.90
- LDL cholesterol level 160 mg/dL (4.14 mmol/L) or higher or other evidence of genetic hyperlipidemia
- Family history of premature ASCVD with onset younger than 55 years in a first-degree male relative or younger than 65 years in a first-degree female relative

The results of the CAC score may help inform the individual patient-physician discussion in this intermediate-risk patient.

In this active construction worker who is asymptomatic, the pretest probability of finding ASCVD is low; because of the increased rate of false-positive test results in low-risk patients, stress testing is not recommended. The use of stress testing to diagnose ASCVD in asymptomatic persons does not reduce mortality. Appropriate risk factor modification, however, does have the potential to reduce cardiovascular risk and mortality.

This patient's blood pressure is adequately treated, and there is no evidence that further lowering of blood pressure results in decreased cardiovascular risk. Therefore, an increase in his lisinopril dosage would not be beneficial.

Although studies of the mechanisms of atherosclerosis suggest that antioxidant therapy might be protective against development of ASCVD, studies have failed to show a benefit of antioxidants as a primary prevention intervention. The use of vitamins A, C, or E, alone or in combination, is therefore not recommended to decrease cardiovascular risk.

KEY POINT

- Coronary artery calcium scoring can improve cardiovascular risk assessment in intermediate-risk patients in whom therapy may be affected by a reclassification of risk.

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Item 84 Answer: D

Educational Objective: Treat symptomatic peripheral arterial disease with a supervised exercise program.

The most appropriate management for this patient with symptomatic peripheral arterial disease is to start a supervised exercise program. Supervised exercise therapy can effectively treat claudication, with increases in pain-free walking time and maximal walking time, and is recommended as part of the initial treatment regimen for intermittent claudication. The CLEVER study demonstrated superior improvement in walking distance with supervised exercise for patients with aortoiliac disease, as compared with stent revascularization or medical therapy alone.

Cilostazol is an oral phosphodiesterase-3 inhibitor that has demonstrated increases in pain-free walking and overall walking distance in patients with claudication in randomized clinical trials, although the gains with exercise are two- to three-fold greater than with cilostazol alone. However, cilostazol is contraindicated in patients with heart failure or a left ventricular ejection fraction below 40%. This contraindication exists because cilostazol has a similar pharmacologic action to the inotropic drugs milrinone and amrinone, which demonstrated increased mortality rates with long-term use in patients with heart failure.

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Patients with stable claudication progress to critical limb ischemia and limb loss at a rate of less than 5% annually. For most symptomatic patients, therefore, noninvasive therapy with exercise and medication is appropriate. If conservative therapy fails or patients have symptoms limiting their lifestyle or employment, revascularization by an endovascular or surgical approach should be considered.

KEY POINT

- Supervised exercise therapy can effectively treat claudication, with increases in pain-free walking time and maximal walking time, and is recommended as part of the initial treatment regimen for intermittent claudication.

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Item 85 Answer: D

Educational Objective: Select proper imaging surveillance for a patient with a bicuspid aortic valve and aortopathy.

This patient with a bicuspid aortic valve should have annual transthoracic echocardiography. Bicuspid aortic valve occurs with other cardiovascular and systemic abnormalities. Specifically, ascending aortic dilation may occur in persons with a bicuspid aortic valve, in combination with aortic valve disease or as an independent condition. Previously considered a secondary event caused by abnormal aortic valve function, the aortopathy associated with a bicuspid aortic valve is now recognized to result from intrinsically abnormal connective tissue. As a result, serial evaluation of ascending aortic diameter should be performed by transthoracic echocardiography (or by CT angiography or magnetic resonance angiography if not adequately visualized by echocardiography). The frequency of surveillance depends upon aortic root and ascending aorta size. Expert consensus guidelines recommend reassessment of the aorta if the aortic root or ascending aorta dimension is greater than or equal to 4.0 cm, with the evaluation interval determined by degree and rate of aortic dilation and by family history. Annual evaluation should occur if the aortic diameter is greater than 4.5 cm. New or changing symptoms and pregnancy are indications for earlier imaging of the aorta. For this patient, in view of the similar findings on transthoracic echocardiogram and chest CT scan, serial transthoracic echocardiography is reasonable. Moreover, transthoracic echocardiography is more cost effective than both CT and cardiac magnetic resonance (CMR) imaging, and serial CT scans can result in significant cumulative doses of radiation in this young patient.

CMR imaging and multidetector CT are appropriate for further assessment of aortic pathology when transthoracic or transesophageal echocardiography is not conclusive. In this patient, CMR imaging and multidetector CT scanning are not indicated because the aortic root and ascending aorta are adequately visualized by transthoracic echocardiography. In addition, annual multidetector CT scanning would needlessly expose the patient to excessive radiation.

Transesophageal echocardiography is an invasive procedure and would be considered if transthoracic imaging was inadequate to measure aortic root size and evaluate the ascending aorta.

Because of the risk of aortic dissection and rupture, reassurance and clinical observation are inadequate follow-up for bicuspid valve–related aortopathy.

KEY POINT

- In patients with a bicuspid aortic valve, serial evaluation of ascending aortic diameter should be performed by transthoracic echocardiography (or by CT angiography or magnetic resonance angiography if not adequately visualized by echocardiography).

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Item 86 Answer: D

Educational Objective: Diagnose obstructive coronary artery disease in a patient with left bundle branch block.

This patient with a left bundle branch block (LBBB) on her baseline electrocardiogram (ECG) should undergo vasodilator nuclear perfusion imaging. In patients with baseline ECG abnormalities such as pre-excitation, LBBB, a paced rhythm, or baseline ST-segment depression greater than 1 mm, ECGs obtained during stress testing cannot be appropriately interpreted, and standard exercise treadmill testing is therefore not appropriate. Instead, these patients must undergo stress testing with additional imaging, such as nuclear perfusion imaging or stress echocardiography.

When myocardial perfusion imaging is used to evaluate patients with LBBB, a vasodilator study using an agent such as adenosine or dipyridamole is necessary instead of an exercise study. This is because perfusion defects that are not related to obstructive coronary artery disease (CAD) can be seen in the septum with exercise. Radiotracers are distributed with blood flow, and when the coronary arteries fill during diastole, the delay in contraction of the septum with LBBB can impair filling and create a defect in the septum in the absence of obstructive CAD. However, vasodilators produce hyperemia and a flow disparity between myocardium supplied by the stenotic vessel as compared with the unobstructed vessel that is not affected by the delay in septal contraction related to LBBB. For this reason, an exercise nuclear perfusion study would not be appropriate in this patient.

Coronary artery calcium scoring quantifies the amount of calcium in the walls of the coronary arteries and correlates well with plaque burden in the coronary arteries. It is an anatomic study with fairly high sensitivity for detecting occlusive

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CAD, although the frequency of false-negative results (significant CAD with a low CAC score) is not known. Therefore, CAC scoring is more frequently used for risk stratification in patients with intermediate risk for atherosclerotic cardiovascular disease. Another anatomic study, coronary CT angiography, is an emerging technology that has high correlation with findings on invasive coronary arteriography and may be increasingly useful in evaluating for occlusive CAD.

KEY POINT

- In patients with suspected coronary artery disease with baseline electrocardiographic (ECG) abnormalities such as pre-excitation, left bundle branch block, a paced rhythm, or ST-segment depression greater than 1 mm, ECGs obtained during stress testing cannot be interpreted; therefore, stress testing with additional imaging is required.

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Item 87 Answer: B

Educational Objective: Evaluate a woman with atypical chest pain with exercise electrocardiography.

This patient should undergo exercise electrocardiography (ECG). Although she has several risk factors for coronary artery disease (CAD), including hyperlipidemia and a family history of premature CAD, her symptoms are not typical for angina, which requires the presence of pain precipitated by exercise or emotion, a substernal location of the pain, and relief with rest or nitroglycerin. Because she has only two of the three diagnostic criteria for angina, she is classified as having atypical angina. Women in her age group with atypical angina have an intermediate pretest probability of CAD (approximately 22%). For patients with an intermediate pretest probability of disease and a normal resting ECG, exercise ECG testing is recommended as the initial test of choice.

Conventional coronary angiography identifies the location and severity of blockages and allows vascular access for percutaneous intervention. Because of the invasive nature of coronary angiography and the inherent risks of vascular complications, it should be reserved for patients with acute coronary syndrome requiring immediate intervention, lifestyle-limiting angina despite medical therapy, or high-risk criteria on noninvasive stress testing. This patient's pretest probability of CAD is intermediate, which is not high enough to warrant immediate coronary angiography as the initial diagnostic test.

The sensitivity and specificity of noninvasive stress testing for the evaluation of chest pain are lower in women than in men. However, the routine use of exercise testing with either nuclear perfusion imaging or echocardiography to assess left ventricular regional wall motion or perfusion imaging is not recommended for women or men in the absence of baseline ECG abnormalities. Although the addition of noninvasive imaging increases diagnostic sensitivity for coronary artery disease, use of exercise nuclear perfusion testing as the initial test has not been found to reduce cardiovascular events compared with exercise ECG testing alone.

Pharmacologic stress testing with imaging is indicated for patients who are unable to exercise. In addition, patients with left bundle branch block undergoing nuclear stress testing should be administered a pharmacologic stressor even if they are able to exercise because of the potential for a false-positive test owing to a septal perfusion abnormality that may occur with exercise. Pharmacologic stress testing is not indicated because this patient is physically able to exercise and does not have a left bundle branch block.

KEY POINT

- Exercise electrocardiographic testing is recommended as the initial test of choice in patients with a normal baseline electrocardiogram and an intermediate pretest probability of coronary artery disease based on age, sex, and symptoms.

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Item 88 Answer: E

Educational Objective: Manage aspirin use for primary prevention in a patient with diabetes mellitus and a low cardiovascular risk.

No further testing or therapy would be most appropriate in this patient. Although she has diabetes mellitus, she has no other major cardiovascular risk factors. Risk assessment for atherosclerotic cardiovascular disease (ASCVD) has traditionally been with the Framingham risk score, although the American College of Cardiology/American Heart Association Pooled Cohort Equations, a new method for assessment that includes additional variables for risk stratification, is increasingly being used. With this method, a 10-year risk of ASCVD of less than 5% is considered low risk, 5% to below 7.5% is considered intermediate risk, and 7.5% and above is designated as high risk. This patient has a calculated 10-year risk of 2.7%, making her low risk for ASCVD. Therefore, no additional testing is indicated at present.

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It is reasonable to give low-dose aspirin to adults with diabetes and no previous history of vascular disease who are at increased cardiovascular risk and without increased risk for bleeding. However, aspirin should not routinely be given to patients with diabetes who are at low risk (men younger than 50 years and women younger than 60 years without other major risk factors such as hypertension or tobacco use). The risks of gastrointestinal bleeding or hemorrhagic stroke outweigh the benefits of aspirin in this low-risk patient.

Coronary artery calcium scoring is reasonable to further define cardiovascular risk in patients with intermediate risk as determined by the Pooled Cohort Equations (5% to <7.5%). However, this patient's risk of ASCVD is considered low; therefore, good adherence to lifestyle factors and monitoring of cardiovascular risk factors are most appropriate in this patient.

There is no role for routine exercise testing in an asymptomatic patient. In patients with low coronary artery disease pretest probability, false-positive results will be more common than true-positive results and may lead to unnecessary downstream testing and treatment.

Although elevated homocysteine levels are associated with cardiovascular risk, no data support the use of folic acid supplementation, which can lower homocysteine levels, to reduce the risk.

KEY POINT

- Aspirin should not routinely be given to patients with diabetes mellitus who are at low cardiovascular risk (men younger than 50 years and women younger than 60 years without other major risk factors such as hypertension or tobacco use).

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Item 89 Answer: D

Educational Objective: Treat low cardiac output in heart failure by reducing afterload.

The most appropriate additional treatment for this patient is nitroprusside. After several days of diuresis, this patient has a normal right atrial pressure (0-5 mm Hg) and pulmonary capillary wedge pressure above normal but within the acceptable range for patients with heart failure (<18 mm Hg) to provide optimal ventricular filling. These hemodynamic parameters suggest that the cardiac output is very low and is the major explanation for the patient's heart failure symptoms. Acute heart failure is typically marked by a combination of volume overload (manifested by an increased pulmonary capillary wedge pressure, usually ≥18 mm Hg) and reduced cardiac output. Part of the reason for reduced cardiac output is a very high systemic vascular resistance, as the systemic circulation increases afterload to maintain blood pressure in the setting of low stroke volume. With correction of the volume overload state, the next step in therapy is to reduce afterload with nitroprusside.

Nitroprusside is an intravenously administered vasodilator that lowers systemic vascular resistance and, therefore, increases cardiac output. This therapy should be used only in the setting of invasive monitoring, including a right heart catheter and possibly an arterial line to closely measure systemic pressure. Counterintuitive to what would be expected, the blood pressure usually rises with nitroprusside because of the improved cardiac performance. Nitroprusside is associated with possible rebound vasoconstriction following discontinuation and potential toxicity due to its metabolism to cyanide with longer term use; therefore, therapy is generally limited to no more than 24 to 48 hours in most patients. Patients with cardiogenic shock may also be treated with an inotropic agent such as dobutamine.

Changing to continuous intravenous furosemide is not indicated because the patient has normal filling pressures manifested by the pulmonary capillary wedge pressure of 16 mm Hg and right atrial pressure of 4 mm Hg. More aggressive diuresis will not impact the principal problem, which is low cardiac output and a high systemic vascular resistance. Studies have evaluated the efficacy of continuous versus intermittent boluses of intravenous diuretics in patients hospitalized with acute heart failure. There was no difference demonstrated in patients' symptoms, kidney function, or length of stay between the two strategies. High- versus low-dose diuretics also have been evaluated. Patients taking high dosages exhibited a trend toward more diuresis and slight worsening of kidney function. Diuresis should be performed using whatever strategy is necessary to remove the fluid.

Dopamine was recently compared with nesiritide and placebo in patients with acute heart failure and mild kidney dysfunction. No benefit was demonstrated with either dopamine or nesiritide compared with placebo for either urine output or protection of kidney function. In general, the results of studies evaluating the use of inotropic therapy for the treatment of patients hospitalized with acute heart failure have been negative. For the routine care of patients hospitalized with heart failure, dopamine, dobutamine, and milrinone have not been shown to be helpful and may be associated with adverse outcomes.

Esmolol is an intravenous β-blocker. Like all β-blockers, it has some negative inotropic activity, and use of this drug might worsen the patient's hemodynamic status, not improve it.

KEY POINT

- In patients with low-output heart failure, nitroprusside can reduce afterload and increase cardiac output; nitroprusside should be used only in the setting of invasive cardiac monitoring.

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Item 90 Answer: A

Educational Objective: Manage liver disease resulting from constrictive pericarditis.

The patient should undergo hemodynamic cardiac catheterization. He has evidence of liver disease most likely caused by constrictive pericarditis. Patients with constrictive pericarditis can develop severe symptoms of right-sided congestion that can lead to chronic hepatic congestion and hepatopathy. When detected early, cirrhosis can be reversible if constrictive pericarditis is identified and treated in a timely manner with surgical pericardiectomy. An important clue that suggests constrictive pericarditis as a contributor to hepatopathy is an elevated jugular venous pulse, which demonstrates the presence of elevated right atrial pressures. The central venous pressure is rarely abnormal in patients with primary liver disease. A hemodynamic study with an echocardiogram is sufficient to diagnose constrictive pericarditis in most patients. For patients such as this one with an indeterminate echocardiogram, the most appropriate next step is an invasive hemodynamic study with cardiac catheterization, which provides the greatest sensitivity and specificity for the diagnosis of constrictive pericarditis.

A liver biopsy may be helpful in patients with liver disease of unknown etiology or to gauge the type and degree of liver injury or fibrosis. A liver biopsy is not performed prior to the completion of less invasive tests, such as a liver chemistry profile and ultrasonography. In this patient, the elevated central venous pressure suggests cardiac rather than primary liver disease, and cardiac catheterization with hemodynamic measurements is more likely to prove diagnostic.

B-type natriuretic peptide level is often normal or minimally elevated in patients with constrictive pericarditis despite the elevated central venous pressure. However, measurement of B-type natriuretic peptide will not establish the diagnosis of constrictive pericarditis or guide therapy.

Judicious use of loop diuretics is important in patients with constrictive pericarditis to reduce dyspnea and edema, but because higher filling pressures are needed to maintain stroke volume, overly aggressive diuresis can reduce cardiac output, causing dizziness and orthostatic hypotension.

KEY POINT

- For patients with suspected constrictive pericarditis who have an indeterminate echocardiogram, the most appropriate next step is an invasive hemodynamic study with cardiac catheterization.

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Item 91 Answer: D

Educational Objective: Evaluate a patient with atypical chest pain and indeterminate findings on exercise stress testing.

This patient with atypical chest pain and indeterminate results on exercise stress testing should undergo stress echocardiography. Baseline abnormalities on the resting electrocardiogram (ECG) can limit the ability to interpret the ECG during exercise. Specific abnormalities on the resting ECG preclude the use of ECG stress testing because of difficulty in accurately interpreting changes that may occur with stress. These abnormalities include the presence of left ventricular hypertrophy with repolarization abnormalities (ST-segment depressions) greater than 0.5 mm, pre-excitation, left bundle branch block, and a paced rhythm. In these settings, exercise stress testing with imaging, either with echocardiography or perfusion imaging, is required. Although patients without these exclusionary findings may undergo stress ECG, baseline changes need to be considered in interpreting the test. This patient had ST-segment depressions less than 0.5 mm at baseline; if there were no further changes with exercise testing, these findings could be interpreted as normal. However, a positive stress test is defined as greater than 1-mm ST-segment depression in two contiguous leads during exercise testing. In this patient, the 1-mm ST-segment depression that developed during exercise is a less reliable predictor of ischemia given the ST-segment baseline abnormalities. Therefore, these changes on stress testing are not definitive and her test result is considered indeterminate. She should therefore undergo repeat stress testing with imaging in order to establish a diagnosis of coronary artery disease (CAD).

The patient does not yet have a diagnosis of CAD and her hypertension is adequately treated on her current regimen; adding treatment with a β-blocker to treat myocardial ischemia would not be indicated.

Cardiac catheterization should be reserved for patients with high-risk features on exercise stress testing, such as a high-risk Duke treadmill score (below -11), hypotension, severe ST-segment depression, and early-onset angina. This patient has atypical chest pain, and cardiac catheterization should be deferred until a diagnosis of CAD is made and the extent and severity of disease are evaluated with stress imaging.

Cardiac magnetic resonance (CMR) imaging is best utilized for diagnoses of the aorta, pericardium, and myocardium, including viability and extent of myocardial fibrosis. Stress CMR imaging can be performed, but its availability is limited.

KEY POINT

- In a patient with indeterminate results on exercise stress testing, a repeat stress test with imaging should be performed to elucidate the diagnosis.

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Item 92 Answer: A

Educational Objective: Manage a patient with an acute coronary syndrome with thrombolytic therapy.

This patient should receive a thrombolytic agent such as tenecteplase and be transferred to a center capable of performing percutaneous coronary intervention (PCI). He has electrocardiographic changes consistent with an acute inferior ST-elevation myocardial infarction (STEMI). Patients with a STEMI presenting within 12 hours of symptom onset should receive reperfusion therapy with either primary PCI or thrombolysis, with PCI being the preferred intervention owing to increased efficacy. When transfer times for primary PCI exceed 120 minutes from presentation, administration of thrombolytic therapy is recommended, such as in this patient presenting to a facility without PCI capability and an inability to transport him for treatment within that time frame.

This patient has no absolute contraindications to thrombolytic therapy, which include previous intracerebral hemorrhage, a known cerebrovascular lesion (such as an arteriovenous malformation), suspected aortic dissection, active bleeding or bleeding diathesis (excluding menses), significant closed head or facial trauma within 3 months, and ischemic stroke within the past 3 months. A relative contraindication for thrombolysis is severe hypertension (defined as a systolic blood pressure >180 mm Hg); however, this patient's systolic blood pressure does not meet this threshold. Even when thrombolytic therapy is administered, treatment guidelines recommend that patients be transferred to a PCI-capable facility because of the potential for thrombolytic failure. Optimal management of patients with STEMI relies heavily upon physician recognition and rapid initiation of reperfusion therapy, with either thrombolytic therapy or PCI. Patients with an acute coronary syndrome and an electrocardiogram compatible with STEMI should be treated with reperfusion therapy without biomarker confirmation, as early biomarker results may be normal in patients with STEMI. Therefore, waiting for the results of cardiac biomarker levels would delay appropriate treatment.

The use of a glycoprotein IIb/IIIa inhibitor, such as abciximab, has not been shown to improve outcomes of patients with STEMI prior to the primary PCI procedure and should be reserved for administration in the catheterization laboratory during primary PCI.

Transfer for primary PCI is a reasonable alternative to thrombolytic therapy in the setting of absolute contraindications to thrombolytic therapy or high-risk clinical features and if an acceptable time to transfer the patient to a PCI-capable hospital can be achieved (first medical contact-to-device time of 120 minutes or less). In studies of patients transferred from a non-PCI facility for primary PCI, more than half of patients with STEMI did not undergo perfusion in 120 minutes or less. In this case, transfer time would be prolonged (>120 minutes); therefore, thrombolytic therapy is the best reperfusion strategy.

KEY POINT

- Patients with an ST-elevation myocardial infarction presenting within 12 hours of symptom onset to non-percutaneous coronary intervention (PCI)-capable hospitals should receive either primary PCI (if available in <120 minutes) or thrombolytic therapy (if primary PCI is not available within 120 minutes).

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Item 93 Answer: A

Educational Objective: Diagnose severe aortic regurgitation.

This patient has aortic regurgitation. The murmur of aortic regurgitation, described as a diastolic decrescendo murmur, is heard best at the third left intercostal space and may be better heard when the patient is at end-expiration, leaning forward. Chronic aortic regurgitation has many associated findings, including widened pulse pressure, bounding carotid and peripheral pulses, and a diffuse and laterally displaced point of maximal impulse. A low-pitched rumbling diastolic murmur ("Austin Flint murmur") can accompany aortic regurgitation and is caused by premature closure of the mitral leaflets due to the regurgitant aortic flow.

The auscultatory findings for mitral stenosis include an opening snap with a low-pitched mid-diastolic murmur (often described as a rumble) that accentuates presystole and is heard best at the apex with the patient in the left lateral decubitus position. It most often occurs in patients with rheumatic valve disease and is frequently associated with atrial fibrillation.

A small patent ductus arteriosus in the adult produces an arteriovenous fistula with a continuous murmur that envelops the S_2 and is characteristically heard beneath the left clavicle. Patients with a moderate-sized patent ductus arteriosus may present with a continuous "machinery-type" murmur best heard at the left infraclavicular area and bounding pulses with a wide pulse pressure.

The sinuses of Valsalva are three aortic dilatations just above the aortic valve cusps. Two of the three sinuses are the origins of the coronary arteries. Regurgitant blood flow into the sinus structures fills the coronary arteries and assists

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in the closure of the aortic valve cusps. Sinus of Valsalva aneurysm is a type of aortic root aneurysm. Rupture of the aneurysm will allow flow between the sinus of Valsalva and either the right atrium or right ventricle, producing a continuous systolic and diastolic murmur heard loudest at the second left intercostal space. Clinical presentation can vary, ranging from asymptomatic to decompensated heart failure. Ruptured sinus of Valsalva aneurysm more frequently involves the left or right coronary cusps and less frequently the noncoronary cusp.

KEY POINT

- The murmur of aortic regurgitation is a diastolic decrescendo murmur heard best at the left third intercostal space; associated findings include widened pulse pressure, bounding carotid and peripheral pulses, and a diffuse and laterally displaced point of maximal impulse.

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Item 94 Answer: B

Educational Objective: Distinguish lumbar stenosis from peripheral arterial disease.

An MRI of the lumbar spine is most likely to confirm the diagnosis in this patient. This patient's normal ankle-brachial index (ABI) bilaterally, normal distal pulses, lack of a bruit, normal skin findings, and clinical history all suggest a diagnosis other than peripheral arterial disease (PAD). Patients with pseudoclaudication (lumbar spinal stenosis) may report bilateral leg weakness associated with walking or with prolonged standing; symptoms are aggravated by prolonged standing and are relieved with bending at the waist. Nearly half of patients have absent deep tendon reflexes at the ankles, but reflexes at the knees and muscle strength are usually preserved. The American College of Physicians recommends that advanced imaging with MRI or CT should be reserved for patients with a suspected serious underlying condition or neurologic deficits, or who are candidates for invasive interventions. In the absence of these indications, back imaging is not indicated.

Measuring the exercise ABI can be useful in diagnosing PAD when the resting ABI is normal and the index of suspicion is high for PAD. This patient's history and examination findings point to a diagnosis other than PAD, so measuring the exercise ABI will not add helpful information at this time.

Segmental limb plethysmography is useful in patients with an established diagnosis of PAD to help localize the site of stenosis. In this test, blood pressures are recorded using plethysmographic cuffs placed at the upper thigh, lower thigh, calf, and ankle. A drop in systolic pressure of 20 mm Hg identifies a zone of significant disease.

An ABI greater than 1.40 is associated with calcification of the arterial wall and may occur in patients with medial calcinosis, diabetes mellitus, or end-stage kidney disease. This finding is uninterpretable and is associated with worse cardiovascular outcomes than a normal ABI; therefore, an appropriate next step after this finding is to either measure great toe pressure or calculate a toe-brachial index (systolic great toe pressure divided by systolic brachial pressure), a test that is typically performed in a vascular laboratory. This patient's ABI is normal, so measurement of the toe-brachial index is not necessary.

KEY POINT

- Patients with pseudoclaudication (lumbar spinal stenosis) may report bilateral leg weakness associated with walking or with prolonged standing; symptoms are aggravated by prolonged standing and are relieved with bending at the waist.

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Item 95 Answer: A

Educational Objective: Manage acute decompensated systolic heart failure with diuretics.

In this patient with recently diagnosed heart failure, the dosage of furosemide should be increased. She has signs of volume overload (elevated central venous pressure, an S_3, peripheral edema, weight gain).

Given the patient's relative hypotension and volume overload, increasing her diuretic dose would be more appropriate than increasing the dose of her ACE inhibitor, which might lead to low blood pressure and would not improve her volume overload.

Although there is a mortality benefit to the use of β-blockers in patients with systolic heart failure, these agents have negative inotropic activity, and initiation of β-blocker therapy is relatively contraindicated in patients with evidence of decompensated heart failure. Once the patient has been appropriately diuresed, a β-blocker can be added. Even patients with a low systolic blood pressure, once euvolemic, can often tolerate low doses of a β-blocker.

Spironolactone is an appropriate agent to add for treatment of stable patients with New York Heart Association (NYHA) functional class II to IV heart failure. This patient, however, has acute volume overload, which should be treated before initiation of this therapy. Although spironolactone has some diuretic activity, at the usual doses prescribed for patients with heart failure (12.5-25 mg/d), it would not have sufficient diuretic effect in this patient.

This patient's presentation demonstrates the importance of an early (within 7 days) post-hospital clinic visit for

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patients after a hospitalization for heart failure. Recognizing volume overload at a point when it can be treated on an outpatient basis is an example of the benefit of this visit. If the patient were euvolemic, adding additional therapy, such as a β-blocker or spironolactone, would be appropriate. This visit also allows the internist to reemphasize to the patient the importance of medication adherence and fluid restriction.

KEY POINT

- In patients with acute decompensated systolic heart failure, the most appropriate treatment is to increase the diuretic dosage to remove the excess fluid.

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Item 96 Answer: A

Educational Objective: Treat a patient with patent foramen ovale and cryptogenic stroke with aspirin.

This patient has features of a cryptogenic stroke and patent foramen ovale (PFO). Antiplatelet therapy, such as aspirin, is first-line therapy for patients with PFO and initial cryptogenic stroke. The foramen ovale usually closes within the first few weeks of life. In 25% to 30% of the population, the foramen ovale remains patent. This is usually an incidental finding.

Data are insufficient to recommend PFO device closure for secondary stroke prevention after a first stroke unless there are exceptional circumstances, such as oxygen desaturation from right-to-left shunt or thrombus trapped in the PFO, or for patients with recurrent cryptogenic stroke on warfarin therapy. Overall, the PFO device closure procedure is safe and short-term complications are rare; however, evidence of long-term follow-up and benefit is lacking. Randomized controlled studies have failed to demonstrate superiority of closure over antiplatelet therapy for secondary prevention after cryptogenic stroke. Uncertainty persists regarding the best management strategy because of limitations of current randomized controlled studies; therefore, a reasonable consideration is to encourage participation in one of the ongoing clinical trials.

Data are insufficient to support warfarin therapy for patients with PFO and initial cryptogenic stroke. Warfarin is the treatment of choice for patients with PFO and recurrent stroke or for patients with stroke and a documented hypercoagulable state.

Surgical PFO closure, including a minimally invasive approach, is another option for patients with PFO and recurrent cryptogenic stroke but the efficacy of surgical closure in these patients has been variable and randomized trials have not been performed.

KEY POINT

- Antiplatelet therapy, such as aspirin, is first-line therapy for patients with patent foramen ovale and initial cryptogenic stroke.

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Item 97 Answer: D

Educational Objective: Manage a bicuspid aortic valve in an asymptomatic adult.

The most appropriate next step in management is to repeat the echocardiogram in 1 year. This patient has a bicuspid aortic valve and is asymptomatic. Patients with a bicuspid aortic valve should undergo surveillance transthoracic echocardiogram imaging of the aortic valve, aortic root, and ascending aorta to exclude aortic valve pathology and ascending aortic aneurysm, which are commonly associated with a bicuspid aortic valve and may be independent of the degree of aortic valve disease. This patient has mild aortic valve stenosis and a slightly dilated ascending aorta. If the aortic root or ascending aortic diameter is less than 4 cm, reimaging should be done approximately every 2 years. If the aortic root or ascending aortic diameter is greater than 4 cm, reimaging should occur yearly or more often as progression of aortic dilation warrants or whenever there is a change in clinical symptoms or findings.

Aortic valve replacement is recommended in asymptomatic patients with severe aortic valve stenosis, generally defined as a valve area below 1 cm^2, who may be at high risk without surgery. This patient does not have severe aortic valve stenosis, so aortic valve replacement is not necessary at this time.

Surgery to repair or replace the ascending aorta in adults with a bicuspid aortic valve is recommended when the ascending aorta diameter is greater than or equal to 5.5 cm or progressive dilatation occurs at a rate of 0.5 cm per year or greater.

Medical therapy has not been shown to reduce the rate of progression of aortic dilation in patients with aortopathy associated with bicuspid aortic valve. In patients with hypertension, control of blood pressure is essential. β-Blockers and angiotensin receptor blockers have conceptual advantages to reduce the rate of aneurysm progression but have not been shown to be beneficial in clinical studies.

KEY POINT

- Patients with an asymptomatic bicuspid aortic valve should undergo surveillance transthoracic echocardiography yearly if the aortic root or ascending aortic diameter is greater than 4 cm.

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Item 98 Answer: A

Educational Objective: Evaluate palpitations with a loop recorder.

This patient's symptomatic episodes are intermittent and short-lived; therefore, a 30-day wearable recorder with looping memory is the best diagnostic strategy to uncover the nature of her palpitations. These recorders are worn continuously and record a continuous "loop" of heart rhythm. When the patient experiences symptoms, she can depress a button and the device captures the rhythm before, during, and after the symptoms. Loop recorders are useful for recording episodes accompanied by syncope or presyncope and for episodes that are too short to be captured by a patient-triggered event recorder.

A patient-triggered event recorder (without looping memory) is useful for recording infrequent episodes that last long enough (1-2 minutes) for the patient to hold the device to the chest and trigger it to capture the heart rhythm. A self-applied event recorder is not useful for brief episodes because the time taken to apply the monitor may be longer than the symptomatic episode.

If a patient has an abnormal cardiovascular examination or is demonstrated to have an arrhythmia, echocardiography should be performed to evaluate for the presence of structural heart disease. In this patient, however, the cardiac examination is normal, and there is no documentation of an arrhythmia at this point. Many patients with symptoms suggestive of arrhythmia are found to have causes for their symptoms that are not related to heart rhythm.

An exercise treadmill stress test would be reasonable if the episodes were precipitated by exertion or exercise, but this patient's episodes are not associated with exertion.

Given the infrequency of this patient's symptoms, 48-hour ambulatory electrocardiographic monitoring is not likely to capture the symptomatic episodes.

In patients with very infrequent or rare episodes (>30 days between episodes), an implanted loop recorder may be appropriate. These devices, which are approximately the size of a pen cap and are implanted under the skin of the chest next to the sternum, have several years of battery life. Although they are invasive, these devices have a higher diagnostic yield than other forms of outpatient heart rhythm monitoring.

KEY POINT

- A looping event recorder is useful for recording episodes of palpitations that are accompanied by syncope or presyncope and for episodes that are too short to be captured by a patient-triggered event recorder.

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Item 99 Answer: D

Educational Objective: Treat native valve infective endocarditis complicated by heart block.

The patient should undergo aortic valve replacement now. Although he is hemodynamically stable and does not require pacemaker support, the presence of a new conduction defect confirms extension of the infection into the perivalvular tissues as suggested by echocardiography. When this occurs, the effectiveness of cure with antibiotics alone is decreased significantly, and early surgical intervention is indicated. Other indications for early surgery in native valve infective endocarditis include valve stenosis or regurgitation resulting in heart failure; left-sided endocarditis caused by *Staphylococcus aureus*, fungal, or other highly resistant organisms; endocarditis complicated by annular or aortic abscess; and endocarditis with persistent bacteremia or fever lasting longer than 5 to 7 days after starting antibiotic therapy. Additionally, early surgery is reasonable in patients with infective endocarditis who have recurrent emboli and persistent vegetations on antibiotic therapy, and may be considered in patients with native valve endocarditis who have mobile vegetations greater than 10 mm in length.

Duration of antibiotic therapy in patients with native valve infective endocarditis is generally 4 to 6 weeks, based upon the specific organism, the site of infection, and any associated complications. Generally, 6-week treatment regimens are used in patients with more virulent or highly resistant organisms and those with cardiac or extracardiac infectious complications. Prolonged treatment for 3 months as therapy for this patient would not be appropriate, even with surgical intervention, and would not be indicated in other patients with native valve endocarditis except in certain situations.

Delaying intervention for 6 weeks of antibiotic therapy or treating with antibiotics alone without surgery would not likely adequately address this patient's endocarditis-related complications. In addition, this approach may result in further decompensation of the patient's clinical status and an increased operative risk for intervention at a later time.

Key to management of patients with infective endocarditis requiring surgery is a multidisciplinary approach involving the internist, cardiologist, infectious disease specialist, and cardiac surgeon.

KEY POINT

- The presence of a conduction block is an indication for surgical therapy in patients with native valve infective endocarditis.

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Item 100 Answer: A

Educational Objective: Treat an acute episode of supraventricular tachycardia.

This patient should be given adenosine. She has hemodynamically stable narrow-complex tachycardia consistent with supraventricular tachycardia. The rhythm is regular and no obvious P waves are visible; therefore, atrioventricular nodal reciprocating tachycardia (AVNRT) is the most likely cause. AVNRT accounts for up to two thirds of cases of supraventricular tachycardia. Patients often report neck pulsations, which are caused by simultaneous contraction of the atria and ventricles. Because the patient failed to terminate her tachycardia with vagal maneuvers, adenosine should be administered. Adenosine is highly effective at termination of nodal-dependent rhythms and can help identify the underlying etiology. For example, continued atrial activity (P waves) during atrioventricular block can help identify atrial flutter and atrial tachycardia. Patients given adenosine should be on a cardiac monitor with a running rhythm strip on paper to document the results. Prior to giving adenosine, patients should be warned that they may experience nausea, flushing, chest pain, or a sense of dread. Patients with bronchospastic lung disease should not receive adenosine.

Although amiodarone would be effective for terminating this patient's arrhythmia, it has many long-term risks, including thyroid, liver, pulmonary, and neurologic toxicity. In this young patient, amiodarone would not be an appropriate option.

Cardioversion is not indicated because the patient is hemodynamically stable, and pharmacologic attempts at cardioversion, such as adenosine, have not been attempted.

Ibutilide is an intravenous Vaughan-Williams class III antiarrhythmic drug FDA approved for pharmacologic cardioversion of atrial fibrillation. The patient has regular supraventricular tachycardia, not atrial fibrillation.

KEY POINT

- Patients with hemodynamically tolerated supraventricular tachycardia refractory to vagal maneuvers should be given adenosine.

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Item 101 Answer: C

Educational Objective: Manage dual antiplatelet therapy in a patient who had a non–ST-elevation myocardial infarction treated with a bare metal stent.

A full year of clopidogrel therapy is indicated in this patient who has sustained a non–ST-elevation myocardial infarction (NSTEMI). Clopidogrel added to aspirin improves outcomes after hospitalization in patients with NSTEMI regardless of the in-hospital treatment approach. Current recommendations from the American College of Cardiology and the American Heart Association state that all patients with an acute coronary syndrome (unstable angina, NSTEMI, or ST-elevation myocardial infarction) treated medically or with a stent (bare metal stent or drug-eluting stent) should be given $P2Y_{12}$ inhibitor therapy (for example, clopidogrel, prasugrel, or ticagrelor) in addition to aspirin for at least 12 months.

Patients who receive a stent in the absence of an acute coronary syndrome (that is, for stable angina pectoris) also require dual antiplatelet therapy with aspirin and clopidogrel until endothelialization of the stent is completed and the risk for acute stent thrombosis decreases. For a bare metal stent placed under these circumstances, clopidogrel should be continued for at least 1 month; for a drug-eluting stent, clopidogrel should be continued for at least 1 year. There is no indication for dual antiplatelet therapy for less than 1 month. Neither ticagrelor nor prasugrel has been studied extensively in patients undergoing coronary stent implantation for stable angina pectoris; therefore, these patients should be treated with clopidogrel in addition to aspirin.

KEY POINT

- Patients with an acute coronary syndrome should be treated with dual antiplatelet therapy (aspirin and a $P2Y_{12}$ inhibitor) for 1 year regardless of initial treatment approach.

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Item 102 Answer: A

Educational Objective: Recognize late complications in a cardiac transplant patient.

This patient should undergo coronary angiography. He underwent heart transplantation 10 years ago and presents with exertional dyspnea. The two most common causes of dyspnea in post-cardiac transplant patients are rejection and cardiac allograft vasculopathy. The prevalence of cardiac allograft vasculopathy is approximately 50% by year 5 post-transplant and is the most common cause of mortality in patients after the first year post-transplant. Because the transplanted heart is denervated at the time of transplant, vasculopathy and subsequent ischemia may occur without the classic symptoms of angina. Therefore, this diagnosis must be suspected in long-term transplant patients presenting with symptoms compatible with ischemia without chest pain. In this patient with exertional dyspnea 10 years after transplantation, the most likely cause is cardiac allograft vasculopathy, and therefore proceeding to coronary angiography to confirm the diagnosis is the appropriate next step.

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Dobutamine stress echocardiography would be a reasonable option in lower-risk patients (such as those with a relatively recent coronary angiography study).

If the patient had undergone heart transplantation within the past year, the suspicion for rejection would be high. However, the incidence of rejection after the first year is low unless patients are not compliant with their immunosuppressive medications. Therefore, endomyocardial biopsy to evaluate for rejection is not the most appropriate step.

Because of the patient's significant history of tobacco use, pulmonary function testing might be a reasonable consideration for evaluation of possible underlying lung disease. However, the rapid onset of respiratory symptoms in a previously asymptomatic patient who is currently a nonsmoker would make this diagnosis less likely, and testing would not be appropriate before excluding a cardiac cause.

The transplanted heart is denervated, and without the normal vagal tone, a normal heart rate for transplant patients is between 90/min and 110/min. Because sinus tachycardia may also be present in patients with pulmonary embolism, it may be more difficult to assess tachycardia as a possible presenting sign in patients who are post-transplant. However, this patient is not at increased risk for pulmonary embolism, and his heart rate of 102/min is not unusual and should not increase suspicion for this diagnosis. Therefore, a ventilation-perfusion lung scan to test for this possibility would not be an appropriate next step.

KEY POINT

- The most common cause of reduced left ventricular function in heart transplant patients after the first year is cardiac allograft vasculopathy.

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Item 103 Answer: C

Educational Objective: Manage a patient with an implantable cardioverter-defibrillator undergoing surgery.

In this patient with an implantable cardioverter-defibrillator (ICD) with planned shoulder surgery, her ICD should be reprogrammed immediately before the procedure to asynchronous pacing with disabling of tachycardia detection and shocking function.

In any patient with a cardiac implanted electronic device, three fundamental questions must be answered in order to appropriately determine perioperative device management. First, what type of device does the patient have (for example, pacemaker versus defibrillator)? Second, is the patient pacemaker dependent? Third, will the surgery be performed with instruments that result in electromagnetic interference in the vicinity of the device or its leads (for example, electrocautery)?

There is often confusion about pacemakers and defibrillators. An ICD is a pacemaker with extra capabilities (detection and treatment of a ventricular tachycardia or ventricular fibrillation). Management of the pacing and defibrillator functions may differ in specific clinical situations. For example, this patient can be considered pacemaker dependent given her history of complete heart block and atrioventricular sequential pacing on her electrocardiogram, requiring continued pacemaker function during surgery. However, her shoulder surgery will be in close proximity to her device and will increase the likelihood of electromagnetic interference that could alter both the pacing and defibrillator functions of her device. Therefore, in order to ensure adequate pacing and avoidance of shocks caused by electrical interference associated with instruments used during surgery, the device should be reprogrammed before the procedure.

Programming the device to asynchronous mode (DOO) will allow continued pacing of the atrium and ventricle but without the device sensing the cardiac response, thereby avoiding suppression of pacing due to electrical interference that the device might interpret as an elevated heart rate (that is, oversensing). Disabling the shock function will eliminate false detection of a tachyarrhythmia due to electrical interference. However, not all patients with pacemaker dependence require asynchronous pacing during surgery, and guidelines for device management before, during, and after surgery continue to evolve. Because of this, it is advisable to consult with the patient's outpatient electrophysiologist in advance of surgery.

Disabling the shock function of an ICD is possible by applying an external magnetic field to the device. The change in function associated with the application of a magnet to an ICD differs from doing so to a pacemaker. Magnet application induces asynchronous pacing (pacing regardless of what is sensed) in pacemakers, whereas magnet application in ICDs disables the shocking function of the device without changing pacing programming. In this patient, although disabling the shocking function is appropriate, doing so will not change the device to an asynchronous mode.

Devices often need to be interrogated after surgery; however, this option is incorrect because reprogramming is needed in this patient before she can proceed to surgery. In any patient whose device is reprogrammed before surgery, the device should be interrogated after surgery and confirmed to be "active."

Advising against surgery is incorrect. Patients with implanted cardiac devices can safely undergo surgery provided the correct precautions are taken. Patients with acute arrhythmias may require stabilization, but in general, an implanted cardiac device in and of itself is not a contraindication to surgery or invasive procedures.

In summary, this patient is pacemaker dependent, has an ICD, and is having surgery in the vicinity of her device. Therefore, the patient's ICD requires reprogramming to an asynchronous mode, disabling of the tachytherapies, and appropriate device interrogation and reprogramming after the surgery.

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KEY POINT

- Patients with an implantable cardioverter-defibrillator who are pacemaker dependent often require reprogramming of their device before surgery.

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Item 104 Answer: B

Educational Objective: Diagnose ostium primum atrial septal defect.

The most likely diagnosis is ostium primum atrial septal defect (ASD). The patient has clinical features of an ASD, presenting with dyspnea, previous atrial fibrillation, and features of volume overload of the right heart with elevation of the central venous pressure and a right ventricular lift. A systolic murmur at the base results from increased flow across the right ventricular outflow tract from the left-to-right shunt. Fixed splitting of the S_2 throughout the cardiac cycle is a characteristic clinical feature of ASD. The apical systolic murmur is from mitral regurgitation and is related to the mitral valve cleft. The electrocardiogram demonstrates left axis deviation, first-degree atrioventricular block, and interventricular conduction delay. This combination of findings, including fixed splitting of S_2, mitral regurgitation murmur, and left axis deviation on the electrocardiogram, are most consistent with an ostium primum ASD.

Patients with coronary sinus ASD have features of right heart volume overload but do not have mitral valve disease and thus will not have a murmur of mitral regurgitation. The electrocardiogram may be normal or demonstrate first-degree atrioventricular block and incomplete right bundle branch block.

Patients with ostium secundum ASD have features of right heart volume overload but do not have mitral valve disease and thus will not have a murmur of mitral regurgitation. The electrocardiogram may be normal or demonstrate first-degree atrioventricular block and incomplete right bundle branch block. Left axis deviation on the electrocardiogram is not found in patients with an ostium secundum ASD.

Patients with patent foramen ovale have a normal echocardiogram and physical examination. These patients are also generally asymptomatic.

Patients with sinus venosus ASD have features of right heart volume overload but do not have mitral valve disease and thus will not have a murmur of mitral regurgitation. The electrocardiogram may be normal or demonstrate first-degree atrioventricular block and incomplete right bundle branch block.

KEY POINT

- Ostium primum atrial septal defect is characterized by the combination of fixed splitting of the S_2, a mitral regurgitation murmur, and left axis deviation on the electrocardiogram.

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Item 105 Answer: A

Educational Objective: Manage ventricular septal defect complicating myocardial infarction.

This patient has developed a clinically significant ventricular septal defect (VSD) and is in cardiogenic shock; he requires emergency surgery to repair the defect. VSD manifests as hemodynamic compromise in the setting of a new holosystolic murmur 3 to 7 days after an initial myocardial infarction (MI). Although surgical mortality is high, urgent cardiac surgery (coronary artery bypass grafting and VSD patch repair) offers the only chance of survival for patients with large post-infarction VSDs, especially in the presence of cardiogenic shock. There is no consensus on the optimal timing of surgery as early surgical repair is difficult because of infarcted myocardium, which is often friable and makes surgical closure of the septal defect difficult. There have been several reports of successful percutaneous closure of VSDs, but anatomy of the VSD and clinical expertise limit widespread use of this procedure in all patients.

Acute ventricular free wall rupture also occurs 3 to 7 days after MI and has a high mortality rate. Patients most commonly present with pericardial tamponade (due to hemopericardium), pulseless electrical activity, and death. Emergent pericardiocentesis and subsequent surgical reconstruction can improve survival. The echocardiographic findings in this patient did not reveal pericardial effusion or tamponade, and his presentation is consistent with VSD.

This patient has an occluded left anterior descending artery and persistent ST-segment elevation; however, the presence of hemodynamic compromise and echocardiographic evidence of VSD requires emergency cardiac surgery. Although coronary artery bypass grafting is usually performed during an attempted repair of the septal defect, percutaneous coronary intervention of the left anterior

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descending artery is not indicated once the VSD has been diagnosed.

The performance of right heart catheterization may aid in the diagnosis of VSD, and the use of a vasopressor such as dopamine may help initially stabilize the patient. However, this patient has a severe hemodynamic impairment and requires emergency cardiac surgery.

KEY POINT

- Urgent cardiac surgery offers the only chance of survival for patients with large postinfarction ventricular septal defects, especially in the presence of cardiogenic shock.

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Item 106 Answer: A

Educational Objective: Treat a black patient with heart failure with hydralazine and isosorbide dinitrate in addition to usual therapy.

This patient should have hydralazine and isosorbide dinitrate added to her medication regimen for the treatment of her heart failure. She has New York Heart Association (NYHA) functional class III heart failure and is black. Hydralazine and isosorbide dinitrate have been demonstrated to improve symptoms and reduce mortality in patients who are black and who are already on maximal therapy with NYHA class III or IV heart failure symptoms. Adverse effects of this therapy include peripheral edema and headaches, but this regimen should be attempted in these patients.

Optimal therapy for patients with heart failure includes treatment with an ACE inhibitor, β-blocker, and an aldosterone antagonist. The addition of an angiotensin receptor blocker, such as losartan, to this combination is generally not recommended, primarily because of concern for hyperkalemia. Additionally, no benefit to this treatment regimen has been documented. It would therefore not be appropriate in this patient.

In patients with heart failure, warfarin treatment is appropriate only in those with another indication, such as atrial fibrillation meeting CHA_2DS_2-VASc criteria, but not with heart failure alone. The routine treatment of patients with heart failure with warfarin is not indicated.

Cardiac resynchronization therapy (CRT) may be an effective therapy in patients with heart failure and a prolonged QRS duration indicating dyssynchrony. Indications include a left ventricular ejection fraction of 35% or less in patients in sinus rhythm, with a left bundle branch block, and with a QRS duration of 150 ms or greater in whom moderate to severe symptoms (NYHA class III or IV) are present despite optimal medical therapy. Because this patient does not have evidence of dyssynchrony or an ejection fraction of 35% or less, she is not a candidate for treatment.

KEY POINT

- Hydralazine and isosorbide dinitrate improve symptoms and reduce mortality in patients with New York Heart Association class III or IV heart failure symptoms who are black and are already on maximal therapy.

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Item 107 Answer: D

Educational Objective: Evaluate for suspected perivalvular abscess in a patient with infective endocarditis.

This patient should undergo transesophageal echocardiography (TEE). He has evidence of a new conduction defect on electrocardiogram suggesting a possible perivalvular abscess complicating *Staphylococcus aureus* infective endocarditis. Perivalvular abscesses may be present in 30% to 40% of patients with infective endocarditis, and the risk may be further increased in those with a bicuspid aortic valve. The diagnosis should be considered in patients with persistent bacteremia, fever, or evidence of conduction system disorders who are being treated with appropriate antibiotic therapy. TEE has a high sensitivity and specificity for identifying perivalvular extension of infection and is the diagnostic study of choice when a perivalvular abscess is suspected.

Cardiac CT has not been extensively studied for use in diagnosing myocardial infection and is not typically used for this purpose. Cardiac magnetic resonance (CMR) imaging, however, is effective in identifying intramyocardial infection, although it is a more complex technology that may have limited availability in some areas. CMR imaging is often used in situations in which a perivalvular abscess is suspected but transesophageal echocardiography is equivocal.

Evidence of a conduction system disorder may be the only indicator of a perivalvular abscess in a patient otherwise responding clinically to treatment for infective endocarditis, as in this patient. Because of the significance of this possible complication, failure to further evaluate conduction system abnormalities in this setting would be inappropriate.

Although transthoracic echocardiography is effective for initial evaluation for endocarditis and assessing for potential complications once endocarditis has been diagnosed (such as valvular or left ventricular dysfunction), TEE is significantly more sensitive for detecting perivalvular abscess because of the closer proximity of the ultrasound probe to the valve structures. It is therefore preferred to transthoracic echocardiography if this diagnosis is a consideration.

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KEY POINT

- Transesophageal echocardiography is the diagnostic study of choice in patients with a possible perivalvular abscess complicating infective endocarditis.

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Item 108 Answer: B

Educational Objective: Diagnose upper extremity peripheral arterial disease.

Measurement of systolic blood pressure in both arms is indicated in this patient at high risk for atherosclerotic cardiovascular disease (ASCVD) who likely has upper extremity peripheral arterial disease (PAD) as the cause of his symptoms. His extremity symptoms are consistent with impaired arterial blood flow with exertion causing claudication in the left arm, and his associated neurologic symptoms suggest the subclavian steal syndrome. In subclavian steal, a stenosis in the left subclavian artery proximal to the take-off of the vertebral artery results in retrograde blood flow from the central nervous system to the arm, resulting in neurologic symptoms. A hallmark feature of upper extremity PAD on physical examination is a difference in systolic blood pressures between the arms, with a differential of greater than 15 mm Hg being typical. Differences in the distal pulses (upstroke and duration) may also be noted when comparing the upper extremities, and a bruit detected over the subclavian artery may be present. Noninvasive vascular testing with Doppler ultrasonography may be confirmatory. Upper extremity PAD, whether symptomatic or asymptomatic, is a marker for significant ASCVD and is associated with an increased risk for future cardiovascular disease. Therefore, primary treatment is aggressive therapy for ASCVD, including antiplatelet therapy. Treatment for clinically symptomatic upper extremity PAD, as in this patient, may include angioplasty with stenting or surgical bypass.

The ankle-brachial index is used to assess for lower extremity PAD and might be abnormal in this patient with likely ASCVD, although this test would not be helpful in evaluating his upper extremity symptoms.

Pulsus paradoxus is an exaggerated drop in systolic blood pressure (>10 mm Hg) during inspiration and may be present in patients with severe pericardial disease (tamponade and occasionally constrictive pericarditis), asthma, and COPD. This patient, however, does not have a history suggestive of these disorders, and evaluation for pulsus paradoxus would not be diagnostically helpful.

Thoracic outlet maneuvers are used to evaluate for neurovascular impingement at the point where the upper extremity neurovascular bundle exits the thoracic cavity. Although thoracic outlet syndrome could be responsible for his vascular symptoms, the obstruction occurring with this syndrome is distal to the vertebral artery and would not explain his accompanying neurologic symptoms.

KEY POINT

- A hallmark feature of upper extremity peripheral arterial disease on physical examination is a difference in systolic blood pressures between the arms (typically >15 mm Hg).

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Item 109 Answer: D

Educational Objective: Manage first-degree atrioventricular block accompanied by bifascicular block.

No intervention is indicated. This octogenarian has first-degree atrioventricular (AV) block (PR interval >200 ms), right bundle branch block, and left posterior fascicular block. The combination of first-degree AV block and bifascicular block is often referred to as "trifascicular block," although this term is not correct because true trifascicular block would imply complete AV block. There is no indication for pacing in patients with first-degree AV block and bifascicular block who have no symptoms due to bradycardia. The risk of this type of block progressing to complete heart block is less than 2% to 3% per year.

The patient is asymptomatic, has no evidence of left ventricular dysfunction, and no clinical evidence of ischemia. Therefore, stress testing, including adenosine perfusion imaging, is not indicated. Because right coronary artery ischemia can cause paroxysms of bradycardia, stress testing for ischemia may be indicated in patients with paroxysmal bradycardia or clinical findings suggestive of ischemia, neither of which is present in this patient. In patients in whom symptomatic bradycardia is a concern, treadmill stress testing may be helpful in evaluating whether there is an appropriate chronotropic response to exercise.

Permanent pacing is only indicated in two clinical situations. First, pacemakers are indicated in patients with symptomatic bradycardia in the absence of a reversible cause. Second, pacemakers are indicated in patients with evidence of AV conduction disturbances that have a high likelihood of progression to complete heart block or life-threatening sudden asystole. Second-degree Mobitz II block, alternating

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bundle branch block, atrial fibrillation with pauses greater than 5 seconds, and complete heart block are all indications for permanent pacing. This patient has none of these conditions, and neither dual-chamber nor single-chamber pacing is indicated.

KEY POINT

- Asymptomatic first-degree atrioventricular block with bifascicular block does not require pacemaker implantation.

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Item 110 Answer: D

Educational Objective: Manage secondary risk reduction in a patient with established coronary artery disease.

The intervention that offers the greatest cardiovascular risk reduction for this patient is to start an ACE inhibitor for secondary prevention after myocardial infarction (MI) and to reduce systolic blood pressure. ACE inhibitors have been shown to decrease both cardiovascular and all-cause mortality in patients with chronic ischemic heart disease, especially in those patients with prior MI, left ventricular systolic dysfunction, or heart failure. Guidelines from the American College of Physicians/American College of Cardiology Foundation/American Heart Association recommend a treatment goal of 140/90 mm Hg or below in patients with stable ischemic coronary heart disease. Although previous guidelines recommended treatment to reduce blood pressure to below 130/80 mm Hg, there is limited evidence to show a benefit of doing so, with the potential for adverse consequences owing to overtreatment of blood pressure in these patients. The 2014 Eighth Joint National Commission (JNC-8) report does not provide specific recommendations for treatment of patients with established atherosclerotic disease, although the recommended threshold for treatment for all patients younger than 60 years is also 140/90 mm Hg. Therefore, this patient would be expected to benefit from therapy to decrease her blood pressure to at least 140/90 mm Hg or below.

While there is observational evidence from the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) Prevention study that patients with prior MI who take fish oil have a 20% reduction in mortality rate, the current American College of Cardiology/American Heart Association guidelines do not currently provide recommendations for use of fish oil after MI. Fish oil is effective in reducing triglyceride levels; however, this patient's triglyceride levels are normal.

Recently released guidelines recommend treatment of patients with established atherosclerotic disease with a high-intensity statin with a goal of lowering the LDL cholesterol level to less than 50% of the baseline level but without treatment to a specific LDL cholesterol level. As this patient has had the expected decrease in LDL cholesterol level on her present regimen, the addition of another agent for managing dyslipidemia, such as niacin, would not be appropriate.

Although moderate alcohol consumption (approximately one to three drinks daily) is associated with a lower risk of coronary heart disease, excessive alcohol intake accounts for approximately 4% of cases of dilated cardiomyopathy. However, reducing this patient's current level of alcohol consumption will not reduce her risk of a future cardiovascular event.

KEY POINT

- Patients with prior myocardial infarction should receive an ACE inhibitor for secondary cardiovascular prevention.

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Item 111 Answer: A

Educational Objective: Manage revascularization in a patient with an acute coronary syndrome with a high TIMI risk score and multivessel disease.

This patient should undergo coronary artery bypass graft (CABG) surgery. In patients with a non–ST-elevation acute coronary syndrome (unstable angina or non–ST-elevation myocardial infarction), the TIMI risk score is used to determine whether a conservative strategy or an early invasive strategy is warranted. This patient has several TIMI risk factors, including aspirin use in the past week, ST-segment deviation, elevated biomarkers, more than three traditional coronary artery disease (CAD) risk factors, and documented CAD with greater than or equal to 50% diameter stenosis; therefore, an early invasive strategy is warranted. In this patient, an oral $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, ticagrelor) was not administered, but if this had been given, the surgery should be delayed 5 days to allow discontinuation and excretion of the antiplatelet medication.

Intra-aortic balloon pump placement may be considered for patients with recurrent cardiac ischemia and poor left ventricular function. However, although this patient had recurrent chest pain during hospitalization, his symptoms improved with intravenous nitroglycerin and medical therapy, and he

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has remained hemodynamically stable. Therefore, intra-aortic balloon pump placement is not indicated.

Because this patient has multivessel disease and a reduced left ventricular ejection fraction, he should undergo CABG rather than percutaneous coronary intervention.

In patients with left main coronary artery stenosis, depressed left ventricular function, and an acute coronary syndrome, the optimal treatment strategy includes revascularization rather than medical therapy.

KEY POINT

- Patients with multivessel coronary disease and a reduced left ventricular ejection fraction should undergo coronary artery bypass graft surgery rather than percutaneous coronary intervention.

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Item 112 Answer: C

Educational Objective: Treat a patient with severe calcific aortic stenosis and aortic regurgitation with surgical valve replacement.

This patient should undergo surgical aortic valve replacement. Surgical aortic valve replacement is the only treatment of aortic stenosis associated with a survival benefit and durable symptom relief. Surgical aortic valve replacement is the treatment of choice for most patients with symptomatic severe aortic stenosis and is associated with low mortality rates for patients younger than 70 years (1%-3%).

Aortic valve repair is an option in a limited number of adult patients with aortic valve disease. In general, it is restricted to patients with aortic regurgitation and anatomically favorable aortic valve and root anatomy and can range from simple cusp plication to complex valve-sparing aortic root replacement. This patient has severe calcific aortic stenosis and a valve that is unlikely to be amenable to repair.

Balloon valvuloplasty, although important in the treatment of pediatric patients with severe aortic stenosis, has a more limited role in adults, either as a bridge to definitive treatment, to differentiate dyspnea symptoms in high-risk patients with comorbid conditions such as COPD, or to treat patients with calcific aortic stenosis with hemodynamic instability or decompensation. While balloon valvuloplasty is a potential consideration for this patient, the presence of significant aortic regurgitation is a contraindication. Improvement in aortic valve area from this procedure is modest, and many patients have residual severe aortic stenosis immediately after valvuloplasty. Balloon valvuloplasty would not be the best option for this patient.

Transcatheter aortic valve replacement (TAVR) is indicated for patients with severe symptomatic aortic stenosis who are considered unsuitable for conventional surgery because of severe comorbidities. Candidates for TAVR must be carefully selected. Surgical risk should be assessed objectively, such as by using the Society of Thoracic Surgeons adult cardiac risk score (STS score) (http://riskcalc.sts.org/STSWebRiskCalc273/de.aspx). Patients with an STS risk score of greater than or equal to 8% may be candidates for TAVR. In addition, TAVR is not approved in patients with concomitant valve disease (such as significant aortic regurgitation or mitral valve disease) and a bicuspid aortic valve. This patient has a bicuspid aortic valve and moderate aortic regurgitation; therefore, she would not be a candidate for TAVR.

KEY POINT

- Surgical aortic valve replacement is the treatment of choice for most patients with symptomatic severe aortic stenosis and is associated with low mortality rates for patients younger than 70 years (1%-3%).

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Item 113 Answer: D

Educational Objective: Diagnose a left atrial myxoma.

This patient most likely has a myxoma that is causing her symptoms and clinical findings. Left atrial myxomas are the most common benign tumors of the heart. These lesions can cause constitutional symptoms, such as fatigue, dyspnea, fever, and weight loss, related to tumor cytokine production; systemic embolization from either tumor fragments or associated thrombi may cause neurologic symptoms or other systemic sequelae. Left atrial myxomas most commonly appear as a mass arising from the atrial septum; the mass can involve the mitral valve intermittently to cause a "tumor plop" that may clinically mimic mitral stenosis. Myxomas may occur as part of the Carney complex, which is an autosomal dominant disorder associated with pigmentation abnormalities (such as blue nevi), schwannomas, and endocrine tumors.

Metastatic adenocarcinoma with cardiac involvement can manifest from direct invasion or hematogenous spread, with symptoms and signs dependent on the site of involvement. Metastatic adenocarcinoma with cardiac involvement, although common in patients with this tumor type (15% of patient at autopsy), would be less likely in this patient given the isolated anatomic location and recent negative malignancy screening results.

Angiosarcomas are malignant tumors that can occur in the atria but are less common than myxomas and typically infiltrate the myocardium, which is normal in this patient.

Lipomas typically are located in the subendocardium, not the atrium, and rarely cause symptoms.

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Papillary fibroelastomas, like myxomas, can be mobile with a pedunculated stalk. However, they most commonly arise on left-sided cardiac valves and the left ventricular outflow tract.

KEY POINT

- The most common benign tumors of the heart, left atrial myxomas can cause constitutional symptoms, such as fatigue, dyspnea, fever, and weight loss, related to tumor cytokine production and neurologic symptoms related to systemic embolization from either tumor fragments or associated thrombi.

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Item 114 Answer: B

Educational Objective: Manage acute pericarditis on an outpatient basis.

This patient should receive clinical follow-up without hospital admission or further diagnostic testing to monitor her response to therapy, evaluate for possible complications, and assess the timing for tapering her medications. Slow tapering over 2 to 4 weeks after initial presentation with improvement in symptoms is usually performed to reduce the risk of recurrent inflammation.

The vast majority of patients with acute pericarditis, including the patient presented, can be managed medically on an outpatient basis. For a subset of patients, high-risk features of acute pericarditis may be present and warrant hospitalization for treatment and monitoring for possible complications; these include fever, leukocytosis, acute trauma, abnormal cardiac biomarkers, an immunocompromised host, oral anticoagulant use, large pericardial effusions, or evidence of cardiac tamponade.

CT can be used to show pericardial thickening in patients with acute pericarditis. However, this finding would not change the diagnosis or appropriate management strategy in this patient.

Medical therapy with anti-inflammatory agents is appropriate for acute pericarditis. However, glucocorticoids are reserved for patients who do not respond to NSAIDs, such as ibuprofen, aspirin, and indomethacin, none of which has been tried yet in this patient. Glucocorticoid therapy may also increase the risk of recurrent pericarditis and should only be considered in highly selected patients with refractory pericarditis.

Pericardiocentesis is indicated only for patients with tamponade or for those in whom the analysis of pericardial fluid can be of assistance in diagnosis and management. Signs of tamponade are not present in this patient whose inferior vena cava is normal in size on echocardiography, whose Doppler ultrasound shows minimal change in mitral inflow with respiration, and whose bedside maneuvers reveal no pulsus paradoxus.

KEY POINT

- Patients with acute pericarditis who do not have high-risk features (fever, leukocytosis, acute trauma, abnormal cardiac biomarkers, immunocompromise, oral anticoagulant use, large pericardial effusions, or evidence of cardiac tamponade) can be managed medically on an outpatient basis with close clinical follow-up.

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Item 115 Answer: C

Educational Objective: Manage a patient with Wolff-Parkinson-White syndrome with syncope.

This patient should undergo an electrophysiology study. He has evidence of pre-excitation on his electrocardiogram with a history of palpitations and syncope. The slurring of the QRS complex (delta wave) represents early ventricular depolarization owing to conduction over the accessory pathway (bypass tract). The presence of a delta wave and symptoms of tachycardia are consistent with Wolff-Parkinson-White syndrome. The episodes could be caused by supraventricular tachycardia (orthodromic or antidromic reciprocating tachycardia) or pre-excited atrial fibrillation. The presence of syncope suggests that these episodes are hemodynamically significant. Identification of syncope in a patient with Wolff-Parkinson-White syndrome should prompt referral to a cardiologist or electrophysiologist.

An electrophysiology study would allow diagnosis of the cause of this patient's palpitations and allow risk stratification for risk of sudden cardiac death. The electrophysiology procedure also affords the opportunity to ablate the accessory pathway and potentially cure his arrhythmia. Stress testing can be an appropriate method for risk stratification in patients with asymptomatic pre-excitation; however, this patient clearly has symptoms and therefore should undergo invasive testing and ablation.

Antiarrhythmic drug therapy is not indicated in this patient because the type and mechanism of the arrhythmia are not known. Catheter ablation is preferred in young persons with Wolff-Parkinson-White syndrome in order to avoid lifelong use of potentially toxic medications. Antiarrhythmic agents are reserved for second-line therapy, particularly in patients with accessory pathways located close to the atrioventricular (AV) node.

Metoprolol and diltiazem are AV nodal blockers and may be unsafe if the patient has anterograde conduction down the accessory pathway during atrial fibrillation. These drugs can block the AV node and promote rapid 1:1 conduction from the atrium to the ventricle during atrial fibrillation and thus induce ventricular fibrillation. AV nodal blockers are contraindicated in patients with pre-excited atrial fibrillation, such as this patient.

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KEY POINT

- Identification of syncope in a patient with pre-excitation should prompt referral to a cardiologist or electrophysiologist.

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Item 116 Answer: C

Educational Objective: Consider reversible causes in the evaluation of heart failure.

The most appropriate diagnostic test to perform in this young patient with new-onset heart failure is to obtain thyroid studies. This patient exhibits signs and symptoms consistent with a diagnosis of hyperthyroidism, including tachycardia, a hyperdynamic precordium, palpitations, weight loss, and loose stools. Hyperthyroidism is a well-described, reversible cause of heart failure due to cardiac overstimulation by excess thyroid hormone that resembles sympathetic stimulation. Hyperthyroidism causes an increase in heart rate and myocardial contractility; systemic vascular resistance often decreases and may result in a widened pulse pressure. Hypothyroidism is also a known cause of heart failure, although it would be less likely in this patient with symptoms more consistent with excess thyroid hormone. Because thyroid function abnormalities are a potentially reversible cause of heart failure, assessment of thyroid function should be considered in patients with new-onset heart failure and clinical findings suggestive of thyroid dysfunction.

Evaluation of unusual causes of heart failure should not be performed routinely but should be pursued when there are suggestions of specific diseases by history or physical examination. The patient has no signs or symptoms suggesting a rheumatologic disorder, and routine screening with an antinuclear antibody level is not indicated. Similarly, this patient does not have a history of flu-like symptoms suggesting a viral etiology, making the potential yield of viral titers quite low. Furthermore, directed treatment options in the presence of positive viral titers are quite limited.

Endomyocardial biopsy is rarely indicated in the evaluation of acute heart failure as it is invasive and is unlikely to be helpful in identifying a reversible cause. It may be considered in patients whose heart failure is unresponsive to medical therapy or is associated with ventricular arrhythmias or conduction block in order to evaluate for giant cell myocarditis.

KEY POINT

- Evaluation of unusual causes of heart failure should not be performed routinely but should be performed when there are suggestions of specific diseases by history or physical examination findings.

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Item 117 Answer: B

Educational Objective: Appropriately perform surveillance imaging in a patient with Marfan syndrome and aortic root dilation.

This patient with Marfan syndrome should undergo surveillance imaging annually. Dilation of the ascending aorta is a systemic feature of Marfan syndrome, and the most life-threatening complication of Marfan syndrome is aortic aneurysm, which can lead to an acute aortic syndrome (aortic dissection, rupture, or both). Accordingly, examination of the ascending aorta and heart valves is mandatory in patients with Marfan syndrome. The severity of aortic disease is in relation to the extent of aortic dilation, the length of the dilated segment, and the location of aortic involvement. Most patients with Marfan syndrome present with enlargement of the ascending aorta; therefore, serial examination is focused mainly on assessing this portion of aorta. American College of Cardiology Foundation/American Heart Association guidelines recommend follow-up imaging 6 months after diagnosis, with annual surveillance thereafter if the aortic root is less than 4.5 cm in diameter and otherwise stable. This threshold is lower than for patients with an aortic aneurysm due to other causes because of the tendency for complications in patients with Marfan syndrome with an aortic root diameter above this level. If the aortic root diameter is 4.5 cm or greater or if the aortic root diameter shows significant growth from baseline, more frequent imaging of the aorta should be considered.

Imaging of the aortic root in patients with Marfan syndrome is usually performed with transthoracic ultrasound because it is able to accurately evaluate this portion of the aorta and is noninvasive. However, for aneurysms above the aortic root, CT or MRI is preferred as they more accurately measure the aortic dimensions in that region.

KEY POINT

- In patients with Marfan syndrome and aortic root dilation, surveillance imaging should be performed 6 months after diagnosis and annually thereafter if the aortic size remains stable.

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Item 118 Answer: B

Educational Objective: Manage a patient with a high-risk score on exercise treadmill testing with cardiac catheterization.

This patient's exercise electrocardiographic (ECG) stress testing results indicate that he has coronary artery disease (CAD), and his Duke treadmill score (-11.5) indicates the presence of high-risk disease. He should undergo cardiac catheterization for diagnosis and possibly revascularization.

Exercise ECG stress testing can be used for the diagnosis of CAD (as in this patient), to evaluate adequacy of medical therapy in patients with known CAD, and to evaluate functional status. When used to evaluate chest pain, the test is considered diagnostic of obstructive CAD (>70% obstruction) if there is greater than 1-mm ST-segment depression with exercise in two contiguous leads. The findings in this patient are consistent with occlusive coronary disease as the cause of his exertional chest pain.

In addition to diagnosis, a positive treadmill study can be used to further risk stratify obstructive CAD. The Duke treadmill score is one method and is calculated as follows: Exercise time in minutes - (5 × ST-segment depression) - (4 × angina score). (Angina score: 0 = asymptomatic; 1 = nonlimiting angina; 2 = exercise-limiting angina.) Scores below -11 are high risk, and those above 5 are low risk. Patients with high-risk scores are likely to have left main or proximal left anterior descending (LAD) artery disease. Other markers of a high-risk exercise study that would be suggestive of proximal LAD artery disease or multi-vessel disease would include a drop in blood pressure with exercise or severe ST-segment depression. Based on his high-risk Duke treadmill score, this patient should be further evaluated with coronary arteriography.

Although this patient should be treated with medical therapy including aspirin, a β-blocker, and a statin, he should also undergo cardiac catheterization because of the high likelihood of severe obstructive CAD.

The use of imaging, such as stress echocardiography or myocardial perfusion imaging, can localize ischemia to a vascular territory and can be helpful to determine affected vascular territory prior to revascularization. Stress testing with imaging can also be helpful in making the diagnosis of CAD in patients with equivocal exercise stress tests or those in whom there is a higher likelihood of a false-positive exercise stress test. However, because of this patient's high-risk ECG stress test, he should undergo catheterization for a definitive diagnosis and possible revascularization. There would be no benefit to a noninvasive imaging test prior to or instead of that intervention.

KEY POINT

- Cardiac catheterization is indicated in patients with a positive electrocardiographic stress test and findings indicative of high-risk coronary artery disease.

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Item 119 Answer: C

Educational Objective: Diagnose peripartum cardiomyopathy.

The most likely diagnosis in this woman who gave birth 2 weeks ago is peripartum cardiomyopathy. Peripartum cardiomyopathy is left ventricular systolic dysfunction identified toward the end of pregnancy or in the months following delivery in the absence of another identifiable cause. This occurs with increased frequency in women with a history of preeclampsia. Patients may be asymptomatic or present with features of heart failure. Prompt initiation of medical therapy is recommended for women with peripartum cardiomyopathy and includes an ACE inhibitor or an angiotensin receptor blocker (after delivery), β-blockers, digoxin, hydralazine, nitrates, and diuretics.

Pulmonary embolism can occur postpartum, particularly if prolonged bed rest is required in the peripartum period. Although both pulmonary embolism and heart failure frequently are marked by dyspnea, this patient's presentation is more indicative of heart failure, with pulmonary congestion and elevated central venous pressure.

Most patients with ischemic cardiomyopathy have symptomatic coronary artery disease, abnormal electrocardiographic findings demonstrating previous myocardial infarction, or regional hypokinesis on echocardiography. These findings are absent in this patient.

Stress-induced cardiomyopathy (takotsubo cardiomyopathy) is characterized by transient cardiac dysfunction with ventricular apical ballooning, usually triggered by intense emotional or physical stress, although in several published cases, no trigger was identifiable. The presenting clinical picture may mimic an acute coronary syndrome, with chest pain, mildly elevated cardiac enzyme levels, and electrocardiographic changes consistent with ischemia. The patient's clinical presentation is not consistent with stress cardiomyopathy.

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KEY POINT

- Peripartum cardiomyopathy is left ventricular systolic dysfunction identified toward the end of pregnancy or in the months following delivery in the absence of another identifiable cause.

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Item 120 Answer: C

Educational Objective: Manage severe symptomatic mitral stenosis.

This patient has severe symptomatic mitral stenosis with a valve that by description appears amenable to percutaneous balloon mitral valvuloplasty (PBMV). Classifying mitral stenosis as moderate or severe can be difficult owing to variance in heart rate and forward flow on transmitral gradient. As such, mean gradients are no longer included in the severity criteria. However, the mean gradient is usually greater than 5 mm Hg to 10 mm Hg in severe mitral stenosis, and the mitral valve area is usually less than 1.5 cm^2 in severe mitral stenosis and 1.0 cm^2 or less in very severe mitral stenosis.

PBMV is indicated for symptomatic patients (New York Heart Association [NYHA] functional class II, III, or IV) with severe mitral stenosis and valve morphology favorable for PBMV in the absence of left atrial thrombus or moderate to severe mitral regurgitation. Valve morphology is evaluated by assessing the degree of valvular calcification, valve thickening, degree of leaflet restriction, and extent of subchordal thickening. The most common cause of mitral stenosis is rheumatic heart disease, in which valve inflammation leads to progressive degenerative changes including leaflet thickening, calcification, and impaired valve function, as seen in this patient.

Given that this patient has severe symptomatic mitral stenosis and that there are no obvious contraindications to therapy, a conservative approach would not be appropriate.

Mitral valve replacement is indicated in patients with symptomatic (NYHA functional class III–IV) severe mitral stenosis when PBMV is unavailable or contraindicated or valve morphology is unfavorable.

Generally, rheumatic mitral valve disease is not as amenable to surgical repair as that from degenerative causes, such as myxomatous mitral valve disease. Moreover, the percutaneous option is preferable in a patient when available.

KEY POINT

- Percutaneous balloon mitral valvuloplasty is the preferred treatment for severe symptomatic mitral stenosis.

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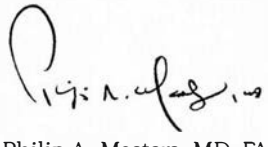

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The learning objectives of MKSAP 17 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence
- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internists and primary care physicians
- Subspecialists who need to remain up-to-date in internal medicine and in areas outside of their own subspecialty area
- Residents preparing for the certification examination in internal medicine
- Physicians preparing for maintenance of certification in internal medicine (recertification)

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Dermatology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 17 in several important ways. MKSAP 17 now includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Dermatology section of MKSAP 17.

- Dermatologic treatments are highly variable in cost; generic topical medications should be considered for a cost-effective approach.
- Food allergies are an uncommon cause of flares in atopic dermatitis; routine food testing without a reliable history of flaring with a particular food should be avoided.
- Less frequent handwashing and application of a thick emollient such as petrolatum are the treatments of choice for irritant hand dermatitis caused by overwashing (see Item 67).
- Systemic therapy, such as phototherapy, traditional systemic agents, or biologics should be reserved for severe (>10% body surface area) psoriasis, psoriatic arthritis, or psoriasis unresponsive to topical therapy.
- Systemic glucocorticoids, systemic retinoids, and phototherapy should be reserved for severe or recalcitrant lichen planus.
- Seborrhea can be treated with over-the-counter selenium sulfide or zinc pyrithione shampoos that are lathered into the skin and allowed to work for a few minutes and then washed out; ketoconazole shampoo and topical cream are also very effective.
- First-line therapy for cellulitis without a draining wound or abscess is a course of antibiotics against both *Streptococcus* spp. and *Staphylococcus* spp. (cephalexin or dicloxacillin, clindamycin, or a macrolide); a 5-day course of antibiotics is as effective as a 10-day course.
- Treatment of most superficial dermatophyte infections includes topical antifungal agents; however, over-the-counter preparations are cost-effective options with good efficacy.
- Minor wounds and burns may be treated with thorough cleansing, application of topical sterile petrolatum, and the application of a nonadherent bandage; nonstick silicone dressings are a more expensive option.
- Dysplastic nevi are benign melanocytic lesions most commonly found on the trunk and extremities; removal should be reserved for those lesions that are changing, symptomatic, or stand out from the patient's other nevi (see Item 32).
- Seborrheic keratoses, solar lentigines, acrochordons, melanocytic nevi, cherry angiomata, dermatofibromas, lipomas, and epidermal inclusion cysts are benign lesions that usually do not require biopsy or treatment.
- Surgical excision is the mainstay of treatment for basal cell carcinoma; Mohs surgery should be reserved for head and neck lesions, large or recurrent tumors, or when cosmetic outcome is crucial; superficial lesions may be treated topically.
- Squamous cell carcinomas typically present as red scaly papules and nodules on sun-exposed skin and are treated with excision; Mohs surgery should be reserved for large tumors with high-risk characteristics in the head and neck region.
- Uncomplicated acute urticaria is a clinical diagnosis based on the presence of pruritic wheals; laboratory studies are almost always normal, and no further diagnostic evaluation is required in most patients before initiating therapy, if needed (see Item 55).
- Management of black hairy tongue consists of tongue brushing as part of aggressive oral hygiene (see Item 5).

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Dermatology

Approach to the Patient with Dermatologic Disease

Introduction

Skin conditions account for a substantial number of physician visits, with patients presenting to internists for evaluation and management of primary dermatologic issues, the skin manifestations of internal disease, or cutaneous adverse reactions from therapeutic regimens. Thus, the ability to recognize common skin findings and the cutaneous clues associated with underlying disorders or their treatment is an important skill required of internists. This section will cover key aspects of dermatology for the internist, with an emphasis on diagnostic recognition, early evaluation, and initial management. This will also include a focus on "when to refer," with an emphasis on recognizing key cutaneous signs that suggest a patient may be more acutely ill or require a more thorough evaluation and consultation with an experienced dermatologist.

Physical Examination

The U.S. Preventive Services Task Force (USPSTF) states that there is insufficient evidence to recommend dedicated screening for skin cancer in the general population. However, there is a growing body of evidence suggesting that patients who are screened have earlier, more treatable skin cancers, and that counseling these patients about preventive measures and self-examination can reduce the number or severity of skin cancers and lead to earlier detection. A sensible approach in average-risk patients is to perform an "integrated skin examination," evaluating the skin during the course of the routine physical examination. While checking blood pressure and pulse, look at the arms; while examining the abdomen, look at the skin of the torso; and while listening to the lungs, look at the back. High-risk patients may warrant more comprehensive and regular evaluation (**Table 1**). A comprehensive skin examination, which takes on average only 1 to 2 minutes, should include evaluation of the scalp below the hair, the mucosa, and the genitals, including looking between skin folds, digits, and on the soles of the feet. Patients should be counseled about how to perform skin self-examinations (generally done once monthly, in a systematic fashion) and to use sun protection (**Table 2**).

The language of dermatology is often a point of confusion for many internists, but recognizing and describing primary lesions is critical to forming an accurate differential diagnosis and can help dermatologists triage referred patients based on the acuity of their lesions.

TABLE 1. Skin Cancer Risk Factors That Warrant Regular Skin Cancer Screening

History of multiple blistering sunburns
Red or light hair; light-colored eyes
Multiple atypical nevi
History of melanoma
History of nonmelanoma skin cancers
Family history of skin cancers or melanoma
Immunosuppression
History of phototherapy

TABLE 2. Sun Protection

Use broad-spectrum ultraviolet protective sunscreen
Use chemical or physical sun blocking agents (or combination)
Use SPF 30 or greater
Apply 30 minutes before sun exposure, reapply every 2 hours; more frequently if wet
Avoid the peak hours (11 AM to 2 PM)
Consider ultraviolet protective clothing

SPF = sun protection factor.

The "primary lesion" refers to the morphology of a skin eruption as it first starts and is an essential clue to a specific diagnosis. Lesions often evolve over time and may cause secondary changes to the skin, either due to the process itself or to external factors such as trauma and scratching; these findings are called "secondary lesions" (**Table 3**). When describing skin lesions, focus on the color, location, and distribution of the lesion, including the primary morphology. "Erythema" implies transient redness of the skin due to inflammation that blanches or lightens with pressure. It is often essential to distinguish erythema from nonblanching purpura, which implies damage to vessels and a substantially different differential diagnosis.

It is not uncommon for patients to have pictures of their lesions or for physicians to have access to mobile devices that allow photography and image transmission. Physicians should be cautious in taking pictures and sending them and must ensure that any patient photography is protected as patient information and sent only through secure telecommunication services or as encrypted e-mail. Photographs are part of the patient's medical record, and copies of all pictures should be maintained with the patient's chart. Whereas teledermatology

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TABLE 3. Lesion Morphology

Primary Lesions	Description
Macule	Small size, flat, change in skin color
	Circular, oval, or irregular
	Border may be distinct or gradually fade to normal skin
Patch	Larger than a macule, 1 cm or larger
	May have very faint fine scale or minimal surface change
Papule	Small bumps, from pinpoint to 1 cm
	Discrete raised lesions
	Lack fluid or pus
	May be flat, umbilicated, grouped, filiform, or scaly
Maculopapular	An eruption with overlapping morphologies
	Admixture of small, flat areas with pinpoint slightly raised bumps
Plaque	Larger raised lesion, 1 cm or larger
	Often flat topped
	"Like a plateau"
Nodule	Larger than a papule
	Usually indistinct borders
	Often arises deeper under the skin and pushes up
Wheal	Transient, edematous, erythematous plaques
	Often oval, arcuate, serpiginous, circular
	"Hives"
Vesicle	Small, fluid-filled papules, ranging from pinpoint to 1 cm
	Often translucent or slightly yellow
	Whitish vesicles are termed "pustules"
Bullae	Larger than vesicles, often 1 cm or larger
	May be thin walled and rupture easily ("flaccid") or tense with thicker top ("tense")
	"Blisters"
Secondary Lesions	**Description**
Scale	Excess keratin from stratum corneum
	May be a fine dusting, a moist greasy scale, or a thick silvery scale
Crust	Dried out serum, blood, or inflammatory cells, often mixed with epidermis and surface bacteria
	May be hemorrhagic (from blood), orange-yellow (from serum or *Staphylococcus* colonization), or thick and black (eschar from chronic wound)
	Ulcers may develop a fibrinous biofilm with polymicrobial colonization, which may represent a moist "crust"
Excoriation	Linear erosions, often crusted, may suggest external trauma and scratching that can lead to loss of the epidermis
Fissure	Linear crack exposing dermis
	Generally occurs where skin is moist and macerated, such as folds, or where skin is very thick and rigid, such as tips or edges of acral sites
Erosion	Loss of the epidermis alone leads to a small, often "punched-out," shallow, moist depression
	Heals without scarring
Ulcer	Complete loss of the epidermis into the dermis
	Can be varying depths, including to deeper tissues in the subcutis
	Heals with scarring
Scar	Skin damaged beyond the basement membrane of the epidermis will generally heal with scarring
	Certain anatomic sites and some black persons are more prone to thicker scarring

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is a valuable tool and holds promise for expanding access in the future, studies are ongoing to determine the accuracy of teledermatology for triage and patient management, and at this time most insurers do not reimburse for teledermatology services.

As in all of medicine, a primary responsibility is to determine the level of acuity of a disorder and whether a patient requires immediate intervention or a higher level of care. This holds true for dermatology as well, and although most dermatologic diseases lack urgency, some disorders represent true emergencies (**Table 4**).

KEY POINTS

- Screening for skin cancer in patients who are at increased risk may allow for diagnosis at a more treatable stage.
- For average risk patients, an "integrated skin examination" involves evaluating the skin for abnormalities during the course of the routine physical examination.

Therapeutic Principles in Dermatology

The initial management of skin conditions is based on the type and severity of the cutaneous lesions. In stable patients, treatment with topical medications is an appropriate approach. Most topical therapies for dermatologic conditions will be "off label" as there is a paucity of evidence for many of these conditions, and most treatment regimens are not FDA approved.

When prescribing topical therapy, patients should be evaluated according to the morphology of the cutaneous eruption, their skin type, and for tolerance of different vehicles. As some dermatologic treatments are highly variable in cost, consideration of the resources available to the patient should also be a factor in shared treatment decision making. Generic topical medications are generally similar in efficacy and should be considered for a cost-effective approach, although formal comparative effective studies are lacking.

The optimal medication and vehicle depend on the type of condition (**Table 5**). For many skin conditions, the vehicle through which a medication is delivered is extremely important. A cream may severely irritate an acutely inflamed eczematous eruption, whereas an ointment will be soothing and well tolerated. A thick, scaly eruption in the scalp is best treated using a foam, allowing easy penetration through the hair onto the inflamed skin. Ointments are the most moisturizing, include the fewest ingredients, and are the least likely to burn when put on inflamed skin. Ointments often have higher potency when compared with the same medication and concentration in a cream or lotion. Patients may prefer creams, gels, and lotions for their feel. Solutions and foams may be easier to apply in hair-bearing areas, especially the scalp. It is important to ask patients what they prefer, as compliance is essential. Patients with different skin types or ethnic backgrounds may have a preference for specific vehicles.

Patients who do not respond to topical therapy should be carefully reevaluated. Skin biopsy is a rapidly available diagnostic test with very low associated morbidity and may provide important information about the pattern of inflammation to help guide treatment. Referral to a dermatologist is appropriate for any skin condition of unclear cause that fails to respond to initial therapy. Additionally, widespread eruptions that are inflammatory, painful, or associated with vesicles, bullae, or purpura, or those occurring in immunosuppressed patients, should also be referred to a dermatologist for rapid evaluation.

TABLE 4. Dermatologic Emergencies

Widespread erythema or erythroderma (drug eruption, bacterial toxin-mediated disease, severe psoriasis)
High fever and widespread rash (severe drug eruptions, rickettsial diseases)
Diffuse peeling or sloughing of skin (toxic epidermal necrolysis, infection)
Dark, dusky, purple areas of painful skin (impending skin loss from infection or severe drug eruption)
Mucosal inflammation, erosions, or ulceration (severe drug eruption, autoimmune blistering disease with high risk of morbid scarring)
Widespread blistering (autoimmune blistering disease, infection, severe drug eruption)
Purpura, particularly "retiform" or lacey, patterned purpura (vasculitis, vasculopathy, infection, autoimmune disease)
Broad areas of exquisitely painful skin out of proportion to clinical examination findings (necrotizing fasciitis)
Angulated purpura of the distal extremities (sepsis, autoimmune phenomena)
Palpable purpura (small vessel vasculitis from infection, medications, or autoimmune reactions)
Immunosuppressed, particularly patients with neutropenia, with skin lesions of unknown cause in the setting of fever, particularly red or purple nodules (skin signs of infection in immunosuppressed hosts)
Purple or necrotic skin lesions in immunosuppressed hosts (angioinvasive fungal infection)
Rapidly growing lesions in immunosuppressed hosts (infection, malignancy)
Worrisome pigmented lesions warrant urgent (not emergent) referral and evaluation (melanoma)

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TABLE 5. Topical Medication Vehicles

Vehicle	Description
Cream	Mixture of oil and water; often appears white and smooth
	Easily applied, rubs in, and is absorbed; high rates of compliance
	May be irritating to acutely inflamed, raw, eroded, open skin; may not penetrate thick scale
Ointment	More oil than water; thick and greasy
	Often leaves a thick and messy residue; hard to put on before clothing
	Most moisturizing emollient; hydrophobic, traps water on the skin
	Less irritating than creams; may be used on actively inflamed, raw skin
Solution	Very liquid, minimally viscous, feels mostly like water
	Easy to use when applying medications over large areas or hair-bearing areas
	If alcohol based, may be drying; certain preservatives lead to irritation but generally solutions are well tolerated
Lotion	Texture between a solution and a cream; somewhat thicker than a solution
	Very variable in terms of irritation and tolerance, depending on brand and medication
	Easy to apply over broad areas
Gel	Semisolid thick preparation; firmer than a solution
	May dry out the skin and frequently may sensitize the skin, often causes stinging, burning, or irritation when applied to inflamed skin
	High rates of compliance when used appropriately on noninflamed skin
Foam	Generally used specifically for hair-bearing areas; easier to apply to places like the scalp than other vehicles
Powder	Often used in skin folds, as it is easy to apply and may dry out moist areas of skin-on-skin friction and sweating

Topical Glucocorticoids

Topical glucocorticoids are important anti inflammatory medications that, because they can be applied directly to the affected area, can offer a powerful treatment with fewer side effects than systemic glucocorticoids. Topical glucocorticoids are grouped into classes from 7 (weak) to 1 (ultrapotent) based on their ability to cause vasoconstriction (**Table 6**).

The choice of a topical glucocorticoid should be made by evaluating the location and thickness of the rash, the age of the patient, and how long the therapy is likely to be needed. In general, thicker dermatoses such as psoriasis, lichen planus, or lichenified atopic dermatitis will require higher potency topical glucocorticoids and longer courses of therapy. Prescribing enough topical glucocorticoid for adequate therapy is vital. Thirty grams of a topical glucocorticoid is enough for one application to the entire body of an adult male. This amount can be extrapolated down to the appropriate amount for a more localized eruption. For widespread eruptions, 454-gram tubs of hydrocortisone and triamcinolone can be dispensed. Fifteen or 30 grams can be prescribed if there is concern for overuse (for example, on the face).

Side effects from topical glucocorticoids include thinned skin, striae distensae (stretch marks), and easy bruising, all mediated in part by decreased collagen production. These side effects are most likely to occur when more potent topical glucocorticoids are used under occlusion, in skin folds, or for extended periods of time. Hypothalamic-pituitary axis suppression has also been documented from even short courses of potent and ultrapotent topical glucocorticoids, especially if occluded or used in areas of thinned skin or over large body surface areas. Topical glucocorticoid use around the eyes can lead to glaucoma and cataracts, and therefore their use should be limited. Although topical glucocorticoids are often implicated in hypopigmentation, more commonly the color change is caused by postinflammatory pigment loss once the primary eruption resolves.

Tachyphylaxis occurs when an individual topical glucocorticoid stops being effective because of prolonged use, and simply switching to a different topical glucocorticoid, even one with the same strength, may be effective.

It is important to understand the potential risks of using topical glucocorticoid and antifungal combinations. Clotrimazole-betamethasone combines an azole antifungal agent with a potent topical glucocorticoid. There are reports of failure in treating dermatophyte infections. If tinea is suspected, using a topical antifungal agent alone is preferred. Fungal infections also often occur in skin folds, such as under the breast or in the inguinal fold, which would be an inappropriate place to apply betamethasone for extended periods owing to the risk of atrophy. Clotrimazole-betamethasone is only approved for 2 weeks when applied in the perineum. There is also a preparation with nystatin and triamcinolone. Nystatin is an anticandidal agent that is ineffective against dermatophytes, and again triamcinolone may lead to stretch marks if overused in skin folds.

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TABLE 6. Classes and Strengths of Topical Glucocorticoids

Group	Generic Name	Brand Name
I	Flurandrenolide tape	Cordran tape
	Clobetasol propionate (0.05%)	Cormax
		Temovate
		Temovate-E
		Olux foam
	Halobetasol propionate (0.05%)	Ultravate
	Augmented betamethasone dipropionate (0.05%)	Diprolene
	Diflorasone diacetate (0.05%)	Psorcon
II	Betamethasone dipropionate (0.05%)	Diprosone
	Halcinonide (0.1%)	Halog
	Fluocinonide (0.05%)	Lidex
		Lidex-E
	Desoximetasone (0.25%)	Topicort
III	Triamcinolone acetonide (0.5%)	Aristocort A
	Betameth valerate (0.1%)	Betatrex
	Fluticasone propionate (0.005%)	Cutivate
	Amcinonide (0.1%)	Cyclocort
	Mometasone furoate (0.1%)	Elocon
IV	Triamcinolone acetonide (0.1%)	Aristocort
		Kenalog
	Flurandrenolide (0.05%)	Cordran
	Amcinonide (0.1%)	Cyclocort
	Prednicarbate (0.1%)	Dermatop-E
	Mometasone furoate (0.1%)	Elocon
	Betamethasone valerate (0.12%)	Luxig foam
	Fluocinolone acetonide (0.025%)	Synalar
	Hydrocortisone valerate (0.2%)	Westcort
V	Triamcinolone acetonide (0.1%)	Aristocort
		Kenalog
	Betamethasone valerate (0.1%)	Betatrex
	Clocortolone pivalate (0.1%)	Cloderm
	Flurandrenolide	
	(0.05%)	Cordran SP
	(0.05%)	Cordran
	(0.025%)	Cordran
	Fluticasone propionate (0.05%)	Cutivate
	Prednicarbate (0.1%)	Dermatop-E
	Desonide (0.05%)	DesOwen
	Hydrocortisone butyrate (0.1%)	Locoid
	Fluocinolone acetonide (0.025%)	Synalar
		Synemol
	Desonide (0.05%)	Tridesilon
	Hydrocortisone valerate (0.2%)	Westcort

(Continued on the next page)

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TABLE 6. Classes and Strengths of Topical Glucocorticoids *(Continued)*

Group	Generic Name	Brand Name
VI	Prednicarbate (0.05%)	Aclovate
	Triamcinolone acetonide (0.025%)	Kenalog
	Fluocinolone acetonide (0.01%)	Synalar
		Capex
		Dermasmooth
		FS
	Flurandrenolide (0.025%)	Cordran SP
	Desonide (0.05%)	DesOwen
VII	Hydrocortisone	
	(2.5%)	Hytone
	(1.0%)	Lacticare HC
	Hydrocortisone + pramoxine	
	(1.0%)	
	(2.5%)	
	5 g Hydrocortisone powder in 454 g acid mantle cream	Pramosone

KEY POINTS

HVC
- Dermatologic treatments are highly variable in cost; generic topical medications should be considered for a cost-effective approach.
- The choice of a topical glucocorticoid should be made by evaluating the location and thickness of the rash, the age of the patient, and how long the therapy is likely to be needed.
- Side effects from topical glucocorticoids include thinned skin, striae distensae (stretch marks), and easy bruising, and are likely to occur when they are used for extended periods of time, especially in skin folds or areas of occlusion.

Common Rashes

Eczematous Dermatoses

Eczematous dermatitis is a type of inflammation characterized by inflamed, dry, red, itchy skin. The terms eczema and dermatitis are often used interchangeably. There are multiple types of eczematous dermatoses (**Table 7**).

In all types of eczematous dermatoses, patients should be told to take short showers or baths in warm (but not hot) water, use a mild soap, and apply moisturizer liberally within 3 minutes of getting out of the bathtub. The skin loses the hydration gained from bathing within 3 minutes, and if moisturizer is delayed longer than this, the skin becomes drier than it was before bathing. There are newer moisturizers containing ceramides that may provide extra benefit in healing the skin barrier. Washcloths, buff puffs, loofahs, and other abrasive cleaning implements should be avoided in patients with eczematous dermatitis because they can inappropriately exfoliate the skin. They may also act as fomites and harbor sources for infection, especially with repeated use.

Atopic Dermatitis

Atopic dermatitis (AD) is characterized by xerotic, pink, scaly skin and is most commonly seen on the periocular areas, posterior neck, antecubital and popliteal fossae, wrists, and ankles (**Figure 1**). The rash often waxes and wanes. Many patients with

TABLE 7. Types of Eczematous Dermatoses

Atopic dermatitis	A specific type of eczematous dermatitis that is genetically driven and often affects areas such as the antecubital and popliteal fossae; typically presents in childhood
Allergic contact dermatitis	A type IV hypersensitivity reaction to an allergen that comes into contact with the skin
Irritant contact dermatitis	Inflammation caused by a direct caustic or irritant effect of a chemical
Xerotic eczema	Extremely dry skin that results in inflammation and pruritus
Nummular dermatitis	An acute and extremely pruritic dermatitis characterized by coin-shaped plaques
Stasis dermatitis	An acute inflammation of the skin caused by chronic venous stasis

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FIGURE 1. Subacute eczema of the flexural folds showing erythema with crusts typical of atopic dermatitis.

AD have a defective skin barrier because of a mutation in filaggrin, which is a protein that helps the epidermis provide a barrier against allergens and irritants. Therefore, patients with a filaggrin mutation often have dry, scaly skin and are at higher risk for contact dermatitis. Patients with AD also have downregulated innate immunity, and therefore their skin is locally immunosuppressed and more susceptible to infection. Because of the impaired barrier, the circulating Langerhans cells in the skin are more easily in contact with environmental antigens, and patients are more likely to become sensitized to environmental allergens such as dust mites, ragweed pollen, and animals. They are also more likely to become sensitized to chemicals put onto their skin leading to contact dermatitis. Staphylococcal colonization of AD is very common. When the skin is scratched, there are breaks in the epidermis that can become infected, as evidenced by honey-colored crusting, oozing erosions, and pustules. Food allergies are an uncommon cause of flares in AD, and blood and skin IgE tests for these allergens have high false-positive rates. Therefore, random food testing without a reliable history of flaring with a particular food can lead to inappropriate food avoidance and patient frustration.

Contact Dermatitis

Although contact dermatitis is common and causes significant morbidity, it is also curable by avoiding the causative chemical. There are two types of contact dermatitis, allergic and irritant. Allergic contact dermatitis is a type IV delayed hypersensitivity reaction to a specific chemical. With repeated exposure to the chemical, a pruritic eczematous dermatitis develops on the exposed area (**Figure 2**). In exuberant cases, the localized inflammation can lead to a secondary "id" reaction, a generalized acute cutaneous reaction in which pinpoint flesh-colored to red papules develop diffusely on the body. Id reactions may be centered on the initial allergic site but may also induce uniform monomorphous small papules especially on the extensor arms, legs, or neck. Irritant contact dermatitis is caused by a direct toxic effect on the epidermis from exposure to a chemical such as a cleaning agent, other caustic substances, or repeated wetting and drying and is not mediated by the immune system. For example, overwashing with harsh soap will often lead to dry, irritated skin, which is not immune mediated.

Causes of Allergic Contact Dermatitis

Urushiol is an allergen in the *Toxicodendron* (formerly classified as *Rhus*) genus of plants. Examples of these plants include poison ivy, poison oak, and poison sumac. Typically this rash presents with geometric lines or splatters of red papules and vesicles, especially on exposed areas. If the urushiol resin oxidizes to the skin, it will turn black and is often mistaken for a spider bite ("black dot poison ivy").

Nickel metal allergy is also very common, especially with the increasingly frequent practice of piercing. Nickel is typically found in jewelry, belts, or snaps, including the inside button on jeans, which rubs against the lower abdomen.

Neomycin and bacitracin are commonly used over-the-counter topical antibiotics that with repeated use, especially on abraded or lacerated skin, can lead to contact sensitization. Patients and physicians often mistake this for a wound infection, but if the area is itchy and there is a geometric, sharply bordered pattern, a contact allergy should be suspected. Transdermal medications such as clonidine or buprenorphine have also been associated with allergic contact dermatitis.

Fragrances such as eugenol, geraniol, and cinnamic aldehyde are common causes of contact dermatitis when used in perfumes and colognes as well as in soaps and moisturizers. Contact dermatitis to aerosolized fragrances will present in an airborne pattern (involving the face, especially the eyelids; neck; and arms). Patients who are allergic to fragrances in soaps and moisturizers will have a more diffuse eruption on the trunk and extremities.

Rubber and chemicals used in the processing of rubber can be found in labels or emblems on clothing, nonslip grips, gloves, or other workplace exposures and may also cause contact allergies.



FIGURE 2. Pinpoint vesicles on a red base on the antecubital fossa are characteristic of acute contact dermatitis.

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Plant materials such as tea tree oil and balsam of Peru, as well as other organic ingredients, have become more popular as people are choosing to use more organic products. These can be potent allergens and go unnoticed by patients who are often using them as topical agents to treat a primary skin eruption, resulting in secondary sensitization.

There are many other allergens, including preservatives in medicines and soaps. When an obvious causative agent cannot be identified, epicutaneous patch testing can be very helpful. This test involves putting small commercially available concentrations of the potential causative chemicals on the back. The allergens are removed after 48 hours, and the areas are evaluated for a rash at 48 hours and again at 72 or 96 hours. The decision about which allergens to apply is based on the distribution of the contact dermatitis. Often the causative agent is not easy to identify prior to testing. For example, a patient may develop a rash because of irritation or rubbing from a new pair of shoes and then apply topical medications or moisturizers and develop a secondary contact dermatitis on the original rash. Therefore, most patients are tested using a standard panel of the most commonly described allergens. Epicutaneous patch testing is not the same as scratch or prick testing, which is used to identify immediate type I IgE-mediated wheal and flare responses.

Hand Dermatitis

Hand dermatitis is characterized by inflamed, scaling, and sometimes fissured skin on the palmar or dorsal hand (**Figure 3**). The most common causes are overwashing, allergic or irritant contact dermatitis, AD, dyshidrotic eczema (pompholyx), and tinea. Repeated or extended washing with soap causes hand dermatitis by friction, removal of the protective skin barrier, and irritation from the surfactant properties of the soap. People who are required to repeatedly wash their hands (such as medical professionals) or those who wash repeatedly because of obsessive-compulsive or autism spectrum disorders often have extremely pronounced hand dermatitis. This type of irritant dermatitis will be especially marked on the dorsal hands where the stratum corneum is thinner than that of the palms. Many chemicals found in common products can cause allergic contact dermatitis. Hairdressers, rubber workers, health care workers, or others exposed to many different chemicals have a higher risk of becoming sensitized. Allergic contact dermatitis manifests with extreme itching and redness. Dyshidrotic eczema (pompholyx) is an extremely itchy eruption of small vesicles on the sides of the fingers and palms that can occur from frequent wetting and drying, sweating, allergies, or as a reaction to tinea pedis. AD typically affects the hands, but other areas may often be affected as well; therefore, the entire body should be examined. Patients who wear rings often have soap and water trapped underneath the ring after washing. This leads to an irritant dermatitis. Removing the ring prior to washing or making sure that no soap or water residue is left under the ring after washing are effective preventive measures.



FIGURE 3. Dyshidrotic hand eczema, characterized by acute episodes of an intensely pruritic eruption on the palms.

Therapy for hand dermatitis starts with identifying a cause. For irritant hand dermatitis, avoiding the irritant by washing less, moisturizing more, and wearing cotton gloves inside of rubber gloves when around chemicals or during activities such as dishwashing can prevent development of a rash. If rubber gloves are worn alone, the hands often sweat and the water is trapped against the skin, leading to further flares of dyshidrosis. Topical petrolatum jelly is an inexpensive and effective way of repairing the damaged skin barrier. A topical glucocorticoid may be necessary for a short period while the triggers are identified or if the skin is very inflamed. Allergic contact dermatitis, AD, and dyshydrotic eczema can all be treated the same way but nearly always require a short course of topical glucocorticoids for symptom relief. Tinea manuum, a fungal infection that characteristically involves the hands, is often recalcitrant to topical therapy because the infection involves an anatomic site with very thick stratum corneum; often topical keratolytic agents are added to help antifungal agents penetrate the skin, and some patients require oral medications.

Xerotic Eczema

Xerotic eczema, also called asteatotic eczema or "winter itch," is characterized by very dry skin that upon close examination may be slightly fissured. Typical areas include the anterior shins, trunk, back, and arms (**Figure 4**). The eruption is extremely pruritic. Aggressive moisturization, along with changing to soaps that contain less surfactant, may be all that is needed to treat the eczema.

Nummular Dermatitis

Nummular dermatitis is characterized by round (not annular or ring-like) scaling plaques that are intensely itchy (**Figure 5**). The skin is so inflamed that pinpoint vesiculation from serum accumulating in the inflamed skin often occurs and can simulate infection. Tinea corporis can be differentiated from

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FIGURE 4. Extensive fine scaling with minimal erythema on the back in a patient with severe xerotic eczema.



FIGURE 5. Nummular dermatitis is characterized by extremely pruritic round or oval patches of eczematous dermatitis, consisting of papules, scaling, crusting, and often serous oozing. Most lesions appear on the trunk or legs and are 2 to 10 cm in diameter.

nummular dermatitis because the rash of tinea corporis is often annular with at least a partially cleared center and scaling at the periphery. Psoriasis is often located on the elbows, knees, scalp, or intergluteal cleft but has larger, thicker white scale. Allergic contact dermatitis can also present with small, round, intensely itchy plaques. The patient therefore should be asked if the location of the rash aligns with any outside contactant (for example, metal from a belt or chair) or if anything is being applied (for example, neomycin, bacitracin, herbal moisturizers, or tea tree oil) that may help to differentiate the rash of nummular dermatitis from that of allergic contact dermatitis. Nummular dermatitis is often recalcitrant to therapy and may require potent topical glucocorticoid treatment.

Stasis Dermatitis

Stasis dermatitis manifests with red, inflamed skin on the lower legs in patients with venous stasis or other causes of lower extremity edema. Decreased venous drainage results in venous hypertension and increased vascular permeability and edema. Because the shins are often one of the driest parts of the body and are easily excoriated, dermatitis in this area related to venous stasis is common. The red area on the anterior shins in patients with stasis dermatitis is often bilateral and warm to the touch but typically is not tender (**Figure 6**). Although stasis dermatitis can simulate infection, cellulitis usually is not present. Patients will often have a normal leukocyte count and be afebrile. Conversely, cellulitis is almost always unilateral and is usually accompanied by fever and leukocytosis. Therapy includes optimizing total body fluids, using compression stockings, elevating the legs, and applying frequent emollients. Topical glucocorticoids sometimes help if severe pruritus or inflammation is present.

KEY POINTS

- Food allergies are an uncommon cause of flares in atopic dermatitis; routine food testing without a reliable history of flaring with a particular food should be avoided. HVC
- Allergic contact dermatitis is a type IV delayed hypersensitivity reaction to a specific chemical, and epicutaneous patch testing can help to identify the causative allergen. *(Continued)*



FIGURE 6. Stasis dermatitis causing erythematous, pebbly, oozing plaques on the bilateral lower legs of a patient hospitalized for cellulitis.

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KEY POINTS *(continued)*

- Hand dermatitis is characterized by inflamed, scaling, and sometimes fissured skin on the palmar or dorsal hand and is most commonly caused by overwashing, allergic or irritant contact dermatitis, atopic dermatitis, dyshidrotic eczema (pompholyx), and tinea.
- Stasis dermatitis is sometimes confused with cellulitis; however, patients with stasis dermatitis do not have tender skin, will have a normal leukocyte count, and will be afebrile.

Papulosquamous Dermatoses

Papulosquamous dermatoses are characterized by scaling papules and plaques due to inflammation of the epidermis.

Psoriasis

Psoriasis is a chronic inflammatory dermatosis that manifests with scaling, variably pruritic plaques that may be recalcitrant to topical therapy (**Figure 7** and **Figure 8**). A total of 1% to 2% of the population is affected, and there is a genetic predisposition given that 50% of offspring will have psoriasis if both parents



FIGURE 7. Scaling papules and plaques of psoriasis coalescent on the elbow and extensor forearm.



FIGURE 8. Scaling patch with pustules at the edge typical of a pustular flare of psoriasis.

are affected. The incidence of psoriasis peaks at around age 20 years and again at age 60 years. There are many different patterns of psoriasis (**Table 8**). Patients with psoriasis have increased inflammatory Th1, Th17, and Th22 cells. This likely explains why psoriasis may be considered to be a multisystem inflammatory response rather than being limited to the skin. A total of 6% to 11% of patients with psoriasis also have psoriatic arthritis. Psoriatic arthritis can be severe and debilitating (see MKSAP 17 Rheumatology). Patients with psoriasis, especially those who have widespread disease, have an increased risk of myocardial infarction and other major cardiovascular events. Emerging data suggest that psoriasis may be associated with the metabolic syndrome, and some have shown links between psoriasis and diabetes mellitus, hypertension, and hyperlipidemia. Therefore, patients with psoriasis should be monitored more closely for cardiovascular disease and other associated risk factors. Psoriasis seems to be more common in obese patients and those who smoke. Weight loss may lead to improvement. Smoking tobacco may worsen psoriasis, and

TABLE 8. Types of Psoriasis

Psoriasis vulgaris	Red, thick, scaling plaques concentrated on the elbows, knees, ankles, shins, and trunk
Inverse psoriasis	Red, thin plaques with variable amount of scale in the axillae, under the breasts or pannus, intergluteal cleft, and perineum
Sebopsoriasis	Red, thin plaques in the scalp, eyebrows, nasolabial folds, central chest, and pubic area
Guttate psoriasis	0.5- to 2-cm red plaques that erupt suddenly on the trunk often after a group A streptococcal infection
Nail psoriasis	Indentations and "oil spots" often involving multiple nails

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patients should also be counseled against smoking especially because of the elevated risk of cardiovascular disease. Patients with psoriasis often perceive that their disease has greater impact on their lives than more severe medical conditions such as hypertension and diabetes, and many feel that their skin condition is undertreated.

The choice for therapy for psoriasis is based primarily on location and severity. Topical therapy is the preferred choice for localized disease and usually consists of intermittent pulses of medium- to high-potency topical glucocorticoids either alternating with or in conjunction with topical vitamin D analogues or keratolytic agents. A typical regimen might be a medium-potency glucocorticoid applied once or twice a day on the weekdays and a topical vitamin D analogue applied on the weekends for flares. Topical glucocorticoids applied continuously pose a higher risk of atrophy and striae, so having "steroid holidays" a few days each week may allow the medications to be used more safely over time. The vitamin D analogues have some benefit in psoriasis but do not cause the same side effects as glucocorticoids. Ointments and creams are preferred on the body, whereas solutions and foams are more appropriate for the scalp. Calcineurin inhibitors are used topically "off label" for inverse psoriasis (psoriasis in the perineum, axillae, or under the breasts).

Patients with psoriasis covering more than 10% body surface area or those with psoriatic arthritis, recalcitrant palmoplantar psoriasis, pustular psoriasis, or psoriasis in challenging anatomic areas (groin, scalp) may be considered for systemic therapy. Systemic agents include phototherapy, traditional systemic agents (retinoids, methotrexate, cyclosporine), or biologic agents, most often tumor necrosis factor (TNF)-α inhibitors and interleukin-12 or interleukin-23 inhibitors. Phototherapy does not cause immunosuppression but requires multiple visits per week; phototherapy does not impact psoriatic arthritis. There may be a long-term risk of skin cancer associated with light therapy, although this is primarily a risk with psoralen-ultraviolet A (PUVA) phototherapy, so light therapy may be safer in patients with darker skin types who have lower initial risk. Systemic therapy with retinoids, methotrexate, or cyclosporine has been used for many years in appropriate patients. TNF-α inhibitors and interleukin-23 inhibitors are also FDA-approved alternatives for psoriasis. Therapy with any of the systemic agents should be guided by a clinician experienced in their use, including appropriate evaluation for contraindications and careful monitoring. The impact of these treatments on the psoriasis-associated comorbidities is as yet unknown.

KEY POINTS

- Psoriasis can be a multisystem inflammatory response limited not just to the skin, and patients who have widespread disease have an increased risk of myocardial infarction and other major cardiovascular events.

(Continued)

KEY POINTS *(continued)*

- Topical therapy is the preferred treatment for localized psoriasis and consists of intermittent pulses of medium- to high-potency topical glucocorticoids either alternating with or in conjunction with topical vitamin D analogues or keratolytic agents.
- Systemic therapy, such as phototherapy, traditional systemic agents, or biologics should be reserved for severe (>10% body surface area) psoriasis, psoriatic arthritis, or psoriasis unresponsive to topical therapy.

HVC

Lichen Planus

Lichen planus (LP) is an acute eruption of purple, pruritic, polygonal papules that most commonly develops on the flexural surfaces, especially the wrists and ankles (**Figure 9**). LP can also occur in the mucous membranes (mouth, vaginal vault, and penis) with white plaques that, if uncontrolled, may ulcerate. The eruption can also develop in the nails, leading to thickening and distortion of the nail plate. LP is most commonly idiopathic but may be induced by medications or possibly infection. LP has been reported in up to 20% of patients with hepatitis C infection in some studies, but other reports have failed to show an association. Medications implicated in causing LP or lichenoid drug reactions are gold salts, captopril, hydrochlorothiazide, and hydroxychloroquine.

LP tends to remit after 1 to 2 years with or without therapy but may last longer, especially if erosive. Therapy with potent topical glucocorticoids is often effective in lessening the lesions and decreasing pruritus but may not be curative. Erosive LP that is active for many years may degenerate into squamous cell carcinoma as a result of chronic inflammation; therefore therapy to control erosive LP is very important. Systemic glucocorticoids, systemic retinoids, and phototherapy can be considered for treatment of severe or recalcitrant LP.



FIGURE 9. Lichen planus presenting as hyperpigmented purple, pruritic polygonal papules and plaques on the ventral wrists.

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KEY POINTS

- Lichen planus is an acute eruption of purple, pruritic, polygonal papules that most commonly presents on the flexural surfaces; topical glucocorticoids are often effective at decreasing the size of the lesions and the associated itch but may not be curative.
- HVC Systemic glucocorticoids, systemic retinoids, and phototherapy should be reserved for severe or recalcitrant lichen planus.

Pityriasis Rosea

Pityriasis rosea (PR) is a reactive eruption of unknown cause, although some experts have suggested an association with a previous viral eruption. It is more commonly seen in the spring and fall and has a predilection for young adults. Clinically, PR often presents with one scaling patch that is a few centimeters wide (herald patch) and is typically mistaken for an area of tinea corporis or contact dermatitis. Many 0.5- to 2.0-cm red scaling patches then erupt along the skin cleavage lines in a "Christmas tree" distribution on the back a few days later and last 1 to 3 months (**Figure 10**). The eruption is often mildly pruritic. The clinical appearance of scaling papules and plaques is similar to that of secondary syphilis, although PR typically spares the face, palms, and soles, whereas the rash of secondary syphilis often affects the palms and soles. Testing should be performed if there is any clinical concern for syphilis. Therapy for PR is challenging, although there are off-label reports of the use of sunlight (allowing the patient to tan with natural light without burning), phototherapy, and systemic macrolide antibiotics. Topical glucocorticoids and antihistamines may help with the pruritus.



FIGURE 10. Pink macules with a collar of scale consistent with pityriasis rosea.

Seborrheic Dermatitis

Seborrheic dermatitis is an inflammatory scaling, itchy dermatosis that most commonly affects the scalp but can also affect the eyebrows, nasolabial folds, chin, central chest, and perineum (**Figure 11**). Seborrhea is thought to be an overreaction of the body to commensal *Malassezia* yeasts that live on the skin. Seborrhea is characterized by waxy, scaling, red patches. The rash often starts in puberty and waxes and wanes over months and years. The rash on the face is very common, especially in the elderly, in immunosuppressed patients (particularly in patients with HIV infection), and in patients with neurologic disorders such as Parkinson disease. Patients will often think they just have consistently dry skin on the face; however, the distribution of a scaling rash on the eyebrows and nasolabial folds extending onto the cheeks and chin is typical of seborrhea and often does not respond to moisturization only.

Seborrhea can be treated with over-the-counter selenium sulfide or zinc pyrithione shampoos that are lathered into the skin and allowed to work for a few minutes and then washed out. Ketoconazole shampoo and topical ketoconazole cream are also very effective. When the skin is more inflamed, a short course of low-potency topical glucocorticoids can be used, but patients should be warned against continued use around the eyes to avoid side effects.

Drug Reactions

There are many different manifestations of medication reactions in the skin. Morbilliform or type IV hypersensitivity reactions are the most common and manifest as pink-to-red macules and papules (often called maculopapular) that are often very pruritic (**Figure 12**). The typical onset is within 7 to 14 days of starting the medication, but if exposure is recurrent, it may be faster. The therapy is to stop the medication and treat

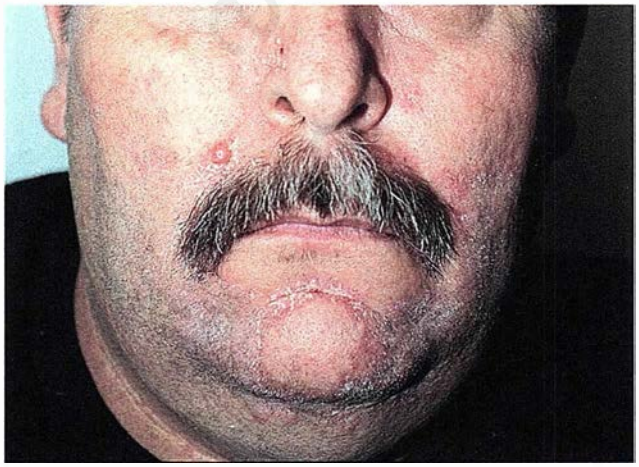

FIGURE 11. Erythematous plaques with dry scale occurring in the beard area and nasolabial folds characteristic of seborrheic dermatitis.

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FIGURE 12. Blanchable erythematous patches on the trunk in a patient with a morbilliform drug eruption.

symptomatically with antihistamines and medium-potency topical glucocorticoids for a brief time while the reaction resolves. Patients should be warned to alert their clinician if they develop fevers, skin pain, blisters, pustules, or mucous membrane involvement.

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (or drug hypersensitivity syndrome [DHS]) is a severe drug-induced hypersensitivity syndrome characterized by a papular eruption, facial edema, lymphadenopathy, internal organ involvement, and hematologic abnormalities such as eosinophilia, lymphocytosis, or thrombocytopenia. The most common implicated drugs are allopurinol, sulfonamides, anticonvulsant agents, and minocycline. DRESS is managed by discontinuing the causative medication immediately and providing symptomatic supportive care. Systemic glucocorticoids should be given because of the high risk of end organ damage. For a more detailed discussion of DRESS or DHS, see Dermatologic Urgencies and Emergencies.

Acute generalized exanthematous pustulosis (AGEP) is an acute eruption of pinpoint pustules that often starts on the head and neck and extend down. The pustules are so minute that sometimes only the resultant peeling is noted (**Figure 13**). AGEP is caused by various medications (most commonly antibiotics, especially penicillins, cephalosporins, and macrolides) or viruses. The list of causative drugs is long and ever-growing and includes such hard-to-identify triggers as contrast dye and dialysates. Therefore, if AGEP is suspected, the clinician should obtain a thorough history of all possible exposures. Generally AGEP begins within 48 to 72 hours of beginning a new drug, which may help identify the culprit. Patients will usually have a fever, and laboratory results will show leukocytosis and occasionally excess bands. The disease self-resolves; however, it may result in extensive peeling, which may be alleviated by the use of emollients.

Fixed drug eruptions (FDE) are purple patches that occur in the same location (fixed) each time a patient is exposed to the same medication. Severe eruptions may have central bullae. Lips, genitals, and hands are commonly involved, but only one spot may develop with the first exposure. If reexposed, however, the original spot will recur along with new areas. Common drug culprits include over-the-counter medications such as pseudoephedrine, NSAIDs, sulfonamides, and other antibiotics, but there is a very long list of medications that are frequently responsible.

Pigmented purpuric dermatoses are characterized by lesions that look like petechiae but are arranged into small patches or plaques (**Figure 14**). The lesions are sometimes itchy but may be asymptomatic. There is no associated platelet abnormality. The lesions are often compared to "cayenne pepper" and tend to resolve with some rust-colored pigmentation. Pigmented purpura may be caused by exposure to viruses or medications such as NSAIDs. The eruption is asymptomatic. There is no specific work-up indicated and no satisfactorily consistent therapy.



FIGURE 13. Pinpoint pustules on a background of erythema in a patient with acute generalized exanthematous pustulosis.



FIGURE 14. Pigmented purpura with fine "cayenne pepper" petechiae within pigmented patches of skin, usually appearing on the extremities.

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KEY POINTS

HVC

- Seborrhea can be treated with over-the-counter selenium sulfide or zinc pyrithione shampoos that are lathered into the skin and allowed to work for a few minutes and then washed out; ketoconazole shampoo and topical cream are also very effective.
- Drug hypersensitivity syndrome (or drug reaction with eosinophilia and systemic symptoms) is a severe life-threatening, idiosyncratic medication reaction.
- The most common medications causing drug hypersensitivity syndrome are sulfonamides, allopurinol, anticonvulsant agents, and minocycline.
- Therapy for drug hypersensitivity syndrome consists of stopping the causative medication immediately; due to the high risk of end organ damage, systemic glucocorticoids are typically needed.

Miliaria

Miliaria is colloquially called "heat rash" or "prickly heat" and is characterized by clogging of the eccrine sweat glands. The clogging may be partially due to overgrowth of *Staphylococcus epidermidis*. The location along the sweat gland that is clogged will determine what type of miliaria is seen. When the gland is clogged superficially, there are minute pustules that are ruptured easily and can be wiped off (miliaria crystallina) (**Figure 15**). Miliaria rubra causes deeper red papules and some pustules when the clog is deeper, and more inflammation is present. Miliaria is often seen in the setting of fever and occlusion. A typical clinical situation is a patient who is immobilized, either from pain or following surgery, and sweat glands are occluded as a result. Therapy is guided toward cooling the affected area, allowing air circulation. If the eruption is severe, topical antibiotics such as clindamycin solution or low-potency topical glucocorticoids may be used.



FIGURE 15. Miliaria crystallina with clear, fragile vesicles but no inflammation.

Acantholytic Dermatosis (Grover Disease)

Acantholytic dermatosis (Grover disease) is a benign pruritic eruption of papules or papulovesicles on the central chest, flanks, and back (**Figure 16**). It is often seen in middle-aged to elderly patients and may be induced by sweating or extreme dryness of the skin. The eruption often flares seasonally. Acantholytic dermatosis is typically self-limited, but therapy with topical glucocorticoids or moisturizers may be effective.

Acneiform Eruptions

Acne

Acne is a chronic inflammatory skin condition characterized by open and closed comedones (blackheads and whiteheads, respectively) and inflammatory lesions, including papules, pustules, and nodules (**Figure 17**). Androgens stimulate increased sebum production; thus, when acne develops in patients outside the typical age range or when the acne is difficult to manage, it is important to look for signs of hyperactivity of the hypothalamic-pituitary-adrenal or the hypothalamic-pituitary-gonadal axis. Examples include Cushing syndrome, congenital adrenal hyperplasia, and polycystic ovary syndrome. Depending on the suspected underlying disorder, measurement of free testosterone, dehydroepiandrosterone sulfate (DHEAS), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels may be appropriate.

The microcomedone is the precursor to acne lesions and is caused by the proliferation and accumulation of keratinocytes that block the outflow of sebum. If sebum accumulation continues, an open or closed comedone will form. The anaerobic bacterium *Propionibacterium acnes* proliferates in the comedone



FIGURE 16. A patient with acantholytic dermatosis (Grover disease) showing recurrent outbreaks of itchy red bumps with peripheral scale on the back.

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FIGURE 17. Extensive acne involvement of upper and mid-back with papules, pustules, nodules, granulation tissue, postinflammatory erythema, hyperpigmentation, and scarring.

and can incite inflammation if there is leakage of the contents into the dermis. This manifests as papules, pustules, and in severe cases, deep cysts, nodules, and interconnecting sinus tracts. Scarring can occur and be disfiguring. Rarely, severe acne may be associated with systemic inflammation (acne fulminans) or sterile inflammation of the bones or joints (**Table 9**).

Treatment begins by considering the types and distribution of lesions, as well as the pregnancy status of the female patient (**Figure 18** and **Table 10**, on page 17). Interventions are selected with the goal of modifying the main causal factors, such as follicular occlusion, sebum production, *P. acnes* proliferation, and inflammation. It is important to educate patients about the expectations of therapy; treatments often take 6 to 8 weeks to demonstrate an effect, need to be used regularly during this time, and are not capable of complete clearance in all patients. In addition, patients can be counseled that neither dietary restriction nor excessive face washing has been shown to be beneficial.

Treatment of acne is important, not only to avoid complications but also because acne has been shown to significantly reduce quality of life measures for those affected. Patients with moderate acne report more mental health and social problems than those with asthma, epilepsy, or diabetes mellitus. Complications from acne are postinflammatory hyperpigmentation and scarring including hypertrophic scars and keloids. Treatment of acne scarring can be performed by dermatologists or plastic surgeons; however, mitigating scar development by early and appropriate treatment is preferred.

First-line treatment for most patients is topical retinoid and topical antimicrobial therapy. Benzoyl peroxide is available over the counter and is an excellent complement to

TABLE 9. Differential Diagnosis of Acne and Acneiform Skin Disorders

Disease	Characteristics
Acne (acne vulgaris)	Very common in adolescents, but also occurs in preadolescents and adults. Women may have premenstrual flare-ups. Physical examination: coexisting open and closed comedones, papules, pustules, and nodular lesions located primarily on face, neck, and upper trunk.
Rosacea	Not true acne; primary lesion is not a comedone but an inflammatory papule; rhinophyma (bulbous, red nose) is a variant. Physical examination: central facial erythema, telangiectasias, papules, and pustules.
Medication-induced acneiform eruption	Onset weeks to months after start of the medication. Comedones are absent; inflammatory papules and pustules commonly appear on the upper trunk and arms when the cause is systemic.
	Possible triggers are glucocorticoids, anabolic steroids, bromides, iodides, isoniazid, phenytoin, azathioprine, cyclosporine, disulfiram, phenobarbital, quinidine, vitamins B_1, B_2, B_6, B_{12}, and D_2, testosterone, progesterone, lithium, epidermal growth factor inhibitors.
Bacterial folliculitis	Common in athletes. Physical examination: follicular papules, pustules, occasional furuncles on any hair-bearing area, especially scalp, buttocks, and thighs. Positive culture for pathogenic bacteria. Most common cause is *Staphylococcus aureus*.
Gram-negative folliculitis	Caused by overgrowth of bacteria during prolonged systemic antibiotic treatment for acne and presents as exacerbation of preexisting acne. Physical examination: many inflamed pustules, most often on the face. Positive culture for gram-negative bacteria, often *Escherichia coli*.
Periorificial dermatitis, idiopathic	More common in women. Physical examination: small (<2 mm) papules and pustules around mouth or eyelids. Similar to acne but without comedones.
Periorificial dermatitis, iatrogenic	Frequent causes are prolonged topical glucocorticoid therapy for atopic dermatitis and inappropriate use of these agents to treat acne. Similar in appearance to idiopathic type.
Cutaneous proliferations	Adenoma sebaceum: numerous pink or skin-colored papules clustered around the nose and chin, associated with tuberous sclerosis. Patients without tuberous sclerosis may have one or up to several fibrous papules on the nose and central face.
	Follicular tumors (fibrofolliculomas and trichodiscomas): numerous skin-colored papules on the face and ears, associated with Birt-Hogg-Dubé syndrome (kidney cancer risk).

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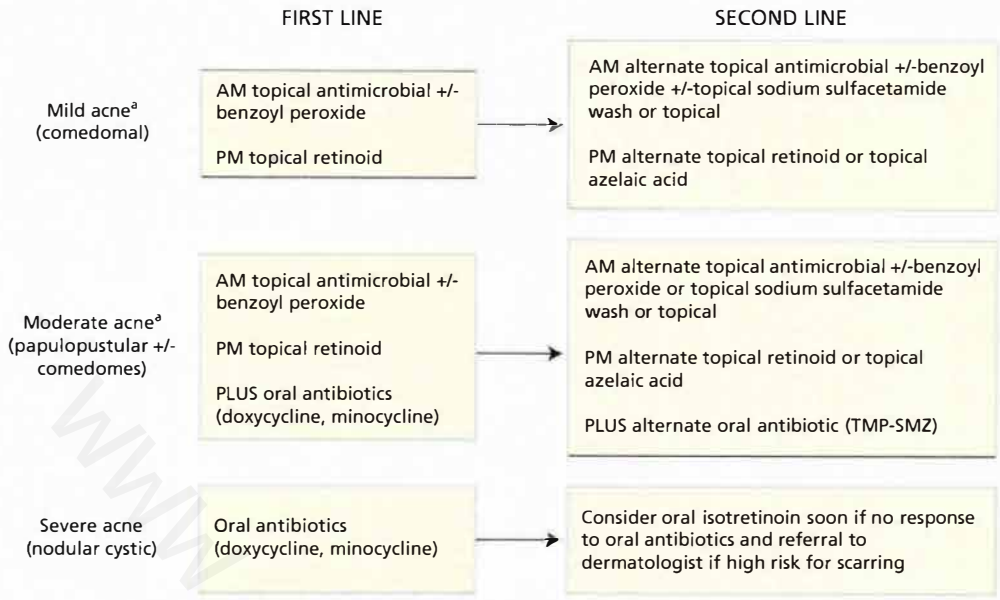

FIGURE 18. First- and second-line treatment for mild, moderate, and severe acne.

TMP-SMZ = trimethoprim-sulfamethoxazole.

[a]Consider oral contraceptives/antiandrogens in female patients. If refractory to treatment, consider gram-negative folliculitis.

treatment with an oral or topical antibiotic, as it reduces the development of bacterial resistance. Salicylic acid is also available over the counter and primarily works by removing and preventing comedones. The most frequent adverse effect of topical acne treatments is irritation. Lower concentrations of benzoyl peroxide (2.5%) are therefore recommended, as the efficacy is similar irritation is less than when formulations with benzoyl peroxide 10% concentration are used.

Topical retinoids are effective for comedonal as well as inflammatory acne. Topical retinoids can prevent acne by reducing follicular plugging and may also have anti-inflammatory effects. Because retinoids are preventive, they need to be applied to the entire acne-prone area and not used as a spot treatment. The most common adverse effects are dryness and irritation.

Antibiotics have been used for decades to treat acne vulgaris. Numerous studies have demonstrated the efficacy of oral antibiotics. Guidelines recommend that the duration of oral antibiotic therapy be limited, specifically that oral antibiotics be used for 3 months and then discontinued for patients with good clinical improvement. The same antibiotic can be used again for patients with good clinical improvement who have a subsequent relapse.

Isotretinoin is an oral retinoid. It is used as a first-line treatment for severe, nodulocystic acne (**Figure 19**) and for inflammatory acne that is recalcitrant to multimodality therapy with topical retinoids and oral antibiotics. The iPLEDGE program is an FDA-approved regulatory program to prevent birth defects from isotretinoin. Providers, patients, and pharmacies must be registered in the iPLEDGE program and complete monthly reports.

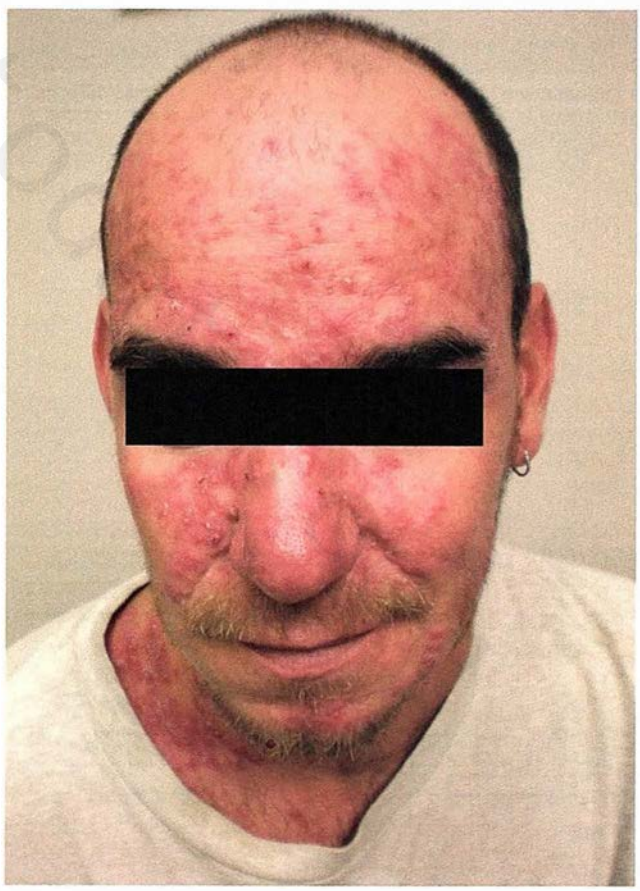

FIGURE 19. Severe nodulocystic acne on the face.

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TABLE 10. Treatment of Acne

Medication[a]	Indication	Side Effects and Comments	FDA Pregnancy Category[b]
Topical retinoids (tretinoin, adapalene, tazarotene)	Mild comedonal acne; use singly or in combination with other treatments	Local irritation; superficial desquamation; may be combined with topical antibiotics	Tazarotene is pregnancy category X and requires pregnancy testing prior to prescription
Topical salicylic acid	Mild comedonal acne; use singly or in combination with other treatments	Mainly in patients with retinoid-intolerant skin	C
Topical azelaic acid	Adjunctive therapy for mild to moderate acne	Local irritation	B
Topical benzoyl peroxide	First-line therapy for mild to moderate acne; use singly or in combination with other treatments	Local irritation and, rarely, contact sensitivity	C
Topical antibiotics (clindamycin, erythromycin)	Therapy for mild to moderate inflammatory acne	Local irritation; promotion of antibiotic-resistant bacteria when used singly, therefore combination therapy with benzoyl peroxide is suggested	B
Topical dapsone	Moderate to severe inflammatory acne; can be part of a regimen with other treatments	Local irritation; G6PD testing is not necessary	C
Oral doxycycline	Moderate to severe inflammatory acne; can be combined with topical agents	Dose-related phototoxicity, vaginal yeast infection, dyspepsia; not for use in children <12 years of age or pregnant women	D
Oral minocycline	Moderate to severe inflammatory acne; can be combined with topical agents	Dizziness, vertigo, discolored teeth, blue-gray skin staining, rare hepatotoxicity and lupus-like syndrome, mild phototoxicity; not for use in children <12 years of age or pregnant women	D
Oral erythromycin	Moderate to severe inflammatory acne; can be combined with topical agents	Gastric upset, diarrhea; can be used in children <12 years of age	B
Oral contraceptives (norethindrone acetate-ethinyl estradiol, norgestimate-ethinyl estradiol)	First-line treatment of moderate to severe acne in adult women or with laboratory evidence of hyperandrogenism	Requires an average of 5 cycles to achieve 50% improvement; adjunctive topical therapy is usually needed	X
Spironolactone	Useful for moderate to severe acne in adult women	Concurrent oral contraceptives recommended	D
Isotretinoin	Treatment of choice for severe, recalcitrant nodular acne; prolonged remissions (1-3 years) in 40% of patients	All prescribers, patients, wholesalers, and dispensing pharmacies must be registered in the FDA-approved iPLEDGE program; cheilitis, dry skin and mucous membranes, hypertriglyceridemia; possible increased incidence of inflammatory bowel disease; depression	X

G6PD = glucose-6-phosphate dehydrogenase.

[a]For specific indications and precautions, please refer to the labeling information of the medications listed.

[b]See MKSAP17 General Internal Medicine for description of FDA Pregnancy Categories.

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Acne can occur in adulthood, although the prevalence decreases with increasing age. Adult acne is more common in women and most commonly affects the lower half of the face or jawline. Androgens are believed to play a significant role in adult female acne; however, most women have normal androgen levels. Combination oral contraceptives and antiandrogens (such as spironolactone) can be useful therapies for adolescent as well as adult women, especially those with perimenstrual acne flares.

KEY POINTS

- Acne manifests as papules, pustules, and in severe cases, deep cysts, nodules, and interconnecting sinus tracts.
- First-line treatment for most patients with acne includes topical retinoid and topical antimicrobial therapy.

Rosacea

Rosacea is a common chronic condition of the facial skin characterized by pink papules, pustules, erythema, and telangiectasias. It is typically found in a bilaterally symmetric distribution on the convexities of the face, namely the forehead, cheeks, nose, and chin. Rosacea is sometimes called "adult acne." Both acne and rosacea have inflammatory papules and pustules, but comedones are *not* seen in rosacea. Rosacea more commonly affects women, especially those 30 to 60 years old.

The pathogenesis of rosacea is unknown. Multiple studies have demonstrated cutaneous inflammation; however, the trigger is highly debated. Alcohol, sun exposure, and other triggers can cause a transient increase in facial erythema but do not cause rosacea.

There are three cutaneous forms of rosacea (erythrotelangiectatic, papulopustular, and phymatous) and an ocular form. All three types of cutaneous rosacea cause some erythema and telangiectasia; however, they differ in the amount and severity of papulopustular lesions and phymatous changes. There is considerable overlap among the three main types, and while progression from one form to another is possible, it is uncommon and often slow.

Erythrotelangiectatic rosacea causes flushing and persistent erythema on the central portion of the face and few inflammatory papules (**Figure 20**). Patients may have swelling, stinging, burning, roughness, scaling, and a history of flushing. Flushing can be triggered by sun, stress, hot weather, alcohol, and warm or spicy foods. Caffeine has not been shown to be a consistent trigger.

Papulopustular rosacea causes central facial erythema with more frequent and numerous papules or pustules; burning and stinging may be present (**Figure 21**).

Phymatous rosacea is characterized by oily thickened skin with prominent pores and telangiectasias, and nodules of thickened skin can accumulate over years. The nose is most commonly affected (rhinophyma) (**Figure 22**), but phymatous rosacea can also occur on the cheeks, forehead, chin, and ears.



FIGURE 20. Erythrotelangiectatic rosacea presents predominantly with patches of erythema and telangiectasia.



FIGURE 21. Papulopustular rosacea causes erythema and pink papules of the convexities of the face, namely, the forehead, nose, cheeks, and chin.

Ocular rosacea reportedly affects 6% to 18% of patients with cutaneous rosacea. Symptoms of ocular rosacea are watery eyes, foreign body sensations, burning, and dryness. Conjunctivitis and styes are common.

The differential diagnosis for rosacea includes disorders that cause central facial erythema or inflammatory papules, such as periorificial dermatitis, cutaneous lupus erythematosus, sarcoidosis, contact dermatitis (eczema), seborrheic dermatitis, actinic damage, and folliculitis due to *Pityrosporum*

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FIGURE 22. Rhinophyma, characterized by hyperplastic sebaceous glands and enlargement of the nose, in a patient with long-standing, uncontrolled rosacea.

or *Demodex* spp. Flushing is a common characteristic of rosacea; the differential diagnosis of this includes carcinoid syndrome, mastocytosis, and pheochromocytoma.

As with most chronic skin diseases, rosacea requires long-term treatment. Treatment is often tailored to target the most prominent manifestations in each patient (**Table 11**). Topical agents are often the first step in treatment. The most frequent side effect of any medication is dryness or irritation. Oral antibiotics are especially effective for ocular rosacea and the papules and pustules of papulopustular rosacea. Oral doxycycline is recommended; a dose of 40 mg twice daily is as effective as 100 mg twice daily but has fewer adverse effects. Topical or oral therapies are less effective for facial erythema and telangiectasia; laser and intense pulsed light are more effective. Laser and surgical debulking can be used to remove excess tissue for those with phymatous rosacea.

KEY POINTS

- Rosacea is a common chronic condition of the facial skin characterized by pink papules, pustules, erythema, and telangiectasias and is typically found on the forehead, cheeks, nose, and chin.
- First-line treatments for rosacea include avoidance of triggers (sun exposure, spicy or warm foods, hot drinks, and alcohol), topical metronidazole, topical sodium sulfacetamide/sulfur, topical azelaic acid and for papulopustular rosacea oral antibiotics.

Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) or "acne inversa" is a chronic inflammatory disease that predominantly affects the apocrine-gland–bearing areas of the skin. The common sites are the axillae, breasts and inframammary creases, inguinal folds, and gluteal cleft (**Figure 23**). It is characterized by comedones, inflammatory papules, nodules, cysts, and scarring. The lesions are painful, and the drainage is often foul smelling. The distribution and severity of disease can range from minor to debilitating.

HS is estimated to affect 1% to 4% of the general population and frequently begins in the second to third decade. It is more common in women. Almost 40% of HS patients report a family history of the disease. About half of patients with HS have breast and armpit involvement and hypertrophic scars. Some also have a high incidence of acne, cysts, and folliculitis. Smoking, depression, obesity, and metabolic syndrome are more common in patients with HS than in the general population. It is therefore important to perform a complete history and physical examination to identify these factors and to determine the full extent and severity of disease.

TABLE 11. Management of Rosacea

	Interventions	FDA Pregnancy Category
Avoidance	Sun-protection (sunscreen or sun-protective clothing)	N/A
	Triggers: Foods (spicy, warm), alcohol, warm environments	N/A
Topical	Metronidazole, 0.75% or 1%	B
	Sodium sulfacetamide/sulfur	C
	Azelaic acid , 15%-20%	B
	Topical calcineurin inhibitors (pimecrolimus, tacrolimus)	C
	Permethrin	B
Systemic	Tetracycline antibiotics (doxycycline, 40 mg)	D
	Macrolide antibiotics	B
	Erythromycin, azithromycin	C
	Clarithromycin	
Laser, light, and surgical	Lasers (PDL, Nd:YAG, CO_2, and others)	Avoided
	Intense pulsed light	
	Electrosurgery	

Nd:YAG = neodymium-doped yttrium aluminium garnet; PDL = pulsed dye laser.

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FIGURE 23. Hidradenitis suppurativa in the axilla demonstrating comedones and scars.

Acne inversa is an apt name because the pathogenesis of HS begins with follicular occlusion but not infection or inflammation of the apocrine glands. Following occlusion, secretions build up in the follicular duct and result in rupture and a subsequent inflammatory reaction that resembles a bacterial abscess. Following this, an acute inflammatory reaction is triggered in the surrounding tissue. The role of bacteria is controversial and is likely a secondary colonization since lesions are initially sterile and antibiotics are not entirely effective in preventing new lesions. In addition to their effects on bacteria, antibiotics may also exert anti-inflammatory effects.

The differential diagnosis includes folliculitis, abscess or carbuncle, ruptured epidermal inclusion cyst, cutaneous manifestations of Crohn disease, and sexually transmitted infections such as granuloma inguinale or lymphogranuloma venereum. HS can be distinguished by the presence of open comedones ("blackheads"), chronic relapses, predisposition for the folds of the body, and recurrence after both antibiotic and surgical therapy.

Many options are available for therapy, although there is little scientific evidence to support their effectiveness, and no treatment is effective for all patients (**Table 12**). Topical and oral antibiotics, topical and oral retinoids, intralesional glucocorticoids, incision and drainage, surgical excision, radiation, laser therapy, and TNF-α inhibitors are all treatment options. Clindamycin-rifampin combination antibiotics, infliximab, and surgical excision have the greatest evidence of effectiveness. Many patients require combination therapy. Potential complications of HS include scarring and contraction resulting in functional limitation, secondary infection, malignant degeneration into squamous cell carcinoma, lymphedema due to chronic inflammation and scarring, and rectal or urethral fistulas.

Common Skin Infections

The skin serves as an external barrier and is colonized with microorganisms that provide an opportunity for infections. Skin infections often are categorized by type of causative microorganism (bacteria, fungus, virus) and by the part of the skin infected.

Bacterial Skin Infections

Normal skin contains numerous microorganisms that comprise the natural microbiome, which helps keep the skin healthy and protects against pathogenic organisms. Although staphylococci or streptococci are commonly involved in skin infections, they are also a part of natural skin flora. Therefore, it is important to perform an appropriate culture to confirm that these microorganisms are the cause of infection with complicated skin and soft-tissue infections including abscesses, extensive areas of involvement, or non-response to antibiotics. It is important to obtain cultures before instituting systemic antibiotics to help with appropriate growth and appropriate

TABLE 12. Treatment Options for Hidradenitis Suppurativa

Disease Severity	Treatment Options/Considerations
Mild Predominantly comedones, small papules or pustules, solitary nodules	Antibacterial washes, topical antibiotics, analgesics, warm compresses, smoking cessation, weight loss
Moderate Multiple nodules, abscesses or cysts, scarring	Oral antibiotics with antibacterial washes and/or topical antibiotics, analgesics, wide local excision Women: Oral contraceptives, spironolactone
Severe Multiple nodules, sinus tracts, scarring	Referral to dermatologist or surgeon for consideration of wide local excision, tumor necrosis factor-α inhibitors, or clinical trial

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antibiotic stewardship. Whenever possible, a culture should be performed by cleaning the skin surface with alcohol and then obtaining a sample from purulent material, yellow-crusted material, or a moist or broken down area of skin. With folliculitis or a collection such as an abscess, unroofing the outer skin may be necessary to obtain the best sample. This is especially important because of increasing resistance to antibiotics, such as methicillin-resistant *Staphylococcus aureus* (MRSA).

Bacterial infections are frequently categorized based on the location and type of infection: folliculitis; abscesses, furuncles, or carbuncles; impetigo; and cellulitis and erysipelas.

Folliculitis

Folliculitis is inflammation of hair follicles characterized by erythematous papules and pustules that are centered around a follicle on the face, chest, back, or buttocks (**Figure 24**).

Folliculitis can be noninfectious or infectious. When infectious, folliculitis is most often caused by *Staphylococcus aureus*, although other bacteria can induce folliculitis. These include *Pseudomonas* (hot tub folliculitis) and gram-negative folliculitis that sometimes occurs as a complication of acne therapy. Folliculitis can also occur from fungi such as *Malassezia* or *Candida* species, or from viruses, including herpesviruses. In addition, folliculitis can be secondary to noninfectious causes including acne vulgaris, eosinophilic folliculitis (seen in patients with HIV infection), or as a reaction to shaving or topical medications.

Although a diagnosis of folliculitis can be made clinically, culture can determine the causative organism and provide antibiotic sensitivity information when there is a lack of response to treatment or when surrounding extensive erythema is present. Biopsy also may be necessary to diagnose the underlying cause and rule out noninfectious causes of folliculitis.

Treatment for bacterial folliculitis includes topical antibacterial agents such as baths with dilute bleach, chlorhexidine washes, or benzoyl peroxide wash as a broad-spectrum antimicrobial agent. Topical mupirocin or clindamycin lotion also can be used. Culture is not necessary when these topical agents are used. For severe cases with widespread involvement or background erythema, oral antibiotics against *Staphylococcus aureus* can be given as a short course. If persistent or recurrent, maintenance with topical washes and/or further evaluation for an alternate diagnosis or for carriers of MRSA may be necessary. Decontamination can be performed as well. Lifestyle changes including avoiding shaving or using shaving cream and a sharp razor and wearing loose clothing to prevent friction also can be incorporated.

KEY POINTS

- Folliculitis is most often caused by *Staphylococcus aureus*, although other bacteria, fungi, and herpesviruses can also induce folliculitis.
- Treatment of folliculitis includes topical antibacterial agents such as chlorhexidine, topical antibiotics, or oral antistaphylococcal antibiotics.

Abscesses/Furuncles/Carbuncles

A carbuncle is a superficial inflammatory mass consisting of several inflamed hair follicles and multiple sites of drainage. A furuncle is an infection centered on a hair follicle with pus extending into the dermis and forming a small abscess. An abscess consists of a collection of neutrophils and purulent material within the dermis or subcutaneous tissue. Most abscesses are infectious in origin, although sterile abscesses can occur in some inflammatory conditions. These all present similarly with an inflamed, tender, fluctuant dermal and subcutaneous nodule and associated warmth (**Figure 25**).

The erythema can be confined to the immediate area overriding the purulent collection or can expand and represent a surrounding cellulitis. Purulent drainage may be easily expressed, and a rim of scale can occasionally be seen. The differential diagnosis includes an inflamed epidermal inclusion or other cyst. Although inflamed cysts can have associated erythema, they often lack the fluctuance observed in abscesses.



FIGURE 24. Pink papules and pustules centered around hair follicles, characteristic of folliculitis.



FIGURE 25. The abscess is characterized by a painful, inflamed nodule with some background erythema.

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To diagnose an abscess, furuncle, or carbuncle, clinical appearance often is sufficient. Incision and drainage of the lesion is necessary. Culture from the purulent material is necessary to guide therapy and establish resistance patterns. For small, uncomplicated abscesses, furuncles, and carbuncles, local therapy with incision and drainage and warm compresses may be sufficient. Culture is still recommended when draining an abscess in case antibiotics are necessary. In immunosuppressed patients or those with associated cellulitis, fever, systemic symptoms, a large size (>5 cm), or multiple abscesses, systemic antibiotic therapy is also required. Hospitalization for initiating intravenous antibiotics may be required depending on the clinical findings. Because *S. aureus* is the most common pathogen in abscesses, antistaphylococcal antibiotics are generally indicated prior to obtaining culture results. The choice of antibiotics depends on the local antibiotic resistance patterns. Given the increased prevalence of MRSA, antibiotics effective against MRSA, including tetracycline-class antibiotics, clindamycin, and trimethoprim-sulfamethoxazole, are used as first-line therapy.

When patients are colonized with MRSA or have close contacts with MRSA (such as daycare centers, prisons, military personnel, athletes, or persons who were recently hospitalized), recurrent abscesses can occur. Multiple recurrent abscesses also can be a sign of systemic immune disorders including HIV infection or underlying diabetes mellitus, and may trigger screening for these disorders. Stringent hygiene practices, such as frequent bathing, keeping any sores covered, and cleaning clothes, towels, and surfaces, are important. Although MRSA decolonization in the community is controversial, use of dilute bleach baths or chlorhexidine and topical mupirocin to the nares may be attempted when serious recurrent infections or repeated infections among a small cohort occur.

Methicillin-Resistant *Staphylococcus aureus* in Hospitalized Patients

Staphylococcus aureus is one of the most common causes of health care–associated infections, including catheter-associated skin and soft-tissue infections. An increasing number of these infections are from MRSA. MRSA carries potential for significant morbidity and mortality among infected hospitalized patients as well as an increased risk to other hospitalized patients because of its virulence, antibiotic resistance pattern, and increasing prevalence among hospitalized patients, especially ICU.

Hospitals mandate varied screening practices, with nares swabs being the most common method, although determining who needs to be screened is controversial. Evidence supporting MRSA screening and its ability to reduce MRSA infection or have an impact on morbidity and mortality is lacking. Some institutions require screening of every admitted patient, whereas others require it only for ICU admissions or those admitted with a prior colonization history. Contact isolation precautions in addition to universal precautions are often used with patients who screen positive for MRSA. Decolonization strategies for patients who screen positive also may be performed, especially for critically ill patients. Universal decolonization with twice daily intranasal mupirocin for 5 days and daily bathing with chlorhexidine in all ICU patients has recently been shown to be useful in preventing more infections.

Empiric antibiotic therapy against MRSA is often selected for most hospitalized patients with skin and soft-tissue infections until culture results are available. Knowledge of local resistance patterns can be helpful in selecting initial therapy.

Impetigo

Impetigo is an acute, highly contagious, and superficial skin infection caused by gram-positive organisms, specifically *S. aureus* or *Streptococcus pyogenes*, or both. It is most common in young, healthy children but may occur in children or adults as superinfected dermatitis (impetiginized lesions) or infect a site of prior trauma such as an insect bite.

Impetigo can be either nonbullous or bullous impetigo. Nonbullous impetigo is the more common type and often affects the face or extremities. It presents as vesicles, pustules, and sharply demarcated areas with overlying honey-colored crust (**Figure 26**).

Bullous impetigo is a toxin-mediated process usually caused by production of an exfoliative toxin by *S. aureus*, which induces erythema and loss of the superficial layer of the epidermis (**Figure 27**).

The same toxin responsible for bullous impetigo can cause staphylococcal scalded skin syndrome, which results in erythroderma and skin peeling in children or occasionally in adults with acute kidney injury.

The diagnosis of impetigo often can be made based on clinical presentation; however, culture of the honey-colored crust can be used to confirm the pathologic organism and



FIGURE 26. Nonbullous impetigo is a superficial infection characterized by a yellowish, crusted surface that may be caused by staphylococci or streptococci.

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FIGURE 27. Clear, fluid-filled blisters with surrounding erythema on the legs of a patient with bullous impetigo.

obtain sensitivity testing, which is important when treating extensive disease or staphylococcal scalded skin syndrome.

Treatment for impetigo includes both topical and systemic therapies. Topical mupirocin often is first-line therapy, and washes with chlorhexidine and bleach baths also can be used. For more extensive infection, oral antistaphylococcal antibiotics are administered.

Systemic infection from impetigo is uncommon; however, ecthyma is a variant of impetigo characterized by an ulcerative lesion with an overlying eschar that extends into the dermis and may be associated with lymphadenitis. Ecthyma differs from cellulitis because of the presence of an overlying ulceration and eschar and involvement of the dermis. It is important to note that this differs from ecthyma gangrenosum, which is a highly morbid infection caused by *Pseudomonas aeruginosa* that occurs in immunosuppressed patients and can be associated with high mortality rate.

Cellulitis/Erysipelas

Cellulitis is an acute, non-necrotizing infection of the skin that involves the deeper dermis and subcutaneous fat, most often caused by *Staphylococcus* or *Streptococcus* spp. This infection often results from superficial breaks or trauma in the skin. The trauma may be from an obvious source (arthropod bite, laceration, tinea pedis, onychomycosis) or may be a microscopic break in the skin with no visible inciting wound. The most common location in adults is an extremity, but in children includes the head and neck. Risk factors for the development of cellulitis include diabetes mellitus, older age, lymphedema, and peripheral vascular disease.

The diagnosis of cellulitis often is made based on the clinical presentation of a well-demarcated erythematous plaque. The four cardinal signs are erythema, pain, warmth, and swelling; associated lymphadenopathy can occur. Systemic symptoms including fever, chills, and malaise also may be present (**Table 13**). A useful clinical tool is to outline the erythema with a marker to monitor progression of the lesion (**Figure 28**).

The presentation of acute stasis dermatitis may mimic cellulitis, although the bilateral erythema and discoloration seen in stasis dermatitis would be atypical for cellulitis. The differential diagnosis of cellulitis also includes contact dermatitis, deep venous thrombosis, and panniculitis. If the diagnosis is in question, a skin biopsy can be performed. Tissue cultures and blood cultures are usually negative in the setting of cellulitis. The source of infection, including stasis dermatitis,

TABLE 13. Differential Diagnosis of Cellulitis

Disease	Clinical Characteristics
Cellulitis	Well-demarcated erythematous plaque with erythema, pain, warmth, and swelling; associated lymphadenopathy can occur. Systemic symptoms including fever, chills, and malaise. Bilateral lower extremity cellulitis suggests an alternative diagnosis.
Stasis dermatitis	Erythematous, scaly, and eczematous patches most common on the lower extremities and affecting both legs with associated hyperpigmentation. Findings can persist for months to years. The medial ankle can be more severely involved, and ulcerations are common in this area. The erythema also can be striking, involving the ankle and extending to below the knee. Sharp demarcation often is less common in stasis dermatitis. Overlying cellulitis can develop in the setting of stasis dermatitis.
Contact dermatitis	Pruritic, geometric, and erythematous patches with superficial scale; differentiated from cellulitis by pruritus as opposed to pain.
Panniculitis (erythema nodosum)	Painful, erythematous subcutaneous, ill-defined nodules present bilaterally. Many panniculitides will resolve with hyperpigmentation. The acute onset of pain and erythema may be concerning for cellulitis, although distinct subcutaneous nodules would be unusual.
Deep venous thrombosis	Pain, swelling, and associated erythema and warmth in one leg, with changes often more prominent in the calf. A brightly erythematous, well-demarcated plaque is not often seen, although red, blue, or violaceous surface changes can be seen.
Herpes zoster	Grouped vesiculo-pustules on an erythematous patch or plaque localized to one area (dermatome). The erythema can be well defined. The presence of grouped, crusted vesiculo-pustules or punched out erosions is uncommon in cellulitis. Bacterial superinfection can occur.

For a complete list of potential entities on the differential diagnosis of cellulitis, please see the bibliography.

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FIGURE 28. Cellulitis of the thigh. The cardinal features of cellulitis include erythema, swelling, warmth, and pain in the affected area.

H CONT. trauma, abrasions, injection drug use, or tinea pedis, should be identified.

First-line therapy for cellulitis without a draining wound or abscess is an antibiotic with coverage against both *Streptococcus* spp. and *Staphylococcus* spp. with a β-lactam antibiotic such as cephalexin or dicloxacillin, clindamycin, or a macrolide antibiotic can be used. A 5-day course of antibiotics is as effective as a 10-day course. If the patient fails to respond to therapy, then expanding coverage for MRSA should be considered or parenteral antibiotics may be necessary. Noninfectious causes of erythema also should be considered in treatment failure cases. In patients with recurrent cellulitis, low-dose daily penicillin also can help prevent disease recurrence.

Erysipelas is a more superficial infection of the lymphatics that often presents as a violaceous-red, edematous, well-demarcated plaque on the face or lower extremities secondary to group A streptococci. Patients are extremely uncomfortable and often have systemic symptoms such as fever and malaise. Clinically, erysipelas may mimic allergic airborne contact dermatitis; however, contact dermatitis causes more diffuse erythema, and patients may be uncomfortable but not systemically ill. Because erysipelas is often due to streptococcal infection, first-line treatment is with penicillin. H

KEY POINTS

- Cellulitis is an acute, non-necrotizing infection of the skin, presenting as well-demarcated erythematous plaque with erythema, pain, warmth, swelling, and associated lymphadenopathy.

HVC
- First-line therapy for cellulitis without a draining wound or abscess is a course of antibiotics against both *Streptococcus* spp. and *Staphylococcus* spp. (cephalexin or dicloxacillin, clindamycin, or a macrolide); a 5-day course of antibiotics is as effective as a 10-day course.
- Erysipelas is an infection of the upper dermis and superficial lymphatics that often presents as a violaceous-red, edematous, well-demarcated plaque on the face.

Erythrasma

Erythrasma is a benign condition caused by a superficial infection with *Corynebacterium minutissimum*. The infection can be asymptomatic or mildly pruritic and is characterized by symmetric, pink-to-brown patches with thin scale and an overlying wrinkled appearance and maceration in intertriginous areas such as the axillae, groin, inframammary areas, and interdigital spaces (**Figure 29**).

Erythrasma will fluoresce to a coral red color with a Wood lamp examination because of bacterial porphyrin production, which is a helpful feature in differentiating it from other causes of intertrigo. First-line treatment of erythrasma is a topical antibacterial agent such as erythromycin, clarithromycin, clindamycin, benzoyl peroxide, or fusidic acid. Oral agents including clarithromycin and erythromycin also could be considered in patients with extensive disease.

Pitted Keratolysis

Pitted keratolysis is a benign, superficial bacterial infection characterized by small pits primarily on the plantar aspects of the feet or palmar aspects of the hands in a setting of increased perspiration (**Figure 30**). This is most often caused by *Kytococcus sedentarius*, *Corynebacterium* spp., or *Actinomyces* spp. Although pitted keratolysis is mostly asymptomatic, an odor and scaling can be associated with this condition. Treatment requires decreasing perspiration by drying the feet with mechanical methods or antiperspirants. Topical clindamycin and erythromycin also are first-line antibacterial agents to clear the infection.

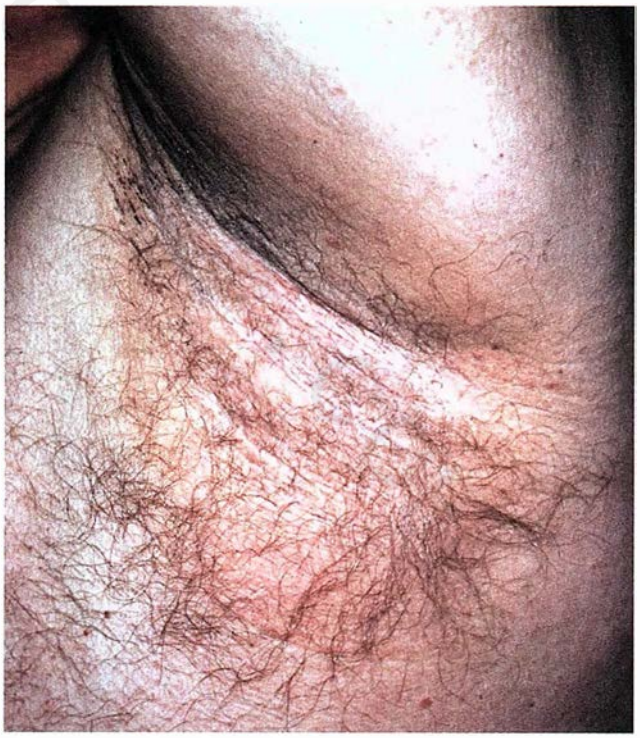

FIGURE 29. Erythrasma presents with sharply demarcated, fine pink-to-brown scaling patches that are typically found in skin fold areas.

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FIGURE 30. Multiple superficial pits on the plantar surface of the foot in a patient with keratolysis, a characteristic malodorous condition caused by *Kytococcus sedentarius*, *Corynebacterium* spp. or *Actinomyces* spp.

Superficial Fungal Infections

Superficial fungal infections are common and typically are caused by dermatophytes or *Candida* spp. The differentiation of superficial infections from deeper or angioinvasive fungal infections that can occur in immunocompromised patients is important, as the presentation, prognosis, and treatment are dramatically different. Superficial fungal infections by dermatophytes infect only the most superficial layers of the skin (stratum corneum, rarely epidermis and hair follicles). Angioinvasive fungal infections, in contrast, have a predilection for superficial and deep blood vessels and will present as violaceous to purple, necrotic patches or nodules, and deep fungal infections will often have both cutaneous changes, such as umbilicated or verrucous papules, and systemic involvement, often of the lungs.

Tinea

There are varied presentations of dermatophyte infections, ranging from mild to severe manifestations. Tinea is categorized according to the area of the body that is impacted, and different types of dermatophytes often are responsible for the respective infections.

Tinea capitis is infection of the hair follicles, typically of the scalp, although eyebrows and eyelashes can be infected. This is most common in children and can present with alopecic areas, broken hair shafts, and scaling. A kerion can result from a tinea capitis infection and is manifested by a boggy, edematous scalp with overlying pustules (**Figure 31**). Associated cervical lymphadenopathy is common and is a useful clinical manifestation to differentiate from seborrheic dermatitis or other causes of alopecia. In children, washing or disposal of items in contact with the scalp (combs, hats, razors) is essential to prevent reinfection.

Tinea corporis classically presents as pruritic, annular erythematous patches with a rim of scale ("ring worm"). Risk factors include close contact in athletes, contact with animals, and immunosuppression. Majocchi granuloma, an erythematous plaque with overlying pustules and papules, is a granulomatous response to dermatophyte infection in the dermis and hair follicles (**Figure 32**). Risk factors include topical glucocorticoid use and shaving of legs in women, which causes spread of the organism. In immunocompromised patients, widespread involvement with varied presentations may occur.

Tinea cruris (jock itch) is dermatophyte infection of the inguinal folds (**Figure 33**). It presents as erythematous patches with a rim of scale and characteristically does not involve the scrotum, in contrast to candidal intertrigo, which can involve the scrotum.

Although tinea cruris is more commonly seen in men, both men and women can develop this infection. The presence of tinea cruris also necessitates examination of the feet as concomitant tinea pedis infection is not uncommon.

Tinea pedis is dermatophyte infection that presents with a flaky scale involving the plantar aspect of the feet



FIGURE 31. Kerion is a result of tinea capitis infection of the hair follicles of the scalp. It is a severe, painful inflammation that appears as raised, pus-filled abscesses.

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FIGURE 32. Majocchi granuloma presents as an annular plaque with erythema that is studded with pustules and papules and is a reaction to a dermatophyte infection in the dermis and hair follicle.



FIGURE 33. Tinea cruris, a dermatophyte infection of the groin, pubic region, and thighs, manifests with an annular lesion with slight scale, an erythematous, advancing edge, and central clearing.

and extending to the sides in a "moccasin" distribution (**Figure 34**). Interdigital involvement with scaling, maceration, and fissuring also is characteristic. Associated onychomycosis caused by the same organism is common. Tinea manuum is a fungal infection of the hands. "Two feet, one hand" tinea is a common presentation of concomitant tinea pedis and tinea manuum. Variants of dermatophyte infection also can occur. Bullous tinea presents with tense bullae, often on the extremities, and represents an exuberant reaction to dermatophyte infection. With extensive infections, an associated hypersensitivity reaction, a "dermatophytid" reaction, can occur away from the site of infection. For example, hand dermatitis also can occur in patients with extensive tinea pedis.

Tinea nigra is another dermatophyte infection presenting as a hyperpigmented, scaly patch, often on the palmar aspect of the hands.



FIGURE 34. Erythematous patches with a scaling rim and associated onychomycosis (thickening of the nails) is seen in tinea pedis.

Diagnosis of dermatophyte infection can be performed by examination of the scale, nail plate, or hair follicle using a potassium hydroxide (KOH) or chlorazol black solution. The presence of branching hyphae is diagnostic. Dermatophyte culture or biopsy also can be performed if the clinical presentation is unusual, if confirmation of the diagnosis is needed, or if KOH examination is equivocal.

Treatment of most superficial dermatophyte infections includes topical antifungal agents such as miconazole, clotrimazole, ketoconazole, or terbinafine. Over-the-counter preparations are cost-effective options with good efficacy. Nystatin is not effective against dermatophytes and should not be used. Combination therapy with topical glucocorticoids and antifungal creams should be avoided because of an increased risk of treatment failures, development of skin atrophy with prolonged use, and increased cost without increased efficacy. Oral antifungal therapy with terbinafine or an azole antifungal agent may be necessary for treating tinea capitis, onychomycosis, Majocchi granuloma, or extensive infection. Oral ketoconazole should not generally be used because of the potential for severe liver toxicity and adrenal gland suppression. In children, oral griseofulvin for tinea capitis also may be used. Tinea pedis will respond to 2 to 4 weeks of topical antifungal therapy, but effective treatment of onychomycosis often requires 12 weeks of oral therapy. Most infections will resolve but may recur and require retreatment. In immunosuppressed patients, recognition and treatment of superficial skin fungal infections is essential, as fungal infections can lead to epidermal breakdown and create a portal of entry for invasive pathogens.

Tinea versicolor is another superficial fungal infection caused by *Malassezia furfur* (formerly *Pityrosporum*) and is most common in warm, humid environments. It presents as hypopigmented, hyperpigmented, or pink patches that are dry and slightly scaly. Although the patches can occur

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anywhere, the neck, upper back, and chest, with extension to the abdomen or extremities, are commonly affected (**Figure 35**). These areas often become more noticeable after exposure to the sun because the organism prevents the skin from tanning. This type of superficial infection is not contagious. A form of folliculitis also occurs (*Malassezia* folliculitis). Diagnosis can be made clinically; however, yeast spores and short hyphae can be easily observed with KOH examination ("spaghetti and meatballs" appearance). Differential diagnosis includes vitiligo, postinflammatory pigmentation, seborrheic dermatitis, and pityriasis alba. Treatment of tinea versicolor with topical antiseborrheic shampoos or lotions such as selenium sulfide or ketoconazole leads to resolution of erythema and scaling, but the pigmentation changes may persist for longer periods of time. Recurrence is common, and retreatment and prevention with topical therapy often is necessary. With widespread involvement, short courses of oral azole antifungal agents (with the exception of ketoconazole as noted earlier) may be necessary.

KEY POINTS

- Diagnosis of dermatophyte infection can be performed by examination of the scale, nail plate, or hair follicle after preparation with potassium hydroxide (KOH) or chlorazol black solution; the presence of branching hyphae is diagnostic.

HVC

- Treatment of most superficial dermatophyte infections includes topical antifungal agents; however, over-the-counter preparations are cost-effective options with good efficacy.

Candidiasis

Cutaneous candidiasis can present in multiple ways: intertriginous areas (**Figure 36**), oral involvement as oral thrush or angular cheilitis, vulvovaginal candidiasis (**Figure 37**), and disseminated disease in immunocompromised, hospitalized patients (see MKSAP 17 Infectious Disease).

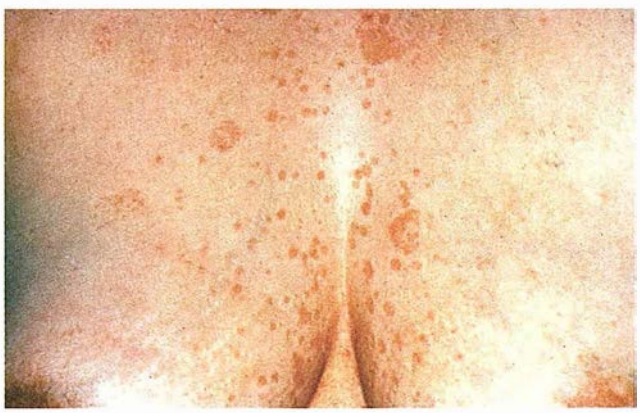

FIGURE 35. Small, light-brown to pink coalescing macules with fine overlying scale on the anterior chest characteristic of tinea versicolor.



FIGURE 36. Bright red papules, vesicles, pustules, and patches with satellite papules in the intertriginous areas under the breasts characteristic of candidiasis.



FIGURE 37. Acute vulvar candidiasis presents with erythema and edema of the vulva with satellite papules and pustules. Associated involvement of the vaginal mucosa is characterized by a discharge that may be thick, adherent, and "cottage cheese-like" or thin and loose, indistinguishable from the discharge of other types of vaginitis.

Cutaneous candidiasis clinically presents as bright red patches with satellite papules and pustules in intertriginous areas. Involvement of the vulva and scrotum is common. Associated vaginal involvement can be characterized by a discharge that may be thick, adherent, and "cottage cheese-like" or thin and loose, indistinguishable from the discharge of other types of vaginitis. Risk factors include chronic moisture and hyperhidrosis, and this may be more common in febrile, hospitalized patients. Diagnosis can be made clinically, and KOH examination showing pseudohyphae and spores can also be diagnostic. Reducing friction and moisture with barrier pastes and powders such as zinc oxide are important. Treatment with topical azole antifungal agents is the preferred first-line therapy. Although nystatin is effective against *Candida* spp., it is not effective for dermatophyte infection.

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Topical azoles should also be used for superficial fungal infections in intertriginous areas. With concomitant vulvar and vaginal involvement (characterized by associated discharge), cutaneous candidiasis may be treated with oral antifungal agents or topical and intravaginal preparations.

Viral Skin Infections

Herpes Simplex Virus

The family of human herpes viruses causes numerous cutaneous infections including herpes simplex virus 1 (HSV1), herpes simplex virus 2 (HSV2), and varicella-zoster viral infections (VZV or human herpes virus 3 [HHV3]). Because they are closely related, the primary skin lesions are similar. The classic presentation is a group of painful, small vesicles on an erythematous base, transitioning to pustules and subsequent crusting of the lesions over time (**Figure 38**).

Because the viruses have a tropism for the nerve dorsal root ganglia, they migrate to this area after initial infection where they can remain latent and cause subsequent reinfection and recurrences. Phases of infection include primary infection (which often is most severe), latent infection in the ganglion when viral shedding can still occur, and viral reactivation leading to a clinical outbreak.

The primary lesions of HSV1 and HSV2 are clinically indistinguishable. HSV1 traditionally causes orofacial lesions, and HSV2 most often causes genital lesions; however, both viruses can lead to either oral or genital lesions. Herpes infection outside of these areas can occur, including infection on the fingers of children (herpetic whitlow) or in exposed skin as a result of skin-to-skin contact, such as in contact sports like wrestling (herpes gladiatorum). Diffuse infection can occur in the setting of an underlying skin disease, such as eczema (eczema herpeticum). The viruses are highly contagious, and transmission is by direct contact of salivary or genital secretions. Asymptomatic viral shedding can occur. Outbreaks can be triggered by stress, fever or other infection, and ultraviolet light exposure. Associated manifestations also can occur, including erythema multiforme.

Primary oral herpes simplex virus infection (herpes gingivostomatitis) can present as a mild or asymptomatic infection or can be severe with fever, malaise, lymphadenopathy, and widespread painful vesicles and erosions on the cutaneous and mucosal lips and gingiva (**Figure 39**). Secondary infection with *Candida* also can occur. Recurrent herpes labialis often causes prodromal pain and stinging, followed by solitary lesions on the vermilion border ("cold sores").

Most primary genital herpes infections are asymptomatic, with up to 70% to 80% of seropositive persons having no recollection of initial infection. Severe initial presentations also can occur with fever, malaise, tender lymphadenopathy, and painful erosions that can be secondarily infected and lead to an inability to urinate or defecate. Recurrent genital herpes is similar to oral herpes with a prodrome, followed by grouped vesicles on an erythematous base, erosions, and crusting. Involvement of the genitals and buttocks can occur. Immunocompromised patients can have severe presentations of both oral and genital herpes, including persistent verrucous nonhealing ulcers.

The differential diagnosis of genital ulcers is important because other sexually transmitted infections must be considered (including syphilis, chancroid, granuloma inguinale, lymphogranuloma venereum). HSV is the most common cause of painful genital ulcers, although chancroid also causes painful ulcers. Other infections often cause nonpainful ulcerations (see MKSAP 17 Infectious Disease). With any sexually transmitted infection, HIV testing also is important.

Diagnosis of HSV can be made clinically, but several tests also are available. Although the Tzanck smear was traditionally used to confirm the presence of a HIV, difficulties with reliable interpretation and its inability to distinguish between HSV1, HSV2, and varicella infections have led to the use of other diagnostic methods. Rapid tests are widely available such as direct-fluorescent antibody (DFA) and polymerase chain reaction (PCR) studies that can provide results in less than 24 hours and can differentiate between the viruses. To adequately perform



FIGURE 38. Herpes simplex viral infection characterized by grouped vesicopustules on an erythematous base that typically have associated tingling or pain.

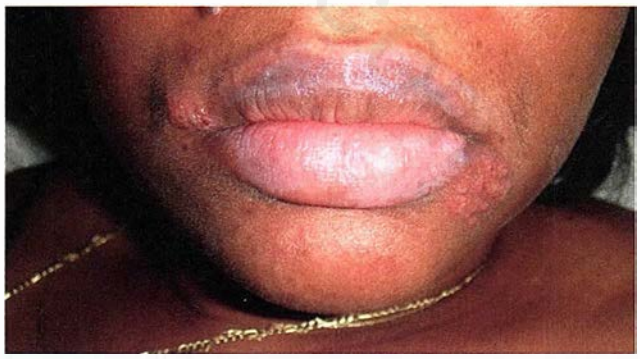

FIGURE 39. Primary herpes simplex virus on the sides of the mouth.

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these tests, a vesicle needs to be unroofed, and material from the blister base (where the virus is present) is sent for examination. Viral culture has traditionally been the gold standard for diagnosis. but the culture can take 48 hours or longer to be interpreted. Culture is still valuable if resistance testing is necessary in patients with recalcitrant or chronic infections (typically immunocompromised patients). Serologic testing is not recommended for diagnosis because seroprevalence rates are high and do not correspond with active infection.

Oral antiviral agents are considered first-line therapies for herpes simplex virus infection and are most effective if instituted at presentation of the prodrome of an outbreak. Oral antiviral agents including acyclovir, valacyclovir, and famciclovir are considered first-line therapies, and dose and duration of treatment are dependent on the type and extent of infection (primary versus recurrent). Topical therapies are less effective in improving symptoms and reducing disease duration. With frequent outbreaks, daily suppressive therapy also can be instituted.

KEY POINTS

- The classic presentation of herpes simplex viral infections is a group of painful, small vesicles on an erythematous base, transitioning to pustules and subsequent crusting of the lesions over time.
- Oral antiviral agents are considered first-line therapies for herpes simplex virus infection and are most effective if instituted at presentation of the prodrome of an outbreak.

Varicella/Herpes Zoster

Varicella-zoster viral infections (VZV) can either be primary (chickenpox) or reactivation (herpes zoster). Primary varicella often is seen in children or young adults, but is now seen less frequently because of vaccination of young children.

Herpes zoster (shingles) is caused by the reactivation of latent VZV. Shingles typically presents with grouped vesicles on an erythematous base in a single dermatome (**Figure 40** and **Figure 41**). Elderly persons and immunocompromised patients are at increased risk, and recurrent outbreaks of herpes zoster should prompt an evaluation for possible malignancy or immunodeficiency. Lesions are infectious until they become crusted over, and persons with herpes zoster should avoid contact with others who may be susceptible including pregnant women or immunocompromised persons.



FIGURE 41. Herpes zoster infection on the flank with grouped vesicles and punched out erosions on an erythematous base.

The clinical presentation of herpes zoster is characteristic. Prodromal symptoms, such as burning, stinging, or tingling, often occur in a localized region, followed by an eruption of grouped vesicles or pustules on an erythematous base. The outbreak is unilateral and does not cross the body's midline. The most common dermatomes affected are in the thoracic region. Facial involvement may require further evaluation. With involvement of the first division of the trigeminal nerve (forehead extending over upper eyelid, or nasal tip involvement), ophthalmologic evaluation is mandatory as herpes zoster ophthalmicus and possible blindness can result. Evaluation by an otolaryngologist may be required if vesicles are noted in the external ear canal, as peripheral facial paralysis and auditory/vestibular symptoms can occur (Ramsay Hunt syndrome). Differentiation between genital herpes and herpes zoster in the sacral dermatomes also may be difficult. Diagnosis can be made clinically, or the tests previously outlined can be used.



FIGURE 40. Herpes zoster infection characterized by vesicopustules on an erythematous base in a dermatomal distribution.

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Disseminated VZV must be considered when more than three dermatomes are affected or more than 20 lesions outside of adjacent dermatomes are present. This is more common in immunocompromised persons who are at risk for associated hepatitis or pneumonia.

Oral acyclovir, valacyclovir, or famciclovir is effective for treating herpes zoster if initiated within 24 to 48 hours of presentation and can shorten the disease course as well as help prevent postherpetic neuralgia. If postherpetic neuralgia develops, gabapentin, pregabalin, tricyclic antidepressants, or topical anesthetics such as topical lidocaine and capsaicin can be helpful. Treatment with gabapentin at presentation of herpes zoster also may reduce the risk of postherpetic neuralgia. A shingles vaccine is available to decrease the incidence of herpes zoster reactivation and decrease the severity and duration of postherpetic neuralgia. The vaccine is indicated for persons 60 years of age and older. However, it is a live attenuated vaccine and is not recommended in immunosuppressed or pregnant persons (see MKSAP 17 General Internal Medicine).

KEY POINTS

- Herpes zoster (shingles) is caused by the reactivation of latent varicella-zoster virus and often presents with grouped vesicles on an erythematous base in a single dermatome.
- When herpes zoster involves first division of the trigeminal nerve (forehead extending over upper eyelid, or nasal tip involvement), ophthalmologic evaluation for eye involvement is mandatory as blindness can result; when more than three dermatomes are involved consider treatment for disseminated varicella-zoster viral infections.
- Oral acyclovir, valacyclovir, or famciclovir, if initiated within 24 to 48 hours of presentation, can shorten the course of herpes zoster and help prevent postherpetic neuralgia.

Warts

Warts are an infection of skin and mucosa caused by human papillomavirus (HPV). There are numerous different HPV subtypes, which may have a predilection for different anatomic sites. HPV is contagious and spread by direct skin contact or contact with infected surfaces, and self-inoculation within an individual can occur. There are many presentations of warts depending on the site and clinical appearance. Verruca vulgaris is an exophytic, hyperkeratotic papule that often develops on the hands but may be found anywhere (**Figure 42**). Verruca plantaris is characterized by larger, hyperkeratotic lesions on the plantar surface of the feet that can be difficult to treat. Differentiation from calluses is possible because warts cause dilated capillaries, which clinically present as black dots and obliteration of normal dermatoglyphics (ridges and furrows on the skin surface forming loops, whorls, and arches). Flat warts (verruca plana) are flat-topped papules that often are spread easily, especially from shaving.

Anogenital warts (condylomata acuminata) are the most common sexually transmitted infection and are most often caused by HPV types 6 and 11. They present as single or multiple papules on the penis, vulva, or perianal area and may be variably sized flat-topped or cauliflower-like papules (**Figure 43**). Lesions are diagnosed based on clinical appearance, but large, atypical lesions or those recalcitrant to therapy should be biopsied to rule out premalignant or malignant transformation.

Although warts may resolve spontaneously, treatment often is required. Over-the-counter preparations of salicylic acid or wart remover can be effective. If resolution does not occur, additional destructive techniques can include cryotherapy, topical application of prescription-strength salicylic acid, cantharidin, podophyllin, or laser therapy. Paring of the hyperkeratoses associated with a wart may be necessary to increase the therapeutic effect. Immune therapies, including

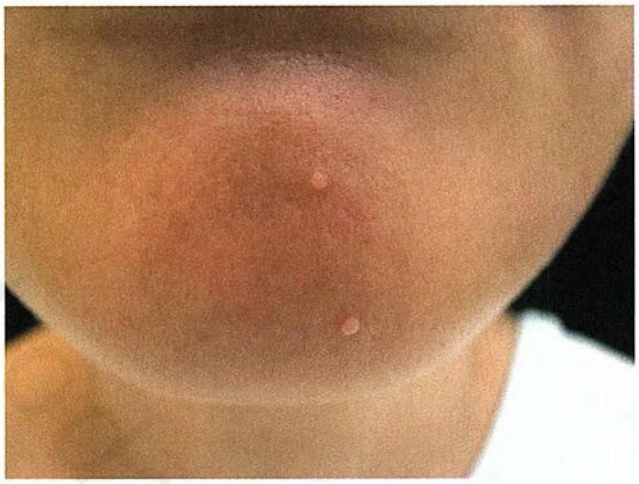

FIGURE 42. Verruca vulgaris lesions are small, skin-colored growths, often occurring in clusters, and are caused by the human papillomavirus.



FIGURE 43. Typical anogenital warts (condyloma acuminata) over the penile shaft and foreskin with adjacent erosions after imiquimod therapy.

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injection of *Candida* antigen and topical imiquimod, also can be effective. Surgical removal of large, bulky lesions also can be used. Numerous therapies have been reported to be effective, but controlled trials are lacking to compare modalities.

HPV vaccination is recommended for young persons (both female and male) ages 9 to 26 years to prevent cervical and anal carcinoma. Anogenital warts also can be prevented if the vaccine is effective against HPV 6 and 11 (see MKSAP 17 General Internal Medicine). It is unclear whether the vaccine confers protection against other strains of HPV.

Molluscum Contagiosum

Molluscum contagiosum is a common poxvirus infection among children, young adults, and immunosuppressed persons. In children, it presents as multiple small, flesh-colored umbilicated papules (**Figure 44**). Inflamed or large lesions and a surrounding eczematous dermatitis can be observed. In young adults, molluscum contagiosum is considered a sexually transmitted infection that also causes similar umbilicated papules in the genital area. Diagnosis can be made by the clinical appearance. Although lesions can self-resolve, this may take months to years. Because lesions are extremely contagious, treatment is recommended. Therapy includes destructive techniques including cryotherapy, salicylic acid, cantharidin, or physical removal with curettage.

Infestations

Scabies

Scabies (*Sarcoptes scabiei*) is transmitted by person-to-person contact. It typically presents as generalized and often intense pruritus with erythematous papulonodules and scaling patches, especially in web spaces, wrists, axillae, nipples, waistline, and genitals (**Figure 45**), with sparing of the head. Burrows (serpiginous lines) may also be seen. Crusted (Norwegian) scabies is a highly contagious variant seen in elderly and immunocompromised persons that presents as hyperkeratotic plaques, especially on the extremities. Infestations occur in nursing homes, hospitals, or institutions, and a high clinical suspicion is necessary to avoid outbreaks, as pruritus often can be very minimal if present.

Diagnosis is suspected when multiple family members in close contact have generalized pruritus. Definitive diagnosis requires identification of the mite, eggs, or feces by microscopic examination (using potassium hydroxide [KOH] or mineral oil) after scraping several lesions (**Figure 46**).

Treatment of the patient and close contacts is required to eliminate the infestation (**Table 14**). Itching can persist for weeks after therapy. The resulting pruritus can be treated with antihistamines, topical glucocorticoids, and, if severe, oral



FIGURE 45. Scabies infestation characterized by erythema, scaling, and small crusted papules between web spaces.



FIGURE 44. Molluscum contagiosum, with pink papules that have a central umbilication.

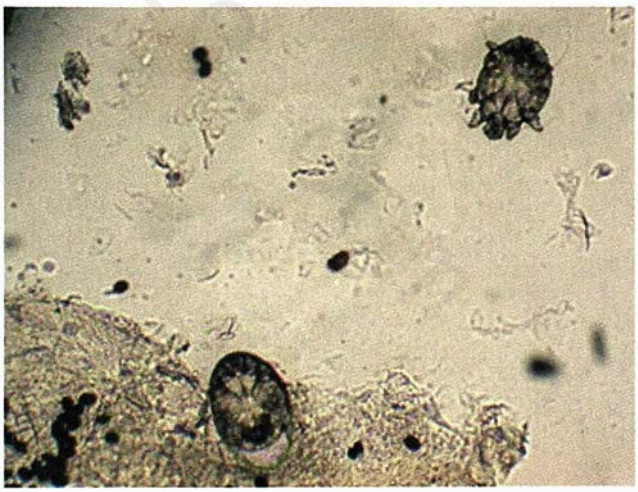

FIGURE 46. Microscopic examination of skin scrapings, showing mites and mite feces (scybala), diagnostic of scabies.

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TABLE 14. Treatment of Scabies and Lice

Medication[a]	Application/Dose	Notes
Scabies		
Permethrin 5% lotion	Apply overnight from neck to feet, then rinse in the morning Repeat in 7-10 days	Considered first-line therapy
Oral ivermectin	Dose: 200 µg/kg Repeat in 7-10 days	Useful for persistent infestation, treatment failure, or intolerance to topical therapy Also may be important adjuvant therapy in crusted scabies Should not be used in pregnant/breastfeeding women or young children
Lindane 1% lotion	Apply overnight from neck to feet, then rinse in morning Repeat in 7-10 days	Not available in some countries because of neurotoxicity
Combination therapy with ivermectin and topical lotions		For treatment of crusted scabies
Lice		
Medication[a]	**Application/Dose**	**Notes**
Permethrin 1% lotion	Apply to affected areas (damp hair for 10 minutes), then rinse Repeat in 7-10 days	Considered first-line therapy unless there is known resistance Should perform nit combing
Pyrethrin 0.3% + piperonyl butoxide 4% shampoo	Apply to damp hair for 10 minutes), then rinse Repeat in 7-10 days	Useful therapy Should perform nit combing
Malathion 0.5% lotion	Apply to affected areas for 8-12 hours, then rinse Repeat in 7-10 days	Flammable Should perform nit combing
Benzyl alcohol 5% lotion	Apply to affected areas, leave on for 10 minutes Repeat in 7-10 days	Should perform nit combing
Spinosad 0.9% topical suspension	Apply to affected areas for 10 minutes, then rinse Repeat in 7 days if live lice are seen	Nit combing not necessary
Topical ivermectin 0.5% lotion	Apply to dry hair Rinse after 10 minutes	Nit combing not necessary
Oral ivermectin	Dose: 200 µg/kg Repeat in 7-10 days	Should not be used in pregnant/breastfeeding women or young children
Lindane 1% lotion	Apply overnight from neck to feet, then rinse in morning Repeat in 7-10 days	Not available in some countries because of neurotoxicity

[a]Treatment of the individual and close contacts at same time is essential for eradication. Washing of clothes, linens, and personal items in hot water should be performed to remove fomites.

glucocorticoids can be used. If new lesions (papules, changes in web spaces) occur, prompt evaluation for reinfestation or bacterial superinfection should occur.

Lice

Lice can be found on the head (*Pediculosis capitus*), body (*Pediculosis corporis*), or pubic area (*Phthirus pubis*) and often present with itching in the involved area. Pubic lice also can be found on eyebrows or eyelashes (**Figure 47**). Head lice often occur among children. Body lice typically live in clothing seams and can transmit infections such as typhus, trench fever, and relapsing fever. Persons living in close contact, including the homeless or refugee populations, are at increased risk.

Diagnosis requires visualization of the lice or the nits (adherent white egg casings) on the hair shafts.

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FIGURE 47. Lice on the eyebrow. The diagnosis of lice is established by identifying crawling lice in the scalp, eyebrows, or pubic hair.

Erythematous bite marks in the affected areas can be a clue to diagnosis. Even after successful treatment, nits can continue to persist.

Treatment of the patient and close contacts is required to eliminate the infestation (see Table 1). Clothes, linens, and personal items should be washed in hot water to remove fomites.

Bedbugs

Bedbug infestations (*Cimex lectularius*) are occurring at increasing rates and are a public health concern. Classic presentation is grouped, pruritic papules in close configuration ("breakfast, lunch, and dinner") on exposed body areas (**Figure 48**). Bites are typically noticed in the morning, as bedbugs feed at night (**Figure 49**). Diagnosis and eradication are difficult and often require a professional exterminator. Evaluation of hotel rooms when traveling for evidence of bedbugs (identifying blood spots under the mattress or identifying molted skin or bedbugs themselves in headboards, baseboards, under the mattress) may be helpful for prevention. Treatment is symptomatic, with topical glucocorticoids and oral antihistamines, as bedbugs do not live on humans.



FIGURE 48. Bedbug bites usually occur in a series ("breakfast, lunch, and dinner"). The lesions are painless, pruritic, urticaria-like papules.



FIGURE 49. Bedbugs are nocturnal. They feed off human blood and tend to live near their food supply.

Bites and Stings

Arthropod bites and stings are common and often self-limited. Both mosquitoes and ticks can be potential vectors for systemic illnesses. Prevention using insect repellents that contain DEET, picaridin, or permethrin-impregnated clothes and wearing long-sleeved clothing is recommended.

Spider Bites

Most spider bites are unnoticed or may appear as pruritic red papules (**Figure 50**). Diagnosis is made upon clinical presentation, and treatment is symptomatic in most patients.

Severe spider bites that cause systemic symptoms are rare. The brown recluse spider, *Loxosceles recluse*, is found in southern and central United States (**Figure 51**) and can cause severe skin necrosis with significant pain and systemic symptoms, including nausea, vomiting, fever, muscle and joint pain, hemolysis, and acute kidney injury (**Figure 52** and **Figure 53**).

Brown recluse spider bites are uncommon because the spiders are timid insects and often are hiding. Most suspected



FIGURE 50. Spider bites presenting as red, pruritic, urticarial papules that are pruritic.

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FIGURE 51. Brown recluse spiders are quite shy, and their bites are often misidentified and overdiagnosed.



FIGURE 52. A brown recluse spider bite (early).



FIGURE 53. Ulceration from a brown recluse spider bite (late).

spider bites actually are misdiagnosed and are caused by other insect bites or infections, including bacterial abscesses. Although diagnosis is usually made clinically, serum enzyme-linked immunoabsorbent assays or biopsy can be performed to confirm a bite. Treatment includes analgesic agents, wound care, and debridement in some cases.

Hymenoptera

Wasp and bee stings are painful but often self-limited. Stingers should be removed rapidly, as venom can continue to be released. Localized reactions include pain, redness, and swelling. Systemic reactions including hives and anaphylaxis can occur in some persons, and such persons should carry an injectable epinephrine pen. Because massive wasp and bee stings can result in multiorgan failure, desensitization using allergy therapy can be performed in persons who have had systemic reactions.

Fire ants, found in the southern United States, can both bite and sting, causing a significant response. These bites cause an initial burning and itchy sensation followed by several pustules. The pustules can mimic other dermatologic diseases including infections. Topical glucocorticoids may be required for symptomatic relief. Persons with severe bites may require oral glucocorticoids.

Worms

Cutaneous larva migrans is an intensely pruritic skin eruption caused by hookworms as a result of walking barefoot in areas where animal feces may be present (such as on beaches). Wearing footwear is therefore recommended. The eruption is linear or serpiginous, and often occurs on the extremities (**Figure 54**). Oral antiparasitic agents (ivermectin as the preferred agent or albendazole as an alternative) can help resolve the eruption. Antihistamines or glucocorticoids can be used to relieve symptoms.



FIGURE 54. Serpiginous, linear red track marks that are pathognomonic for cutaneous larva migrans.

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Cuts, Scrapes, and Burns

Minor cuts, scrapes, and burns often require only gentle cleansing with soap and water and local wound care using sterile petrolatum jelly and a nonadherent bandage over the wound. A contact layer is the first layer on top of the wound. The contact layer allows the wound to stay moist to aid in healing without sticking to it. Examples include petrolatum gauze or sterile petrolatum applied to a nonadherent dressing. Nonstick silicone sheets are an excellent first layer on top of a noninfected wound and can be placed over a topical antibiotic. This will aid in healing and may help lessen scarring, but silicone sheets are more expensive than petrolatum and their superiority has not been proved. The contact layer can be covered by a secondary nonadherent dressing that can be taped in place.

Cuts and Scrapes

For minor wounds that are not contaminated, thorough cleansing and application of topical sterile petrolatum is often sufficient. Topical antibiotics can be used for wounds that are contaminated or in locations such as around the perineum, major skin folds, or mouth that may be colonized with pathogenic bacteria, increasing the risk for secondary infection. Topical antibiotics such as neomycin and bacitracin are inexpensive over-the-counter agents with activity against gram-positive and selected gram-negative organisms but may lead to contact allergy. Mupirocin is effective against gram-positive organisms and has little risk of contact sensitivity, but bacterial resistance is emerging. Silver sulfadiazine is a broad-spectrum antibiotic with activity against gram-positive and gram-negative organisms including *Pseudomonas aeruginosa*. Silver sulfadiazine has been rarely associated with bone marrow suppression and severe drug reactions. Retapamulin is a newer topical antibiotic that covers gram-positive organisms but is more expensive. If pustules, drainage, or pain develops, wound culture is indicated to diagnose an infection. Red, itchy papules and increased drainage within a few days after application of a topical antibiotic may be caused by a topical antibiotic allergy.

The decision to suture or glue a laceration is based on the depth, likelihood of dehiscence, ability to cleanse the wound, and long-term cosmesis. Wound adhesives can be used for minor cuts that are not under tension, whereas sutures are indicated for larger, deeper cuts.

Burns

Patients with thermal burns can be triaged based on the amount of body surface area affected, specific body part involved (face or perineum may need more advanced care), and depth of the burn. Superficial burns affect only the epidermis and appear red. Superficial partial thickness burns involve the epidermis and superficial dermis, manifesting with clear fluid-filled blisters on a red base. Deep partial-thickness burns involve the deeper dermis, appear whiter, and are less blanchable. Full-thickness burns affect the deep dermis into the subcutaneous fat, are not blanchable, and appear white or yellow. Patients with severe or widespread burns should be referred to a burn unit. Estimating the body surface area affected can be done using the size of the patient's palm as 1% for small burns. The rule of 9s (each arm is 9%, each leg is 18%, anterior and posterior trunk are each 18%, the head is 9%, and the groin is 1%) can be used for more extensive burns.

Minor burns can often be treated in an outpatient setting. For burns that are in areas with high infection risk, such as perioral, perineal, or axillary locations, or the hands and feet, application of a topical antibiotic such as mupirocin or silver sulfadiazine is reasonable. Silver sulfadiazine has a sulfa moiety and therefore can cause severe allergic reactions or other sulfa medication effects. For clean, minor burns that can be easily covered and have a low risk of infection, applying sterile petrolatum and covering the area with a nonstick dressing are reasonable. Silicone-based dressings are available and may provide better healing but are more expensive than petrolatum and a nonstick dressing.

Patients with severe burns over broad body surfaces should be referred to an expert, and hospital admission should be considered to allow for advanced wound care, maintain fluid and electrolyte balance, and monitor for infection.

KEY POINTS

- Minor wounds and burns may be treated with thorough cleansing, application of topical sterile petrolatum, and the application of a a nonadherent bandage; nonstick silicone dressings are a more expensive option. HVC
- Thermal burns are characterized by the amount of body surface area affected, specific body part involved (face or perineum may need more advanced care), and depth of the burn; superficial burns appear red, deep burns appear white or yellow and are nonblanchable.

Common Neoplasms

Benign Neoplasm

Seborrheic Keratoses

Seborrheic keratoses are benign brown scaly papules and plaques commonly found in older adults (**Figure 55**). They have a wide range of shades and morphologies and vary in size from a few millimeters to several centimeters. Despite their brown color, they are of keratinocytic lineage rather than melanocytic lineage. Although harmless, they may occasionally resemble more worrisome pigmented lesions such as melanoma and are therefore often biopsied. They may become irritated when traumatized; if this occurs, they are often treated with cryotherapy.

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FIGURE 55. Seborrheic keratoses are brown, scaly, waxy papules that commonly occur in older persons. They frequently have a "stuck on" appearance and often are verrucous (warty) as well. Seborrheic keratoses typically demonstrate horned cysts (epidermal cysts filled with keratin) on the surface that can best be visualized with a magnifying glass.

Melanocytic Nevi

Melanocytic nevi, often referred to as "moles," are found in persons of all ages. They are benign collections of melanocytes and histologically consist of nests of melanocytes occurring at the dermal-epidermal junction (DEJ) and dermis. Although they occur most commonly in sun-exposed areas, they may arise anywhere on the skin or mucous membranes; they are also occasionally found on the iris, retina, or the lining of internal organs. Nevi most commonly start to appear in childhood and increase in number through adolescence and young adulthood. Junctional nevi are flat and often dark brown in color. Compound nevi are raised (papules) and may be irregularly pigmented. Dermal nevi are soft and flesh-colored and may resemble skin tags. The terms "junctional," "compound," and "dermal" refer to the location of the melanocytic nests: junctional nevi have nests located at the DEJ, compound nevi have nests at the DEJ and in the dermis, and dermal nevi have the nests in the dermis. Nevi undergo a benign maturation process from junctional to compound to dermal over a period of many years.

Dysplastic Nevi

Dysplastic nevi are melanocytic nevi that display one or more of the atypical clinical features seen in melanoma (the "ABCDEs") (see Malignant Melanoma), along with cytologic atypia and architectural disorder seen on histology. They are often asymmetric, irregularly bordered, and more than one shade of brown, and may be quite large in diameter (**Figure 56**). Although benign, they are important for several reasons. Patients with multiple dysplastic nevi are at risk for developing melanoma and should be monitored closely. Some of these patients have dysplastic nevus syndrome (DNS); criteria for this syndrome include a history of melanoma in one or more first- or second-degree relatives, the presence of a large number of nevi (>50), multiple nevi having atypical clinical features, and multiple nevi that have atypical histologic features. Many dysplastic nevi have a dark brown center and a surrounding ring of light brown, a pattern that is often referred to as a "fried egg" appearance. Histologically, dysplastic nevi are graded as having mild, moderate, or severe atypia. Although melanomas may arise within dysplastic nevi, the risk of this occurring within any given lesion is quite small. Removal is reserved for those lesions that display particularly worrisome features, are changing in size and color, are symptomatic, or stand out from the patient's other nevi.

Halo Nevi

Halo nevi are benign melanocytic nevi that are in the process of being attacked and eliminated by the immune system. Their name derives from the fact that the hallmark of this process is the formation of a white ring around the mole in question (**Figure 57**). The halo gradually enlarges, and the mole shrinks until all that is left is a depigmented area on the skin that resembles a small area of vitiligo. These lesions are particularly common in children. Halo nevi have sometimes, although not always, been observed at remote sites when patients have a melanoma, as the lymphocytes may be reacting to atypical melanocytes. Therefore, although most of these lesions occur in isolation, patients with halo nevi should have a thorough skin examination.

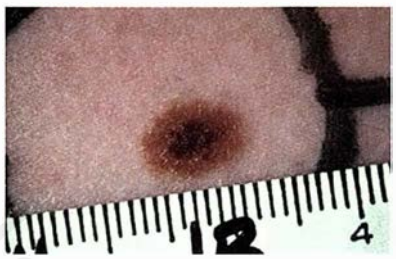

FIGURE 56. Dysplastic nevi are commonly larger than 6 mm with mottled pigment and irregular margins.



FIGURE 57. Halo nevus with white ring surrounding the lesion.

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Sebaceous Hyperplasia

Sebaceous hyperplasia is a benign condition consisting of flesh-colored or yellow papules found on the face in patients with rosacea. These papules often have a central umbilication that is visible upon close inspection and may have telangiectasias on the surface as well (**Figure 58**). Although they are benign, they may be mistaken for basal cell carcinoma because of their shape, location, and presence of telangiectasias. Lesions caused by sebaceous hyperplasia differ from basal cell carcinomas in that they lack the translucency ("pearliness") that is often seen in the latter lesions. They are often removed for cosmetic reasons.

Neurofibromas

Neurofibromas are benign nerve sheath tumors that present as soft, flesh-colored papules on the trunk and extremities. Isolated lesions are common in the general population and are not associated with any underlying disease. They resemble skin tags and dermal nevi and are often confused with these lesions clinically; upon closer inspection, they are sometimes found to have a very faint violet or erythematous hue (**Figure 59**). The presence of numerous neurofibromas suggests a diagnosis of neurofibromatosis type 1 (**Figure 60**). Additional findings that suggest this diagnosis include multiple café-au-lait macules, Lisch nodules (raised, pigmented hamartomas of the iris), and axillary freckling. Neurofibromas are benign and do not require treatment.

Acrochordons (Skin Tags)

Acrochordons (skin tags) are benign, flesh-colored papules that arise in areas of friction, such as the neck, axillae, and groin (**Figure 61**). They are harmless but often bothersome from a cosmetic standpoint. They may also occasionally become tender when traumatized. The presence of numerous lesions, particularly in the setting of obesity and acanthosis nigricans, is associated with insulin resistance and obesity.

Cherry Hemangiomas

Cherry hemangiomas are benign hereditary vascular papules composed of clusters of capillaries that commonly arise on the



FIGURE 58. Sebaceous hyperplasia presents as a yellow-to-pink papule with a central dimple.



FIGURE 59. Isolated neurofibromas present as soft, compressible flesh-colored papules resembling skin tags or dermal nevi.

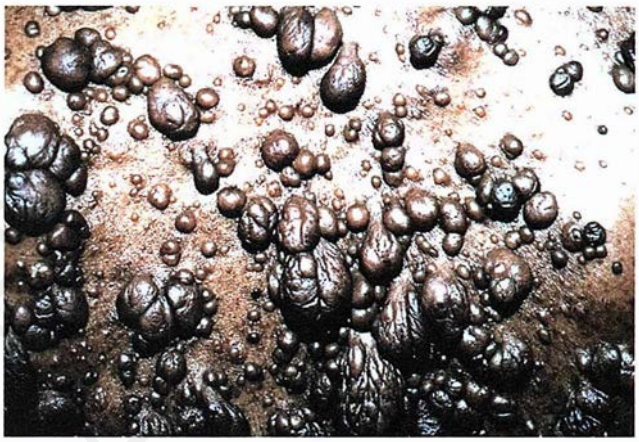

FIGURE 60. Multiple neurofibromas in a patient with neurofibromatosis type 1.



FIGURE 61. Acrochordon is a flesh-colored papule that arises in areas of friction, such as the neck, axillae, and groin. Multiple lesions are often present.

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trunk of older persons. If traumatized, they will often bleed vigorously. Capillary hemangiomas are the most common type and are bright red in color (**Figure 62**). Lesions that consist of venules may be blue or violet. Neither variety is associated with other lesions or dieases, and treatment is not needed.

Dermatofibromas

Dermatofibromas are firm papules that arise after minor trauma, most commonly on the lower extremities. Histologically, they comprise dermal dendritic histiocytic cells with surrounding collagen bundles; the cause is unknown. They are typically flesh colored or slightly brown and often have a slightly darker brown ring encircling the main part of the lesion (**Figure 63**). When squeezed, they tend to pucker, a phenomenon known as the "dimple sign" (**Figure 64**). They do not require treatment.

Solar Lentigines

Solar lentigines are brown, well-demarcated macules and patches that occur on sun-exposed skin of older persons, particularly the face and dorsal hands (**Figure 65**). Previously, they were often referred to as "liver spots" because their color resembles that of liver. Although benign, they are a marker for someone who has relatively fair skin and has received a significant amount of sun exposure over the years. They frequently occur near more worrisome lesions such as actinic keratoses or skin cancers. Lentigines with atypical features or broad, growing lentigines (particularly on the face of older, light-skinned persons) should be biopsied to rule out lentigo maligna, a form of melanoma.



FIGURE 62. Cherry hemangiomas are bright red vascular papules commonly found in adults on the trunk and extremities.



FIGURE 63. Dermatofibromas appear as firm nodules about the size of a pencil eraser. They are frequently hyperpigmented or may have pigmentation at the periphery.



FIGURE 64. The "dimple sign" is a characteristic clinical feature of dermatofibromas.

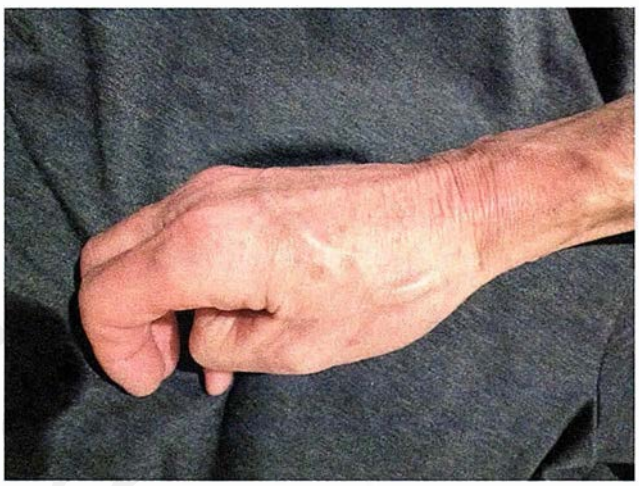

FIGURE 65. Solar lentigines are brown macules and patches that occur in sun-exposed areas in elderly fair-skinned persons. Although benign, they may occasionally be difficult to distinguish from lentigo maligna. Useful discriminating characteristics include more homogeneous pigmentation and lighter color.

Hypertrophic Scars and Keloids

Hypertrophic scars are thick, firm, smooth papules and plaques that occur at sites of trauma; they represent excessive scar tissue formation beyond the normal healing process. They are more common in areas of tension such as the chest and the upper back and are also more common in persons with darker skin tones. They may be tender or pruritic and tend to resolve

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slowly over time. Unlike keloids, they are limited to the extent of the injury rather than extending beyond it. They are often treated with intralesional triamcinolone injections.

Keloids represent a more severe form of hypertrophic scarring in which the lesion extends beyond the borders of the original injury. They are firm, smooth, often tender nodules (**Figure 66**). Relatively minor trauma is often enough to trigger their formation. Ear piercing, for example, is a common inciting factor and can lead to the formation of a nodule many times larger than the injured area. Keloids may be treated with intralesional triamcinolone, excision, and laser surgery (see Dermatologic Problems of Special Populations).

Pyogenic Granulomas

Pyogenic granulomas are bright red vascular lesions that arise suddenly and grow rapidly; they often appear during pregnancy or in the setting of certain medications (such as antiretroviral therapy) (**Figure 67**). The name is misleading, as they are neither pyogenic nor granulomatous. They resemble cherry hemangiomas but are often more friable and tend to bleed more easily. They are treated with biopsy or electrocautery. They are benign lesions and do not have any negative implications.

Epidermal Inclusion Cysts

Epidermal inclusion cysts are benign nodules with a central punctum and a chamber containing keratinaceous material (**Figure 68**). They are often incorrectly referred to as "sebaceous cysts," a term that is erroneous because they possess keratin rather than sebum. When punctured, they often eject a copious amount of foul-smelling keratinaceous material; the odor is derived from the presence of anaerobic bacteria. The cyst wall may occasionally rupture, leading to the formation of a tender red swollen nodule that resembles a furuncle. They are benign but are frequently removed if they grow too large. Definitive treatment requires removal of the cyst wall; simple incision and drainage typically results in recurrence.



FIGURE 66. Keloids may develop claw-like extensions or dumbbell-shaped ends.



FIGURE 67. Pyogenic granulomas are red and friable benign vascular tumors that arise spontaneously and grow rapidly.

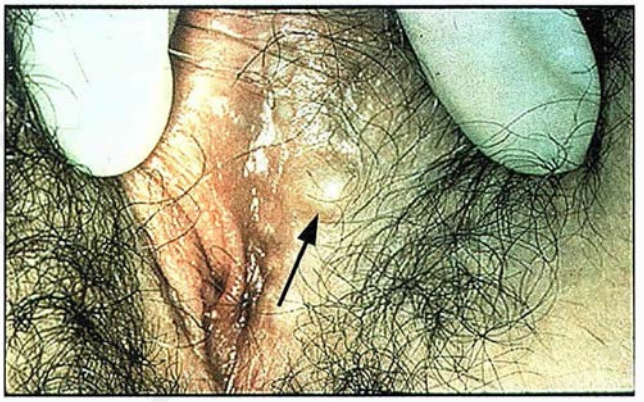

FIGURE 68. Epidermal inclusion cysts present as firm, nontender lumps. If they rupture, a local inflammatory response to the necrotic debris released can mimic infection. They often occur in the groin in both men and women.

Lipomas

Lipomas are benign collections of subcutaneous fat. They often occur as single lesions, but some patients may develop multiple lesions, particularly on the arms. Angiolipomas are a variant that may be tender. They are benign and do not require treatment but are often removed either for cosmetic reasons or to rule out a malignancy if atypical features are found.

KEY POINTS

- Dysplastic nevi removal should be reserved for those lesions that are changing, symptomatic, or stand out from the patient's other nevi.

(Continued)

HVC

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KEY POINTS *(continued)*

HVC
- Seborrheic keratoses, solar lentigines, acrochordons, melanocytic nevi, cherry angiomata, dermatofibromas, lipomas, and epidermal inclusion cysts are benign lesions that usually do not require biopsy or treatment.

Skin Cancers

Basal Cell Carcinoma

Basal cell carcinomas (BCCs) are the most common type of skin cancer. They arise from the basal layer of the epidermis and typically occur in sun-exposed areas on older persons with fair skin (**Figure 69**). BCCs may also be seen in younger persons who have an unusually high level of sun exposure or a genetic predisposition toward developing them. The risk of developing BCCs correlates strongly with cumulative sun exposure. Although they rarely metastasize, most have the ability to cause significant local tissue destruction if not removed. A skin biopsy is performed to confirm the diagnosis and the histologic subtype.

Most BCCs are of two histologic subtypes, nodular and superficial. Nodular BCCs are the most common. They typically present as "pearly" (translucent) telangiectatic papules (**Figure 70**); over time, they may develop a central area of erosion with rolled-up borders (sometimes referred to as a "rodent ulcer") (**Figure 71**). Superficial BCCs are well-demarcated, irregularly bordered, red patches; they tend to enlarge radially rather than invading into deeper structures (**Figure 72**). Several other subtypes of BCC may also be seen. Micronodular and infiltrative BCCs may resemble nodular BCCs clinically, but behave more aggressively, often with significant invasion of the surrounding dermis or subcutaneous tissue (**Figure 73**). Morpheaform BCCs often appear as flesh-colored or slightly erythematous plaques that resemble a scar. These are extremely infiltrative tumors and may extend much further into surrounding areas than their clinical appearance would suggest. Some BCCs are pigmented and may clinically resemble malignant melanoma.



FIGURE 69. A pearly telangiectastic plaque characteristic of nodular basal cell carcinoma. Photo courtesy of Christopher J. Miller, MD.

Treatment of BCCs depends on many factors, including the histologic subtype, location, size, cosmetic considerations, and patient's age and comorbidities. Surgery is generally the mainstay of treatment. Mohs surgery, a form of margin-controlled



FIGURE 70. Nodular basal cell carcinoma. Note the prominent telangiectasias on the surface. Photo courtesy of Christopher J. Miller, MD.



FIGURE 71. Classic nodular basal cell carcinoma. These lesions often have a rolled-up border and translucent appearance; ulceration may develop over time. Photo courtesy of Christopher J. Miller, MD.



FIGURE 72. Superficial basal cell carcinoma. Note the reddish-violet color and relatively well-demarcated border. Photo courtesy of Christopher J. Miller, MD.

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FIGURE 73. Over time, basal cell carcinomas can become quite large and ulcerate. They can cause significant local tissue damage. Photo courtesy of Christopher J. Miller, MD.

surgery that minimizes loss of normal tissue, is particularly useful for tumors in areas with limited surface area such as the head and neck, for large or recurrent tumors, or when cosmetic outcome is crucial. Superficial BCCs are often treated with cryotherapy, topical imiquimod, topical 5-fluorouracil, or photodynamic therapy. Nodular BCCs on the trunk and extremities are often treated with electrodesiccation and curettage. Radiation may be considered for patients with large tumors or those for whom surgery is not an option. Metastatic BCCs may be treated with vismodegib, which is a recently FDA-approved oral medication that interferes with the hedgehog signaling pathway; this signaling pathway is aberrant in most BCCs.

KEY POINTS

- Basal cell carcinomas typically occur in sun-exposed areas on older persons with fair skin, and although they rarely metastasize, most have the ability to cause significant local tissue destruction if not removed.
- Nodular basal cell carcinoma is the most common histologic subtype, typically presenting as "pearly" (translucent) telangiectatic papules that may develop a central area of erosion with rolled-up borders.

(Continued)

KEY POINTS *(continued)*

- Surgical excision is the mainstay of treatment for basal cell carcinoma; Mohs surgery should be reserved for head and neck lesions, large or recurrent tumors, or when cosmetic outcome is crucial; superficial lesions may be treated topically.

HVC

Actinic Keratoses and Squamous Cell Carcinoma in Situ

Actinic keratoses are red scaly macules and papules that occur in sun-exposed areas, generally in older persons (**Figure 74**). They have a "gritty" texture and are often easier to palpate than to see; they are typically diagnosed clinically rather than with biopsy (**Figure 75**). They are a precancerous condition; approximately 1% to 5% of these lesions will progress to invasive squamous cell carcinoma. Individual lesions are often treated with cryotherapy. In patients with a large number of actinic keratoses, treatment with topical preparations (such as 5-fluorouracil or imiquimod) or photodynamic therapy is often performed. Lesions that do not resolve with treatment require biopsy to rule out invasive squamous cell carcinoma.

Squamous cell carcinoma in situ (Bowen disease) is an advanced precancer or a noninvasive squamous cell carcinoma. It typically appears as reddish brown, well-demarcated, scaly patches on sun-exposed areas. Treatment is the same as for actinic keratoses, although surgery is occasionally required

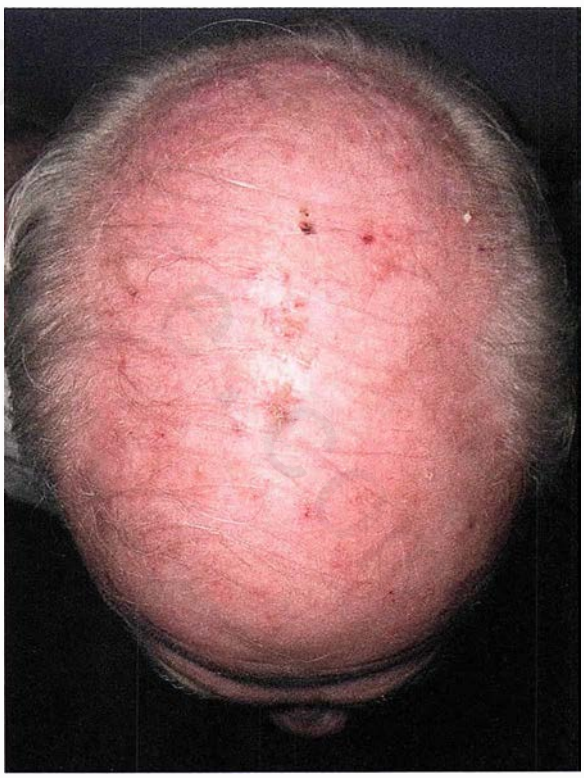

FIGURE 74. Multiple actinic keratoses on the scalp, a common location. Photo courtesy of Christopher J. Miller, MD.

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FIGURE 75. Actinic keratoses present as scaly red macules on sun-exposed areas; the dorsal hands are a common location. Photo courtesy of Christopher J. Miller, MD.

for lesions that are refractory to therapy. Lesions that develop exuberant scale or other atypical features should be biopsied to rule out invasive SCC (**Figure 76**).

Squamous Cell Carcinoma

Squamous cell carcinomas (SCCs) are the second most common type of skin cancer and the most common type of skin cancer seen in persons who are immunocompromised following solid organ transplant. They arise from epidermal squamous cells and typically present as red scaly papules and nodules on sun-exposed areas. Compared with BCCs, they tend to have more scale and lack the translucency seen in BCCs (**Figure 77**).

Although cumulative sun exposure remains the most important risk factor, additional factors are immunosuppression, arsenic exposure, human papillomavirus infection, and ionizing radiation exposure. SCCs may arise in chronic wounds or scars; a particularly aggressive form of SCC known as a Marjolin ulcer may arise in scars from burn injuries. Unlike most types of skin cancer, SCCs may occasionally be painful.

Although many tumors grow slowly and are relatively nonaggressive, certain subtypes may grow extremely rapidly and metastasize. High-risk features include tumor diameter greater than 2 cm, invasion beyond the subcutaneous fat, poor tumor differentiation, and perineural invasion (**Figure 78**). Tumors on the ear, lip, temple, and anogenital locations are also often associated with more aggressive growth for unknown reasons (**Figure 79** and **Figure 80**).

Because of their potential for aggressive behavior and metastasis, SCCs are generally treated surgically, with excision or Mohs surgery depending on the tumor size, location, and characteristics. High-risk lesions, particularly those with significant perineural invasion, may also be treated with adjuvant radiation therapy. Patients who are not candidates for surgery or in whom clear surgical margins are not achievable may be treated with radiation as the primary therapy.



FIGURE 77. Squamous cell carcinomas typically appear as scaly red nodules on sun-exposed skin. They often ulcerate. Photo courtesy of Christopher J. Miller, MD.



FIGURE 76. Squamous cell carcinoma in situ presents as a red or reddish-brown scaly flat plaque, typically in sun-exposed areas. It may be difficult to distinguish from superficial basal cell carcinoma. Photo courtesy of Christopher J. Miller, MD.



FIGURE 78. Squamous cell carcinomas arising in scars or chronic wounds can be particularly aggressive. Photo courtesy of Christopher J. Miller, MD.

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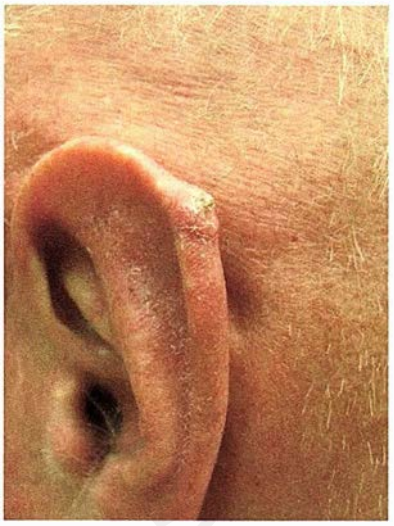

FIGURE 79. Scaly plaque typical of squamous cell carcinoma.



FIGURE 80. Squamous cell carcinoma more commonly occurs on the lower lip and may present as a nodule, ulcer, or indurated plaque. Photo courtesy of Christopher J. Miller, MD.

KEY POINTS

HVC
- Squamous cell carcinomas typically present as red scaly papules and nodules on sun-exposed skin and are treated with excision; Mohs surgery should be reserved for large tumors with high-risk characteristics in the head and neck region.
- Squamous cell carcinomas are the most common type of skin cancer seen in persons who are immunocompromised following solid organ transplant.

Keratoacanthomas

Keratoacanthomas generally appear as rapidly growing red nodules with a prominent central plug of scale and crust; their appearance is sometimes described as "volcaniform" since they resemble the cinder cone of a volcano (**Figure 81**). After a period of rapid growth, keratoacanthomas usually stabilize and then slowly involute, eventually resolving completely, even without treatment. Since some lesions fail to resolve completely and may persist and metastasize, they are usually treated with surgical excision.



FIGURE 81. Red scaly "volcaniform" nodule with central crust typical of keratoacanthoma. Photo courtesy of Christopher J. Miller, MD.

Malignant Melanoma

Although malignant melanoma is the third most common type of skin cancer, it is responsible for the majority of deaths because of its tendency to metastasize. Malignant melanoma is now the most common type of cancer in young women. It is estimated that approximately 1 in 49 persons will develop melanoma in their lifetime. Risk factors include having fair skin, a history of blistering sunburns, a family history of melanoma, numerous nevi (50+), or atypical-appearing nevi (dysplastic nevus syndrome). Although it can arise anywhere in the skin or mucous membranes, it most commonly occurs in sun-exposed areas. The back is the most common location in men, and the legs are the most common location in women. Persons with darker skin types tend to develop melanoma most commonly on acral sites such as the hands or the feet.

The clinical features that suggest melanoma are represented by the mnemonic "ABCDE," where "A" stands for Asymmetry, "B" for irregular Border, "C" for multiple Colors, "D" for Diameter greater than 6 mm, and "E" for Evolution, meaning increasing size (**Figure 82**). The more of these features a pigmented lesion possesses, the more worrisome it is for melanoma. Unfortunately, melanomas do not always adhere to these criteria; they may be red or flesh colored, smaller than 6 mm, perfectly symmetric, or homogeneously colored. Thus, a low threshold for biopsy should be present for any atypical-appearing skin lesion, changing or symptomatic nevus, or any mole that stands out from the background nevi pattern of the particular patient.

Melanoma may be further classified into several different subtypes. Lentigo maligna often arises on the face of elderly

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FIGURE 82. Classic malignant melanoma with asymmetry, an irregular border, multiple colors, and large size. Photo courtesy of Christopher J. Miller, MD.

persons. It tends to follow a more indolent course than other types of melanoma and may be present for many years before developing an invasive component. As the name would imply, it clinically often resembles a solar lentigo.

Superficial spreading melanoma is the most common type of melanoma and the most likely form to exhibit the atypical features identified by the "ABCDEs." It grows radially for a period of time, but ultimately develops an invasive component (**Figure 83**). Nodular melanomas are the most aggressive form and have an invasive component from the beginning; they are responsible for the majority of deaths from melanoma (**Figure 84**). Acral lentiginous melanomas are the most common type of melanoma seen in patients with darker skin tones and usually occur on the hands and feet (see Dermatologic Problems of Special Populations).

There are several prognostic features that predict how likely a melanoma will spread. The most important of these is the depth of invasion of the lesion, also known as the Breslow depth. The presence of ulceration and a mitotic rate greater than 1/mm^2 are additional negative prognostic indicators (**Figure 85**). Patients with melanomas are staged based on a tumor, nodal, and metastasis (TNM) system. Melanomas that are stage IB or higher are often candidates for sentinel node biopsy; patients with a negative sentinel node biopsy may not require complete lymph node dissection.

The skin biopsy is an important part of the diagnostic work-up for melanoma. Ideally, an atypical pigmented lesion should be removed using an excisional biopsy, in which the entire lesion is removed. Since this is not always practical or possible, additional options are sometimes used. These include



FIGURE 84. Nodular melanomas often present as uniformly dark blue or black, "berrylike" lesions that most commonly originate from normal skin. They can also arise from a preexisting nevus.



FIGURE 83. Superficial spreading melanoma with prominent asymmetric shape. Photo courtesy of Christopher J. Miller, MD.



FIGURE 85. The papular areas within a melanoma tend to correlate with the deepest depth of invasion. Photo courtesy of Christopher J. Miller, MD.

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punch biopsy, in which a sample of the lesion is removed using a cylindrical blade and sent for analysis. Although this type of biopsy generally provides a sample of adequate depth, there is concern about sampling error given that the area removed may not necessarily be representative of the remainder of the lesion. Similarly, although shave biopsies are often readily available and easy to perform, this technique carries the risk of transecting the melanoma if a deep enough sample is not taken. This would result in an underestimate of the true depth of the lesion, which could have implications regarding further work-up and management. A modified version of this technique, a "scoop" biopsy, is often employed; this technique is characterized by extension of the shave into the deep dermis or subcutaneous tissue to reduce the risk of transecting the specimen. If lentigo maligna is suspected, a broad shallow shave biopsy is often the preferred technique for two reasons: (1) the atypical cells are found at the dermal-epidermal junction, so transection is less of a concern; and (2) punch biopsies are prone to sampling error with this type of melanoma because of the occasionally subtle appearance and inconsistent distribution of the atypical cells.

Treatment of melanoma depends on the stage. Stage I and stage II lesions are treated surgically, with the margin of excision dependent on the depth of invasion of the lesion. Stage III melanoma is treated with a wide local excision, lymph node dissection, and occasionally adjuvant interferon alfa. Stage IV melanoma is treated with chemotherapy or immunotherapy; significant progress has been made recently in this area, and several new agents were recently FDA approved for the treatment of metastatic melanoma. Radiation plays a limited role in the management of melanoma and is generally used for palliation.

KEY POINTS

- The clinical features of malignant melanoma are Asymmetry, irregular Border, multiple Colors, Diameter greater than 6 mm, and Evolution or increasing size, or "ABCDE."
- The depth of invasion of the lesion (Breslow depth) is an important prognostic feature that predicts how likely a melanoma is to have spread.
- Stage I and stage II melanomas are treated surgically, with the margin of excision dependent on the depth of invasion of the lesion; stage III melanoma is treated with a wide local excision, lymph node dissection, and occasionally adjuvant interferon alfa; and stage IV melanoma is treated with chemotherapy or immunotherapy.

Pruritus

Pruritus, or the sensation of itch, can be severe and can reduce quality of life to the same extent as chronic pain. Pruritus is transmitted through C fibers in peripheral nerves and is a symptom of many skin and nonskin conditions. A history and physical examination can help narrow the likely possibilities (**Table 15**). All types of pruritus may result in scratching; therefore, findings of scratching on examination, such as excoriation, prurigo nodularis, and lichen simplex chronicus, may result from any of these causes.

Pruritus is a common problem for elderly persons. Xerosis (dry skin) is a common cause of itch in this age group. Itch without a rash may occur, and it is important to investigate for occult internal diseases (**Table 16**) and medications that may be contributing to the symptom. In patients taking multiple medications, it can be challenging to determine which drug(s) may be contributing to pruritus, as patients may develop medication-induced itch even after months or years on a drug. Opiates, calcium channel blockers, and, in some studies, statin medications are not uncommon causes.

When primary skin lesions are absent and pruritus is generalized, systemic causes of pruritus are suspected. An internal disease or medication is the cause in 14% to 24% of patients; the risk is less likely for younger patients, those with pruritus for less than 6 weeks, or persons with a recent history

TABLE 15. Classification of Pruritus

Classification	Examples
Dermatologic	Xerosis, eczema, psoriasis, urticaria, infestations
Neuropathic	Brachioradial pruritus, notalgia paraesthetica, postherpetic neuralgia, multiple sclerosis, trigeminal trophic syndrome
Psychogenic	Neurotic excoriations, prurigo nodularis, delusions of parasitosis
Systemic	Medications, liver disease (cholestatic or noncholestatic), HIV infection, chronic kidney disease, hematologic disorders (polycythemia vera, anemia), Hodgkin and non-Hodgkin lymphoma, internal parasite infection, and hyperthyroidism
Mixed	Combinations of two or more of the above

TABLE 16. Suggested Evaluation of Patients with Generalized Pruritus Without a Primary Rash

Complete blood count with differential
Serum iron, serum ferritin, total iron-binding capacity
Thyroid-stimulating hormone
Kidney function tests (blood urea nitrogen and serum creatinine levels)
Liver chemistry tests (serum total and direct bilirubin, alkaline phosphatase, γ-glutamyltransferase, aspartate aminotransferase, alanine aminotransferase)
Chest radiograph
Age- and sex-appropriate malignancy screening, with more advanced testing as indicated by symptoms (weight loss, early satiety)

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of a sick contact or travel. Liver diseases, primarily disease processes that result in cholestasis, can cause significant pruritus without primary skin lesions, but examination may demonstrate jaundice. Kidney disease can cause pruritus and, similar to liver disease, it is the final common pathway of organ failure that is associated with itch rather than a specific disease. Patients with end-stage kidney disease are most likely to be affected by pruritus ("uremic pruritus"). The investigation begins with the history including medication history (**Table 17**). A review of systems should be performed to investigate for thyroid disorders, lymphoma, kidney and liver diseases, and diabetes mellitus. Initial laboratory evaluation for occult systemic disease is outlined in Table 2. HIV antibody assay and chest radiography for lymphoma should also be considered. Hodgkin lymphoma is the malignant disease most strongly associated with pruritus.

Neuropathic pruritus describes itch that is caused by dysfunction of a peripheral or central nerve(s). Neurogenic itch is often localized to the alteration of a small number of nerves often from nerve injury and impingement; examples include surgery, accidental trauma, arthritis, neuropathy, or infection (postherpetic neuralgia). Brachioradial pruritus is localized pruritus of the forearm; radiologic changes in the cervical spine have been reported and may be due to arthritis or trauma including repeated minor traumas from sports or work.

Psychogenic itch describes localized or generalized pruritus associated with a concomitant diagnosis (or symptoms of) depression, anxiety, or somatoform disorders (**Figure 86**). The pruritus is often accompanied by great concern or anxiety by the patient and may flare in association with periods of reported stress. Self-reported depression is present in about 40% of persons with psychogenic pruritus. Psychogenic itch is often more severe during periods of inactivity such as when the patient is resting or attempting to fall asleep. It is important to examine patients carefully and to avoid missing a dermatologic or systemic cause of itch in those with concomitant psychiatric disease. One clue to diagnosis is that patients with psychogenic itch often present with erosions or ulcerations only in areas that can be reached by the patient.

When a dermatologic cause is found, therapy is tailored to the dermatosis. Topical glucocorticoids have anti-inflammatory effects and are a frequent therapy for patients with a primary dermatosis or evidence of inflammation. Glucocorticoids used for treatment of neurogenic or psychogenic pruritus may not result in improvement but will cause cutaneous adverse effects such as atrophy, striae, or hypopigmentation. In addition to glucocorticoids, there are several topical and systemic treatment options (**Table 18**). These can be used as monotherapy for nondermatologic causes or as adjuncts to treatment of dermatologic causes.

TABLE 17. Medications Most Commonly Associated with Pruritus (>15% Frequency)

Opioids
BRAF inhibitors (vemurafenib)
CTLA-4 antagonist (ipilimumab)
EGFR inhibitors (cetuximab)
HMG-CoA reductase inhibitors
Hydroxyethyl starch (HES)



FIGURE 86. Patients with psychogenic itch often report nonhealing sores, such as those seen on this patient's arm. The lesions often have a linear or irregular shape from repeated manipulation. Scars from previous episodes are often seen among the active lesions.

Patient education is critical to the management of any pruritic condition. Patients should be taught that scratching causes skin damage and inflammation (**Figure 87**), which contribute to an "itch-scratch-itch" cycle. It is also important to discuss the feasibility of widespread topical therapy. Topical medications may be difficult to apply because of limited range of motion, and systemic therapies are limited by sedative side effects and the risk of drug interactions resulting from polypharmacy.

KEY POINTS

- When pruritus without a rash occurs, a review of systems, physical examination, and laboratory tests should be done to investigate for thyroid disorders, lymphoma, kidney and liver diseases, and diabetes mellitus.
- Patients may develop medication-induced pruritus even after months or years on a drug.
- Glucocorticoid treatment of neurogenic or psychogenic pruritus often will not result in improvement but will cause cutaneous adverse effects, such as atrophy, striae, or hypopigmentation.

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TABLE 18. Treatment of Pruritus

Skin Directed	Comments
Changes in skin care: decreased use of or change in soaps and increased use of moisturizers and emollients	Soaps can be drying and contribute to pruritus. Patients can be counseled to limit soap use to the underarms, groin, and buttocks and to apply a moisturizer immediately after bathing. These changes are especially helpful for any patient with dry skin.
Topical glucocorticoids and topical calcineurin inhibitors	Treat cutaneous inflammation.
Menthol (1%-3%)-containing creams	Antipruritic effects, sensation of cooling.
Topical anesthetics (pramoxine, lidocaine)	Act as a local anesthetic, reduce sensory nerve transmission of itch.
Ultraviolet light (UVB)	Can be effective for dermatoses such as psoriasis and eczema as well as pruritus of kidney or hepatic origin.
Systemic	**Comments**
Antihistamines (diphenhydramine, hydroxyzine, doxepin)	Most effective for urticaria, otherwise relief is likely due to sedative effects.
Antidepressants	May alter the perception of pruritus in the cerebral cortex.
Tricyclic (mirtazapine, amitriptyline)	
SSRI (fluoxetine, paroxetine)	
Neuroleptics (gabapentin, pregabalin)	May inhibit central or peripheral nerve processing of itch.
Opioid receptor effectors (naltrexone, naloxone, butorphanol)	May inhibit central nerve transmission of pruritus signals through μ- and κ-opioid receptors.

SSRI = selective serotonin reuptake inhibitor.



FIGURE 87. Linear excoriations in a patient with cholestatic liver disease.

Urticaria

Urticaria (hives) are localized areas of edema associated with pruritus caused by mast cell degranulation and release of inflammatory proteins, including histamine, leukotrienes, complement, and prostaglandins. Each individual area of edema characteristically lasts less than 24 hours, although the state of "erupting in hives" may persist for days or weeks. The lesions often flare in one area while resolving in another, giving the perception that they are "moving around." Individual lesions can be very large (many centimeters) and may appear annular or polycyclic. The center of a lesion of urticaria is blanchable pink or clear skin (**Figure 88**).

These features distinguish urticaria from erythema multiforme (see Dermatologic Urgencies and Emergencies) in which the lesions have a purple, dusky, or bullous center and are fixed and not blanchable. Physical maneuvers that can help with diagnosis include circling lesions and seeing if they have resolved within 24 hours, and gently scratching uninvolved skin with the wooden end of a cotton swab or tongue



FIGURE 88. Edematous pink polymorphous papules and plaques on the neck caused by urticaria.

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depressor to see if urticaria can be induced in the scratched area (dermatographism). If the skin just turns red, this is not a positive test. The scratching must cause an edematous, red plaque (wheal). Histopathology of urticaria is often very subtle, and biopsy is rarely useful unless attempting to diagnose or exclude urticarial vasculitis.

Urticaria is divided into acute (the total course <6 weeks) and chronic (the total course lasting >6 weeks). The most common causes of urticaria are infections (viral, bacterial, parasitic, mycobacterial, including chronic occult infections) and medications such as NSAIDs, aspirin, and intravenous contrast (**Figure 89**). Foods and environmental exposures (animal dander or dust mites) may also be implicated. Acute urticaria in adults is almost always due to a viral infection or medication reaction, generally a medication taken within hours of the development of hives. Food-induced allergic reactions can be severe. Urticaria has also infrequently been associated with autoimmune thyroid disease and malignancies, particularly lymphoma. Physical urticaria is induced by a physical stimulus such as the sun, sweating, physical pressure, or cold temperature.

The diagnosis of urticaria is clinical and is based on the evanescent nature of characteristic wheals, itching, and supportive features such as dermatographism. In patients who have a negative review of systems, no fevers, and no extracutaneous symptoms, an extensive evaluation is not needed; evaluation should focus on pertinent positive findings on review of systems.

Treatment of urticaria is most effective with long-acting antihistamines since they help treat active disease and prevent new flares of urticaria. Typical first-line therapy is a long-acting H_1 blocker. If this fails, the combination of H_1 and H_2 blockers is often more effective. Short-acting antihistamines such as diphenhydramine and hydroxyzine are effective in treating acute urticaria, but because they are short acting, they are often not dosed consistently enough to prevent flaring. Systemic glucocorticoids and immunosuppressive agents have been used for urticaria, but in most patients, maximizing the dose of the long-acting antihistamines is equally effective and safer.



FIGURE 89. Drug-induced urticaria presenting as blanchable red patches on the flank.

Angioedema is a deeper and more exuberant form of localized urticaria with severe soft-tissue swelling due to inflammatory mediator–induced vascular permeability, often caused by food or medication allergies or Hymenoptera stings. Angioedema can be life threatening when it involves the airway and compromises breathing. Treatment for severe or life-threatening angioedema is systemic epinephrine and glucocorticoids; patients should be counseled to carry emergency medications with them if they are at risk for angioedema.

Hereditary angioedema differs from mast cell–associated angioedema. It is caused by the unregulated activation of the complement cascade due to lack of or ineffective function of C1 esterase inhibitor, leading to increased vascular permeability. It may cause sporadic, localized swelling involving the head and neck and may be differentiated from mast cell–associated angioedema by the lack of pruritus and absence of typical urticarial lesions. Diagnosis is by testing for quantitative and functional levels of C1 esterase inhibitor and C4 complement levels, although this evaluation is indicated only in patients with a compatible clinical history and examination findings and is not required in individuals with the more common presentation of urticaria.

KEY POINTS

- The diagnosis of urticaria is clinical and based on the presence of pruritic wheals (skin edema with blanchable, pink, or clear skin in the center that come and go); there is no need for an extensive evaluation in patients with a negative review of systems, no fevers, and no extracutaneous symptoms. HVC
- Treatment of urticaria is most effective with long-acting antihistamines.

Autoimmune Blistering Diseases

The autoimmune blistering diseases result from autoantibodies to different antigens in the skin and have similar but distinct presentations. Clinically, they are characterized by persistent pruritic to painful blisters with erosions and variable mucosal and ocular involvement and scarring (**Table 19**). These diseases often arise in older persons.

Identification and diagnosis of these disorders are important because of the associated morbidity and mortality. Although most of these diseases are idiopathic, medications can also cause variants of almost all the disorders (**Table 20**, on page 51), and a thorough medication history and review are essential. Referral for evaluation and optimal management is important.

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TABLE 19. Characteristics of Autoimmune Blistering Diseases

Disease	Clinical Characteristics	Pathology	Comments
Pemphigus vulgaris	Tender, fragile blisters and erosions seen in oral mucosa and skin; mucous membrane lesions much more common than in bullous pemphigoid; Nikolsky sign (rubbing of the skin results in blister formation) is positive	Suprabasilar clefting compared with subepidermal clefting seen in bullous pemphigoid DIF/IIF: intercellular pattern within the epidermis	Incidence varies by country and ethnicity and is estimated to be 0.5 to 3.2 cases per 100,000 persons per year
Pemphigus foliaceus	Scaling and crusted lesions on face and upper trunk, and erythroderma with no mucosal involvement; Nikolsky sign is positive	High granular or subcorneal clefting compared with suprabasal clefting seen in PV DIF/IIF: intercellular pattern within the epidermis	Incidence varies by country with estimated occurrence of 0.5 to 6.6 cases per million persons per year. Endemic pemphigus foliaceus (fogo selvagem) occurs in central and southwestern Brazil and Columbia and has a higher incidence with up to 50 cases per million persons per year and up to 3.4% of the population affected.
Paraneoplastic pemphigus	Painful oral, conjunctival, esophageal, and laryngeal erosions occur more commonly than in pemphigus vulgaris; it is a polymorphous skin eruption marked by confluent erythema, bullae, erosions, and intractable stomatitis; patients also have respiratory problems that may be fatal	Mixed pattern of both suprabasal acantholysis and interface dermatitis DIF/IIF: IgG binds in intercellular pattern within the epidermis; reactants at the dermal-epidermal junction. The combination of intercellular and subepidermal deposition of immunoreactants is a clue to the diagnosis.	High mortality rate (up to 90%) and association with underlying neoplasms: non-Hodgkin lymphoma (42%), chronic lymphocytic leukemia (29%), Castleman disease (10%)
IgA pemphigus	A vesicopustular eruption with clear blisters that rapidly transform into pustules; trunk and proximal extremities are most commonly involved with relative sparing of the mucous membranes	Subcorneal collection of neutrophils DIF shows deposition of intercellular IgA at the epidermal surfaces	Newly described disease with unknown frequency
Bullous pemphigoid	Tense blisters preceded by intense pruritus or urticarial lesions most commonly seen in the elderly on the trunk, limbs, and flexures; does not usually present with oral lesions	Subepidermal bullae without acantholysis and with prominent eosinophils DIF shows linear IgG deposition at the basement membrane zone	One of most common autoimmune blistering diseases with up to 4.3 cases per 100,000 persons per year
Epidermolysis bullosa acquisita	Mechanically induced bullae and erosions mostly on extensor areas that heal with scarring and milia	Subepidermal cleavage without acantholysis DIF shows IgG deposition at the basement membrane zone that localizes to the base on salt-split skin	Rare disease with unknown frequency Can be associated with inflammatory bowel disease
Cicatricial pemphigoid	Presents with bullae, erosions, milia, and scarring seen on mucous membranes and conjunctivae of middle-aged to elderly persons; oral mucosa is almost always involved; conjunctival lesions are also common	Histology is similar to bullous pemphigoid DIF may reveal patterns similar to bullous pemphigoid, linear IgA bullous dermatosis, or epidermolysis bullosa acquisita	Rare disease with estimated incidence of 0.9 to 1.1 cases per million persons per year Increased risk for malignancy in some patients Prompt treatment should be initiated to avoid permanent ocular and oral scarring

(Continued on the next page)

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TABLE 19. Characteristics of Autoimmune Blistering Diseases *(Continued)*

Disease	Clinical Characteristics	Pathology	Comments
Dermatitis herpetiformis	Severely pruritic grouped vesicles or erosions on elbows, knees, back, scalp, and buttocks; lesions occur in crops and are symmetrically distributed; often the vesicles are not seen because the process is so itchy that they are almost immediately broken	Histology shows neutrophilic infiltrate at the tips of the dermal papillae causing subepidermal separation DIF shows granular IgA deposition	Common blistering disease with 10-11 cases per 100,000 persons per year Nearly all patients with dermatitis herpetiformis will have celiac disease
Linear IgA bullous dermatosis	Pruritic, discrete, or clustered bullae in a herpetiform pattern ("cluster of jewels"); annular or polycyclic lesions with vesicles and bullae at the periphery are common	Subepidermal bullae with neutrophils Can be indistinguishable from DH, EBA, or bullous lupus DIF shows linear IgA deposition	In adults, the estimated incidence is 0.6 cases per 100,000 persons per year Ocular involvement can occur. A variant can occur in children called chronic bullous dermatosis of childhood
Porphyria cutanea tarda (and pseudoporphyria)	Erosions and bullae on hands and forearms, and occasionally face and feet that heal with milia, hyperpigmentation, hypopigmented scars. Porphyria cutanea tarda (but not pseudoporphyria) can also present with hypertrichosis on the face	Subepidermal bullae with little inflammation; dermal papillae protrude upward into the blister cavity and thickened upper dermal capillary walls DIF: deposition of immunoglobulins and complement around the dermal capillaries and linear at the basement membrane zone	Common disorder with estimated incidence of 1 case per 25,000 persons per year Not a true autoimmune blistering disorder but should be included in the differential diagnosis Can be associated with hepatitis C infection

DIF = direct immunofluorescence; IIF = indirect immunofluorescence; DH = dermatitis herpetiformis; EBA = epidermolysis bullosa acquisita; PV = pemphigus vulgaris.

Recognition and Diagnosis

Autoimmune blistering disorders should be suspected in any patient with persistent or recurrent blisters involving the skin, eyes, or oral and genital mucosa. The clinical presentation can vary depending on the underlying disorder, ranging from large urticarial plaques to flaccid blisters that may almost instantly rupture and appear as erosions to intact tense bullae. The extent of body surface area involved can vary in autoimmune blistering disorders. There may be minimal involvement of only localized blisters on the extremities to more extensive involvement of nearly the entire body surface area. As the blisters resolve, erosions, hyperpigmentation, and in some patients, scarring can occur. Pain can predominate when erosions and broken skin are present. In addition, some disorders (bullous pemphigoid) can present with significant pruritus. Thorough examination of the eyes, oral mucosa, and genital/perianal mucosa should be performed because permanent scarring can result leading to blindness and vaginal or oral contractures. Mucosal variants also can occur, and evaluation for an underlying autoimmune condition should be considered in patients with persistent mucosal erosions. In pemphigus, the blisters are flaccid and result in early blister erosion with subsequent superficial crusting (**Figure 90**), whereas in bullous pemphigoid, urticarial-like lesions, tense bullae, and a peripheral eosinophilia may be present (**Figure 91**). Cicatricial pemphi-



FIGURE 90. The flaccid intradermal blisters of pemphigus vulgaris are readily broken, leaving large weeping, denuded lesions and crusting.

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TABLE 20. Drug-Induced Autoimmune Blistering Disorders

Condition	Medications
Pemphigus	Thiol group (D-penicillamine, captopril, gold, pyritinol)
	Amoxicillin
	Ampicillin
	Cephalosporins
	Rifampin
Pemphigoid	Furosemide
	Amoxicillin
	Ampicillin
	Phenacetin
	Penicillin
	Penicillamine
	PUVA
	β-Blockers
	Terbinafine
Cicatricial pemphigoid	Penicillamine
	Indomethacin
	Practolol
	Clonidine
	Topical pilocarpine
Linear IgA bullous dermatosis	Vancomycin
	Captopril
	Amoxicillin
	Ampicillin
	Diclofenac
	Lithium
Pseudoporphyria	Furosemide
	Naproxen
	Oxaprozin
	Tetracycline
	Voriconazole

PUVA = psoralen-ultraviolet A light.

goid can be localized to the scalp and cause significant scarring. Epidermolysis bullosa acquisita and porphyria cutanea tarda (and pseudoporphyria, which presents the same as porphyria cutanea tarda but is medication induced) present with small blisters in areas of friction such as the dorsal hands, and scars and milia form with resolution of blisters (**Figure 92**).

Differentiation of the autoimmune blistering diseases can be made based on clinical features, but definitive diagnosis requires histopathologic examination and in some patients serologic testing for pathogenic antibodies. Depending on the location of the targeted antigen, flaccid or tense bullae will be present clinically, and the corresponding separation can be



FIGURE 91. Tense bullae on erythematous base with some areas of eroded skin are seen in bullous pemphigoid.



FIGURE 92. A chronic blistering skin disease on sun-exposed skin with erythema, bullae, erosions, and small milia, especially the back of the hands, consistent with porphyria cutanea tarda.

appreciated using histopathology. In pemphigus, flaccid blisters correspond with suprabasilar separation (**Figure 93**), whereas tense bullae correspond with subepidermal blisters in bullous pemphigoid and epidermolysis bullosa acquisita.

Two biopsies often are performed: one of lesional skin for histology and one of perilesional normal skin in order to perform direct immunofluorescence and identification of specific immunoglobulins that react with the skin. Both the type of immunoreactants (IgG, C3, IgA) and the pattern are helpful in diagnosis.

Serum from affected patients also can assist in diagnosis. The blood can be reacted with different substrates and will determine if circulating antibodies are present (indirect immunofluorescence). Tests such as serum enzyme-linked immunosorbent assays have been developed that detect the presence of specific antibodies in pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid and may correlate with disease activity.

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FIGURE 93. The superficial blisters in pemphigus foliaceus result in multiple erosions and crusting (similar to "corn flakes"). Intact vesicles are not seen regularly.

Although many of these disorders are idiopathic, they may be associated with other diseases that need to be considered. Pemphigus, bullous pemphigoid, and linear IgA bullous dermatosis have been reported in association with other autoimmune diseases including diabetes mellitus, rheumatoid arthritis, and thyroid disease.

Several of these disorders have also been associated with malignancy. Paraneoplastic pemphigus is highly associated with underlying leukemia, lymphoma, and Castleman disease. Cicatricial pemphigoid, and more rarely epidermolysis bullosa acquisita, may be seen in patients with an underlying cancer. Age-appropriate screening and a thorough review of systems are important in these patients. Patients with dermatitis herpetiformis almost uniformly have underlying celiac disease, although it may be asymptomatic in up to one third of patients, and this should be appropriately evaluated. Additionally, epidermolysis bullosa acquisita has been reported in association with inflammatory bowel disease.

Treatment

Management of autoimmune blistering disorders depends on the extent of skin and mucosal involvement, patient comorbidities, and the specific underlying blistering disorder. Medications that suppress the immune system are often required. In drug-induced cases, cessation of the causative medication is essential, but additional immunosuppressive therapy may still be required.

For limited disease, potent topical glucocorticoids may be sufficient. In most patients, systemic therapy is required, often with multiple therapies. Because of its quick onset of action, prednisone is usually the initial therapy. Additional medications, including immunosuppressants such as azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil are often necessary to control the disease. Intravenous immune globulin and anti-inflammatory agents such as tetracycline class antibiotics also have been used. Recently, rituximab has been shown to be effective in pemphigus and could potentially be helpful in other autoimmune blistering diseases. Ocular cicatricial pemphigoid often requires rapid, aggressive therapy, or scarring can quickly develop. Dapsone is effective in conditions with a predominance of neutrophils in the inflammatory infiltrate including dermatitis herpetiformis, IgA pemphigus, and linear IgA bullous dermatosis. In dermatitis herpetiformis, a gluten-free diet is first-line treatment because of the association between dermatitis herpetiformis and celiac disease and an increased risk of bowel lymphoma, but additional therapy often is required.

Disease remissions can occur, but long-term immunosuppressive therapy often is required. Because of the erosions and breakdown in the skin barrier, secondary bacterial and viral infections can occur in these patients, and a high index of suspicion and cultures are often necessary for evaluation.

KEY POINTS

- The autoimmune blistering diseases are characterized by persistent pruritic to painful blisters with erosions and variable mucosal and ocular involvement and scarring.
- Medications that suppress the immune system are often required to treat autoimmune blistering diseases; in drug-induced cases, cessation of the causative medication is essential, but additional immunosuppressant therapy may still be required.

Cutaneous Manifestations of Internal Disease

Rheumatology

Lupus Erythematosus

The cutaneous manifestations of lupus erythematosus (LE) are essential for clinicians to recognize because skin findings are key diagnostic criteria. Because the subtypes of lupus are important to distinguish, the dermatologic examination is crucial. Skin lesions may be either specific or nonspecific. "Lupus-specific" skin lesions are cutaneous signs of lupus that are characteristic of the disease and when biopsied show diagnostic histologic findings ("interface reaction" of lymphocytes at the dermal-epidermal junction causing damage

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to the base of the epidermis). In addition, patients with lupus can also experience "lupus nonspecific" skin lesions representing cutaneous sequelae of the disease (**Table 21**).

The malar rash of acute cutaneous lupus consists of bright erythematous patches over both cheeks and the nasal bridge, almost always sparing the nasolabial folds (in contrast to the more violaceous facial erythema of dermatomyositis, which often involves that crease) (**Figure 94**). Other commonly mistaken entities include rosacea, which often has inflammatory papules and small pustules, as well as telangiectasias, both of which are rare to absent in lupus, and seborrheic dermatitis, which is often characterized by a greasy scale and tends to involve the nasolabial folds, eyebrows, and often the scalp as well.

The classic "discoid lupus" lesion is a dyspigmented patch or plaque that may be either atrophic or hyperkeratotic, with associated scarring within lesions. These occur in sun-exposed areas such as the face and scalp or within the conchal bowl of the ear (**Figure 95**).

A less widely known subtype of cutaneous lupus is subacute cutaneous LE (SCLE). The typical clinical eruption consists of circular or polycyclic scaly erythematous patches and papulosquamous plaques over the forearms, chest, or especially the upper back, in a V-shaped configuration.

TABLE 21. Types of Lupus Lesions

Lupus-Specific Skin Lesions	Nonspecific Cutaneous Manifestations of Lupus
Malar "butterfly" rash (acute lupus)	Livedo reticularis
Annular scaly patches (subacute lupus)	Vasculitis
Psoriasiform patches (subacute lupus)	Urticaria (generally atypical urticarial lesions lasting more than 24 hours and leaving bruising)
Discoid lesions (chronic cutaneous lupus)	Lobular panniculitis
	Oral ulcers
	Alopecia



FIGURE 94. Erythematous plaques involving the bridge of the nose and malar areas with sparing of the nasolabial folds characteristic of acute cutaneous lupus erythematosus.



FIGURE 95. Discoid lupus erythematosus with active lesions characterized by erythematous-to-violaceous inflammatory patches and plaques with raised borders and scaling, and chronic areas of damage consisting of hyper- or hypopigmented-to-dyspigmented, scarred, atrophic, depressed plaques.

Less common variants of cutaneous lupus are lupus panniculitis, with inflammation confined to the fatty areas, which often presents with dell-like (shallow, smooth) depressions of the proximal extremities; bullous lupus erythematosus, which may present with blisters within or around the more classic lupus lesions; and tumid lupus, which presents with deeply indurated subcutaneous plaques.

Patients with the malar rash of acute LE should receive a thorough evaluation for systemic involvement. These patients are at high risk for lupus nephritis and severe internal disease. Diagnosis of SCLE should prompt evaluation of patients' medications, as this eruption is associated with a long list of potential causative medications, including hydrochlorothiazide, calcium channel blockers, ACE inhibitors, terbinafine, and the TNF-α inhibitors. Patients with SCLE are often photosensitive and frequently will be seropositive for antinuclear antibody (ANA), anti-Ro/SSA, or anti-La/SSB antibodies. Antihistone antibody positivity is nonspecific but may be a clue that the reaction is associated with a medication, although this is only present in about one third of patients (even if a medication may be the cause). A subset of patients with SCLE will have kidney involvement, and a thorough evaluation is warranted. Recognition of this entity is essential as patients may be inappropriately treated for systemic lupus erythematosus (SLE) when they have drug-induced SCLE, and discontinuation of the inciting causative medication is paramount. Patients with discoid lesions of chronic cutaneous lupus frequently develop irreversible scarring and may require early aggressive therapy even in the absence of significant systemic involvement.

Lupus, like many autoimmune skin diseases, is exacerbated by ultraviolet (UV) light. Patients with stable disease may experience severe disease flares when on trips to sunny

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locations or as the seasons shift toward spring and summer. Photoprotection is an essential part of therapy. Patients should be counseled to avoid sun exposure, wear UV-blocking clothing, and apply and re-apply broad-spectrum sunblock (including extended-spectrum UVA-blocking chemical sunscreens, often in conjunction with physical blocking agents such as zinc oxide and titanium oxide). Most medications for cutaneous lupus are used "off label." Topical glucocorticoids, topical tacrolimus, topical retinoids, and injections of glucocorticoids may help improve individual lesions or limited skin disease. First-line systemic therapy is with antimalarial agents, usually hydroxychloroquine. Patients with refractory disease will sometimes respond to thalidomide; additional options include alternate or combination antimalarial drugs, methotrexate, mycophenolate mofetil, cyclosporine, dapsone, and combination immunosuppressant therapy. Patients who fail to respond to antimalarial agents, or those with extensive skin involvement or signs of scarring, should be referred to a specialist.

KEY POINTS

- Patients with the malar rash of acute lupus erythematosus should receive a thorough evaluation for systemic involvement; they are at high risk for lupus nephritis and severe internal disease.
- Subacute cutaneous lupus erythematosus is a drug-induced, photosensitive eruption of circular, scaly, erythematous patches over the forearms, chest, or upper back; potential causes such as hydrochlorothiazide, calcium channel blockers, ACE inhibitors, terbinafine, and the TNF-α inhibitors should be identified and discontinued immediately.
- Sun protection, topical glucocorticoids, and hydroxychloroquine are used to treat cutaneous lupus erythematosus.
- First-line systemic therapy for cutaneous lupus erythematosus is with antimalarial agents, usually hydroxychloroquine.

Dermatomyositis

Dermatomyositis can occur as the classic form, with skin involvement and muscle inflammation, or as amyopathic or hypomyopathic dermatomyositis, with either cutaneous disease only or with minimal muscle inflammation, respectively. Amyopathic dermatomyositis is almost as common as classic dermatomyositis, and recognition of the cutaneous features is essential (see MKSAP 17 Rheumatology).

The pathognomonic cutaneous features of dermatomyositis are the heliotrope rash and Gottron papules. The heliotrope rash is named after a purple flower, heliotrope, which moves to face the sun, an apt name that captures both the characteristic color of the cutaneous inflammation in dermatomyositis and the important role that ultraviolet light may play in exacerbating this disease. The heliotrope rash is a distinctive purple or lilac erythema of the eyelids that may be accompanied by edema (**Figure 96**).

Gottron papules are erythematous-to-slightly-violaceous, flat, atrophic-appearing papules concentrated over taut, stretched extensor surfaces, particularly the interphalangeal joints or elbows (**Figure 97**). Patients frequently exhibit inflammation of the proximal nail fold, which may be flat, atrophic, and pink, and often shows periungual telangiectasias or frayed cuticles.

Patients with dermatomyositis often exhibit cutaneous inflammation directly overlying the joints of the hands (namely, the proximal interphalangeal, distal interphalangeal, and metacarpophalangeal joints), whereas patients with lupus often exhibit cutaneous inflammation in the overlying space *between* the joints. Patients with dermatomyositis will frequently have areas of poikiloderma with ill-defined patchy erythema and "salt-and-pepper" dyspigmentation accompanied by telangiectasias on the chest or upper back. There may be slightly violaceous erythema over the "V" of the neck, chest, and the upper



FIGURE 96. The heliotrope rash of dermatomyositis is a distinctive purple or lilac, symmetric erythema of the eyelids that may be accompanied by slight edema, generally focused around the orbits.



FIGURE 97. Gottron papules are violaceous slightly scaly plaques over the bony prominences on the hands.

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back (the "Shawl sign") (**Figure 98**) or on the lateral hips (the "holster sign"). Patients may have violaceous erythema of the face, frequently involving the nasolabial fold, upper extremities, and trunk. Scalp erythema is very common in dermatomyositis. Patients with dermatomyositis frequently report lesional pruritus. These patients typically have normal serum creatine kinase and aldolase levels, but may have evidence of subclinical muscle inflammation on MRI or electromyogram. Notably, patients may have amyopathic dermatomyositis with no evidence of muscle involvement; recognition of this entity is absolutely essential as patients with amyopathic dermatomyositis are at the same risk of internal disease as patients with the classic form.

"Mechanic's hands," or thickened, scaly, hyperkeratotic skin on the tips of the fingers, is associated with interstitial lung disease, and physicians should consider baseline imaging and pulmonary function testing, including DLCO measurement in these patients.

Dermatomyositis is often difficult to treat. Similar to those with LE, patients with dermatomyositis should practice strict sun avoidance, wear protective clothing, and frequently apply broad-spectrum sunscreen. Topical glucocorticoids may be effective in some patients. Systemic therapy is limited to off-label treatment and usually consists of antimalarial agents (such as hydroxychloroquine, chloroquine, quinacrine), or methotrexate or mycophenolate mofetil; there are anecdotal reports describing the use of intravenous immune globulin, dapsone, and some of the newer biologic agents.

KEY POINTS

- The pathognomonic cutaneous features of dermatomyositis are the heliotrope rash and Gottron papules.
- Dermatomyositis may often be treated effectively with sun protection and topical glucocorticoids; systemic therapy usually consists of antimalarial agents.



FIGURE 98. Dermatomyositis: erythema of the "V" of the neck and chest. There are photodistributed erythematous macules and patches with areas of poikiloderma on the sun-exposed part of the upper chest.

Vasculitis and Vasculopathy

Vasculitis, an inflammation of the blood vessels, can be caused by different types of inflammatory cells, and the inflammation may occur in different-sized blood vessels. The clinical manifestations, histology, serologies, organs affected, and treatment depend on the size of the blood vessel affected. Vasculopathy is an injury to the blood vessel from intravascular or luminal processes. This can be a depositional process, such as calciphylaxis, in which the vessel wall is infiltrated with calcium and subsequent thromboses, or a thromboembolic process, wherein clots form or embolize to damage the vasculature, such as in cryoglobulinemia or antiphospholipid antibody syndrome.

Livedo Reticularis

Livedo reticularis is a subtle, lacy network of faintly pink or bluish red vessels, usually seen on the lower legs (**Figure 99**). It is due to sluggish blood flow through the vessels, but



FIGURE 99. Livedo reticularis is a cutaneous reaction pattern that produces a pink or bluish-red, mottled, netlike pattern on the skin. It is caused by slow blood flow through the superficial cutaneous vasculature. It most commonly affects the lower extremities.

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extravasation of blood does not occur, differentiating it from purpura or ecchymoses. Livedo reticularis can sometimes be elicited by keeping a leg in the dependent position; if this resolves when the leg is straightened horizontally, it is likely to be a normal or physiologic process rather than a pathologic process. Livedo reticularis is a nonspecific finding and may be seen in any condition in which there is altered blood flow through the superficial vasculature. Although typically transient, livedo reticularis may sometimes persist, and if advanced or long-standing, ulceration may rarely occur (**Table 22**).

Purpura

Purpura is the result of vascular compromise, either from vessel inflammation or plugging, causing subcutaneous microhemorrhage. The nonblanching red or purple skin lesions result from the presence of extravascular erythrocytes within the dermis. Purpuric lesions should be distinguished from ecchymoses, as ecchymotic lesions are typically small, superficial, nonpalpable, and display multiple colors ranging from red and purple to yellow and green from the breakdown of heme. The smallest purpuric macules are petechiae, which are pinpoint nonblanching red macules usually seen in the setting of low or abnormal platelet counts. Purpuric macules and flat patches may occur on sun-exposed areas (actinic or solar purpura) or in patients on chronic glucocorticoid therapy (due to thin, fragile skin and vasculature).

Small Vessel Vasculitis

A palpable area of the purpura, usually a small pinpoint barely perceptible papule within the purpuric macule, may be a clue to an active superficial skin or small vessel vasculitis. Small vessel vasculitis (also called leukocytoclastic vasculitis or cutaneous leukocytoclastic angiitis) is inflammation of the smallest blood vessels. This inflammation may affect the skin, but thorough evaluation of all other small vessels is essential. The palpable purpuric lesions tend to occur rapidly and simultaneously, often initially or more prominently in dependent areas and areas of pressure (including elastic waistbands and sock lines). Small vessel vasculitis symptoms may range from asymptomatic to mild itch to burning and tenderness (**Figure 100**). Rapid diagnosis is important, as small vessel vasculitis may affect internal organs. Diagnosis is made by skin biopsy. Any purpuric lesions with a palpable component require thorough investigation and may warrant a dermatology consultation.



FIGURE 100. Palpable purpura on the lower leg and dorsal foot. The nonblanching red macules and small papules indicate areas of small vessel vasculitis and extravasated blood due to vessel injury.

TABLE 22. Selected Diseases and Conditions Associated with Livedo Reticularis

Disease/Condition	Example
Neurohumoral diseases	Pheochromocytoma, carcinoid syndrome
Hematologic diseases	Polycythemia vera, leukemia, thrombocytosis
Hypercoagulable states	Antiphospholipid antibody syndrome
Paraproteinemias	Multiple myeloma and associated type 1 cryoglobulinemia
Autoimmune diseases	Systemic lupus erythematosus, dermatomyositis, scleroderma, Sjögren syndrome, Still disease, rheumatoid arthritis, Felty syndrome
Infections	Parvovirus B19, hepatitis C, syphilis, meningococcemia, pneumococcal sepsis, tuberculosis
Drug reactions	Amantadine, quinidine, warfarin, minocycline
Vasculitides	Polyarteritis nodosa, granulomatosis with polyangiitis, microscopic polyarteritis, eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome), Takayasu disease, temporal arteritis
Calciphylaxis	End-stage kidney disease with abnormal calcium-phosphorus product
Cholesterol emboli	Often following an intravascular procedure such as angiography
Endocarditis	—
Microvascular occlusion syndromes	Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, heparin necrosis, paroxysmal nocturnal hemoglobinuria
Cryoglobulinemia	—

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CONT.

Another form of small vessel inflammation is urticarial vasculitis, which presents with either persistent urticarial plaques lasting longer than 24 hours or urticaria that presents with tingling pain rather than pruritus and resolves with bruise-like hyperpigmentation. Biopsy is important, as urticarial vasculitis is associated with underlying autoimmune disease, most commonly SLE, in 50% of patients.

Small vessel vasculitis is frequently idiopathic but may occur in the setting of infection or sepsis, underlying autoimmune disease, medication reactions, or, rarely, malignancy. Patients should be evaluated for extracutaneous manifestations, with particular attention to kidney involvement, and the laboratory evaluation may include a urinalysis, comprehensive metabolic panel, complete blood count, serum complement levels, antinuclear antibody titer, and evaluation for intravascular infection when appropriate. A thorough history and review of systems are necessary to assess for internal manifestations and to identify any potential triggers. Drug-induced vasculitis is not common, but there is a wide range of potential culprit medications to consider (antibiotics, particularly penicillins; NSAIDs; hydralazine; anti-TNF-α agents; and some targeted chemotherapeutic agents). In the inpatient setting, small vessel vasculitis is frequently seen in patients with infective bacterial endocarditis or antibiotic use. If endocarditis or antibiotics is a potential culprit, consultation with an experienced dermatologist is essential. For mild cases, it may be appropriate to continue antibiotics and monitor for progression; if the vasculitis improves, it may have been due to the endocarditis. If the vasculitis worsens or affects organs beyond the skin (that is, if there is kidney involvement), changing the antibiotic regimen should be considered. Depending on the severity of the eruption, skin-limited cutaneous small vessel vasculitis can be managed with rest and elevation, topical glucocorticoids, NSAIDs (unless implicated as a potential causative agent), or antihistamines. As the pathologic process is neutrophil-mediated, colchicine or dapsone may be effective in select patients. Patients with severe eruptions, including rare bullous eruptions or ulcerative lesions, or those with widespread disease may require systemic glucocorticoids. Most patients with small vessel vasculitis have resolution after a single episode or when the trigger is identified; approximately 10% of patients will have a chronic, intermittent course.

KEY POINTS

- Palpable purpura is a manifestation of small vessel vasculitis, and rapid diagnosis with skin biopsy is essential as the vasculitis may progressively affect internal organs (kidneys) and require systemic treatment.
- Skin-limited cutaneous small vessel vasculitis can be managed with rest and elevation, topical glucocorticoids, NSAIDs, or antihistamines.

Cryoglobulinemia

Cryoglobulins are cold-precipitating immunoglobulins that typically remain soluble at body temperature but may precipitate in the peripheral vasculature away from the warmer body core. This intravascular precipitation leads to small vessel fibrin thrombi and clotting, vascular injury that may include an active inflammatory vasculitis, and downstream tissue ischemia (**Figure 101**). Clinically, this presents as either palpable purpura (if there is an inflammatory small vessel vasculitis due to specific types of cryoglobulins that lead to complement fixation) or retiform, angulated purpura (see MKSAP 17 Rheumatology).

Rheumatoid Arthritis

The skin is involved in a subset of patients with rheumatoid arthritis (RA), either from cutaneous manifestations of the disease or complications of treatment. Rheumatoid nodules are the most common cutaneous manifestation of RA, occurring in up to one third of patients. These are typically firm subcutaneous nodules found over extensor joints or tendons (**Figure 102**). They may come and go in parallel with the underlying joint inflammation during treatment. The phenomenon of "accelerated nodulosis," or skin nodules developing rapidly while the



FIGURE 101. Large area of jaggedly branching, angulated retiform purpura consistent with a vascular injury process. In this patient, type 1 cryoglobulins precipitated in the small vessels of the skin, leading to intravascular clot formation and vessel injury, with overlying skin necrosis.



FIGURE 102. Firm, flesh-colored papules over the extensor elbow joint consistent with multiple rheumatoid nodules in a patient with rheumatoid arthritis.

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arthritis is being treated and responding, has been noted as a side effect of many RA medications, particularly methotrexate. Other forms of granulomatous dermatitis seen in RA are palisaded neutrophilic and granulomatous dermatitis, characterized by symmetric, crusted, umbilicated, pink papules around the elbows, and interstitial granulomatous dermatitis, which classically manifests as a linear erythematous cord on the trunk. A rare skin manifestation of RA is rheumatoid vasculitis, which is generally seen in patients with chronic, severe RA. It may present as ulcerated purpura or severe livedo reticularis. Patients with RA who are treated with TNF-α inhibitors may develop a secondary psoriasiform eruption, including severe palmoplantar pustular dermatitis.

Sclerosing Disorders

Sclerosing disorders are discussed comprehensively in the MKSAP 17 Rheumatology section. Patients with all forms of sclerosing disorders may exhibit skin findings ranging from "puffy hands" of early diffuse systemic sclerosis (scleroderma), to diffuse skin tightening of advanced diffuse systemic sclerosis, to the characteristic calcinosis, Raynaud phenomenon, esophageal dysfunction syndrome, sclerodactyly, and telangiectasias of limited diffuse systemic sclerosis (CREST).

Morphea, or localized scleroderma, usually presents as a focal patch of skin thickening without internal manifestations. Morphea may occur as one or a few patches (circumscribed), widespread patches (generalized), linear or diffuse patches (pansclerotic). When morphea extends over joint spaces, it can impact the muscles, bones, and joint mobility. Recognition is important, as patients are at risk of being misclassified as having systemic sclerosis and thus are inappropriately treated. It is important to exclude scleroderma and CREST syndrome, and then management should be focused on symptom control, range of motion preservation (if a joint is affected), and prevention of new lesions with immunomodulatory or immunosuppressive agents. While there is limited evidence of efficacy, patients may be treated with glucocorticoids, hydroxychloroquine, methotrexate, phototherapy, and sometimes anti-TNF agents, or other immunomodulatory or immunosuppressive agents, depending on the severity and extent of the disease.

Nephrology

Both chronic kidney disease and advanced liver disease are commonly associated with intense, severe pruritus, attributed to the accumulation of toxins. Patients with end-stage kidney disease often exhibit dry, xerotic skin and commonly have secondary skin changes from chronic itching and scratching, including excoriations, prurigo nodules, and lichenified patches. Some patients may develop hyperpigmented umbilicated papules with a central keratin core, or Kyrle disease, in which collagen fibers are extruded through the epidermis. Pruritus from kidney disease should be managed with lukewarm baths, gentle soaps, and thick, bland emollients; severe pruritus may require topical glucocorticoids or phototherapy. Two entities encountered in chronic kidney disease warrant particular mention, calciphylaxis and nephrogenic systemic fibrosis.

Calciphylaxis

Calciphylaxis typically occurs in patients with advanced kidney dysfunction and elevated calcium-phosphorus products (>60-70 mg^2/dL^2). Calciphylaxis occurs as a result of abnormal deposition of calcium within the lumen of arterial vasculature, which then compromises flow and leads to an increased risk of luminal thrombosis and downstream ischemia, resulting in subsequent painful tissue necrosis. Notably, a single measurement of normal calcium and phosphorus levels does not exclude the diagnosis. Patients receiving dialysis may have marked fluctuations in serum mineral levels, and the calcium-phosphorus levels may be normal at the time of calciphylaxis diagnosis but may have been markedly abnormal at the onset of disease that developed weeks before patient presentation. Calciphylaxis is rare, occurring in less than 5% of patients on dialysis, but is associated with a 60% to 80% 1-year mortality rate. Generally, patients have nonhealing skin ulcers that develop an eschar and secondary bacterial colonization and eventual infection and sepsis. Clinically, lesions of calciphylaxis are exquisitely painful subcutaneous nodules or plaques with overlying red-brown discoloration and often superimposed angulated purpuric patches, often with central necrosis. Patients with advanced calciphylaxis may have ulceration or large, thick, black eschar formation. Lesions usually occur in high-fat areas and are commonly seen on the lower extremities (especially the thighs) (**Figure 103**). Sodium thiosulfate may be helpful in treating the disease, possibly partially by causing the deposited calcium within the vessels to re-mineralize, mobilize, and be removed through dialysis. Other treatments are the use of a low-calcium dialysate and efforts to reduce overall serum calcium and phosphorous levels.



FIGURE 103. Calciphylaxis manifests as painful subcutaneous nodules or plaques with overlying red-brown discoloration and often superimposed angulated purpuric patches, often with central necrosis.

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maintaining a normal parathyroid hormone level (by either chemical or surgical parathyroidectomy), cautious use of bisphosphonates in select patients, and avoiding potential triggers (such as systemic glucocorticoids and warfarin). Meticulous wound care and surgical evaluation with limited debridement are also important; hyperbaric oxygen may also be beneficial. The use of thrombolytic agents may aid reperfusion but carries a high risk of severe bleeding complications.

KEY POINTS

- Calciphylaxis typically occurs in patients with advanced kidney dysfunction and elevated calcium-phosphorus products.
- Calciphylaxis lesions are painful subcutaneous nodules or plaques with overlying red-brown discoloration and angulated purpuric patches, often with central necrosis; patients with advanced disease may have ulceration or black eschar formation.

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis (NSF) is a relatively recently described entity first recognized in the early 2000s. The first patients were described in the late 1990s as presenting with what was termed a "scleromyxedema-like" illness of kidney disease, with distal skin pain and thickening and loss of mobility (**Figure 104**). Epidemiologic studies implicated the use of gadolinium-based MRI contrast agents administered in the setting of acidemia from kidney disease as a key trigger; however, the limited numbers of affected patients compared with the number of contrast MRI studies performed in patients with end-stage kidney disease suggest that other important etiologic factors are required for NSF to occur. Since the recognition of the role of gadolinium and avoidance of this contrast agent in patients with kidney insufficiency, there has been a marked reduction in the number of new cases of NSF. NSF is gradually progressive, and whereas some case reports suggest possible benefit with a number of different therapeutic modalities, including phototherapy (UVA therapy in particular), photopheresis, and antifibrotic agents, kidney transplantation seems to be the most effective treatment.



FIGURE 104. Nephrogenic systemic fibrosis presents with tightening and thickening of the skin, sometimes with clinically apparent fleshy or yellow papules and plaques, predominantly on the extremities.

Kidney transplantation is associated with specific dermatologic risks. Patients who undergo solid-organ transplantation are at increased risk for the development of cutaneous malignancies, particularly nonmelanoma skin cancer. Kidney transplant recipients are up to 30 times more likely to develop squamous cell carcinoma than healthy hosts, possibly due in part to the oncogenic properties of human papillomavirus, which may be found within some squamous cell carcinomas in this patient population. The immunosuppressive regimen is a key factor as well, with specific medications having higher risks and some offering potential preventive benefits (OKT-3 and tacrolimus carry an increased risk and rapamycin offers a mild protective effect). All patients receiving an organ transplant should be counseled about sun protective measures and receive an annual skin check.

KEY POINTS

- The use of gadolinium-based contrast agents has been identified as a key trigger of nephrogenic systemic fibrosis.
- Patients who undergo solid-organ transplantation are at increased risk for the development of cutaneous malignancies, particularly nonmelanoma skin cancer.

Pulmonology

Sarcoidosis

Sarcoidosis is an inflammatory disease characterized by granuloma formation in multiple organs; approximately 30% of patients will have cutaneous involvement. Recognition of skin disease is essential, as it is much easier to obtain a tissue diagnosis by skin biopsy than by an internal surgical sampling. Sarcoidosis has been called "the great imitator," and a multitude of skin lesions have been described. Classic cutaneous sarcoidosis appears as violaceous papules around the nose including the ala, or periorbitally and periorificially (around the oropharynx and nasal openings) (**Figure 105**). Sarcoid lesions may also preferentially develop in sites of trauma, such as scars or tattoos. The term "lupus pernio" is a source of potential confusion. Lupus generally refers to systemic lupus erythematosus. Pernio generally refers to a condition of purple papules on the distal digits in some patients who live in cold, wet climates; and lupus vulgaris is a form of tuberculosis of the skin. Lupus pernio has little to do with these, however. Lupus pernio is sarcoidosis of the nose and central face, with violaceous subcutaneous plaques or nodules, often with some overlying scaling. This is more common in black persons and is important to recognize, as persons with lupus pernio frequently have a chronic, refractory course. Limited cutaneous sarcoidosis may be treated with topical glucocorticoids; more extensive disease warrants systemic therapy, with hydroxychloroquine the most appropriate first-line agent. Patients who fail to respond may be treated with thalidomide,

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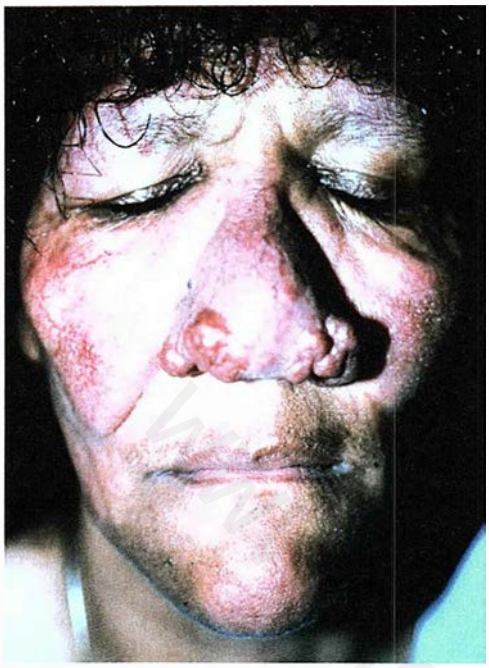

FIGURE 105. This patient has lupus pernio, with sarcoid lesions throughout the nose and cheeks, along with discrete sarcoid papules on the nasal tip and over the nasal ala.

methotrexate, or occasionally TNF-α inhibitors. Additional therapeutic options for some patients include tetracycline-class antibiotics, retinoids, phosphodiesterase inhibitors, and other immunosuppressive agents. Treatment depends on which organs are affected, with the more important or severely affected organ systems determining therapeutic consideration.

KEY POINT

- Classic cutaneous sarcoidosis appears as violaceous papules around the nose or periorbitally and periorificially; it may also develop in sites of trauma, such as scars or tattoos.

Erythema Nodosum

Erythema nodosum (EN) is the most common form of panniculitis, or inflammation of the fat, with most inflammation concentrated on the intralobular septae. Because the inflammation is deep under the skin, the clinical manifestation seen on the surface is often ill-defined erythema with some substance on palpation, which may fade from an active inflammatory red-pink to a more dull brown over time. The lesions are frequently tender when actively inflamed. Most commonly, EN occurs bilaterally and symmetrically on the anterior shins; however, it may also appear in any fatty areas (**Figure 106**). Although lesions will often come and go, most resolve over 4 to 6 weeks. EN is a nonspecific reaction pattern, with inflammation in the fat occurring in response to some systemic process. Multiple causes have been associated with EN, including systemic inflammatory diseases, reactions to medications or hormones, and occult or symptomatic infections. EN can also be idiopathic (**Table 23**).



FIGURE 106. Erythema nodosum manifests as red, ill-defined, tender nodules of varying size typically on the anterior shins.

TABLE 23. Selected Causes of Erythema Nodosum

Infections
Streptococcal pharyngitis
Tuberculosis
Pulmonary fungal infections (coccidioidomycosis, blastomycosis, histoplasmosis)
Gastrointestinal bacterial infections (*Yersinia* enterocolitis, *Salmonella* gastroenteritis)
Psittacosis
Cat scratch fever
Leprosy
Drugs
Antibiotics (penicillin, sulfonamides)
Estrogen-containing medications (oral contraceptives, hormone replacement therapy)
Systemic Conditions
Inflammatory bowel disease
Pregnancy
Sarcoidosis
Connective tissue disorders (dermatomyositis, lupus erythematosus, scleroderma)
Malignancy (rare)
Sweet syndrome
Behçet syndrome

The most common associations are streptococcal infection, hormones (including oral contraceptives, hormone replacement therapy, or pregnancy), inflammatory bowel disease, sarcoidosis, and medication reactions. The appearance of EN in patients with sarcoidosis generally portends an acute presentation with a good long-term prognosis with lower risks of chronic disease. EN, arthritis, hilar lymphadenopathy, and fevers constitute Löfgren syndrome, which is more common in patients of Northern European descent (see Sarcoidosis).

Although EN itself is frequently self-limited, patients may be managed with NSAIDs, rest, elevation, and sometimes gentle compression. Patients with recalcitrant disease may require treatment with systemic immunomodulatory drugs; some patients may respond to saturated solution of potassium iodide, colchicine, or dapsone.

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KEY POINTS

- Erythema nodosum is characterized by tender subcutaneous nodules with ill-defined overlying erythema.
- The most common associations of erythema nodosum are streptococcal infection, hormones, inflammatory bowel disease, sarcoidosis, and medication reactions.

Gastroenterology

Inflammatory bowel disease (IBD) may present with cutaneous manifestations. Erythema nodosum (EN) is one of the more common skin findings in patients with IBD, occurring in either Crohn disease or ulcerative colitis in up to 20% of patients. Crohn disease may also present with distinctive linear pustules and erosions of the oral mucosa and gingiva, termed "pyostomatitis vegetans," with cutaneous Crohn disease (typically granulating ulcers periorificially) or perianal skin tags. Patients with both ulcerative colitis and Crohn disease may develop inflammatory neutrophilic dermatitis, particularly pyoderma gangrenosum.

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is an autoimmune neutrophilic dermatosis in which neutrophils invade and fill the dermis, leading to marked tissue edema and possible ulceration (**Figure 107**). PG may also present with bullous lesions, pustulonodules, and vegetative plaques. The typical history is a small pustule or red nodule that may develop after trauma and rapidly expands causing an edematous, infiltrated, actively inflamed border and a painful, exudative wet ulcer. Classically the border is described as violaceous and, because of the nature of the inflammation, the epidermis often overlies the ulcer, with a "hanging border" or residual thin anastomosing strands of epidermis remaining over the expanding ulcer (see Foot and Leg Ulcers).

As PG resolves, it tends to heal with atrophic scarring in a cross-like or cribriform pattern. One helpful clinical feature for diagnosing active PG may be the presence of "pathergy," or the occurrence of lesions at sites of trauma. Pathergy is seen in many neutrophilic dermatoses (PG, Sweet syndrome, and Behçet syndrome in particular), but only 20% to 30% of patients with PG will exhibit pathergy. Peristomal PG occurs around ostomy sites and may be a particular form of pathergy. The constant exposure of bowel contents to the skin and need for adhesives to bind the ostomy bags to the area can create a clinical challenge when ulcers develop.

Diagnosing PG is challenging, and all patients with suspected PG should be evaluated for potential underlying causes (**Table 24**). There are no definitive tests, and PG is a diagnosis of exclusion; excluding other causes almost always requires a skin biopsy and tissue culture. It is essential to rule out other diseases before making a diagnosis of PG and to reevaluate the diagnosis during treatment. PG is usually glucocorticoid responsive, and failure to respond to therapy should prompt evaluation for an alternative diagnosis. PG may be idiopathic, but it is associated with an underlying disease in 50% of patients.



FIGURE 107. Pyoderma gangrenosum, presenting as a painful, exudative ulcer with a purulent base and ragged, edematous, violaceous, "overhanging" border.

Management is threefold: evaluate for underlying disease, treat the PG inflammation, and manage the resulting wound. Treating PG can be a challenge, and if there is an associated underlying disease, therapy should be directed at controlling that process. PG is often responsive to topical or intralesional glucocorticoids. Cyclosporine and infliximab may also be effective, with infliximab having the highest quality evidence, although most clinicians use systemic glucocorticoids as first-line therapy. Second-line treatment includes other immunomodulatory drugs such as thalidomide, mycophenolate mofetil, azathioprine, methotrexate, intravenous immune globulin, and other biologic agents. Because the pathologic process is neutrophil-dependent, dapsone or colchicine therapy sometimes provides benefit, including potential dual benefit for dapsone as *Pneumocystis* pneumonia prophylaxis for patients requiring long-term glucocorticoids for disease control. Local supportive care is also essential to achieve ulcer resolution. Many patients will have PG inflammation controlled, and that is when systemic immunosuppressants should be tapered. Wound healing may take longer and require intensive local wound care. Important measures include achieving adequate pain control; maintaining a clean, noninfected ulcer base (potentially with antimicrobial soaks, topical antimicrobial agents, and absorptive dressings); and minimizing edema in the affected limb with compression as tolerated.

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TABLE 24. Pyoderma Gangrenosum Evaluation
Diagnostic Criteria (2 major, 4 minor)
Major:
- History of rapidly progressing, painful ulcer with irregular, violaceous, undermined border
- Exclusion of other causes of ulcerations (typically vasculitis, neoplasm, infection)
Minor:
- Skin biopsy showing sterile neutrophilic inflammation
- Presence of pathergy or healing with cribriform scarring
- Presence of systemic diseases associated with pyoderma gangrenosum (inflammatory bowel disease, IgA paraproteinemia, internal malignancy, systemic lupus erythematosus, or other autoimmune disease)
- Response to systemic glucocorticoid therapy (1-2 mg/kg/d, anticipate 50% size decrease within 4 weeks)
Systemic Evaluation
All patients:
- Complete blood count, comprehensive metabolic profile
- Biopsy, often including a separate deep-tissue culture
Dictated by history, presentation, review of systems:
- Age- and sex-appropriate cancer evaluation
- Evaluation for inflammatory bowel disease with upper endoscopy and colonoscopy (almost always indicated)
- Chest radiography for lung pathology or malignancy
- Serum and urine protein electrophoresis for paraproteinemia (especially IgA)
- Hematologic studies for coagulation abnormalities (including antiphospholipid antibodies)
- Bone marrow aspiration and biopsy
- Extended serologic testing for alternative explanations or associated autoimmune diseases (RF/CCP, ANA, ANCA, cryoglobulins)
- Vascular flow studies (if on the leg) to exclude component of vascular insufficiency mimicking pyoderma gangrenosum or impacting wound healing
RF/CCP = rheumatoid factor/anti-cyclic citrullinated peptide; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody.

KEY POINTS

- Pyoderma gangrenosum presents as a painful, exudative ulcer with a purulent base and ragged, edematous, violaceous, "overhanging" border; it may be idiopathic but is associated with an underlying disease in some patients.
- Pyoderma gangrenosum is responsive to glucocorticoids, and cyclosporine and infliximab may also be effective.

Dermatitis Herpetiformis

Dermatitis herpetiformis (DH) is an eruption characterized by pruritic papules and transient, almost immediately excoriated blisters on the elbows, knees, and buttocks (**Figure 108**). Histologically, neutrophils are found in the papillary dermis, and direct immunofluorescence may reveal granular IgA depositions. Patients with DH have intense pruritus and almost immediately respond to treatment with dapsone. DH is strongly associated with gluten sensitivity and celiac disease, and patients should be evaluated for celiac disease and maintain a gluten-free diet, or they are at increased risk for small bowel lymphoma (see Autoimmune Blistering Diseases).

Patients with cirrhosis also frequently have skin involvement. These patients often have xerosis and develop diffuse, intense pruritus, potentially partially due to accumulation of bile salts in the skin. Chronic scratching leads to thickened, lichenified plaques and individual hypertrophic hyperpigmented, excoriated prurigo nodules. This form of pruritus is



FIGURE 108. Group crusted, excoriated papules in a patient with dermatitis herpetiformis. The vesicles are so superficial and fragile and patients have such intense pruritus that the vesicles are rarely seen intact.

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best managed with aggressive topical emollients, and patients with refractory disease may benefit from phototherapy. Patients with advanced liver disease may also develop spider telangiectasias (red papules with tiny networks of capillaries extending outward), jaundice, erythema of the thenar or hypothenar eminences, and changes to the nail plate such as Terry nails, in which the nail bed turns opaque.

Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT) is a rare skin disease associated with liver disease. It may develop from extensive alcohol use, hemochromatosis, or hepatitis C virus (HCV) infection. Only rarely is PCT a genetic disease caused by reduced activity of the enzyme uroporphyrinogen decarboxylase; however, 80% of cases are acquired, most of which are from chronic HCV infection. PCT presents with skin fragility and small, transient, easily ruptured vesicles in sun-exposed areas, mainly on the hands (**Figure 109**). When the lesions rupture, there is usually scarring, shallow erosions, and occasional white papules from pinpoint epidermal inclusion cysts from abnormal healing (milia). Excess hair growth, or hypertrichosis, may be seen on the tops of the hands or cheeks. Laboratory testing may show elevated uroporphyrin levels. A skin biopsy showing a paucinflammatory subepidermal bullae can confirm the diagnosis. Treatment is aimed at limiting iron overload by phlebotomy; antimalarial agents such as hydroxychloroquine may also be beneficial. PCT that develops in the setting of HCV may warrant treating the infection.

Treatment of HCV infection may result in secondary skin side effects that are important to consider. Interferon alfa treatment is associated with the development of granulomatous dermatitis and in some patients, sarcoidosis. A relatively new agent for treating HCV infection, telaprevir, has been associated with skin eruptions in a significant percentage of treated patients, with some reports indicating as many as 35% to 50% of these patients developing a cutaneous eruption. Some of the reported eruptions have been severe, with potentially life-threatening skin reactions developing in a few patients. Patients receiving telaprevir for HCV infection should be followed closely, and any skin eruption warrants a thorough evaluation.



FIGURE 109. A chronic, blistering skin disease, with multiple scars and lesions of varying stages, on sun-exposed skin, especially on the back of the hands, consistent with porphyria cutanea tarda.

Hematology/Oncology

Recognizing paraneoplastic dermatoses may lead to earlier diagnoses, and management of paraneoplastic eruptions is critical in the care of patients with internal malignancies. Cutaneous signs of malignancy include both features of hereditary syndromes with cutaneous manifestations and an associated increased lifetime risk of internal malignancy, and cutaneous inflammatory reaction patterns that develop in the setting of malignancy (**Table 25**). Paraneoplastic eruptions

TABLE 25. Genetic Diseases with Cancer Associations and Skin Findings[a]

Condition	Clinical Findings	Associated Malignancy/Comments
Muir-Torre syndrome (Lynch syndrome)	Sebaceous neoplasms and keratoacanthomas (squamous cell carcinoma subtype)	Adenocarcinomas of the gastrointestinal tract or other tumors of the genitourinary tract. Lung, breast, and hematologic malignancies may occur.
Cowden syndrome	Tan facial papules (tricholemmomas) and oral papillomas or cobblestoning	Adenocarcinomas of the breast or thyroid and/or polyps of the gastrointestinal tract
Birt-Hogg-Dube syndrome	Fine white sclerotic facial papules (fibrofolliculomas or trichodiscomas); spontaneous pneumothoraces	Kidney cancer
Reed syndrome	Tender cutaneous papules (leiomyomas); uterine fibroids	Kidney cancer
Tuberous sclerosis complex	Multiple cutaneous lesions (facial angiofibromas, ash leaf spots, hypopigmented macules, subungual papules); cortical tubers and seizures; female patients may develop lymphangioleiomyomatosis	Kidney cancer

[a]This table is a brief review focused on genetic diseases that can present in adulthood; this is not a comprehensive list of genetic skin diseases with cancer associations.

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may precede, parallel, or follow a diagnosis of cancer. Potential paraneoplastic skin eruptions warrant age- and sex-appropriate screening studies, with additional diagnostic testing depending on the specific skin reaction pattern (**Table 26**).

Sweet Syndrome

Sweet syndrome, or acute febrile neutrophilic dermatosis, is one of the classic "neutrophilic dermatoses," driven by neutrophilic infiltration and cytokine inflammation. Other neutrophilic dermatoses include pyoderma gangrenosum; erythema elevatum diutinum (a vasculitis that predominantly affects the skin overlying extensor joint spaces); neutrophilic eccrine hidradenitis (typically seen following chemotherapy exposures); and subcorneal pustular dermatosis (which usually causes relapsing pustular plaques of the folds of skin in middle-aged and older women). Neutrophilic inflammation

TABLE 26. Paraneoplastic Disorders: Conditions That Are Strongly Linked to Internal Malignancy

Condition	Clinical Findings	Associated Malignancy/Comments
Acanthosis nigricans	Velvety or verrucous hyperpigmentation of intertriginous areas, weight loss, glossitis	Adenocarcinoma, usually GI or GU, most commonly of stomach; occurs also in patients with endocrinopathy
Leser-Trélat sign	Rapid appearance or inflammation of multiple seborrheic keratoses; often occurs in conjunction with acanthosis nigricans	Same cancer association as acanthosis nigricans; seborrheic keratoses are common lesions; Leser-Trélat sign is very rare
Tripe palms	Rugose folds on the palms and soles; may occur with or without acanthosis nigricans	If occurring with acanthosis nigricans, same cancer association; if occurring without acanthosis nigricans, squamous cell carcinoma of the head and neck or lungs
Bazex syndrome (also known as acrokeratosis paraneoplastica)	Psoriasiform, violaceous scaling on the acral surfaces (fingers, toes, nose, and ears); keratoderma may also be present	Squamous cell carcinoma of the upper respiratory tract or upper GI tract; effective therapy of an associated cancer is followed by resolution of the dermatosis
Carcinoid syndrome	Episodic flushing, often accompanied by diarrhea and bronchospasm; can eventually result in telangiectasia or permanent ruddiness	Pulmonary carcinoid tumors or carcinoid tumors metastatic to the liver; tumor removal is followed by resolution of the skin and systemic findings
Ectopic ACTH syndrome	Generalized hyperpigmentation	Small cell lung cancer; tumor removal can result in improvement of the pigmentation
Necrolytic migratory erythema	Intertriginous erythema, scales, and erosions; glossitis and angular cheilitis are common	Glucagon-secreting tumor of the pancreas
Neutrophilic dermatoses	Sweet syndrome; atypical pyoderma gangrenosum (bullous lesions with a blue-gray border, often on the hands, arms, or face)	Myeloid leukemia, myelofibrosis, and refractory anemias; these disorders also occur without malignancy in 80% to 90% of patients
Paget disease of the breast	Erythematous, irregularly bordered plaque on the nipple	Represents an extension of a ductal adenocarcinoma of the breast
Extramammary Paget disease	Erythematous scaly patch or plaque on the perineal skin, scrotum, or perianal area	Cancer of the GI or GU tract is present in 25% of patients; it is not contiguous with the dermatosis; the dermatosis is a malignancy and needs appropriate excision or ablation
Paraneoplastic pemphigus	Severe mucosal erosions, tense and flaccid bullae that may be widespread	Non-Hodgkin B-cell lymphoma, Castleman disease, chronic lymphocytic leukemia
Dermatomyositis	Heliotrope rash, Gottron papules and sign, photodistributed violaceous erythema; scaly erythema of the scalp with diffuse alopecia; periungual telangiectasias and cuticular overgrowth	20% to 25% of patients with dermatomyositis had, have, or will have a malignancy; ovarian cancer is overrepresented; paraneoplastic course is possible but unusual
Necrobiotic xanthogranuloma	Purple-orange nodules and plaques, often on the upper eyelids, which frequently ulcerate	90% of patients have an associated paraproteinemia (generally IgG κ) and may develop multiple myeloma
Amyloidosis	"Pinch purpura" in sites of thin skin such as the periorbital area, usually accompanied by macroglossia and smoothing of the tongue	Seen in multiple myeloma or systemic amyloidosis
Scleromyxedema	Waxy fine papules over the face, neck, and upper trunk	Most patients have an associated paraproteinemia (generally IgG λ) and may develop overt multiple myeloma

ACTH = adrenocorticotropin hormone; GI = gastrointestinal; GU = genitourinary.

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CONT.

can predominate in other multiple skin eruptions, including Behçet syndrome, erythema nodosum, linear IgA bullous dermatosis, dermatitis herpetiformis, and more. Sweet syndrome may be idiopathic or occur in association with an underlying disease; the syndrome typically develops after an upper respiratory or gastrointestinal infection or in the setting of hematologic abnormalities, particularly myelodysplastic syndrome and myelodysplastic syndrome evolving into acute myeloid leukemia. Sweet syndrome has also been associated with solid malignancies and medications (particularly neutrophil-stimulating medications such as granulocyte-colony stimulating factor (G-CSF) and all-*trans* retinoic acid). Patients will have high fevers, leukocytosis with a left shift, elevated inflammatory markers, and often muscle or joint pain, along with the skin eruption. The skin lesions are described as "juicy" indurated edematous red-purple plaques and nodules, sharply demarcated from the adjacent skin. Biopsy will show a neutrophilic infiltrate with prominent superficial papillary dermal edema. This intense edema high up in the skin is what causes the characteristic "swollen, juicy" appearance clinically. Intensely inflamed lesions may ulcerate and resemble PG (**Figure 110**).

As with PG, pathergy may occur and offer a clue to the diagnosis. Unlike PG, lesions of Sweet syndrome resolve without scarring. All patients with Sweet syndrome should have a complete blood count and should be evaluated for potential underlying malignancy, particularly acute myeloid leukemia. Flares of Sweet syndrome can sometimes parallel the underlying disease, but Sweet syndrome may also develop as patients are being treated for the leukemia. Flares may be due to endogenous cytokine signaling, such as elevated levels of G-CSF in response to cytotoxic bone marrow ablative chemotherapy for leukemia. Sweet syndrome is dramatically glucocorticoid responsive, and patients often have immediate relief after just one dose, with resolution of fevers and dramatic reduction in skin lesions. Alternatives to glucocorticoids in patients who are unable to successfully taper off include saturated solution of potassium iodide, dapsone, colchicine, and NSAIDs. Select patients may require cyclosporine, mycophenolate mofetil, and TNF-α inhibitors or possibly targeted antineutrophilic biologic agents such as anti-interleukin-1 anakinra.



FIGURE 110. Red-purple "juicy" nodule characteristic of Sweet syndrome lesions. The marked edema is typical, leading to a "pseudovesicular" appearance.

Skin findings in patients undergoing treatment for cancer are importatnt as well. Cutaneous eruptions can have severe impacts on patients undergoing chemotherapy, and failure to recognize or manage these side effects can lead to treatment interruptions or suboptimal dose reduction (**Table 27**). Almost all chemotherapeutic agents have been reported to cause the entire spectrum of classic cutaneous adverse drug reactions, such as morbilliform exanthems and urticarial eruptions. Multiple agents have also been associated with development of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Patients who are undergoing chemotherapy are often severely immunocompromised, and careful evaluation and management of the skin is essential to prevent and recognize infections. Violaceous nodules or areas of purpura, particularly if with necrosis, should be evaluated immediately to exclude rapidly progressive invasive infections. Careful skin examination for sites of breakdown or trauma, such as in the skin folds or web spaces, can help prevent superficial skin infections from serving as a portal of entry for systemic infection.

Patients who undergo bone marrow transplants have additional skin-specific issues. Graft-versus-host disease is one of the most common complications of bone marrow transplantation and may present initially or solely in the skin. Patients will classically develop erythema of the ears, upper back and neck, outer shoulders or outer arms, and dorsal feet or hands, and the erythema may be folliculocentric initially. Patients should be evaluated for signs of engraftment in the marrow (cell count recovery) and for liver or gastrointestinal involvement. Acute graft-versus-host disease rarely develops within the first 2 weeks following transplantation, but once count recovery has started, it is a common cause of significant morbidity and treatment-related mortality. Patients may have a morbilliform eruption, which can be clinically challenging to distinguish from cutaneous adverse drug reactions. The timing, morphology, distribution, and associated symptoms (such as diarrhea or liver chemistry abnormalities) can help differentiate these two entities; skin biopsy may be of use although there are not definitive features.

Chronic graft-versus-host disease generally occurs in the skin as either lichen planus-like lesions or scleroderma-like changes. Patients may develop chronic inflamed erythematous-to-violaceous papules or plaques with overlying scale, which may be accompanied by inflammation of the eyes, mouth, or genitals.

KEY POINTS

- Lesions of Sweet syndrome can appear as "juicy" indurated edematous red-purple plaques and nodules, sharply demarcated from the adjacent skin.

(Continued)

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TABLE 27. Select Dermatologic Chemotherapy Reactions

Reaction	Chemotherapeutic Agents
Dermatomyositis-like eruption	Hydroxyurea
Neutrophilic dermatoses (PG, Sweet syndrome)	G-CSF, GM-CSF, ATRA, thalidomide, lenalidomide, bortezomib
Acneiform eruption	EGFR inhibitors
Paronychia	EGFR inhibitors
Pseudoporphyria	5-Fluorouracil
Cutaneous lupus	5-Fluorouracil, capecitabine
Hand-foot syndrome/acral erythema	Cytarabine, 5-fluorouracil, capecitabine, methotrexate, docetaxel, paclitaxel, anthracyclines
Neutrophilic eccrine hidradenitis	Cytarabine, multiple other agents
Hand-foot skin reaction	Sorafenib, sunitinib
Serpentine supravenous hyperpigmentation	5-Fluorouracil
Flagellate hyperpigmentation	Bleomycin
Alopecia	Multiple agents
Morbilliform	Multiple agents
Urticarial	Multiple agents
SJS-TEN	Multiple agents
Erythema multiforme	Multiple agents
Vasculitis	Multiple agents

ATRA = all-trans *retinoic* acid; EGFR = epidermal growth factor; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

KEY POINTS *(continued)*

- Sweet syndrome has been associated with acute myeloid leukemia, solid tumors, chemotherapy, and infections.

Endocrinology

The skin is affected by a host of endocrinologic conditions, ranging from the association between autoimmune skin diseases such as vitiligo and alopecia areata with thyroid disease, to gynecomastia from hormonal imbalances, or the diffuse hyperpigmentation of Addison disease. This section will focus on diabetes mellitus and thyroid disease.

Diabetes Mellitus

Patients with diabetes mellitus can develop a wide range of skin findings such as the velvety hyperpigmentation of acanthosis nigricans, which tends to present in the intertriginous areas, particularly in the axillae, in obese persons with diabetes (**Figure 111**). This may be accompanied by skin tags, which are common in obese persons.

Some findings are connected to the underlying etiopathogenesis of the disease. For example, patients with type 1 diabetes are at increased risk for development of vitiligo (asymptomatic depigmented patches periorificially or in sites of trauma caused by autoimmunity against melanocytes).



FIGURE 111. Acanthosis nigricans, characterized by a velvety brown plaque in an obese patient.

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Patients with diabetes may develop orange, atrophic plaques on their anterior shins (necrobiosis lipoidica). Patients with necrobiosis lipoidica often have retinal or kidney damage as well. Other cutaneous findings associated with diabetes are bullous diabeticorum (large, asymptomatic, noninflammatory bullae on the lower extremities) and scleredema (an uncommon skin finding characterized by edematous induration of the upper back). Diabetic dermopathy (multiple hyperpigmented macules on the anterior shins) is one of the most common cutaneous findings.

Patients with diabetes are at an increased risk of skin infection, such as interdigital and intertriginous infection with *Candida* and dermatophytes. Early recognition is essential, as untreated cutaneous fungal infections may serve as a portal of entry for bacteria, resulting in cellulitis. Intertriginous erythematous eruptions with scale should be evaluated, and if due to tinea, the lesions should be treated with topical antifungal agents (such as ketoconazole), which often requires repeated use to clear and maintain normal skin.

KEY POINTS

- Acanthosis nigricans presents as skin thickening and darkening of the intertriginous areas, particularly the axillae.
- Necrobiosis lipoidica refers to orange, atrophic plaques on the anterior shins of patients with diabetes mellitus that are often associated with retinal or kidney damage.

Thyroid Disease

Hyperthyroidism can lead to warm, moist, smooth, thin skin, often with hyperhidrosis. The hair will grow thin and feel soft, and nail fragility may develop. Cutaneous myxedema can occur anywhere but typically is concentrated on the anterior shins, with the skin appearing indurated with compressible plaques that may have a "peau d'orange" appearance from intradermal mucin deposition.

Thyroid acropachy is a rare finding in some patients with Graves disease, characterized by swelling of the soft tissues of the hands and feet with associated digital clubbing due to periosteal bone formation (**Figure 112**). Patients with hypothyroidism develop cool, dry, pale skin, which may progress to ichthyosis or plate-like scaling resembling fish scales. The hair becomes dry and brittle and may fall out. Loss of the lateral third of the eyebrows is common. Generalized myxedema can lead to a waxy, swollen appearance with puffy lips and edematous and droopy eyelids.



FIGURE 112. Clubbing is seen specifically in patients with Graves disease.

Infectious Disease

HIV Infection

Patients with HIV infection (generally with CD4 cell counts <200/μL) may have a marked photosensitivity and develop a striking photodermatitis with thickening and lichenification of sun-exposed areas. Patients presenting with new or worsening psoriasis should be evaluated for HIV risk factors, and HIV testing should be offered. Severe outbreaks of seborrheic dermatitis (erythema with greasy scale in the scalp or "T-zone" of the central face) may occur in patients with HIV infection as well, and patients with refractory or extensive seborrhea require prompt evaluation. Patients with other sexually transmitted infections, including genital warts, warrant evaluation for HIV infection as well.

The rash of acute HIV seroconversion is nonspecific, characterized by asymptomatic erythematous macules and small papules over the upper trunk, face, and proximal extremities, sometimes including the palms, and often accompanied by striking oral aphthous ulcers. HIV antibody testing may be negative in acute seroconversion, and viral load testing or delayed antibody testing is essential.

Patients with HIV infection frequently have pruritus. Chronic pruritus and subsequent lichenification and areas of thickened plaques of lichen simplex chronicus or papules of prurigo nodularis are common. Pruritus may be from skin superinfection and chronic bacterial folliculitis, HIV-related xerosis, or as a result of medications. Two specific pruritic eruptions are pruritic papular eruption of HIV (a common chronic papular rash seen in 10% to 45% of patients, which is characterized by symmetric skin-colored or hyperpigmented papules on the trunk and extremities) and eosinophilic pustular folliculitis (characterized by recurrent, extremely pruritic red or hyperpigmented papules on the face and upper chest) (**Figure 113**). Patients with HIV infection are at risk for secondary skin infection with molluscum, superficial bacterial infections, and superficial fungal infections and have a high rate of herpes simplex and herpes zoster virus infections and reactivation. These infections may present with more widespread disease and atypical clinical features in patients with advanced HIV infection. Patients with very low CD4 cell counts are also at risk for secondary cutaneous malignancies including cutaneous lymphoma and Kaposi sarcoma (caused

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FIGURE 113. Pruritic papular eruption of HIV. The folliculocentric papules and excoriated, hyperpigmented remnants of previous lesions are clustered on the chest and trunk. Photo courtesy of Robert Micheletti, MD.

by human herpesvirus 8) (**Figure 114**). These patients often have an increased risk of squamous cell carcinoma (frequently HPV associated), including squamous cell carcinomas of the digital tips and under the nails and of the penis, perineum, and perianal region.



FIGURE 114. Kaposi sarcoma is characterized by violaceous to hyperpigmented plaques. The central plaque shown here has a vascular-appearing, violaceous papule within it.

KEY POINT

- The rash of acute HIV seroconversion is characterized by asymptomatic erythematous macules and small papules over the upper trunk, face, and proximal extremities, often accompanied by striking oral aphthous ulcers.

Dermatologic Urgencies and Emergencies

Retiform Purpura

Purpura is characterized by nonblanchable, red-purple macules or papules that result from the leakage of erythrocytes into the skin. The term "retiform" describes the angulated or netlike configuration that reflects the vascular structure in the skin. The color is often a dark brick-red or purple (**Figure 115**). It is important to recognize these colors as they may indicate local skin ischemia due to occlusion or breakdown of vascular integrity that may lead to necrosis, which may become life-threatening if not aggressively treated. Various conditions can cause retiform purpura, many of which disrupt arterial blood flow (**Table 28**). Thrombotic and embolic causes should be considered first. Thrombotic causes include alterations to the coagulation cascade such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and drug-induced thrombosis (warfarin or heparin). Embolic causes include cardiac sources of emboli (bacterial or marantic endocarditis, atrial myxoma), as well as cholesterol emboli that may be dislodged after an intravascular procedure. Cholesterol emboli may cause multisystem changes such as eosinophilia, acute kidney injury, stroke, intestinal ischemia, and amaurosis fugax. Ecthyma gangrenosum and pyoderma gangrenosum are other diseases that can cause dark, dusky, or purple lesions but do not have a retiform configuration.



FIGURE 115. Retiform purpura on the lower legs due to vasculitis.

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TABLE 28. Causes of Retiform Purpura and Associated Findings

Etiology	Associated Findings and Causes
Angioinvasive fungal infection	Infection caused by *Mucorales*, *Aspergillus*, *Fusarium*, *Pseudallescheria*
	Neutropenic, solid-organ transplant recipients, burn victims
	Infects locally but can become systemic
Necrotizing fasciitis	Pain out of proportion to examination
	History of preceding trauma
	Can be a mixed infection or due to *Streptococcus*
	Surgical emergency; imaging can be supportive but should not delay surgical exploration
Immune-mediated vasculitis	Polyarteritis nodosa
	ANCA-associated vasculitides:
	Eosinophilic granulomatosis with polyangiitis
	Granulomatosis with polyangiitis
	Microscopic polyangiitis
	Connective tissue disease-associated (systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis)
	Evaluate for ANCA, signs of connective tissue disease, other end-organ damage (kidney, lung, eye, gastrointestinal, musculoskeletal)
Calciphylaxis	Associated with advanced kidney disease
	Extremely painful
	Extensive forms occur on central, adipose sites (breast, abdomen, hips)
	Limited forms often occur distally
Thromboembolism	DIC, purpura fulminans
	Systemic inflammation due to infection or other insult
	Evidence of organ ischemia and uncontrolled bleeding from multiple sites
Drugs	Levamisole-adulterated cocaine: tender purpura on the ears is prominent
	Warfarin skin necrosis: rare, occurs in first week of therapy, commonly involves adipose areas such as the breasts, abdomen, and hips
	Heparin necrosis: rare, onset in the first 5 to 10 days of therapy, can occur at the sites of injection or elsewhere, may or may not be associated with thrombocytopenia

ANCA = antineutrophil cytoplasmic antibody; DIC = disseminated intravascular coagulation.

CONT.

The history can yield important clues to the cause such as infection, thrombotic disease, recent intravascular procedures, spontaneous abortion, solid organ or hematologic malignancy, or prescribed medication or illicit drug reactions. Laboratory tests, directed by the history and physical examination, are indicated to investigate the cause and assess for end-organ damage. In select patients, skin biopsy may be helpful in establishing the diagnosis. Large incisional biopsies, which include the dermis and subcutis, are preferred over punch biopsies. An additional specimen is sent for tissue culture if infection is suspected.

KEY POINT

- Retiform purpura often indicates infection, thrombotic disease, recent intravascular procedures, spontaneous abortion, solid organ or hematologic malignancy, or prescribed medication or illicit drug reactions.

Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

Erythema multiforme (EM) can be recognized by the target lesions on the palms and soles as well as mucosal erosions, most frequently in the mouth (**Figure 116**). In contrast, typical target lesions are rare in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS and TEN are distinguished by the amount of skin involved by blisters or erosions (**Table 29**). SJS is defined as affecting less than 10% body surface area (BSA), and TEN affects more than 30% BSA. When 10% to 30% BSA is involved, it is considered SJS-TEN overlap with a mortality rate between the two. SJS and TEN are rare, with a prevalence of 1:100,000 for SJS and 1:1,000,000 for TEN. The conditions on the SJS-TEN spectrum can cause significant pain and scarring of involved mucosal surfaces, although the mortality risk is associated with the more severe end of the

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FIGURE 116. Erythema multiforme can cause target lesions on the palms and soles that can vary in size and may have a central erosion.



FIGURE 117. Hemorrhagic crusts and erosions of the lips and mouth are common in Stevens-Johnson syndrome and toxic epidermal necrolysis.

H CONT.

spectrum. The causes of SJS and TEN are not definitely known; however, several cells and signaling pathways have been implicated in triggering keratinocyte death. Some of the possible apoptotic mechanisms include Fas-Fas ligand, damage by perforin or granzyme B, and granulysin. Cytokines and reactive oxygen species have also been linked to keratinocyte injury.

A drug or an infection can trigger EM. EM erupts 1 to 3 weeks following an infection such as herpes simplex virus or *Mycoplasma pneumoniae*. Children are affected equally by drugs and infections; however, drugs are a more frequent cause in adults. Most patients with EM are between 20 and 40 years of age. Target lesions on the palms and soles are often 1 to 6 cm in size. A central purpuric or dusky zone, surrounded by a pale ring and a peripheral red ring, forms the "target." The center often becomes vesicular or eroded. Target lesions are prominent on the palms and soles, whereas red macules and papules occur elsewhere on the body but favor the extremities. Mucosal erosions are painful, and intact vesicles or bullae on mucosa are rare.

SJS and TEN are potentially lethal because of widespread skin inflammation, necrosis, and erosion (**Figure 117** and **Figure 118**).



FIGURE 118. Toxic epidermal necrolysis can result in large areas of skin detachment, such as those seen here on the trunk.

TABLE 29. Comparison of Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

	Erythema Multiforme (EM)	Stevens-Johnson Syndrome (SJS)	Toxic Epidermal Necrolysis (TEN)
Morphology	Typical 3-zoned target	Atypical targets and confluent erythema with sloughing	Extensive, confluent erythema with sloughing
Distribution	Favors extremities	Trunk and extremities; up to 10% body surface area involvement[a]	Trunk and extremities; at least 30% body surface area involvement[a]
Mucosal disease (oral, eye, genitourinary)	1 or 2 sites	2 or more sites	2 or more sites
Constitutional symptoms	+	++/+++	+++
Etiology: Infection (%)	50	26	6
Drugs implicated in (%)	50	74	94
Mortality rate (%)	0	5-13	25-39

[a]SJS-TEN Overlap: 10% to 30% body surface area involvement, remaining features the same as SJS.

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CONT.

TEN is almost exclusively caused by medications (**Table 30**), whereas SJS is normally triggered by medications but may occasionally be caused by vaccines or infection. Patient factors such as HIV infection, kidney disease, active autoimmune disease, and human leukocyte antigen type (HLA-B*1502 and HLA-B*5801) also contribute to increased risk. Patients of Asian and South Asian ancestry who are positive for HLA-B*1502 have up to a 10% risk for SJS-TEN when exposed to aromatic anticonvulsants (carbamazepine, phenytoin, and phenobarbital). These patients should be tested for the presence of HLA-B*1502 antigen before these drugs are initiated. HLA-B*5801 positivity predicts risk of SJS-TEN upon exposure to allopurinol.

When due to drugs, SJS and TEN occur within 8 weeks of drug initiation, often between 4 and 28 days. Patients may report flulike symptoms for 1 to 3 days prior to the skin eruption. Initially, red-purple macules or papules develop on the trunk and extremities, which enlarge and coalesce. Skin pain is prominent. Vesicles, bullae, and erosions reflect the epidermal necrosis seen on biopsy. Nikolsky sign (the shearing off of the epidermis with lateral pressure, as by the examiner's thumb on the skin) is present. Two or more mucosal surfaces, such as the eyes, nasopharynx, mouth, and genitals, are involved in more than 80% of patients (**Figure 119**). Systemic inflammation can result in pneumonia, hepatitis, nephritis, arthralgia, and myocarditis.

Diagnosis and Treatment

Diagnosis of EM is usually made clinically. A biopsy is often performed when SJS or TEN is suspected. Frozen sections of fresh tissue can provide diagnostic information more rapidly than routine histology. The biopsy demonstrates acantholysis and epidermal necrosis, the degree of which depends on the age of the lesion. The biopsy can help to distinguish the spectrum of dermatoses from urticaria, urticarial vasculitis, drug hypersensitivity reaction, graft-versus-host disease, or autoimmune bullous diseases, but histopathology cannot distinguish among the entities in the SJS-TEN spectrum.

SCORTEN is a severity-of-illness score validated for TEN. It incorporates blood Sugar (plasma glucose >252 mg/dL), presence of Cancer, Older age (>40 years), heart Rate (>120/min), Ten percent or more BSA involvement on day 1, Electrolytes (serum bicarbonate <20 mEq/L), and blood urea Nitrogen (>28 mg/dL) (**Table 31**). If the diagnosis of TEN is made, the SCORTEN scale is a validated, severity-of-illness tool for TEN and SJS. The mortality rate is directly correlated with the number of SCORTEN variables that are fulfilled.

If *M. pneumoniae* is the trigger of EM or SJS, then antimicrobial therapy is helpful. Systemic glucocorticoids are highly effective for decreasing inflammation and pain even when patients have an infectious trigger for EM. For EM, short courses (3 to 4 weeks) of systemic glucocorticoids early in the course should be considered. EM can recur, and in approximately 70% of patients this is associated with herpes simplex virus infection. These patients may benefit from suppressive antiviral therapy.

TABLE 30. Medication Classes Reported to Cause Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Medication Class	Examples
Aromatic antiepileptic drugs	Carbamazepine, fosphenytoin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin
Oxicam NSAIDs	Meloxicam, piroxicam, tenoxicam
Acetic acid NSAIDs	Diclofenac, indomethacin, lonazolac, etodolac, aceclofenac, sulindac, ketorolac
Antibiotics	Sulfonamides; fluoroquinolone; aminopenicillins, cephalosporins, macrolides, minocycline
Antiviral agents	Nevirapine, abacavir
Miscellaneous	Pantoprazole, sertraline, allopurinol



FIGURE 119. Stevens-Johnson syndrome causing erosions on the tongue, lips, and red-brown patches on the surrounding facial skin.

TABLE 31. SCORTEN Severity of Illness Scale

Plasma glucose	>252 mg/dL (14.0 mmol/L)
Cancer or associated malignancy	Yes
Older age	>40 years
Heart rate	>120/min
Detached or compromised body surface	>10%
Blood urea nitrogen	>28 mg/dL (10.0 mmol/L)
Electrolyte (serum bicarbonate)	<20 mEq/L (20 mmol/L)

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CONT.

If a medication is implicated, the first step is cessation of the offending drug. Supportive therapy, such as avoiding dehydration and the use of topical analgesics for oral disease, is important for all patients. Skin findings commonly will worsen even if the trigger is removed. More aggressive supportive care, such as that received in a burn center or ICU, has consistently been shown to improve survival. Fluid, electrolyte, and nutritional support are critical. The role of glucocorticoids or intravenous immune globulin is controversial. Early intervention is essential, and many experts believe that intravenous immune globulin dosed appropriately may help arrest the process; however, firm data are lacking. Decisions regarding therapy should be multidisciplinary and include consultation with a dermatologist. Infection is a significant cause of mortality. A low threshold is recommended for performing cultures and initiation of empiric antibiotics. Use of prophylactic antibiotics is not recommended. Scarring is a complication, especially for mucosal surfaces such as the eyes and genitourinary tract. Ophthalmologic or urologic consultation should be obtained when involvement of these sites is suspected.

KEY POINTS

- Erythema multiforme (EM) can be recognized by the target lesions; a drug or infection (herpes simplex virus or *Mycoplasma pneumoniae*) can trigger EM.
- Stevens-Johnson syndrome and toxic epidermal necrolysis are potentially lethal because of widespread skin inflammation, necrosis, and erosion; the two syndromes are distinguished by the amount of skin involved.

DHS (or DRESS Syndrome)

Drug hypersensitivity syndrome (DHS) or drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe, life-threatening, idiosyncratic medication reaction. The pathophysiology may involve drug-triggered viral replication and an exuberant host antiviral response with widespread inflammation. The most common culprit medications include sulfonamide antibiotics, allopurinol, and anticonvulsants, but many more medications have been implicated. DHS is unique in that the onset is usually 2 to 6 weeks after starting the causative medication. Because of this delayed onset, it is often underrecognized or misdiagnosed. The eruption is usually an exuberant morbilliform eruption with prominent facial edema, lymphadenopathy, fever, and, in severe cases, hypotension (**Figure 120**). DHS can be confused with lymphoma, viral eruptions, or hemophagocytic lymphohistiocytosis. Rarely, hemophagocytic lymphohistiocytosis can be due to a drug. Patients with suspected DHS should have a complete blood count with differential to evaluate for eosinophilia or atypical lymphocytosis. Liver chemistry tests, serum creatinine level, and urinalysis



FIGURE 120. Generalized papular eruption in a patient with drug reaction with eosinophilia and systemic symptoms (DRESS).

should be performed. Given the severity of DRESS-associated myocarditis, some experts suggest that baseline echocardiography should be performed on every patient. Because of the fever and lymphadenopathy, therapy for DHS is to stop the causative medication immediately. Systemic glucocorticoids are typically needed (often 1-2 mg/kg, tapered slowly over multiple weeks to months). Because there is a 10% mortality rate, any patient started on a high-risk medication who develops fever and a rash should be evaluated for DHS. There are reports of the widespread inflammation of DHS causing delayed autoimmune reactions, including thyroid disease and diabetes mellitus, which requires regular follow-up long after the eruption resolves.

DHS is often an underrecognized cause of fever of unknown origin, and if not properly diagnosed, can be fatal. The possibility of DHS must be kept in mind in patients in the ICUs who are on many medications. DHS caused by an aromatic antiepileptic agent can also pose a serious threat due to cross-reaction with other antiepileptics. For example, if phenytoin causes DHS but is appropriately stopped, neither phenobarbital nor carbamazepine should be substituted because of the risk of cross-reaction.

Erythroderma

Erythroderma is characterized by erythema, indicating inflammation, of at least 80% to 90% of the skin surface (**Figure 121**). Peripheral edema, skin erosions, scaling, and lymphadenopathy are common findings. Dehydration, heat loss, and skin infections are potential complications and can compromise the skin barrier and lead to systemic infections and tissue damage. Erythroderma is more common in men than women; the average age of onset is 55 years. Erythroderma is a reaction pattern, and the specific cause can be elusive. The most common causes are medication reactions or an existing skin condition that has flared, most commonly atopic dermatitis or psoriasis following an abrupt

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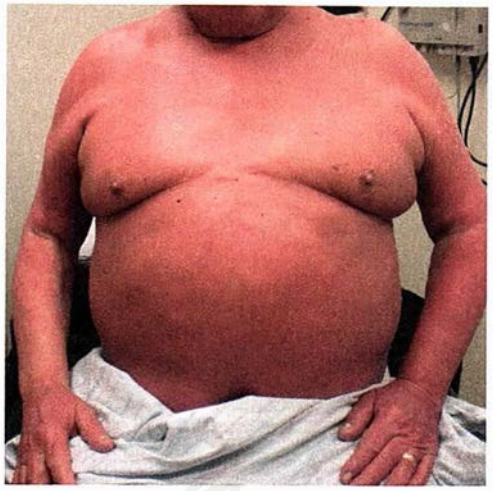

FIGURE 121. Erythroderma of the trunk and arms caused by mycosis fungoides, a form of cutaneous lymphoma.

CONT. discontinuation of systemic glucocorticoids. The cause is idiopathic in 25% to 40% of patients even after a rigorous evaluation. History and physical examination provide critical clues to the cause (**Table 32**). Alopecia, nail dystrophy, and thickening of the palms and soles are indicative of a long-standing cause such as cutaneous T-cell lymphoma, graft-versus-host disease, psoriasis, or pityriasis rubra pilaris. Pityriasis rubra pilaris is a chronic papulosquamous dermatosis that often begins on the scalp and with time becomes generalized. It can be distinguished from psoriasis by the prominent, firm, orange-red, follicle-based papules that coalesce with intervening "islands" of normal skin. Drug reactions, staphylococcal scalded skin syndrome, and autoimmune bullous diseases often have a more acute onset without a long-standing history of preceding dermatosis. Because erythroderma is acute, thick scaling of the palms and soles or nail changes do not occur.

TABLE 32. Causes of Erythroderma

Existing dermatosis
Psoriasis, atopic eczema, allergic contact dermatitis, lichen planus, pityriasis rubra pilaris
Drug reaction
Exanthem, drug hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, TEN
Infection
Staphylococcal scalded skin syndrome, tinea corporis, scabies, viral infection
Autoimmune disease
Pemphigus foliaceus, pemphigus vulgaris, bullous pemphigoid, linear IgA disease, lupus erythematosus, dermatomyositis
Malignancy
Cutaneous T-cell lymphoma (mycosis fungoides), paraneoplastic syndrome with internal malignancy
Sarcoidosis, graft-versus-host disease
Idiopathic

TEN = toxic epidermal necrolysis.

Diagnosis and Management

Several diagnostic studies, guided by the clinical history and examination, are potentially helpful. A complete blood count with differential can assess for leukocytosis, which can be reactive or due to an occult hematologic malignancy. Eosinophilia can be a sign of a drug hypersensitivity reaction, scabies infestation, or cutaneous T-cell lymphoma. Imaging studies such as a chest radiograph can assess for lymphadenopathy (reactive or from lymphoma) or occult malignancy in other organs. A skin scraping can demonstrate dermatophytosis or the *Sarcoptes scabiei* mites that cause scabies. Immunofluorescence studies can distinguish possible autoimmune disease, and patch testing is done for a suspected contact allergy causing generalized eczema. Biopsy can be helpful in erythroderma, but nonspecific changes are common (30% to 40% of biopsies). It is not uncommon for patients to have multiple biopsies over time before a definitive diagnosis is made.

Management in conjunction with a dermatologist is frequently necessary. Treatment of infection, as well as management of fluid and electrolyte imbalance, is critical. Thick emollients help to restore skin barrier function. Topical glucocorticoids and systemic antihistamines can improve pruritus. Since drug hypersensitivity is a common cause, drug cessation is a frequent maneuver. Systemic therapy depends on the suspected cause and severity of symptoms. Additional therapies may include ultraviolet light therapy, systemic glucocorticoids, oral retinoids, and systemic immunosuppressants such as methotrexate, azathioprine, and mycophenolate mofetil.

KEY POINTS

- Erythroderma is characterized by erythema of 80% to 90% of skin surface with peripheral edema, erosions of the skin, scaling, and lymphadenopathy.
- Treatment of infection, as well as management of fluid and electrolyte imbalance, is critical in managing erythroderma; thick emollients help to restore skin barrier function, and topical glucocorticoids and systemic antihistamines can improve pruritus.

Hair Disorders

Hirsutism

Hirsutism, or excessive hair growth in women, affects about 8% to 10% of women. In androgen-dependent sites,

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the fine vellus hairs are converted to thicker, coarser terminal hairs such as those on the underarms. The most to least common sites are the lower abdomen and areola, the chin and upper lip, and between the breasts and on the lower back (**Figure 122**). Polycystic ovary syndrome (PCOS) is the cause of 50% to 70% of cases of hirsutism. The differential diagnosis includes several conditions associated with elevated levels of androgens as well as idiopathic and familial causes (**Table 33**). The evaluation should begin by reviewing the menstrual and reproductive history, medication history, and family history, as well as performing a comprehensive physical examination and assessing for breast discharge, acne, clitoromegaly, weight gain, or striae. Therapeutic options include removal of surface hairs (shaving, depilatories, waxing, or tweezing), bleaching (camouflage), and medications (eflornithine cream,

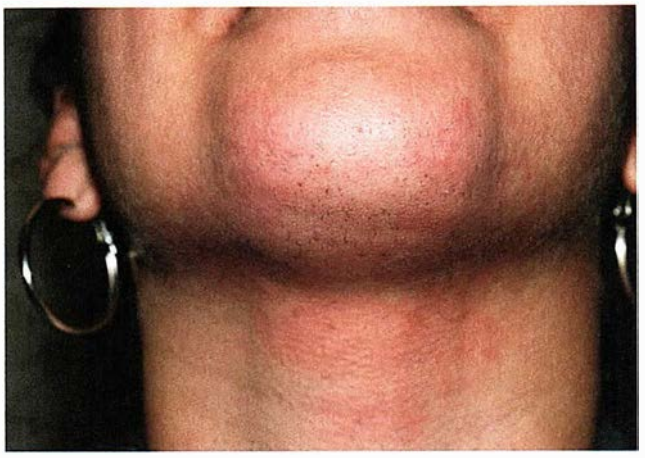

FIGURE 122. Dark, terminal hairs on the chin in a woman with hirsutism due to polycystic ovary syndrome.

TABLE 33. Diagnosing Excessive Hair Growth in Women

Differential Diagnosis of Excess Hair Growth	Associated Causes and Findings	Possible Testing/Assessments
Hirsutism (androgen-dependent sites)	Polycystic ovary syndrome: chronic anovulation, hyperandrogenemia, menstrual irregularities, infertility, obesity	DHEAS Serum total and free testosterone
	Ovarian tumors (many types): persistent bloating, early satiety, abdominal pain	Pelvic examination, ultrasound CA-125 measurement
	Cushing syndrome: acne, striae, moon facies, abdominal obesity, muscle wasting	24-hour urine free cortisol Low-dose dexamethasone suppression test
	Adrenal adenoma	Imaging
	Congenital adrenal hyperplasia: salt-losing crisis, ambiguous genitals, precocious puberty, oligo- or amenorrhea	17-Hydroxyprogesterone level ACTH stimulation test
	Prolactinoma: galactorrhea, visual changes, amenorrhea	Serum prolactin level
	Drug-induced: testosterone, DHEAS, danazol, corticotropin, high-dose glucocorticoids, androgenic progestins, acetazolamide, anabolic steroids	
Idiopathic/Familial	Present since puberty Slow development/progression Normal menses Family history	Testosterone, 17-hydroxyprogesterone, DHEAS levels
Hypertrichosis (non-androgen-responsive hair)	Porphyria: blistering, skin fragility, scarring	24-hour urine porphyrins, possibly stool or blood porphyrin levels
	Hyperthyroidism: weight loss, anxiety, tachycardia, increased sweating	Thyroid function testing, thyroid antibodies
	Drug-induced: cyclosporine, phenytoin, diazoxide, minoxidil, hexachlorobenzene, penicillamine, methyldopa, metoclopramide, reserpine	History
Acquired hypertrichosis lanuginosa (rare)	Excessive growth of fine lanugo hair (white or blonde, 1-2 cm long) on all hair-bearing surfaces including the face	Associated with malignancy, especially colorectal cancer Colonoscopy Age-appropriate and symptom-directed cancer screening

ACTH = adrenocorticotropic hormone; DHEAS = dehydroepiandrosterone.

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spironolactone, finasteride). It is important to inform women that finasteride is an FDA pregnancy category X drug and that spironolactone (pregnancy category C) has demonstrated feminization of male rat fetuses. Electrolysis and laser hair removal are more durable methods but are expensive and not permanent (see MKSAP 17 Endocrinology and Metabolism).

KEY POINTS

- Polycystic ovary syndrome is the cause of 50% to 70% of cases of hirsutism.
- Therapeutic options for hirsutism are removal of surface hairs, bleaching, and medications such as eflornithine cream, spironolactone, or finasteride.

Alopecia

Alopecia or hair loss can manifest as either a reduced amount or complete loss of hair in a specific location on the scalp. Even mild alopecia can be associated with decreased quality of life and self-esteem. Diagnosis can be simplified by first determining if the alopecia affects localized or diffuse areas of the scalp and, second, if the process is scarring. Scarring alopecia results in the loss of hair and follicle openings (ostia) and appears as very smooth patches of skin (**Figure 123**). A 4-mm punch biopsy from an area of active alopecia (*not* from areas suspicious for scar) can yield useful information regarding diagnosis, therapy, and prognosis if the diagnosis is uncertain following the history and physical examination (**Table 34**). A biopsy should also be performed is there is a clinical suspicion for scarring or lack of response to or worsening with treatment.



FIGURE 123. Scarring alopecias cause destruction of the follicles and result in a smooth patch of skin. Some follicles that were spared from the inflammation stud the surface of this patch of scarring alopecia.

KEY POINTS

- In diagnosing alopecia, first determine if the alopecia is localized or diffuse, and, second, if it is scarring or nonscarring.
- A 4-mm punch biopsy from an area of active alopecia can yield useful information regarding diagnosis, therapy, and prognosis of alopecia.

Localized/Limited Alopecia

Nonscarring

Alopecia areata (AA) is a chronic autoimmune disorder that results in smooth, hairless patches of skin (**Figure 124**, on page 77). The scalp is the most common site. In contrast to tinea capitis, there is no scale. At the periphery of the patch, there may be "exclamation point" hairs, which are characteristic of AA. The hair shaft of exclamation point hairs narrows the closer the shaft is to the skin surface. This tapering resembles the upper portion of an exclamation point and is thought to be due to inflammation around the hair follicle. Individual patches can spontaneously resolve within 12 months; however, new patches may develop. Onset is often before age 30 years but is rare before 3 years of age. An autoimmune mechanism is supported by the increased rate of other autoimmune diseases; for example, autoimmune thyroid disease is three times more common in those with AA.

Severe forms of AA can result in large patches of hair loss involving more than 50% of the scalp, complete loss of scalp hair (alopecia totalis), or loss of all body hair (alopecia universalis). These forms are uncommon and occur in about 10% to 15% of all persons with AA.

Syphilis is an uncommon cause of alopecia. On examination, there are patchy or "moth-eaten" areas of alopecia over the entire scalp. Other findings of secondary syphilis may be present.

Traumatic alopecia encompasses traction alopecia (from tension), trichotillomania (from compulsive twisting and pulling), and damage from chemicals or heat. Traumatic alopecia, regardless of the cause, is initially reversible but can progress to a scarring alopecia if the trauma continues. Patches of alopecia are rarely completely bald but have short, broken hairs mixed with longer hairs (**Figure 125**, on page 77). Traction alopecia develops at the peripheral edges of a hairstyle, such as the frontotemporal hairline with ponytails or buns and in geometric patterns across the scalp with braids. Traction alopecia can affect persons of any race or either sex. In contrast, the distribution of trichotillomania can be "bizarre" with linear, irregular, or asymmetric shapes. Treatment is directed at the source of the trauma (see Table 2). Rarely, internal malignancies may metastasize to the scalp and lead to alopecia at the metastatic site.

Scarring

Discoid lupus erythematosus (DLE) is the most common type of chronic cutaneous lupus. On the scalp, DLE manifests as

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TABLE 34. Management of Selected Types of Alopecia

Type of Alopecia	Treatment Options	Possible Systemic Associations
Androgenetic alopecia	Men: Topical minoxidil 5%,[a] finasteride,[a] dutasteride Women: Topical minoxidil 2%,[a] spironolactone Both: Hair transplant, cosmetic camouflage	Men: Increased rate of prostate cancer (if onset in the 20s) Women: Polycystic ovary syndrome
Alopecia areata	<50% scalp involvement: watchful waiting, topical glucocorticoids ± topical minoxidil, anthralin, intralesional triamcinolone >50% scalp involvement: topical immunotherapy (squaric acid or DPCP, topical glucocorticoids, ± topical minoxidil, phototherapy, wigs or other cosmetic camouflage, intralesional triamcinolone for brows, latanoprost for eyelashes	Autoimmune disease (hyperthyroidism, hypothyroidism, vitiligo, pernicious anemia, diabetes mellitus) Atopic eczema
Telogen effluvium	Remove or correct potential trigger Watchful waiting	Anemia, thyroid disease, significant weight loss, eating disorders, parturition, high fever, major surgery, blood loss, mental stress Medications: Anabolic steroids or supplemental androgens Antithyroid medications Antiepileptics β-blockers Oral retinoids Warfarin
Tinea capitis	Oral therapy with terbinafine, fluconazole, or itraconazole for about 6 weeks Oral therapy with griseofulvin for ~12 weeks	Screen close contacts
Discoid lupus erythematosus	Sunscreen or other sun-protection Glucocorticoids: Topical are first line Intralesional for recalcitrant or thick lesions Oral glucocorticoids are reserved for patients with rapid progression Antimalarial agents Retinoids: topical or oral if severe	Systemic lupus erythematosus (5%-10%) ROS for symptoms Examination for signs Urinalysis, ANA
Traumatic alopecia	Traction/styling alopecia: decrease tension from styling practices Trichotillomania: Cognitive behavioral therapy If severe or recalcitrant, antidepressants or anxiolytics may be helpful	Concomitant psychiatric disorder is more common in adults than children Consider referral to psychiatrist or psychologist
Lichen planopilaris	Topical, intralesional, or oral glucocorticoids, hydroxychloroquine, immunosuppressants	Check for concomitant lichen planus on the skin, nails, and oral and genital mucosa
Frontal fibrosing alopecia	Hydroxychloroquine, 5-α reductase inhibitors	
Central centrifugal cicatricial alopecia	Topical and intralesional glucocorticoids, oral tetracyclines, hydroxychloroquine, immunosuppressants, avoidance of associated styling practices	Use of hair straightener or relaxer Use (especially prolonged use) of styles with high tension on the hair

[a]FDA-approved treatment for that condition/indication.

DPCP = diphenylcyclopropenone; ROS = review of systems; ANA = antinuclear antibody.

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FIGURE 124. This patient with alopecia areata (AA) has patches of hair loss with preservation of the follicular ostia and "exclamation point" hairs at the peripheral edge, which are typical of AA.



FIGURE 125. This patient has traction alopecia from years of pulling her hair back in a bun. She demonstrates a decreased density of hair at the periphery where the tension was the greatest.

scaling, erythematous, hyper- and hypopigmented patches with alopecia. Multiple lesions are more likely than a single lesion. DLE may be present on other sun-exposed areas or in the conchal bowl of the ear. Glucocorticoids (topical, intralesional, or oral) are the most common therapy. Sun protection is a critical part of management for DLE.

Acne keloidalis nuchae is a chronic, scarring folliculitis that causes hairless areas of scar on the nape of the neck. It mostly affects black men but can occur in other populations (see Special Populations).

Diffuse Alopecia

Nonscarring

Androgenetic alopecia (AGA) can affect both men and women. It is the most common alopecia in men. The prevalence varies by sex and ethnicity. The prevalence in white men is 50% at age 50 and more than 70% at age 70. The prevalence is lower in women and Asian men. AGA is due to the effect of androgens on genetically susceptible hairs and results in shorter, thinner hairs that grow for shorter periods of time. The mechanism is not as clear for women. On examination, there are "miniaturized" hairs and in men, areas of complete hair loss. In men, the temples and vertex are often affected. In contrast, in women the top of the head is affected, and balding is not complete. A classic examination finding is "widening" of central part compared with the occipital part.

Telogen effluvium (TE) is the most common cause of diffuse alopecia in adult women. The differential diagnosis includes AGA and an uncommon and diffuse form of AA. TE is caused by a rapid shift of many hairs from a growing phase to a resting phase with a subsequent wave of increased "shedding." Patients often report sudden and excessive shedding from all over the scalp. History may reveal a triggering event 3 months prior to the start of the alopecia. In contrast to AGA, the frontal and occipital parts are similar in width and quality. TE often spontaneously resolves in about 6 to 12 months if the trigger is removed or treated.

Scarring

Lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) are variants of lichen planus that affect the hair (see Common Rashes). Patients may have significant pain, burning, or pruritus. On examination, there is mild scaling and erythema, which may be subtle and concentrated around follicular ostia. FFA predominates in postmenopausal women and causes alopecia at the frontotemporal hairline and eyebrows. LPP has a more scattered distribution around the entire scalp (**Figure 126**). Treatment of both LPP and FFA is challenging, and relapses are common.

Central centrifugal cicatricial alopecia is a scarring alopecia. It begins on the vertex (or crown) of the scalp and expands outwardly over time (**Figure 127**). The female to male ratio is about 3:1. The cause is unknown but is likely multifactorial



FIGURE 126. Lichen planopilaris is a cause of scarring alopecia and often demonstrates redness around the follicles.

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FIGURE 127. Hair loss due to central centrifugal cicatricial alopecia (scarring alopecia).

and may include styling practices. Treatment is challenging and often not curative.

Nail Disorders

The nail is a complex anatomic structure composed of the nail matrix, nail plate, nail bed, and nail folds. The nail folds comprise both the proximal and lateral folds. The nail plate originates from the matrix that is located under the proximal nail fold (cuticle). Thus, proximal nail fold inflammation of any etiology (hand eczema, psoriasis) can cause dystrophy of the nail plate. The nail plate grows over the nail bed. The finger- and toenails grow 3 and 1 mm per month, respectively. Starting in the third decade, the rate can slightly decrease with each year of age. Nail disorders can be caused by various diseases, and it is important that a correct diagnosis is made (**Table 35**). Nail problems are rare in children.

TABLE 35. Nail Changes Associated with Possible Systemic Diseases/Conditions

Type of Nail Change	Possible Causes
Transverse indentations (Beau line, onychomadesis)	Description: Transverse linear depressions in the nail plate; at the same level of the nail in most or all of the nails
	Associated with: Local injury or any severe systemic insult such as infection, surgery, chemotherapy
Pitting	Description: Small, punctate indentations in nail plate
	Associated with: Psoriasis, lichen planus, alopecia areata
Splinter hemorrhages	Description: Red-brown, short, fine lines in the nail bed, due to injury in nail bed vessels
	Associated with: Trauma, psoriasis, lichen planus, infective endocarditis, chronic kidney failure, autoimmune connective tissue diseases
Color change:	
Brown/black	Subungual hematoma, nevus, melanoma, drug-induced (azidothymidine, minocycline)
Yellow	Aging, dermatophyte infection, yellow nail syndrome
White nails	
Punctate	Description: Nonuniform, small white macules on some nails, appear in different places on different nails, due to day-to-day trauma
Half-and-half nails (Lindsey nails)	Description: White change comprises proximal half of the nail and the distal half is pink, red, or brown.
	Associated with: chronic kidney failure
Terry nails	Description: Mostly white nail with a distal rim of normal color at the distal edge.
	Associated with: Liver disease, chronic heart failure, and normal aging
Clubbing	Description: Spongy thickening of distal digit due to hypervascularization
	Associated with: Pulmonary diseases, congenital heart disease, arteriovenous malformations, cirrhosis, inflammatory bowel disease, celiac disease, infective endocarditis, lung cancer, pachydermoperiostosis
Koilonychia (spoon nails)	Description: Upward curving of the periphery of nail to mimic the bowl of a spoon
	Associated with: Chronic occupational injury, iron deficiency anemia
Cuticle changes; ragged torn cuticles	Also known as Samitz sign
	Associated with: Dermatomyositis
Periungual (around nail) erythema with dilated, tortuous vessels	Increased number of visible vessels near the cuticle
	Associated with: Dermatomyositis and scleroderma
Periungual (around nail) erythema with numerous fine vessels	Increased number of visible vessels near the cuticle
	Associated with: Lupus erythematosus

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Aging

With aging, the thickness, curvature, surface, and color of the nail plate can change. The underlying mechanisms are unknown. The nail plate may become thicker or thinner. The normal texture of the nail can become rougher and more friable, resulting in striations and splitting. The color of the nail may become paler or yellow. These changes may predispose to onychomycosis, pain, and subungual hemorrhage.

Connective Tissue Diseases

The proximal nail fold can demonstrate signs of systemic lupus erythematosus, dermatomyositis, or scleroderma. The proximal nail fold can appear erythematous and with magnification demonstrate irregular, twisted, and dilated vessels. The cuticle can become dry and ragged with dermatomyositis (Samitz sign) (**Figure 128**).

Infection

Onychomycosis

Onychomycosis is a fungal infection of the nails. It affects 10% to 20% of adults and is the most common nail infection. Infection is more common in older men with comorbidities such as diabetes mellitus, peripheral vascular disease, and immunosuppression. Dermatophytes cause more than 90% of fungal nail infections. Yeasts and molds are uncommon causes. The fungus may enter the nail from a tinea infection elsewhere in the body or from the environment. The most common pattern is distal subungual onychomycosis; the distal corner of the nail becomes yellow, lifted, and develops subungual debris. This can then spread proximally and laterally to involve the entire nail plate. Proximal subungual onychomycosis evolves similarly but begins at the proximal nail fold (the cuticle). This is a rare pattern and is associated with the effects of HIV infection and the severely immunocompromised patients. Treatment is rarely medically necessary and is often pursued for cosmetic reasons. Infection should be confirmed, especially if considering systemic therapy, by processing the nail or subungual debris with potassium hydroxide (KOH), staining with periodic acid–Schiff (PAS), or fungal culture. Topical therapies traditionally have been limited in their efficacy and require long treatment durations. Efinaconazole is a new topical agent with a better response rate then ciclopirox. These topical agents are available by prescription. Terbinafine cream is available over-the-counter and has slightly better efficacy then azole creams. Systemic terbinafine is the most effective oral therapy, whereas itraconazole is a second-line agent. Continuous terbinafine therapy is more effective than pulse therapy. Toenails are treated for 12 weeks, and fingernails are treated for 6 weeks. Topical agents can be an effective therapy for superficial white onychomycosis and early subungual onychomycosis.

Paronychia

Acute paronychia often presents as a painful swelling of the nail fold (**Figure 129**). It often follows minor trauma and affects only a single finger. *Staphylococcus aureus* is a frequent cause. Management consists of warm compresses or soaks, incision and drainage, or topical or systemic antibiotics. In contrast, chronic paronychia affects multiple fingers and manifests as red, swollen nail folds that lack a cuticle. It causes ridging and dystrophy of the nail plate. Chronic irritation from water or



FIGURE 128. This patient has dermatomyositis and has redness of the periungual skin as well as tortuous, dilated, and thrombosed vessels in the proximal nail fold.



FIGURE 129. Bulbous focal swelling of the periungual skin of one finger due to acute bacterial paronychia.

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chemical contact is the primary cause. *Candida* species or gram-negative bacteria can cause secondary infection. Management includes minimizing wet-work and the use topical glucocorticoids to minimize inflammation and topical antifungal or antiseptic agents.

KEY POINTS

- Onychomycosis, a fungal infection of the nails, is more common in older men with comorbidities such as diabetes mellitus, peripheral vascular disease, and immunosuppression.
- Acute paronychia often follows minor trauma and affects only a single finger; *Staphylococcus aureus* is a frequent cause.

Inflammatory Dermatoses

Lichen planus (LP) causes nail disease in about 10% of patients with generalized LP (see Common Rashes). The nail plate can become thinner or be completely destroyed (**Figure 130**). The cuticle may become attached to the nail plate (pterygium). Red streaking of the nail can also occur. It is important to examine the rest of the skin and mucosae for signs of LP.

Nail changes occur in about 75% of persons with psoriasis. The most common nail abnormality observed on both fingernails and toenails is subungual hyperkeratosis. Toenails more often demonstrate thickening and discoloration (whitening or yellowing), whereas pitting and ridging are more common on fingernails. Persons with psoriatic nail dystrophy are often older and are more often affected by psoriatic arthritis. Some of the nail damage can result from onychomycosis. About 20% of those with psoriatic nail dystrophy have positive fungal cultures.



FIGURE 130. Thinning, shortening, and hyperpigmentation of the nails from lichen planus.

Malignancy

Acral Lentiginous Melanoma

Acral lentiginous melanoma (ALM) is the most common form of melanoma in Asian, Hispanic, and black populations. It can originate in the nail and present as a longitudinal brown stripe that is either solitary or different from other brown lines (darker, broader, changing) (see Special Populations).

Squamous Cell Carcinoma

Squamous cell carcinoma of the nail unit often begins at the nail fold and is associated with a history of trauma, arsenic ingestion, radiation exposure, chronic paronychia, and human papillomavirus (HPV) infection (**Figure 131**). It manifests as an irregular pink keratotic patch or papule that can be mistaken for a wart. Warts, however, are discrete, skin-colored papules with punctate brown dots (thrombosed vessels). If a wart is not responding to therapy as expected, a biopsy or referral to a dermatologist is appropriate. Immunosuppressed patients with HPV/warts around the nail plate may be at higher risk of developing squamous cell carcinoma in those locations and should be monitored closely.

Disorders of Mucous Membranes

Evaluation of the mucous membranes is an important part of the skin examination because findings can be potentially harmful and a clue to systemic disease.



FIGURE 131. This pink plaque on the finger and dystrophic nail was treated as a wart, but a biopsy demonstrated squamous cell carcinoma.

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Melanotic Macule

Melanotic macules are well-circumscribed, often round, evenly hyperpigmented lesions that can occur on oral or genital mucosa. In the oral cavity, they are most common on the lower lip, although they may be seen on the gingiva, buccal mucosa, or tongue. Single or multiple lesions can be observed. No treatment is necessary, but biopsy can be performed if there are irregular or changing spots (**Figure 132**).

Amalgam Tattoo

Amalgam tattoos are the most common source of localized pigmentation on the buccal mucosa. They result from traumatic implantation of amalgam into the soft tissue. It clinically presents as a gray to bluish or black macule adjacent to a restored tooth. Diagnosis can be made clinically, or confirmation can be made with biopsy and pathology. No treatment is necessary.

Leukoplakia and Erythroplakia

Leukoplakia is an adherent white plaque on the mucosa that most often is a benign, inflammatory response to triggers such as trauma or tobacco use. It can be premalignant and lead to intraoral squamous cell carcinoma in approximately 20% of patients. Premalignant leukoplakia is more common in certain anatomic sites (floor of the mouth or ventral tongue). The differential diagnosis includes oral candidiasis, which manifests as nonadherent white plaques. Oral hairy leukoplakia is an Epstein-Barr virus infection that occurs almost uniquely in patients with HIV infection. It presents as adherent linear white plaques on the lateral surface of the tongue (**Figure 133**).

Erythroplakia is a red, velvety plaque, which has a higher probability of underlying dysplasia at the time of diagnosis. In both leukoplakia and erythroplakia, biopsy is necessary to evaluate for dysplasia, and erythroplakia should always be biopsied when clinically observed.

Aphthous Ulcers

Aphthous ulcers (canker sores) are common, benign, noninfectious shallow ulcerations of unknown etiology with surrounding erythema that occurs on nonkeratinizing oral and genital surfaces (labial/buccal mucosa, sides of tongue, floor of mouth) (**Figure 134**). Diagnosis is made clinically, although testing to rule out infections can be performed. Aphthous ulcers may be self-limited when the lesions are few or infrequent. When they become recurrent, painful outbreaks that interfere with eating and quality of life, therapy such as topical glucocorticoids or topical lidocaine can be used; oral therapies including colchicine also can be considered when the ulcers are recalcitrant to topical therapies. Severe, recurrent oral



FIGURE 133. Oral hairy leukoplakia in a patient with AIDS. Oral hairy leukoplakia is a precancerous lesion that presents as white patches on the oral mucosa with changes in the surface texture.

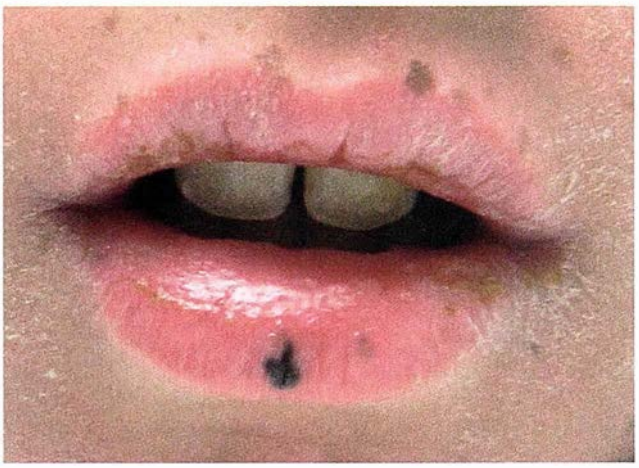

FIGURE 132. Melanotic macule occurring on the vermilion border of the lower lip.



FIGURE 134. Aphthous ulcers are characterized by painful, discrete, shallow, round-to-oval ulcers with a grayish base typically less than 1 cm in diameter.

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ulcers may suggest a systemic disease such as Behçet syndrome (associated with eye symptoms and arthralgia), or Crohn disease, HIV infection, or erythema multiforme. The differential diagnosis includes herpes simplex ulcers, which can present as grouped vesicles typically on the keratinizing surfaces, and sexually transmitted infections.

KEY POINT

- Severe, recurrent oral aphthous ulcers may suggest a systemic disease such as Behçet syndrome, Crohn disease, HIV infection, or erythema multiforme.

Lichen Planus

Lichen planus is an inflammatory condition that can affect the skin, nails, or mucosa (see Common Rashes). Clinical presentations include white lines and patches (Wickham striae) or painful erythema and erosions (erosive variant) (**Figure 135**). With mucosal-only disease, evaluation for contact allergens should be considered. Biopsy establishes the diagnosis. Therapies are glucocorticoids (systemic and topical) and immunosuppressive agents in severe disease. Follow-up is important as squamous cell carcinoma can occur in long-standing ulcerative lesions.

Actinic Cheilitis and Squamous Cell Carcinoma

Actinic cheilitis is a premalignant condition that presents with chronic erythema and recurrent scaling of the lower lip. This differs from angular cheilitis, which is inflammation involving one or both corners of the mouth and often related to bacterial or fungal infections. Treatment with topical chemotherapy agents (5-fluorouracil), imiquimod, laser therapy, photodynamic therapy, or cryotherapy is recommended.

Development of a mucosal nodule or ulcer should raise the suspicion of invasive squamous cell carcinoma (SCC). Mucosal SCC also can develop as a result of chronic inflammatory conditions (lichen planus, lichen sclerosus) or in the oral cavity in association with tobacco or alcohol use or human papillomavirus infection. Biopsy is required for diagnosis, and excision often is necessary. SCC of the lip is often underrecognized and leads to delayed diagnosis, more extensive surgery, and a high metastatic rate (see Common Neoplasms).

KEY POINTS

- Actinic cheilitis is a premalignant condition and presents as chronic erythema and recurrent scaling of the lower lip; management is with topical chemotherapy agents, imiquimod, laser therapy, photodynamic therapy, or cryotherapy.
- Development of a nodule or ulcer on the lip area should raise the suspicion of invasive squamous cell carcinoma.

Lichen Sclerosus

Lichen sclerosus is an inflammatory condition that often presents as a white, atrophic patch on the genital and perianal skin, although extragenital lesions can occur (**Figure 136**). It differs from lichen planus in its clinical presentation of white patches that circumferentially involve the vaginal introitus and perianal area ("figure 8" appearance) or the head of the penis. Prepubertal girls and postmenopausal women appear to be at highest risk. The differential diagnosis includes vitiligo, which causes depigmented rather than atrophic plaques. Biopsy establishes the diagnosis and can differentiate it from other inflammatory disorders, as lichen sclerosus has distinct histopathologic features compared with lichen planus. Treatment is with potent topical glucocorticoids (similar to first-line treatment for lichen planus), and frequent clinical follow-up is

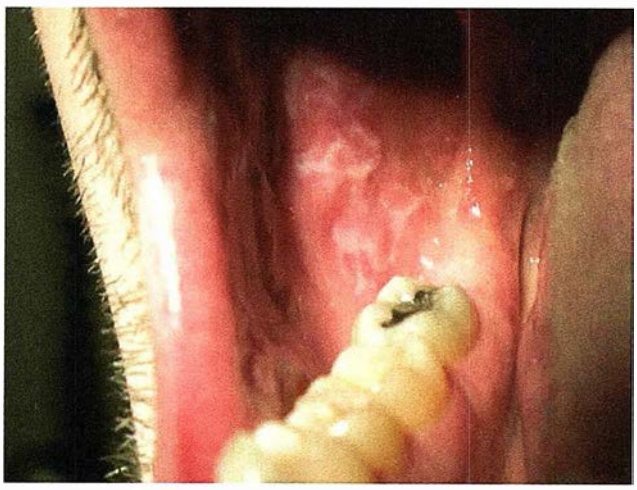

FIGURE 135. Oral lichen planus on the buccal mucosa with prominent reticulated white lines of Wickham striae.



FIGURE 136. Lichen sclerosus is a chronic inflammatory mucocutaneous disease characterized by "parchment-like" or "cigarette paper" skin. Courtesy of CDC Public Health Image Library.

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necessary. If left untreated, permanent scarring can occur. SCC may occur in long-standing lesions.

Black Hairy Tongue

Black hairy tongue is a harmless but distinctive presentation of overgrowth of filiform papillae and bacteria or fungi, causing a dark and hairy appearance (**Figure 137**). Poor hygiene, tobacco use, coffee and tea consumption, dry mouth, and medications such as antibiotics can contribute to the appearance. Management includes better oral hygiene, such as tongue scraping, and modifying risk factors, including tobacco and medication use.

Geographic Tongue

Geographic tongue (benign migratory glossitis) is a common, benign inflammatory condition of the dorsal tongue that presents with migratory areas of smooth red surfaces and white patches, creating a map-like appearance (**Figure 138**). Although generally asymptomatic, a burning sensation can occur, and it may be exacerbated by hot or spicy foods. It has been reported in association with psoriasis. Management consists of analgesics and avoidance of triggers.

Oral Candidiasis

Oral candidiasis can present in a variety of ways. The most common presentation is that of white, nonadherent plaques on the tongue, palate, and gingiva with a burning sensation (thrush) (**Figure 139**). It also can present as angular cheilitis, which are painful erythematous patches in one or both corners of the mouth; concomitant bacterial super-infection also can occur. Risk factors are immunosuppression (HIV infection or transplantation), oral glucocorticoid use, antibiotic use, and xerostomia with thrush, and poor-fitting dentures with drooling for angular cheilitis. Diagnosis can be made using potassium hydroxide (KOH) examination, and treatment with oral antifungal preparations such as azole troches or nystatin swish and swallow mouthwash is effective. Oral antifungal agents can be used in patients with severe or recalcitrant candidiasis.

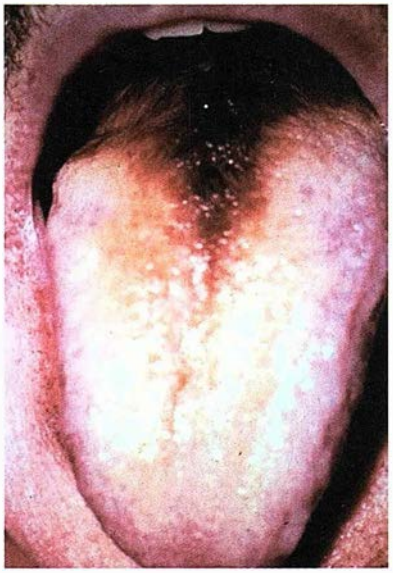

FIGURE 137. Black hairy tongue is most commonly associated with antibiotic use, coffee and tea consumption, poor oral hygiene, and smoking.

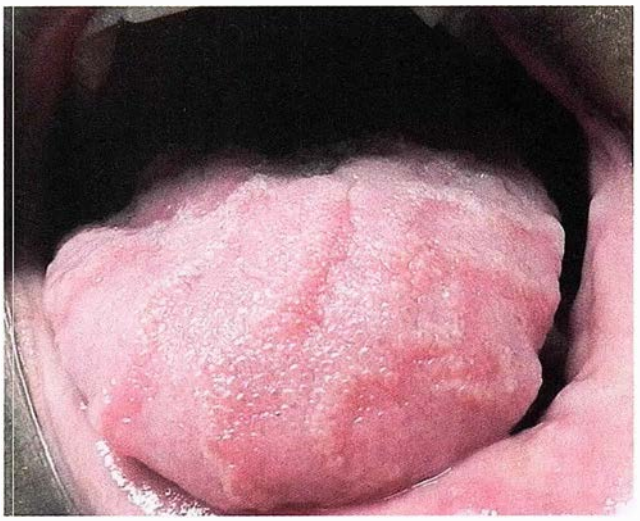

FIGURE 138. Geographic tongue (benign migratory glossitis) showing irregularly shaped, map-like migratory patches on the dorsal tongue.

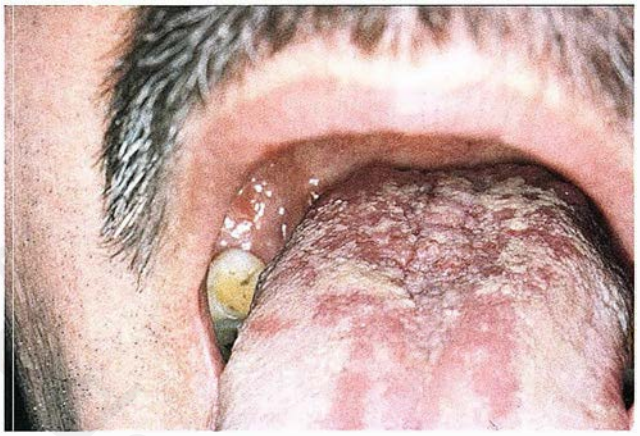

FIGURE 139. Oral candidiasis (thrush) most commonly presents as a white, fluffy, nonadherent film on the tongue, buccal mucosa, or palate.

Foot and Leg Ulcers

Lower extremity ulcerations may be divided into several categories, including venous stasis ulcers, arterial insufficiency ulcers, neuropathic ulcers, infectious ulcers, ulcers due to malignancy, drug-induced ulcers, ulcers associated with sickle cell anemia, and ulcers resulting from inflammatory conditions such as pyoderma gangrenosum (see Cutaneous Manifestations of Internal Disease). Discriminating among them is important, as the treatments differ widely depending on the underlying cause.

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Venous Stasis Ulcers

Ulcerations are one of the most common complications of long-standing venous stasis disease. Most patients have a history of stasis dermatitis and often have some level of scarring and dyspigmentation on the bilateral lower extremities (see Common Rashes). The same mechanism of impaired venous drainage causing changes in vascular permeability with stretching of the skin may lead to loss of integrity of the dermal barrier and development of ulceration. Venous stasis ulcers usually occur on the distal lower leg, particularly the medial aspect of the ankle, and may result from a minor trauma, a medical procedure, or an acute stasis dermatitis flare. The symptoms vary from negligible discomfort to significant pain. The ulcers tend to have an irregular border and surrounding hyperpigmentation, and the skin and subcutaneous tissues are thickened, resulting in lipodermatosclerosis (fibrosing panniculitis of the subcutaneous tissue) (**Figure 140**). Patients often have varicose veins and peripheral edema.

Treatment is directed toward three main areas: reducing the peripheral edema, creating a wound environment that is conducive to healing, and treating any secondary infection that may be present.

Reduction of peripheral edema is achieved by the use of compression stockings, pneumatic compression boots, and compression dressings (Unna boots). In some patients with evidence of hypervolemia, low salt diets, and diuretics (hydrochlorothiazide or furosemide) may be indicated. Since some patients may have a significant degree of arterial insufficiency as well, determination of their arterial circulation status by measuring the ankle-brachial index may be helpful in patients with significant risk factors for arterial disease to ensure that excessive compression (and resultant arterial ischemia) is not performed. Venous ultrasonography is generally not indicated, however, since the clinical examination is ordinarily sufficient to establish venous insufficiency.

Creating a desirable wound environment is critical to encourage healing. Wounds should be moist but not overly saturated. Wounds that are dry may be covered with hydrogel or hydrocolloid dressings to increase the moisture content. Debridement of necrotic tissue may be necessary. Alginate and foam dressings may be used when excessive exudate is present.

Cultures of many chronic wounds, such as stasis ulcers, will typically reveal a polymicrobial mixture of bacteria; in most patients this represents colonization rather than acute infection. Nevertheless, keeping the bacterial burden low is a desirable goal, since having a significant bacterial burden likely interferes with wound healing. Reduction of the bacterial burden is achieved (when needed) by temporary and judicious use of silver impregnated dressings or similar local antimicrobial preparations. Topical antibiotics should be used with caution, however, because of the potential for the development of contact dermatitis and resistant bacteria and thus should be avoided if possible. Clues to suggest active infection are worsening pain, swelling, and copious exudate; these findings would be an indication for oral antibiotics.



FIGURE 140. Lipodermatosclerosis with ulcer, resulting from chronic thickening of the skin in chronic venous stasis dermatitis.

KEY POINTS

- Venous stasis ulcers occur on the distal lower leg and are typically associated with signs of chronic venous insufficiency.
- Treatment consists of compression, creating a wound environment that is conducive to healing, and treating any secondary infection that may be present.

Arterial Insufficiency Ulcers

Arterial insufficiency ulcers develop in patients with a history of significant atherosclerotic disease of the extremities and are caused by a lack of blood flow to these areas. They tend to be painful; discomfort may increase with elevation of the legs, compression, or any other maneuver that further limits circulation. Unlike venous stasis ulcers, which often have somewhat irregular borders and a significant amount of surrounding postinflammatory hyperpigmentation and lipodermatosclerosis, arterial insufficiency ulcers have a "punched out" appearance with surrounding erythema. The extremities as a whole often appear pale, and the skin is thin, taut, and shiny and lacks hair (**Figure 141**). Pedal pulses are often difficult to appreciate, the toes are cold, and capillary refill is poor. If arterial insufficiency is suspected, diagnosis can be confirmed by measuring

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FIGURE 141. Arterial insufficiency ulcers appear sharply demarcated or "punched out," and the surrounding skin is red, taut, and tender.

the ankle-brachial index. The ulcers are treated with debridement and dressings similar to venous stasis ulcers; the same antibacterial preparations are also used when necessary. One important distinction, however, is that compression will increase pain and worsen arterial insufficiency ulcers, whereas the opposite is true with venous stasis ulcers. Surgical revascularization to improve the lower extremity circulation is often necessary to facilitate wound healing.

KEY POINTS

- Arterial insufficiency ulcers have a "punched out" appearance with surrounding erythema.
- In patients with arterial insufficiency ulcers, surgical revascularization to improve the lower extremity circulation is often necessary to facilitate wound healing.

Neuropathic Ulcers

Neuropathic ulcers arise from recurrent trauma in patients who have lost sensation in a given limb. Diabetes mellitus is the most common underlying predisposing factor, but other causes of nerve damage, or less common disorders such as tertiary syphilis, may be responsible. The ulcers are painless and typically occur in areas prone to trauma, such as the plantar aspects of the feet or friction points created by poorly fitting orthotic devices (**Figure 142**). Treatment consists of debridement, use of appropriate dressings, and protection



FIGURE 142. Neuropathic ulcers have a hyperkeratotic rim and occur over pressure points such as the metatarsal heads.

from further trauma. Daily examination of the feet in patients with diabetes is encouraged. The ulcers can be quite deep and occasionally extend into the bone; thus, early identification and treatment are crucial to prevent development of osteomyelitis and avoid potential amputation.

KEY POINTS

- Neuropathic ulcers are painless and typically occur in areas prone to trauma, such as the plantar aspects of the feet or friction points.
- Daily examination of the feet in patients with diabetes mellitus is encouraged to check for neuropathic ulcers; early identification and treatment are crucial to avoid potential amputation.

Other Causes of Lower Extremity Ulcers

Pyoderma gangrenosum is an extremely painful ulcerating inflammatory condition seen most commonly in patients with inflammatory bowel disease; it may also be associated with rheumatoid arthritis, hematologic malignancies, and liver disease. It should be suspected in patients with the appropriate history and also when no other obvious cause for ulceration exists. Pyoderma gangrenosum may be confused with various other causes of ulceration such as stasis ulcers, infections, and pressure ulcers. Squamous cell carcinomas may also arise on the lower extremities and present as ulcers that clinically may appear nearly identical to the other types; thus, biopsy should be considered when ulcers fail to improve despite appropriate therapeutic measures. Certain organisms, including fungi and atypical mycobacteria, can cause chronic ulcers and should be suspected in patients who have an appropriate travel history or who are immunocompromised (see Cutaneous Manifestations of Internal Disease).

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Dermatologic Problems of Special Populations

Treatment of Dermatologic Conditions in Pregnancy

Pregnant and nursing women need special consideration because potential medication-related teratogenicity can limit the treatment options for dermatologic diseases. Dermatologic conditions can be chronic and unchanged during pregnancy, and pregnancy itself can induce normal changes (**Table 36**). The FDA assigns categories for every medication to indicate the potential of a drug to cause birth defects if used during pregnancy. These categories and the risk-to-benefit ratio should be considered before prescribing medications to any woman of childbearing potential, including those attempting pregnancy, pregnant women, or nursing mothers. The specific trimester and developmental stage should be considered as medications carry different risks depending on the developmental period.

FDA pregnancy category X medications should never be used in pregnant or nursing women, and those specifically prescribed in dermatology are methotrexate, thalidomide, and retinoids (**Table 37**). Importantly, men who are potential fathers should not take methotrexate. There are regulatory systems that monitor certain medications such as iPledge for isotretinoin and STEPs for thalidomide because of the significant potential detriment to fetuses.

Management with topical agents often is considered before prescribing systemic medications because they are lower risk, with the exception of tazarotene (category X). Glucocorticoids are pregnancy category C, but are generally thought to be safe, especially topical formulations. The lowest required amount for therapeutic efficacy is used. Antihistamines also are considered safe in pregnancy (except hydroxyzine in the first trimester), but they should be avoided in breastfeeding mothers because of risks of sedation in infants.

Tetracyclines are frequently used in dermatology; however, they should be avoided because of the risk of staining the teeth and bone during fetal development (category D). Trimethoprim-sulfamethoxazole should also be avoided because it can interfere with folic acid metabolism (category C). Other antibiotic classes such as the penicillins (category B) and cephalosporins (category B) are safer choices during pregnancy. Spironolactone may be used to treat acne but should not be used for acne in pregnant women because of risks of feminization in a fetus.

TABLE 37. Selected FDA Pregnancy Category X Drugs to Avoid During Pregnancy and Lactation

Acitretin
Danazol
Estrogens
Finasteride
5-Fluorouracil
Flutamide
Isotretinoin
Methotrexate
Stanozolol
Tazarotene (topical)
Thalidomide

TABLE 36. Normal Dermatologic Changes Observed During Pregnancy

	Finding	Characteristics
Hyperpigmentation	Melasma	"Mask of pregnancy," brown patches on face and neck, occasionally extremities
	Linea nigra	Line of pigmentation on the abdomen that may extent centrally from the pubis to xiphoid
	Nipples, areolae, axillae, genitals	Skin may darken in pregnancy; moles also may darken
Striae gravidarum	Stretch marks	May start pink to red and then become paler over time
Hair and Nails	Hair	May thicken during pregnancy, and then loss of hair about 3 months postpartum is common (telogen effluvium)
	Nails	May grow faster during pregnancy
Vascular changes	Spider angiomas	Common on face, neck, extremities
	Hemorrhoids and varicose veins	Occur in about 40% of women
	Palmar erythema	Increased redness on palms seen in two thirds of women
	Edema	Diffuse swelling can occur; lower leg edema is common
	Vaginal erythema (Chadwick sign) and blue discoloration of cervix (Goodell sign)	Due to increased blood flow and congestion
	Gingival hyperemia and edema	Occurs in some extent to all women; pyogenic granulomas also can occur

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If dermatologic surgical procedures during pregnancy are indicated, low doses of local anesthetics, including lidocaine and epinephrine are safe to use; however, sedatives and opioids should be avoided in pregnant and breastfeeding women.

KEY POINTS

- FDA pregnancy category X medications should never be used in pregnant or breastfeeding women, and those specifically prescribed in dermatology are methotrexate, thalidomide, and retinoids.
- Management with topical agents often is considered before prescribing systemic medications to pregnant women because they are lower risk than systemic medications, with exception of topical tazarotene (FDA pregnancy category X).

Aging

Several common and uncommon skin conditions become more prevalent during aging, and the skin structure and function change with age. Autoimmune blistering diseases are rare, but bullous pemphigoid is more common after the age of 60 years, and the risk increases each year thereafter. The most common skin conditions to affect older patients are pruritus, inflammatory dermatoses, fungal infections, and bacterial and viral infections.

Changes Due to Chronologic Aging and Photoaging

A myriad of changes occur in the skin over time; these can be due to chronologic aging alone or influenced by the cumulative effects of ultraviolet light exposure (**Table 38**).

Xerosis (dry skin) is more common in older patients and is often associated with pruritus (see Pruritus). Actinic purpura is caused by age-related capillary fragility and bleeding under atrophic skin. It is common on the forearms and dorsal hands, but may be seen anywhere on the body (**Figure 143**). It is not a sign of vasculitis, a bleeding disorder, or nutritional deficiency, and does not require additional evaluation or therapy. Stellate pseudoscars are jagged or linear atrophic scars that primarily occur on the forearms of patients with chronic actinic damage. Patients may or may not recall antecedent trauma. Stellate pseudoscars are often seen in conjunction with actinic purpura.

TABLE 38. Common Skin Findings of Intrinsic Aged Versus Photoaged Skin

Intrinsic Aging	Photoaging
Thinned epidermis	Coarse furrows
Loss of subcutaneous fat	Fine wrinkles
Fine wrinkles	Diffuse pigmentation; "bronzing"
Dry, flaky skin	Lentigines
Loss of elasticity	Pebbly texture of skin (elastosis)
Skin pallor	Solar purpura
Decreased skin temperature	Telangiectasia

Inflammatory Skin Conditions

Xerotic eczema occurs in areas of excessively dry skin. The lower legs are common areas. Patients with severe xerotic eczema can develop poorly demarcated, scaly patches interspersed with superficial red fissures in a netlike distribution (**Figure 144**). The appearance has been likened to cracked porcelain or a dry lake bed (see Common Rashes).

Seborrheic dermatitis is more common as age increases. Greasy scaling of the scalp, brows, nose, and cheeks may develop. Areas such as the axillae and central chest may be affected (see Common Rashes).

Infection

Herpes zoster and postherpetic neuralgia are more frequent in older persons, and the risk of these conditions can be reduced with immunization (see MKSAP 17 General Internal Medicine). Infestations by scabies, lice, or bedbugs can occur in group



FIGURE 143. Actinic purpura on the forearm of a patient with an iatrogenic fistula.



FIGURE 144. Severe xerotic eczema is characterized by redness and a "tile-like" pattern on dry skin (xerosis) with evidence of trauma from scratching. This typically occurs during midwinter in northern climates.

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living arrangements. Fungal infections of the feet and toenails are very common in older populations; however, not all nail changes are caused by fungus. The nail changes in color, texture, and thickness with age. These changes can be mistaken for onychomycosis (see Nail Disorders).

Skin of Color

Melanocytes are responsible for the wide variety of skin colors observed. The variation in skin color among individuals is due to variability in the size, distribution, and melanin concentration of the melanosomes. Melanin absorbs and scatters energy from ultraviolet (UV) light, so persons with darker skin have a lower risk of sun damage, but are more likely to develop pigmentation alteration, both hyper- and hypopigmentation. Persons with skin of color can be affected by novel and common skin conditions. Inflammatory dermatoses can have a more subtle appearance since the pink-red color that is a sign of inflammation can be difficult to see on darker skin (**Figure 145**). The most common skin problems in people with skin of color are acne, dyschromia or any alteration in skin color (darker or lighter), seborrheic dermatitis, atopic dermatitis, or other causes of dermatitis.

Differences in Pigmentation

Persons with skin of color often have normal variations in skin color with areas of hyperpigmentation along the gingiva and lines of demarcation on the trunk and extremities. Traumatic or inflammatory skin damage can also cause pigment alteration. Scrapes, bug bites, or acne often heal with hyperpigmentation. Areas of active inflammation from seborrhea, eczema, or psoriasis may develop hypopigmentation. Topical or intralesional glucocorticoids can also cause hypopigmentation, which can be difficult to distinguish from the effects of a rash; upon cessation of the medication the dyschromia will improve. Partial or complete depigmentation is also seen in idiopathic guttate hypomelanosis, which manifests as 2- to 6-mm hypopigmented macules on the trunk and extremities.

Vitiligo affects about 1% to 2% of the general population but is more difficult to treat for patients with darker skin color because of the dramatic difference in the depigmented (white) skin and preserved areas of natural pigmented skin (**Figure 146**). The peak onset is between 10 and 30 years of age, and the most common form is a generalized form that has a predilection for the eyes, nostrils, and mouth and is often bilaterally symmetric. Topical glucocorticoids are the most frequent therapies for vitiligo and can be used for patients with limited or generalized disease. Ultraviolet light therapy is frequently used for generalized disease since it can be difficult to apply medications diffusely. When depigmentation affects nearly the entire body and is unresponsive to treatment, depigmentation of the remaining normal skin is considered.

Treatment of hyperpigmentation is challenging. Depigmenting agents such as hydroquinone, azelaic acid, and kojic acid target different steps in the production of melanin. Topical retinoids can be used in combination with depigmenting agents for additional effect. Procedures including chemical peeling and laser therapy, can be effective but can be expensive, and adverse effects can be severe. Cosmetic camouflage is an affordable option for most patients. Sunscreen can reduce the recurrence of pigment.

Acne Keloidalis Nuchae and Pseudofolliculitis Barbae

Both acne keloidalis nuchae (AKN) and pseudofolliculitis barbae (PFB) are characterized by firm, skin-colored, pink, or hyperpigmented papules that are often centered on hair

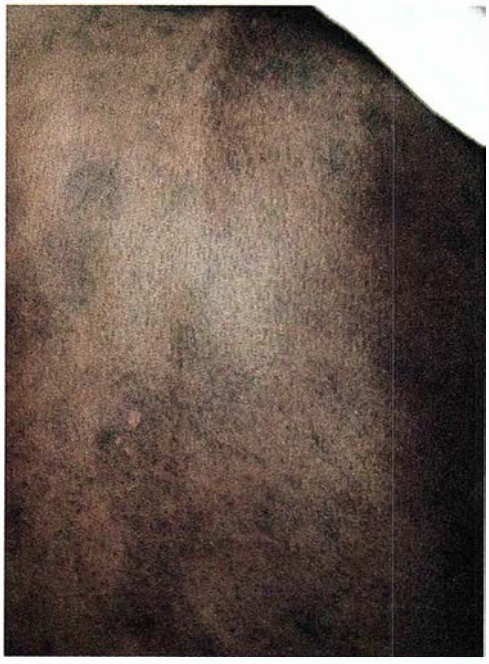

FIGURE 145. Erythema due to inflammation can be difficult to distinguish in people with more skin color. This patient has secondary syphilis manifesting as dark brown patches without erythema.



FIGURE 146. Symmetric patches of generalized vitiligo on the eyelids.

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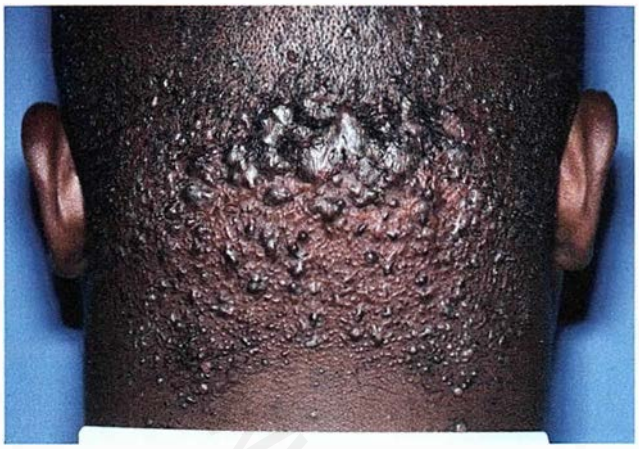

FIGURE 147. Skin-colored papules and plaques on the posterior scalp and nape of the neck from acne keloidalis nuchae.



FIGURE 148. Large keloid on the earlobe as a result of an ear piercing.

follicles. AKN often occurs on the posterior scalp and neck (**Figure 147**), whereas PFB occurs on the face and anterior neck. These conditions are most likely caused by the trauma of an ingrown hair. The hair follicle in people with skin of color is often curved, and the hair grows out of the skin in a spiral. Rather than spiral outward smoothly, occasionally the hair punctures the side of the follicle and can incite an inflammatory response and subsequent skin lesions that range from small papules to large keloids (see Hair Disorders). The differential diagnosis includes acne and bacterial folliculitis. Acne will often occur at any site on the face rather than being limited to areas of terminal hairs. Infectious folliculitis presents with red papules and pustules; however, it is often distributed across an area such as the scalp or trunk rather than preferentially in the beard or posterior scalp. Acne and folliculitis do not usually heal with fibrotic papules. Therapy aims to minimize inflammation and secondary infection, flatten scars, and alter damage done by hairs. Topical and oral antibiotics, glucocorticoids (topical or intralesional), changes in shaving habits, and laser hair removal can be used, often in combination.

Keloids

Black persons are at least twice as likely as white persons to develop keloids. Keloids are an overgrowth of dermal collagen often in response to skin injury such as piercing, tattoo, surgery, or acne (**Figure 148**). The upper trunk, neck, and ears are frequent sites. Keloids can be asymptomatic, painful, or pruritic. In contrast to hypertrophic scars and typical scars, keloids extend beyond the border of the original injury. There is no single preferred treatment. Options include topical and intralesional glucocorticoids, laser therapy, intralesional chemotherapy, and radiation therapy. Intralesional glucocorticoids are often the first-line therapy but must be repeated about every 8 weeks and three to four injections are needed to demonstrate significant improvement. Topical glucocorticoids are generally ineffective for keloids but can be effective for hypertrophic scars. Surgical excision alone is avoided as recurrence is frequent, and surgery is often paired with intralesional glucocorticoids. Similar to surgery, laser therapy, for example with a pulsed dye laser, is often paired with intralesional glucocorticoids.

Skin Cancers

Although less common, both nonmelanoma and melanoma skin cancers occur in skin of color populations. Although skin cancer rates are lower, cancers are often found later than in white populations. Both patients and physicians need to be suspicious of growing, bleeding, or ulcerating lesions.

The frequency of basal cell carcinoma (BCC) is inversely correlated with the degree of pigmentation in the skin; those most commonly affected are fair-skinned white persons, followed by Hispanics, and the least frequently affected are black persons. Pigmented BCC is more common in those with darker skin. Otherwise the behavior and treatment are the same, and metastasis is rare.

Darkly pigmented persons can develop squamous cell carcinoma (SCC); however, in contrast to the UV-induced type seen in the white population, SCC often develops in areas of chronic inflammation or scarring and is found more often on the legs. SCC developing in these settings has a metastasis rate of 20% to 40%, compared with a rate of 1% to 4% in white persons with UV-induced SCC.

Acral lentiginous melanoma (ALM) constitutes 5% to 10% of all melanomas yet is the most common type in those with skin of color. The most common sites are the palms, soles, and nails (**Figure 149**). Melanoma rates are lower in persons of color than in the white population; however, the average time to diagnosis is 2 years. Even after adjusting for age, stage, site, and socioeconomic status, the 5-year survival rates of blacks and Hispanics are lower than those of white persons.

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FIGURE 149. Acral lentiginous melanoma presents on an acral site such as the foot or hand and may involve the nail. It often has an irregular shape, color variation, and in later stages may ulcerate.

Melanonychia

Melanonychia refers to brown or black coloration of the nails. Longitudinal melanonychia is a common form in which brown lines traverse the nail proximally to distally. This is a normal variant that is found in 50% of black persons. The thumb and forefinger are most commonly affected (**Figure 150**). The condition is often bilateral. The prevalence and number of nails affected increases with age. The differential diagnosis includes other pigmented lesions of the nail such as a nevus, acral lentiginous melanoma, postinflammatory hyperpigmentation, pigmented squamous cell carcinoma, blood extravasation from trauma, and drug pigmentation. A biopsy of a pigmented band in the nail should be considered only if a single digit is affected, if it developed during the fourth decade or later, if there is associated nail dystrophy, if the diameter is 4 mm or greater, if the characteristics of the band changes, or if there is a personal or family history of melanoma.



FIGURE 150. Longitudinal melanonychia showing hyperpigmentation at the proximal nail fold, a clinical sign suggesting the presence of subungual melanoma.

KEY POINTS

- Acne keloidalis nuchae and pseudofolliculitis barbae are characterized by firm, skin-colored, pink, or hyperpigmented papules centered on hair follicles in people of color.
- Keloids, resulting from a skin injury such as piercing, tattoo, surgery, or acne, are twice as likely to occur in the black population.
- Acral lentiginous melanoma is the most common type of cancer in persons with skin of color.

The Homeless

Skin problems, most commonly infections and infestations, are the main reasons the homeless seek medical attention. The foot is the most frequent site of disorders such as ulcers, cellulitis, erysipelas, and gas gangrene. Poor foot hygiene, inadequate footwear, and excessive moisture are frequent and result in high rates of tinea pedis (30% to 40%) and pitted keratolysis (20%). Infestations with scabies, lice, and bedbugs are frequent and affect 25% of those in a shelter. The body louse can transmit *Bartonella quintana*, which has caused trench fever, bacillary angiomatosis, endocarditis, and chronic afebrile bacteremia in the homeless. Epidemic typhus caused by *Rickettsia prowazekii* and relapsing fever caused by *Borrelia recurrentis* are also louse borne.

Pruritus is a common problem of the homeless and may be attributed to a primary skin dermatosis, medications or illicit drug use, or occult or uncontrolled internal disease. Pruritus is often accompanied by bacterial infection from poor hygiene and secondary infection of excoriations. Common skin dermatoses, such as psoriasis, seborrheic dermatitis, and atopic eczema, occur in the homeless. It isn't known if inflammatory dermatoses are more frequent in this population; however, it is possible that common dermatoses are more severe because of poor hygiene, exposure to cold, moisture, and difficult medical access.

Dermatologic Diseases of Overweight Patients

Intertrigo

Intertrigo is an inflammatory process found in skin fold areas such as the inframammary region, abdominal pannus, and crural folds. It is particularly problematic in hot, moist conditions, and thus annual exacerbations during the summer are commonly seen. The rash consists of confluent, well-demarcated erythema, generally symmetrically distributed. Secondary infection by yeast can often occur and is generally characterized by multiple small red macules that surround the main rash (satellitosis). Treatment consists of keeping the area dry and well-ventilated. Antifungal powders may be useful in controlling moisture and are frequently used to reduce the likelihood

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of flares. Low- or mid-potency topical glucocorticoid creams may be used for a short period of time, but prolonged use should be avoided to prevent skin thinning and stretch mark formation. If secondary infection with yeast is present, concomitant treatment with topical antifungal agents may be added.

Stasis Dermatitis

Obese persons and those with poor venous circulation are particularly prone to stasis dermatitis. Treatment consists of compression stockings and topical glucocorticoids (see Common Rashes). Long-standing untreated peripheral edema can also lead to massive localized lymphedema and elephantiasis nostras verrucosa, a debilitating condition characterized by substantial swelling of the lower extremities with skin thickening and the development of multiple warty-appearing nodules in the affected area.

Acrochordons

Acrochordons (skin tags) are commonly found in obese persons in areas of recurrent friction, such as the axillae and groin. They may also be seen on the eyelids and around the neck. Although harmless, they are often of cosmetic concern. The combination of acanthosis nigricans and skin tags around the neck and in the axillae is often seen in obese patients with diabetes mellitus.

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 62-year-old woman is evaluated for multiple areas of scaling and rough skin on her forehead and cheeks, the backs of her hands, and forearms. These areas are painless but persist despite application of moisturizer. She is in good overall health and takes no medications. She has a history of multiple sunburns.

On physical examination, vital signs are normal. Skin findings are shown.



The remainder of the physical examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Actinic keratosis
(B) Seborrheic keratosis
(C) Squamous cell carcinoma
(D) Superficial basal cell carcinoma

Item 2

A 19-year-old man is evaluated for a 3-year history of firm bumps in his hairline at the back of his neck. He is concerned because they are increasing in number and occasionally are itchy. Skin findings are shown.



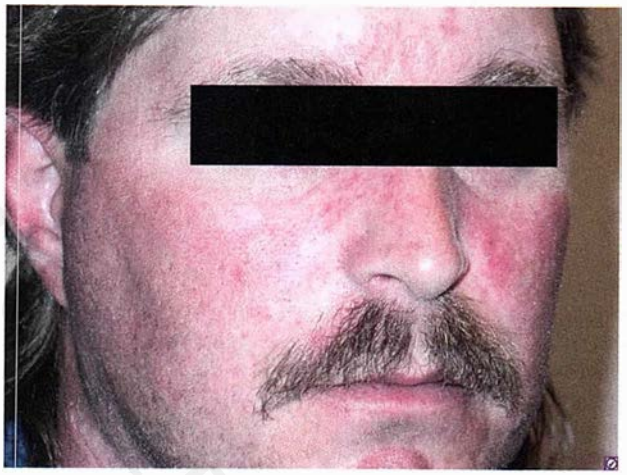
The rest of his skin examination is normal.

Which of the following is the most likely diagnosis?

(A) Acne keloidalis nuchae
(B) Acne vulgaris
(C) Bacterial folliculitis
(D) Keloids

Item 3

A 41-year-old man is evaluated because of his "red face." He notices that his face gets redder when he goes out in the sun, gets out of the shower, or drinks hot coffee. He is most bothered by the pimples he gets on his cheeks and chin. His skin is not itchy or painful. He takes no medications, drinks three or four beers on the weekend, and otherwise feels well. General physical examination findings are unremarkable. Skin findings are shown.



Which of the following is the most likely diagnosis?

(A) Acute cutaneous lupus erythematosus
(B) Periorificial dermatitis
(C) Rosacea
(D) Seborrheic dermatitis

Item 4

A 75-year-old woman is evaluated for a 7-month history of an ulcer on the inner portion of her right ankle. In addition to the ulcer, she notes that an oozing, weeping rash periodically develops in the surrounding area, and that a similar rash sometimes occurs on her other leg. She also experiences intermittent lower extremity edema on the legs bilaterally. Medical history is significant for long-standing type 1 diabetes mellitus and hypertension. Medications are insulin glargine, metformin, and lisinopril.

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On physical examination, vital signs are normal. BMI is 32. Pedal pulses are palpable, and the patient has good capillary refill in the toes. The ulcer is not tender. She has multiple venous varicosities. Skin findings are shown.



Which of the following is the most likely diagnosis?

(A) Arterial ulcer
(B) Neuropathic ulcer
(C) Pyoderma gangrenosum
(D) Venous stasis ulcer

Item 5

A 72-year-old man is evaluated for discoloration of the tongue and bad breath. He notes the gradual onset of the tongue changes, with development of significant halitosis in recent weeks. He otherwise feels well and has no other symptoms. Medical history is unremarkable. He smokes a half-pack of cigarettes per day and drinks two to three glasses of wine or beer each night. He takes no medications.

On physical examination, the patient is afebrile and vital signs are normal. The appearance of the tongue is shown.



Dentition is poor, but there are no other lesions in the oral cavity. There is no lymphadenopathy in the head or neck. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Amoxicillin-clavulanate
(B) Biopsy of the discolored area
(C) Brushing of the tongue
(D) Fluconazole

Item 6

A 30-year-old man presents to the clinic with a concern about the appearance of his fingernails. His fingernails on both hands have been pitting, yellowing, and lifting off the nail bed for the past 6 months. He has not tried to treat his nail changes.

On physical examination, there are no changes in his toenails or the skin of his feet. There are well-demarcated pink, scaling plaques on his elbows and knees. Fingernail findings are shown.



Which of the following is the most likely cause of this patient's fingernail changes?

(A) Candidal infection
(B) Eczema
(C) Psoriasis
(D) Tinea manuum

Item 7

A 20-year-old male farmer is evaluated for a several-month history of increasing odor and wetness involving both of his feet during the summer months. He otherwise feels well and has no pain or other foot-related symptoms. Medical history is unremarkable, and he takes no medications.

Oh physical examination, vital signs are normal. Examination of the feet is notable for a significant malodor. Skin findings are shown (see top of next page).

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The remainder of his examination is noncontributory.

Which of the following is the most appropriate topical treatment?

(A) Clotrimazole cream
(B) Clotrimazole-betamethasone cream
(C) Erythromycin lotion
(D) Hydrocortisone cream

Item 8

A 27-year-old woman is evaluated for a 1-week history of an intensely pruritic rash on her eyelids. She applied a new brand of eye makeup just prior to the onset of the rash. She immediately discontinued its use and has been applying a moisturizing lotion to both eyelids since then without improvement in her symptoms. She notes no other areas of rash and generally feels well. The patient has no significant medical history and takes no medications.

On physical examination, vital signs are normal. There is erythema, mild edema, and some serous crusting over the upper eyelids bilaterally. No erythema is present on the scalp, face, neck, upper back, shoulders, arms, or fingers. The remainder of the examination is normal.

A 2-week course of which of the following is the most appropriate treatment for this patient?

(A) Betamethasone dipropionate
(B) Clobetasol propionate
(C) Halobetasol propionate
(D) Hydrocortisone valerate

Item 9

A 72-year-old man sustains a laceration on his left index finger while preparing chicken. He immediately washes the area and applies neomycin and an occlusive bandage. He changes the bandage and reapplies the medication twice daily. Two days later, he develops itching and redness at the wound site. He has had no fever or other systemic symptoms. Medical history is significant for well-controlled type 2 diabetes mellitus. His only medication is metformin.

On physical examination, vital signs are normal. The left index finger shows a 1.0-cm superficial wound with well-approximated margins without purulence or drainage, and no pain on palpation. There are pinpoint papules and vesicles in an area extending 0.5 cm around the laceration site in a rectangular pattern approximating the bandage. There is no lymphangitic streaking. The remainder of the physical examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Allergic contact dermatitis
(B) Group A streptococcal infection
(C) Herpes simplex virus infection
(D) *Staphylococcus aureus* infection

Item 10

A 44-year-old woman is evaluated for a 2-year history of hair loss. She has noticed hair loss on the top of her scalp, but not from the sides or back of her scalp. Her father and brother have "bald spots," but she states that her mother and grandmother are "normal."

On physical examination, vital signs are normal. Her scalp findings are shown.



Which of the following is the most likely cause of the patient's alopecia?

(A) Alopecia areata
(B) Androgenetic alopecia
(C) Frontal fibrosing alopecia
(D) Telogen effluvium

Item 11

A 34-year-old man is evaluated for several slow-growing lesions on his penis. He first noticed the wart-like growths 3 years ago, and they have progressively enlarged. He was treated with topical cryotherapy six times and topical imiquimod over the past year without improvement; the

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lesions have continued to enlarge. Medical history is significant for HIV infection. Medications are tenofovir, emtricitabine, and efavirenz.

On physical examination, vital signs are normal. Multiple red to brown verrucous papules with underlying induration and focal erosions are present on the penile shaft.

There is no lymphadenopathy. There are no other skin findings, and the remainder of the physical examination is normal.

Laboratory studies are significant for a CD4 cell count of 875/μL (0.875×10^9/L) and an undetectable viral load.

Which of the following is the most appropriate management?

(A) Biopsy
(B) Cryotherapy
(C) Human papillomavirus (HPV) vaccination
(D) Topical triamcinolone cream

Item 12

A 53-year-old woman is evaluated for an ulcer on the bottom of her foot. Medical history is significant for type 2 diabetes mellitus and hypertension. Medications are metformin and lisinopril.

On physical examination, blood pressure is 128/78 mm Hg; other vital signs are also normal. A painless ulcer is present on the plantar aspect of the right foot. Skin findings are shown.



Pedal pulses are intact.

Which of the following is the most likely diagnosis?

(A) Arterial ulcer
(B) Neuropathic ulcer
(C) Squamous cell carcinoma
(D) Venous stasis ulcer

Item 13

A 20-year-old woman is evaluated for growth of dark brown hairs on her cheeks and neck. The growth began 5 years ago, and she finds it bothersome. She has tried to manage the growth by using depilatory creams. She otherwise feels well, her medical history is unremarkable, and she takes no medications. She notes irregular menstrual cycles, having fewer than six periods in a calender year. There is no history of similar hair growth affecting the women in her family.

On physical examination, vital signs are normal. BMI is 30. Skin findings on the face are shown.



Breast development and external gynecologic examination are normal. The remainder of the physical examination is normal.

Which of the following is the most likely cause of this patient's facial hair?

(A) Familial hair growth pattern
(B) Hyperthyroidism
(C) Polycystic ovary syndrome
(D) Porphyria

Item 14

A 35-year-old woman is evaluated for a rash on her hands and arms. The previous day she was clearing vines in her backyard. The skin eruption is red and intensely itchy, and she has scratched multiple areas. She experiences a burning sensation when she applies moisturizer. The patient has a history of depression for which she takes sertraline.

On physical examination, vital signs are normal. Skin findings are shown.



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The remainder of the examination is unremarkable.

Which of the following is the most appropriate topical therapy for this patient's skin eruption?

(A) Bacitracin
(B) Diphenhydramine
(C) High-potency glucocorticoid ointment
(D) Low-potency glucocorticoid cream

Item 15

A 61-year-old woman with long-standing pedal edema is evaluated for redness on the bilateral lower legs. She notes that the edema worsens over the course of the day but is improved with elevation of her legs. She reports no pain or pruritus, no calf tenderness, no shortness of breath, no palpitations, and otherwise feels well. Medical history is significant for obesity but is otherwise unremarkable. She takes no medications.

On physical examination, vital signs are normal. BMI is 36. There is no jugular venous distention. The lungs are clear, and an S_3 is not present. Pedal pulses are normal, and there is no calf tenderness. Skin findings are shown.



The remainder of the physical examination is noncontributory.

Which of the following is the most appropriate treatment?

(A) Compression stockings
(B) Oral cephalexin
(C) Oral furosemide
(D) Topical mupirocin

Item 16

A 49-year-old woman has a 20-year history of painful papules and nodules of the perineum and perianal skin. Her underarms are not involved. She develops several concurrent nodules every other month, and these prevent her from working for a week or more. Occasionally some of the nodules will spontaneously drain foul-smelling fluid. The nodules have been unresponsive to antibacterial soaps and lotions and topical and systemic antibiotic therapy, and recur following incision and drainage. The patient has no other medical problems other than obesity and cigarette smoking.

On physical examination, vital signs are normal. BMI is 30. Skin findings are shown.



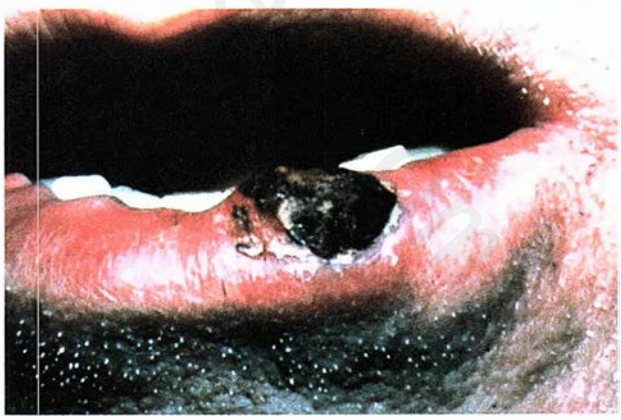
Which of the following is the most likely diagnosis?

(A) Bacterial abscesses
(B) Bacterial folliculitis
(C) Hidradenitis suppurativa
(D) Ruptured epidermal cysts

Item 17

A 68-year-old man is evaluated for a 6-month history of a rapidly growing nodule on the lower lip. He notes mild tenderness surrounding this area. Medical history is significant for a 40-pack-year history of smoking, moderate alcohol consumption, and significant sun exposure. He is otherwise in good health and takes no medications.

On physical examination, vital signs are normal. The nodule is shown.



The remainder of the physical examination is unremarkable.

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Which of the following is the most appropriate next step in management?

(A) Bacterial culture
(B) Cryotherapy
(C) Electrodesiccation and curettage
(D) Lesional biopsy
(E) Topical 5-fluorouracil

Item 18

A 62-year-old woman is evaluated for a 4-month history of decreased exercise tolerance, joint stiffness, mild weakness, and a rash on her hands. She has noted increasing difficulty carrying heavy objects and feels exhausted after climbing stairs. Although her joints are stiff, she has not had any joint swelling. Her rash developed around the time of her other symptoms and has not responded to over-the-counter topical agents. She has no other symptoms, including cough or dyspnea. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 109/72 mm Hg, pulse rate is 82/min, and respiration rate is 20/min. Oxygen saturation is 98% on ambient air. Cardiopulmonary examination is unremarkable. Joint examination is normal. Skin findings are shown.



Laboratory studies:

Creatine kinase	320 U/L
Antinuclear antibodies	Positive (titer of 1:640)
Anti-dsDNA antibodies	Negative
Anti-Ro/SSA antibodies	Negative
Anti-La/SSB antibody	Negative
Complete blood count	Normal
Metabolic profile	Normal

A plain chest radiograph is normal.

Which of the following pulmonary conditions is associated with this patient's clinical presentation?

(A) Bronchiectasis
(B) Diffuse alveolar hemorrhage
(C) Hilar lymphadenopathy
(D) Interstitial lung disease
(E) Pleuritis

Item 19

A 53-year-old woman is evaluated for a slowly enlarging, telangiectatic, pearly, ulcerated 1-cm plaque on the left temple. It bleeds periodically when traumatized. Medical history is significant for atrial fibrillation. She takes warfarin daily. She is otherwise in good health.

On physical examination, vital signs are normal. Cardiac examination shows an irregular heart rate but is otherwise normal. The remainder of the examination is unremarkable.

Biopsy of the lesion reveals a basal cell carcinoma with micronodular and infiltrative features.

Which of the following is the most appropriate treatment for this lesion?

(A) Cryotherapy
(B) Electrodesiccation and curettage
(C) Mohs micrographic surgery
(D) Radiation therapy
(E) Topical imiquimod

Item 20

A 32-year-old woman is evaluated at a well-patient visit. Both her parents have a history of nonmelanoma skin cancer within the past year, and she is seeking counseling regarding skin cancer prevention. She has a history of remote sunburns and had previously tanned as a teenager. She requests advice on how to approach sun protection to limit both future skin cancer risk as well as to prevent wrinkles and cosmetic photodamage.

The patient has no other significant medical history and takes no medications.

On physical examination, vital signs are normal. She has mild scattered wrinkling, scattered solar lentigines, and an average number of benign-appearing nevi.

Which of the following is the most appropriate advice for this patient?

(A) Maintain a baseline tan
(B) Sunscreen with sun protection factor (SPF) 2 to 14
(C) Sunscreen with SPF 15 or greater
(D) Sunscreen with SPF 15 or greater plus UVA protection

Item 21

A 67-year-old woman is evaluated for a chronic rash under her breasts and arms, and in the groin and upper thigh region. She notes that the rash is intermittent and tends to be worse in the summer months. Medical history is significant for type 2 diabetes mellitus, hypertension, and hyperlipidemia. Medications are metformin, lisinopril, and simvastatin.

On physical examination, vital signs are normal. BMI is 39. Skin findings are shown (see top of next page).

The remainder of the examination is normal.

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Which of the following is the most likely diagnosis?

(A) Allergic contact dermatitis
(B) Atopic dermatitis
(C) Cellulitis
(D) Intertrigo

Item 22

A 53-year-old man is evaluated for itching lasting 5 months. He reports that his whole body is itchy and that a short course of emollients and antihistamine medication did not improve his symptoms. He feels well otherwise. Review of systems is negative including findings for fever, fatigue, and unintentional weight loss. He does not take any medications.

On physical examination, vital signs are normal. Examination of the skin reveals no signs of xerosis or inflammation. Excoriations are noted on his legs, shoulders, and back. The remainder of the physical examination, including thyroid and lymph node examinations, is normal.

A complete blood count, metabolic profile, serum thyroid-stimulating hormone level, liver chemistry tests, and HIV antibody assay are normal.

Which of the following is the most appropriate next step in management?

(A) Chest radiograph
(B) CT scan of the chest, abdomen, and pelvis
(C) Skin biopsy
(D) No further testing

Item 23

A 19-year-old man is evaluated for a month-long history of rash. He states that the rash is extremely itchy; he has areas of involvement under his arms, around his waist, on his wrists, between his fingers, and on his palms. Medical history is unremarkable, and he takes no medications. He has not attempted to treat the rash. He is temporarily homeless and has been staying with different friends or in the local shelter. Two months ago, he left the apartment of a friend who had a similar rash.

The general physical examination is unremarkable. Skin examination shows scattered, excoriated lesions that spare the feet. Skin lesions on the hand are shown.



Which of the following is the most likely diagnosis?

(A) Allergic contact dermatitis
(B) Bedbug bites
(C) Scabies infestation
(D) Tinea manuum

Item 24

A 72-year-old woman is evaluated for a pruritic rash on the abdomen. She reports previous episodes of similar symptoms in the past. Medical history is significant for type 2 diabetes mellitus and hypertension. Medications are metformin, valsartan, hydrochlorothiazide, and a clonidine patch.

On physical examination, vital signs are normal. Skin findings are shown.



The remainder of the physical examination is unremarkable.

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Which of the following is the most likely cause of this patient's skin findings?

(A) Allergic contact dermatitis
(B) Fixed drug eruption
(C) Irritant dermatitis
(D) Tinea corporis

Item 25

A 25-year-old man is evaluated in the emergency department for fever of 48 hours' duration and a rash for 24 hours. His illness began with fever followed by fine, red, itchy papules on the trunk, arms, and legs. The rash soon became painful. This morning, he awoke with the rash on his face and sores in his mouth, and when he touched his skin it peeled off. Two weeks ago, he began minocycline and tretinoin cream for acne. He has no other medical problems.

On physical examination, he is toxic appearing and in pain. Temperature is 39.4 °C (102.9 °F), blood pressure is 110/60 mm Hg, pulse rate is 116/min, and respiration rate is 18/min. His eyes are red, and his mouth and lips are covered with a bloody film. Representative skin findings are shown.



Which of the following management options is most likely to benefit this patient?

(A) Infliximab
(B) Intravenous methylprednisone
(C) Intravenous vancomycin and ceftriaxone
(D) Supportive care and discontinuation of minocycline

Item 26

A 52-year-old woman is evaluated for a 1-month history of a spreading rash on her back, chest, and arms. She has been using over-the-counter topical glucocorticoids without relief. She does not have any other associated symptoms and otherwise feels well. Medical history is significant for hypertension. Medications are hydrochlorothiazide and metoprolol.

On physical examination, temperature is 37.1 °C (98.7 °F), blood pressure is 141/83 mm Hg, pulse rate is 72/min, and respiration rate is 18/min. Skin findings are shown (see top of next column).



There are no lesions in the scalp or ears, no finger or nail changes, no joint inflammation, and no oral ulcers. The remainder of the physical examination is unremarkable.

Laboratory studies:

Antinuclear antibodies	Positive (titer of 1:320)
Anti-Ro/SSA antibodies	Positive
Anti-La/SSB antibodies	Negative
Antihistone antibodies	Negative
Creatine kinase	Normal

Which of the following is the most likely diagnosis?

(A) Dermatomyositis
(B) Pemphigus foliaceus
(C) Psoriasis
(D) Subacute cutaneous lupus erythematosus

Item 27

A 78-year-old woman is hospitalized for management of acute worsening of chronic kidney disease. On the third hospital day, she develops a painful nodule under the tape adjacent to the site of a peripheral intravenous catheter on her left forearm. Medical history is also significant for hypertension and type 2 diabetes mellitus. She currently takes amlodipine, insulin, and furosemide.

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 125/85 mm Hg, pulse rate is 70/min, and the respiration rate is 12/min. A tender, fluctuant, erythematous nodule with 2 cm of surrounding erythema is present on the left forearm. There is no lymphadenopathy. The remainder of the physical examination is noncontributory.

The leukocyte count is 13,000/μL (13×10^9/L). The nodule is incised and drained. Microscopic examination shows numerous leukocytes and small gram-positive cocci; culture results are pending.

Which of the following is the most appropriate antibiotic therapy for this patient?

(A) Amoxicillin-clavulanate
(B) Cephalexin

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(C) Meropenem
(D) Vancomycin

Item 28

A 20-year-old man is evaluated for a 6-week history of a patch of alopecia on his scalp. The hair loss was asymptomatic. He has not tried to treat it, and he has noticed some hairs re-growing in the patch. He has no history of hair loss. There is no family history of hair loss, but his mother has hypothyroidism. He takes no medications.

The general physical examination is unremarkable. Scalp findings are shown.



Which of the following is the most likely diagnosis?

(A) Alopecia areata
(B) Androgenetic alopecia
(C) Discoid lupus erythematosus
(D) Telogen effluvium
(E) Tinea capitis

Item 29

A 74-year-old woman is evaluated in the hospital for management of a painful skin lesion on her left lower leg that has been present for 3 weeks. The initial lesion began as a small darkened area that progressively increased in size with worsening pain. Her pain is now so severe that she is unable to walk. Medical history is significant for end-stage kidney disease requiring hemodialysis, type 2 diabetes mellitus, and hypertension. Medications are insulin, calcitriol, calcium carbonate, erythropoietin, aspirin, and lisinopril, although the patient has significant difficulty with medication adherence.

On physical examination, temperature is 37.3 °C (99.1 °F), blood pressure is 143/80 mm Hg, pulse rate is 102/min, and respiration rate is 15/min. The left lower extremity lesion is shown (see top of next column).

Which of the following is the most likely diagnosis?

(A) Calciphylaxis
(B) Cutaneous vasculitis
(C) Pyoderma gangrenosum
(D) Spider bite



ITEM 29

Item 30

A 21-year-old woman is evaluated for mosquito bites on her arms and legs that she received 1 week ago that she has been scratching regularly. One of the bites on her left thigh is now is painful with a small amount of drainage. She otherwise feels well, has no significant medical history, and takes no medications.

On physical examination, vital signs are normal. A weeping red papule with overlying honey-colored crust is present on the anterior left thigh. There is no surrounding or extension of the redness, no lymphadenopathy, and no systemic symptoms. The remainder of the examination is unremarkable.

Which of the following is the most appropriate treatment?

(A) Cephalexin
(B) Doxycycline
(C) Mupirocin ointment
(D) Triamcinolone ointment

Item 31

A 20-year-old man is evaluated for a new scaling rash on the trunk. He had been well until 3 weeks ago when he developed subjective fever for 2 days with cough and rhinitis that resolved without treatment. One week later, he developed a spot on the right shoulder, and now the rash has spread to his entire trunk and proximal extremities. He has not noted any lesions in the genital area. Medical history is unremarkable, and he takes no medications. He is sexually active.

On physical examination, vital signs are normal. Skin findings are shown (see top of next page).

He has no oral or genital lesions. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Hepatitis C virus antibody testing
(B) Polymerase chain reaction testing
(C) Rapid plasma reagin testing
(D) No further evaluation

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ITEM 31

Item 32

A 27-year-old man is evaluated for numerous moles scattered over his chest, back, abdomen, and extremities. He is concerned about the possibility of developing melanoma, although he does not believe that any of the moles have recently changed in size or appearance. His mother and two of his brothers also have similar lesions. Family history is significant for two early melanomas in his mother. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Skin findings are shown.



The remainder of the physical examination is normal.

Which of the following is the most appropriate next step in management?

(A) Monthly self examinations and referral to a dermatologist
(B) Partial biopsy of multiple pigmented lesions
(C) Removal of the largest pigmented lesions
(D) Removal of as many pigmented lesions as feasible

Item 33

A 40-year-old man is evaluated for several ulcers located near his ostomy site. He has a 15-year history of ulcerative colitis and underwent elective proctocolectomy with ostomy placement 3 months ago to decrease his risk of colorectal cancer. His ostomy has functioned well without previous problems. The ulcers, which are moderately painful, developed 1 month ago and have failed to respond to topical care, including barrier methods and changing adhesives. He is otherwise healthy and takes no medications.

On physical examination, vital signs are normal. BMI is 19. Skin findings are shown.



Which of the following is the most appropriate treatment?

(A) Replace ostomy to the opposite side
(B) Rituximab
(C) Surgical debridement
(D) Topical clobetasol

Item 34

A 35-year-old woman is evaluated for a 6-month history of skin changes on her legs. She initially noted scaling and thickening of the skin on her anterior shins that has persisted despite application of a topical moisturizer and an over-the-counter glucocorticoid. She was evaluated at a walk-in clinic approximately 3 months ago. Antifungal agents and topical glucocorticoids were prescribed, which she applied without relief. She reports that the involved areas have continued to thicken. Medical history is significant for type 1 diabetes mellitus, hyperthyroidism, and vitiligo. Medications are insulin glargine and methimazole.

On physical examination, temperature is 37.3 °C (99.1 °F), blood pressure is 132/90 mm Hg, pulse rate is 90/min, and respiration rate is 20/min. BMI is 19. The thyroid is diffusely enlarged without nodularity. The remainder of the general physical examination is normal. Skin findings are shown (see top of next page).

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Which of the following is the most likely diagnosis?

(A) Lipodermatosclerosis
(B) Necrobiosis lipoidica
(C) Pretibial myxedema
(D) Stasis dermatitis

Item 35

A 52-year-old man is evaluated for multiple extremely itchy spots on his arms, legs, chest, and neck. His symptoms started approximately 1 month ago. He continues to develop new groups of lesions daily along with healing of previous areas. His wife also recently began to experience similar findings. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Examination of the skin shows multiple lesions scattered primarily across the lower neck, the proximal arms, and the lower legs. Representative lesions are shown.



The remainder of the physical examination is normal.

Which of the following is the most likely cause of these lesions?

(A) Bedbugs
(B) Body lice
(C) Fleas
(D) Scabies
(E) Spider bites

Item 36

A 66-year-old man is evaluated for a 6-week history of a red, very itchy rash "all over" his body. It began as patches and plaques but over the past 2 weeks has progressed to a generalized red skin rash. The pruritus keeps him awake at night. His only other medical problem is hypertension for which he has taken hydrochlorothiazide for the past 12 years.

On physical examination, vital signs are normal. Generalized lymphadenopathy is present, and there is 1+ edema involving the feet and legs to the knees. Skin findings are shown.



Which of the following is the most likely diagnosis?

(A) Angioedema
(B) Drug-induced subacute cutaneous lupus erythematosus
(C) Erythroderma
(D) Pityriasis rosea

Item 37

A 52-year-old woman had a burning sensation involving the right side of her forehead and the tip of her nose for 2 days, followed by increased redness and the development of lesions involving the tip of her nose. Medical history is significant for hypertension, and her only medication is ramipril.

On physical examination, vital signs are normal. Skin examination shows an erythematous patch on the right side of the forehead with scattered overlying grouped vesicles and a vesicle on the tip of the nose with background erythema. Mild conjunctival erythema is noted. The remainder of the physical examination is unremarkable.

In addition to starting antiviral medications, which of the following is the most appropriate next step in management?

(A) Administer herpes zoster vaccine
(B) Start mupirocin
(C) Urgent ophthalmologic evaluation
(D) Urgent otolaryngology evaluation

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Item 38

A 38-year-old woman is hospitalized for a rash that developed during antibiotic treatment for pyelonephritis. She was diagnosed 1 week ago and was started on a 10-day course of trimethoprim-sulfamethoxazole based on urine culture results. Although her urinary tract symptoms have resolved, yesterday she noted the onset of a widespread, itchy rash. She also notes some facial swelling but has no difficulty breathing. Medical history is otherwise unremarkable, and she is taking no other medications.

On physical examination, temperature is 38.5 °C (101.3 °F). Her mucous membranes are normal. She has 3-cm lymph nodes in the anterior cervical and axillary regions and a liver edge palpable 4 cm below the costal margin. Skin findings are shown.



In addition to discontinuing the antibiotic, which of the following is the most appropriate next step in the management of this patient?

(A) Complete blood count and liver chemistry tests
(B) Lymph node biopsy
(C) Skin biopsy
(D) No further testing

Item 39

A 62-year-old woman is evaluated for pain with sexual intercourse and genital itching. Her symptoms began several years ago and have been progressively worsening. She has used lubricants and topical moisturizers without improvement. She notes no vaginal discharge or odor. She has no significant medical history and takes no medications.

On physical examination, vital signs are normal. The general physical examination is unremarkable. Skin findings are shown (see top of next column).

There is no vaginal discharge or odor.



Which of the following ointments is the most appropriate treatment?

(A) Clobetasol, 0.05%
(B) Hydrocortisone, 1%
(C) Mupirocin
(D) Nystatin

Item 40

A 32-year-old man is evaluated for a painful purple area on the penis and the thigh that appeared 2 days ago. He describes a burning and stinging sensation associated with the lesion. He recalls having a similar episode several months ago that resolved spontaneously. He otherwise feels well. Medical history is unremarkable, and his only medication is as-needed ibuprofen for occasional musculoskeletal pain. He has had no sexual partners in the past 6 months.

On physical examination, vital signs are normal. Skin lesions are shown.



There is no inguinal lymphadenopathy. The remainder of the physical examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Contact dermatitis
(B) Fixed drug eruption
(C) Herpes simplex virus infection
(D) Primary syphilis

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Item 41

A 52-year-old man is evaluated in the hospital for several skin lesions on his back, chest, and arms. The patient has acute myeloid leukemia and was hospitalized after developing neutropenic fever 10 days following his initial course of chemotherapy. The skin lesions first appeared the day his fever started. Medications are vancomycin and cefepime.

On physical examination, temperature is 38.4 °C (101.2 °F), blood pressure is 110/70 mm Hg, pulse rate is 95/min, and respiration rate is 18/min. A representative skin lesion is shown.



Laboratory studies:

Hemoglobin	8.2 g/dL (82 g/L)
Leukocyte count	400/μL (0.4×10^9/L) with 95% neutrophils
Platelet count	10,000/μL (10×10^9/L)
Metabolic profile	Normal
Urinalysis	Normal

Chest radiograph is normal. Blood cultures show no growth to date.

Which of the following is the most likely diagnosis?

(A) Candidiasis
(B) Keratoacanthoma
(C) Pyogenic granuloma
(D) Sweet syndrome

Item 42

A 32-year-old man is evaluated for a 2-week history of a rash on his face and midchest. He describes the rash as consisting of small, reddish "lumps" that are intensely itchy; they develop and begin to resolve with development of new lesions. He otherwise feels well. Medical history is significant for a recent diagnosis of HIV infection. Medications are tenofovir, emtricitabine, efavirenz, and trimethoprim-sulfamethoxazole. On physical examination, vital signs are normal. The patient has 1- to 3-mm papules and pustules on the face and central chest. There is no crusting or scaling in the web spaces, and no lesions on the umbilicus or penis. There is no lymphadenopathy or facial swelling. The remainder of the physical examination is unremarkable.

Laboratory studies:

Hemoglobin	Normal
Leukocyte count	3200/μL (3.2×10^9/L) with 9% eosinophils
Platelet count	Normal
CD4 cell count	170/μL
HIV viral load	8000 copies/mL
Creatinine	Normal
Liver chemistry tests	Normal

Which of the following is the most likely diagnosis?

(A) Drug-induced acne
(B) Drug reaction with eosinophilia and systemic symptoms (DRESS)
(C) Eosinophilic pustular folliculitis
(D) Scabies infestation

Item 43

A 20-year-old male college student on the wrestling team is evaluated for a superficial skin infection. He has a history of several episodes of folliculitis and furunculosis over the past year that has required systemic treatment. His recurrent infections were treated with various oral antibiotics, including cephalexin, clindamycin, and trimethoprim-sulfamethoxazole. He currently takes no medications, has no drug allergies, and is otherwise in good health.

On physical examination, vital signs are normal. There are multiple, scattered erythematous papulopustules and nodules on the buttocks and upper thighs, some with a collarette of scale. He has no background erythema or lymphadenopathy. The remainder of the physical examination is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Culture a pustule
(B) Perform a Tzanck smear
(C) Start linezolid
(D) Start vancomycin

Item 44

A 31-year-old woman is evaluated during a routine physical examination. She feels well but notes skin changes on her legs that have been present for several years. The skin changes persist regardless of position or temperature. Medical history is unremarkable except for three episodes of first trimester spontaneous pregnancy loss. She takes no medications.

On physical examination, vital signs are normal. The general medical examination is normal. Skin findings are shown (see top of next page).

The skin changes are more prominent when she is sitting or standing, but persist while supine. They don't go away when she is warmed. There is no lower extremity edema.

Which of the following is the most likely diagnosis?

(A) Amyloidosis
(B) Antiphospholipid antibody syndrome

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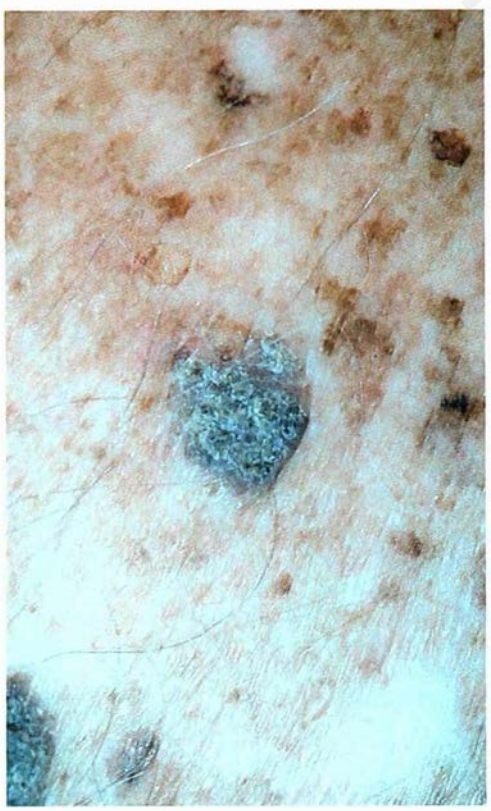
(C) Autoimmune thyroid disease
(D) Systemic sclerosis

Item 45

A 76-year-old woman is evaluated for a new lesion on her trunk. The lesion appeared a few months ago and has grown steadily. It may be itchy and becomes irritated when traumatized and sometimes bleeds. The patient is otherwise in good health. She takes no medications.

On physical examination, vital signs are normal. Skin findings are shown.



The remainder of her physical examination is normal.

Which of the following is the most likely diagnosis?

(A) Dermatofibroma
(B) Malignant melanoma
(C) Pigmented basal cell carcinoma
(D) Seborrheic keratosis
(E) Solar lentigo

Item 46

A 35-year-old man is evaluated for a 1-day history of a rash on the trunk and extremities. A few days earlier, he had a nonpurulent cough and rhinitis that resolved without treatment. Each individual skin lesion is very pruritic and lasts only a few hours before disappearing. He has no difficulty with swallowing or breathing. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. There is no evidence of lip or tongue swelling. The lungs are clear without wheezing. Skin findings are shown.



The remainder of the physical examination is unremarkable.

Which of the following is the most appropriate management?

(A) Amoxicillin
(B) Cetirizine
(C) Prednisone
(D) Ranitidine

Item 47

An 80-year-old man is evaluated for a facial skin rash. He reports dry skin, scaling, and redness most notably around his eyebrows and nose. He has regularly applied moisturizer without improvement. He washes his face with gentle soap and moisturizes with petrolatum jelly. The skin in the affected areas is not pruritic or painful. The patient has a history of hypertension and hypothyroidism. Medications are hydrochlorothiazide and levothyroxine.

On physical examination, vital signs are normal. Skin findings are shown (see top of next page).

The remainder of the physical examination is unremarkable.

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Which of the following is the most appropriate treatment for this patient?

(A) Benzoyl peroxide gel
(B) Ketoconazole cream
(C) Metronidazole gel
(D) Mupirocin ointment
(E) Triamcinolone ointment

Item 48

A 68-year-old man is evaluated for a slowly growing nodule on his nose. The lesion has been present for 6 months and is asymptomatic. Medical history is unremarkable, and he takes no medications. He does not smoke or drink.

On physical examination, vital signs are normal. The remainder of his examination is normal. Skin findings are shown.



Which of the following is the most likely diagnosis?

(A) Angiofibroma
(B) Basal cell carcinoma
(C) Sebaceous hyperplasia
(D) Squamous cell carcinoma

Item 49

A 28-year-old woman is evaluated for an acne flare on her face. She is approximately 8 weeks pregnant. She has had acne for several years, which was well-controlled when she was using a combination benzoyl peroxide-clindamycin gel, salicylic acid wash, and tazarotene cream. She stopped all of these after her preconception counseling. Skin findings are shown.



Which of the following is the most appropriate therapy for this patient?

(A) Azelaic acid cream
(B) Oral doxycycline
(C) Tazarotene cream
(D) Tretinoin cream

Item 50

A 24-year-old man is evaluated in the office for blisters that have developed on his lips and tongue. He has not had any similar episodes previously. He developed a tingling and burning sensation of the lip that was followed by redness and development of blisters. The patient has a recent diagnosis of HIV infection but has not started any medications.

On physical examination, vital signs are normal. Skin lesions are shown (see top of next page).

The remainder of the examination is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bacterial culture
(B) Direct-fluorescent antibody testing
(C) Herpes simplex virus serologic testing
(D) Viral culture

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ITEM 50

Item 51

A 62-year-old man was admitted to the ICU for high fevers associated with sepsis following hip replacement surgery. Since the procedure he has been relatively immobile except when receiving physical therapy. Two days after surgery, he developed fine superficial vesicles on the back. Except for pain following the procedure, he has felt well. Medical history is otherwise unremarkable, and his only medication is as-needed acetaminophen-oxycodone.

On physical examination, temperature is 37.9 °C (100.2 °F). The rest of his vital signs are normal. Skin findings are shown.



The surgical site is clean and dry. The remainder of the examination is unremarkable.

Which of the following is the most likely cause of this acute eruption?

(A) Allergic contact dermatitis
(B) *Candida albicans* infection
(C) Miliaria crystallina
(D) *Staphylococcus aureus* folliculitis

Item 52

A 67-year-old man is evaluated for an ulcer on his right ankle. The ulcer developed several weeks ago and does not appear to be healing despite application of a topical dressing. He reports that the ulcer is painful and is worse with leg elevation and improved with the leg in a dependent position. Medical history is significant for hypertension and a 40-pack-year smoking history. His only medication is amlodipine.

On physical examination, vital signs are normal. Skin findings are shown.



The remainder of the examination is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Biopsy of ulcer edge
(B) External compression
(C) Measurement of the ankle-brachial index
(D) Oral antibiotics

Item 53

A 32-year-old woman is evaluated for a 1-week history of a rash affecting both feet. She recently traveled to Jamaica for vacation and was well during that trip, but noted the onset of symptoms after returning home. The rash is mildly painful but intensely itchy and is keeping her awake at night. She has no other symptoms and otherwise feels well. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Skin findings are shown (see top of next page).

The remainder of the physical examination is normal.

Laboratory studies are significant for a leukocyte count of 9000/μL (9.0×10^9/L) with 9% eosinophils.

Which of the following is the most appropriate treatment?

(A) Cephalexin
(B) Ivermectin
(C) Prednisone
(D) Terbinafine

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ITEM 53

Item 54

A 50-year-old man is evaluated for a firm, darkly pigmented papule on his back that has been growing steadily over a period of several months. His medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. The skin lesion is a 0.5-cm darkly pigmented, raised plaque with irregular borders and inconsistent coloration. The remainder of his physical examination, including the rest of his skin examination, is unremarkable.

A skin biopsy is performed and shows malignant melanoma on pathologic examination.

Which of the following is the primary feature used to determine prognosis?

(A) Lesion depth
(B) Mitotic rate
(C) Presence of ulceration
(D) Radial diameter of the lesion

Item 55

A 22-year-old woman is evaluated for a red, itchy rash on her chest, back, abdomen, arms, and legs for 1 week. She notes that an area of redness and swelling arises and lasts less than 24 hours, followed by development of a new area in a new location. She has no lip, tongue, or throat swelling. She is unable to recall any new medication, food, or other exposures prior to onset of the rash. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. There is no lip or tongue swelling. The lungs are clear without wheezes. Skin findings are shown (see top of next column).

The remainder of the examination is normal.

Which of the following is the most appropriate next diagnostic step?

(A) Chest radiograph
(B) Complete blood count with differential
(C) Food allergy testing



(D) Thyroid function tests
(E) No further evaluation

Item 56

A 45-year-old woman is evaluated for a "dark spot under her nail." She is healthy, feels well, and takes no medications. She thought the streak started after she "banged" her finger, but it has not gone away after 6 months.

On physical examination, she has a hyperpigmented longitudinal band on her index finger that is 4 mm wide. Vital signs are normal. Nail findings are shown.



Which of the following is the most appropriate next step in the management of this dark nail streak?

(A) Culture of nail clipping
(B) Histologic examination of nail clipping
(C) Nail matrix biopsy
(D) Observation

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Item 57

An 80-year-old woman is evaluated in the emergency department for a red, blistering rash. Her symptoms began 1 week ago with significant itching with the subsequent development of blisters that do not break easily. The blisters have occurred on her chest, abdomen, and extremities; she has not noted any blisters involving her lips or mouth. The patient has no other significant medical history.

On physical examination, vital signs are normal. Representative skin findings are shown.



There are no oral or mucosal lesions. The remainder of the physical examination is normal.

Which of the following is the most likely diagnosis?

(A) Bullous pemphigoid
(B) Pemphigus foliaceus
(C) Pemphigus vulgaris
(D) Toxic epidermal necrolysis

Item 58

A 34-year-old man is evaluated for asymptomatic skin changes in his groin that have been present for weeks to months. He has a long-standing history of plaque psoriasis without psoriatic arthritis, for which he uses a combination of topical medications. A few months ago, he developed redness and pruritus in his groin and tried using some of his psoriasis medications to treat the itching. For the plaque psoriasis, he uses clobetasol ointment twice daily on weekends and calcipotriene cream twice daily on weekdays.

On physical examination, vital signs are normal. There are large red plaques with silvery scale over the elbows, knees, and around the umbilicus. Skin findings are shown (see top of next column).

There is no nail pitting, joint swelling, redness, or tenderness. The remainder of the examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Contact dermatitis
(B) Inverse psoriasis
(C) Striae distensae
(D) Tinea cruris

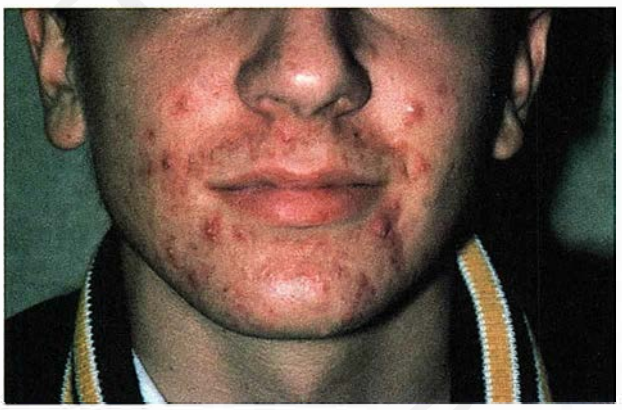


ITEM 58

Item 59

A 24-year-old man is evaluated for persistent acne. He has been treated for approximately 1 year with multiple therapies but has noticed minimal improvement. Medical history is unremarkable. His medications for the past 6 months are oral doxycycline, tretinoin cream, clindamycin lotion, and benzoyl peroxide wash.

On physical examination, vital signs are normal. His general medical examination is unremarkable. Skin findings are shown.



Which of the following is the most appropriate next step in management?

(A) Add metronidazole cream
(B) Change to tazarotene cream
(C) Switch doxycycline to oral minocycline
(D) Discontinue current medications and start oral isotretinoin

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Item 60

A 55-year-old man is evaluated for a 6-week history of blisters on his hands. The blisters are tender, break easily after they develop, and occur in different regions on the backs of his hands. Medical history is notable for alcoholic liver disease. The patient does not use tobacco but drinks 6 beers daily. He takes no medications.

On physical examination, temperature is 36.4 °C (97.5 °F), blood pressure is 98/70 mm Hg, pulse rate is 85/min, and respiration rate is normal. BMI is 22. Cardiopulmonary examination is normal. The abdominal examination is significant for mild splenomegaly; there is no evidence of ascites. The patient has slight darkening of his skin and scattered spider telangiectasias. Mild hypertrichosis is evident on the face. The hand findings are shown.



There are no oral erosions or ocular inflammation.

Which of the following is the most likely diagnosis?

(A) Allergic contact dermatitis
(B) Bullous lupus erythematosus
(C) Bullous pemphigoid
(D) Porphyria cutanea tarda

Item 61

A 32-year-old man is evaluated for a 2-month history of a persistent skin rash. He describes the rash as lesions that develop rapidly, are very itchy with burning and tingling, last for 2 to 3 days, and then leave bruises once they resolve. He has felt feverish at times since the rash started and had also had some stiffness and pain in his hands and fingers. Medical history is unremarkable, and his only medications are cetirizine daily and diphenhydramine as needed, which have not helped the condition.

On physical examination, temperature is 37.9 °C (100.2 °F), blood pressure is 138/83 mm Hg, pulse rate is 85/min, and respiration rate is 18/min. Skin findings are shown (see top of next column).

There are also numerous ecchymoses and hyperpigmented patches at sites where he reports lesions to have resolved. The skin of the face is uninvolved, and there are



no oral ulcers. Joint examination reveals mild tenderness of the wrists bilaterally but no synovitis. Range of motion is full and intact. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Gluten-free diet
(B) Radioallergosorbent test (RAST)
(C) Skin biopsy
(D) Thyroid function tests

Item 62

H

A 53-year-old woman is evaluated in the emergency department for a 1-week history of increased swelling, redness, and pain in her lower legs. She has not had trauma to her legs and has not noted any drainage. She has not had fevers and has otherwise felt well. Medical history is significant for heart failure. Medications are ramipril, metoprolol, and furosemide, which she has not been taking recently as she has not had her prescriptions refilled.

On physical examination, vital signs are normal. The neck veins are prominent. Mild bibasilar crackles are present. There is no inguinal lymphadenopathy, and the remainder of the general examination is unremarkable. Skin findings are shown.



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H CONT.

Which of the following is the most likely diagnosis?

(A) Cellulitis
(B) Contact dermatitis
(C) Deep venous thrombosis
(D) Stasis dermatitis

Item 63

A 24-year-old woman with longstanding atopic dermatitis is evaluated for an acute worsening of her disease in the past week. She has had increased pruritus and now has multiple painful areas within the involved skin. She has been applying petrolatum jelly and triamcinolone ointment and washing with gentle cleansers without improvement. She is otherwise well and takes no medications.

On physical examination, vital signs are normal. She has eczematous plaques with scattered pustules in the involved areas. The remainder of the physical examination is unremarkable.

Which of the following is the most likely cause of this patient's acute flare?

(A) Herpes simplex virus infection
(B) Soap allergy
(C) *Staphylococcus aureus* infection
(D) Topical glucocorticoids

Item 64

A 20-year-old woman is evaluated for a 3-year history of pink papules and pustules on her face and neck. Her menstrual periods are regular, and she feels well. She says she gets a few "pimples" at a time, but they leave dark marks that take months to fade. She has not had any prior treatment, and she is not using any over-the-counter products. Skin findings are shown.



Which of the following is the most appropriate treatment?

(A) Bleaching cream
(B) Topical antimicrobial agent
(C) Topical glucocorticoid
(D) Topical retinoid

Item 65

A 47-year-old man is evaluated for a several-month history of itching and scaling on his feet that has not been improving with moisturizing lotion. He has no significant medical history and takes no medications.

On physical examination, vital signs are normal. Skin findings are shown.



There is scaling and fissuring between the toes as well.

Which of the following is the most appropriate topical treatment?

(A) Betamethasone
(B) Clotrimazole
(C) Clotrimazole-betamethasone
(D) Nystatin

Item 66

H

A 57-year-old man is evaluated in the emergency department for a rash on his legs, arthralgia, myalgia, and fever of 4 days' duration. Over the past week, he has developed pain and numbness in the left foot, and he has tripped several times when walking.

On physical examination, temperature is 37.7 °C (99.8 °F), blood pressure is 150/100 mm Hg, pulse rate is 88/min, and respiration rate is 18/min. Cardiopulmonary examination is normal. The liver is palpable. Skin findings are shown (see top of next page).

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H CONT.

Which of the following is the most likely dermatologic diagnosis?

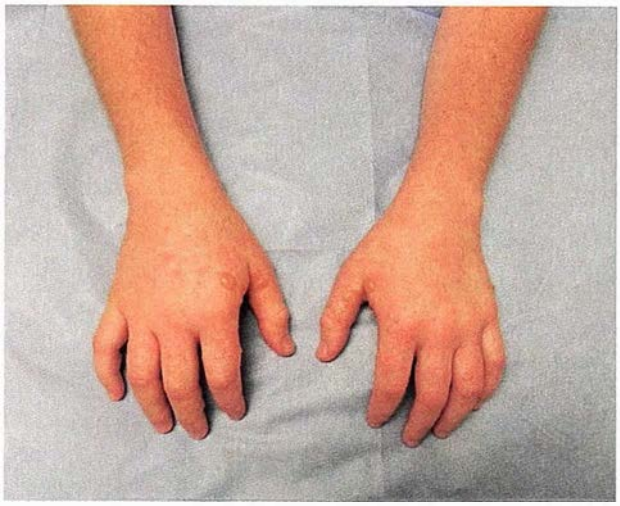
(A) Erythema multiforme
(B) Lichen planus
(C) Traumatic ecchymosis
(D) Vasculitis

Item 67

A 34-year-old woman is evaluated for very dry, painful hands. She works in a daycare center and washes her hands 15 to 20 times daily, often for 2 to 3 minutes at a time. She has been applying lotion multiple times daily with no relief of the pain. She has a history of obsessive-compulsive disorder and takes no medications.

On physical examination, vital signs are normal. She has xerosis on the dorsal aspect of her hands with lichenification, erythema, and fissuring.

The remainder of the physical examination is unremarkable.



In addition to decreasing the frequency of hand washing, which of the following is the most appropriate therapy?

(A) Petrolatum moisturizer
(B) Topical diphenhydramine
(C) Topical lidocaine gel
(D) Topical neomycin

Item 68

H

A 44-year-old man was admitted to the hospital 2 weeks ago with fever and a new heart murmur and was diagnosed with native valve endocarditis. He was treated initially with broad-spectrum antibiotics with narrowing of his antimicrobial therapy to intravenous nafcillin based on culture and sensitivity results. He was discharged on the third hospital day to complete a 6-week course of intravenous antibiotic therapy. Although he had done well since discharge, he presents 11 days later with new fever and a rash.

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 115/78 mm Hg, pulse rate is 110/min, and respiration rate is 12/min. There is mild facial edema and lymphadenopathy of his cervical and axillary lymph nodes. The lungs are clear. Cardiac examination shows mild tachycardia and a grade 2/6 systolic murmur, unchanged from his last examination. Skin examination reveals diffuse erythema on his trunk, proximal extremities, and face. The remainder of his examination is unremarkable.

Laboratory studies:

Leukocyte count	12,100/μL (12.1×10^9/L) with 54% neutrophils, 31% lymphocytes, and 15% eosinophils
Albumin	Normal
Alanine aminotransferase	147 U/L
Aspartate aminotransferase	156 U/L
Bilirubin	Normal

Repeat blood culture results are pending.

Which of the following is the most likely diagnosis?

(A) Drug reaction with eosinophilia and systemic symptoms
(B) Morbilliform drug exanthem
(C) Stevens-Johnson syndrome
(D) Vasculitis

Item 69

A 44-year-old woman is evaluated for pruritus that has been present for about 3 months. She reports that she feels the itch on her upper back only, and the only thing that gives her relief is to scratch hard enough to "make it bleed." She says there were no preceding papules, pustules, or rash. Antihistamines, emollients, topical glucocorticoid ointment, and application of ice provided no relief. Her symptoms developed shortly after she lost her job. She has a history of depression and anxiety for which she sometimes takes fluoxetine.

On physical examination, vital signs are normal. The general physical examination is normal. Skin findings are shown (see top of next page).

Which of the following is the most likely diagnosis?

(A) Fluoxetine-induced morbilliform drug eruption
(B) Neuropathic itch

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(C) Occult colorectal adenocarcinoma
(D) Psychogenic itch

Item 70

A 32-year-old woman is evaluated for a 6-month history of a new rash on her elbows, knees, and scalp. The rash is intensely pruritic, and she is concerned that it has resulted from insect bites. She has not noticed any other skin lesions but does relate a 4.5-kg (10-lb) unintentional weight loss over the past 6 months. Medical history is significant for irritable bowel syndrome for which she takes loperamide as needed.

On physical examination, the patient is afebrile and vital signs are normal. Skin findings are shown.



There is no mucosal involvement, and the remainder of the skin examination is normal. The general physical examination is otherwise unremarkable.

Which of the following associated conditions is most likely in this patient?

(A) Celiac disease
(B) Hepatitis C
(C) Non-Hodgkin lymphoma
(D) Ulcerative colitis

Item 71

A 32-year-old woman is evaluated for a rash on her face and arms of 2 months' duration. The rash developed progressively and has not responded to topical moisturizers and an over-the-counter glucocorticoid. The patient also has a moderate nonproductive cough, but otherwise feels well. Medical history is significant only for a 15-pack-year smoking history, although she quit smoking 4 months ago. She takes no medications.

On physical examination, vital signs are normal. BMI is 23. The lungs are clear. Skin findings are shown.



Her hair is normal, and she has no scarring or lesions in the ears or on the cheeks.

A chest radiograph is shown (see top of next page).

Which of the following is the most likely diagnosis?

(A) Dermatomyositis
(B) Hodgkin lymphoma
(C) Limited systemic sclerosis
(D) Sarcoidosis
(E) Systemic lupus erythematosus

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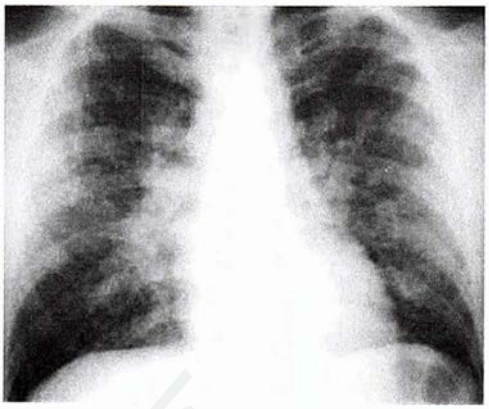

ITEM 71

Item 72

A 30-year-old woman is evaluated for a 3-year history of chronic lesions on her scalp, cheeks, and ears. She has lost hair and is concerned she may become bald. She has been treated with a number of topical medications, including topical hydrocortisone and tacrolimus. The patient does not have any antecedent triggers or associated systemic symptoms. Medical history is unremarkable. Her sister has systemic lupus erythematosus. She takes no medications and is not currently using any topical therapy for her rash.

On physical examination, vital signs are normal. Skin findings are shown (see top of next column).

She has no oral ulcers and no lesions below the head and neck. The remainder of the examination is unremarkable.



Laboratory studies:

Antinuclear antibodies	Positive (titer of 1:160)
Anti-Ro/SSA antibodies	Negative
Anti-La/SSB antibodies	Negative
Anti-dsDNA antibodies	Negative
Anti-Smith antibodies	Negative
Complete blood count	Normal
Urinalysis	Normal

Which of the following is the most appropriate treatment?

(A) Dapsone
(B) Hydroxychloroquine
(C) Prednisone
(D) Vitamin D supplementation

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Answers and Critiques

Item 1 Answer: A

Educational Objective: Diagnose actinic keratosis.

This patient has actinic keratoses (AKs). AKs are precancerous lesions that generally occur in fair-skinned persons on sun-exposed areas such as the face, dorsal arms, hands, legs, and upper back. They are strongly correlated with cumulative sun exposure; the more sun exposure an individual has had, the more numerous they are. A small percentage of lesions (1% to 5%) may evolve into invasive squamous cell carcinomas. However, they never develop into other types of skin cancer such as basal cell carcinoma or melanoma, although many of the factors that predispose one to develop AKs are also risk factors for these other malignancies. The diagnosis of AKs is generally based on the clinical history and the typical tactile and visual appearance of the lesions; biopsy is not routinely needed. Liquid nitrogen is most commonly used to treat AKs, although other destructive methods (shave removal or curettage) are options, and topical therapies (5-fluorouracil, imiquimod) are often used for extensive disease. Efforts to decrease risk for developing AKs include sun avoidance and diligent use of sunscreen.

Seborrheic keratoses are a benign proliferation of keratinocytes that typically appear as hyperpigmented, well-circumscribed, "stuck on" lesions that most commonly develop on the trunk, upper extremities, and face. This patient's skin lesions are not consistent with this appearance, and their location on the dorsal surface of the hands would be uncommon.

Squamous cell carcinomas (SCCs) are typically larger and present as papules or nodules rather than macules. Also, in immunocompetent persons, it is rare to find multiple SCCs occurring simultaneously. Distinguishing between advanced AKs (also referred to as hypertrophic AKs) and early SCCs can sometimes be challenging. Therefore presumptive AKs that fail to respond to treatment should be biopsied to rule out early SCC.

Superficial basal cell carcinomas (SBCCs) often present as scaly macules and sometimes can resemble AKs. SBCCs tend to be more reddish-violet in color, and in contrast to AKs which are often seen in large numbers, patients typically have only a few of these at any given time.

KEY POINT

- Actinic keratoses are premalignant, erythematous, scaly macules that occur on sun-exposed areas of older persons with fair skin.

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Item 2 Answer: A

Educational Objective: Diagnose acne keloidalis nuchae.

This patient has acne keloidalis nuchae (AKN), which is characterized by firm, skin-colored, pink, or hyperpigmented papules that are often centered on hair follicles. AKN often occurs on the back of the neck and is similar in appearance to pseudofollicular barbae, which occurs on the hair-bearing face and anterior neck. These conditions are most likely due to ingrown hair and are more frequent in persons of color with curly hair owing to the shape of the hair and hair follicle. AKN can cause keloid formation associated with chronic folliculitis at the back of the neck. Therapy aims to minimize inflammation and secondary infection, flatten scars, and alter damage done by hairs. Topical and oral antibiotics, glucocorticoids (topical or intralesional), changes in shaving habits, and laser hair removal can be utilized, often in combination. Changes to shaving habits that are recommended include liberal use of shaving cream, avoidance of stretching the skin when shaving, and use of a single-blade razor rather than a multi-blade razor.

The differential diagnosis includes acne vulgaris and bacterial folliculitis. Inflammatory acne consists of erythematous pustules, nodules, or cysts (deeper and often painful) and are the result of inflammation in and around the hair follicles. This patient has only inflammatory papules and lacks comedones, which would be expected if this was acne. Bacterial folliculitis presents with red papules and pustules centered on hair follicles. The beard, pubic areas, axillae, and thighs are most often affected. Acne and folliculitis do not usually heal with fibrotic papules.

Keloids are areas of exuberant scar formation. A keloid is a tuberous growth of scar tissue that extends beyond the limits of the original injury. Any type of injury to the skin, including internal (acne) or external (trauma or surgery), can trigger keloids. Keloids most frequently occur on the earlobe and upper torso. People of African or Asian descent have a higher risk of keloid formation.

KEY POINT

- Acne keloidalis nuchae is characterized by firm, skin-colored, pink, or hyperpigmented papules that are often centered on hair follicles and appear most frequently on the back of the neck in people of color.

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Item 3 Answer: C

Educational Objective: Diagnose rosacea.

This patient has rosacea, which presents as central facial erythema with transient papules or pustules. Burning and stinging may be present. The pathogenesis of rosacea is unknown. There are two types, erythematotelangiectatic (vascular) and papulopustular (inflammatory) rosacea. Vascular rosacea presents as persistent flushing, especially of the central face, with prominent telangiectasias. Pustules and papules are seen in the inflammatory variant, but in contrast to acne, rosacea pustules are not follicular based. Bulbous thickening of the nose (rhinophyma) can also occur. Eye involvement, with dry, gritty-feeling eyes and conjunctival injection, is common. Multiple studies have demonstrated that rosacea is associated with cutaneous inflammation; however, the trigger is highly debated. Alcohol, sun exposure, and other triggers can cause a transient increase in facial erythema but do not cause rosacea. Flushing is a common characteristic of rosacea; the differential diagnosis of this includes carcinoid syndrome, mastocytosis, and pheochromocytoma. The differential diagnosis for rosacea also includes entities that cause central facial erythema and/or inflammatory papules, namely acne, periorificial dermatitis, cutaneous lupus erythematosus, sarcoidosis, contact dermatitis (eczema), seborrheic dermatitis, actinic damage, and folliculitis due to *Pityrosporum* or *Demodex* spp.

The malar rash of acute cutaneous lupus erythematosus, typically seen in patients with systemic lupus erythematosus, is a transient erythematous patch over the cheeks that often spares the nasolabial fold. Certain forms of rosacea may resemble the rash of malar erythema, but patients with rosacea will often have a prominent telangiectatic component, as well as inflammatory papules, pustules, and occasionally rhinophymatous changes of the nose.

Periorificial dermatitis shares some clinical characteristics with rosacea. It occurs in both young children, commonly around the mouth and eyes, and adults, who are usually affected around the mouth. Monomorphous pink papules (1 to 2 mm) that sting or burn rather than itch are grouped around the mouth or eyes. Periorificial dermatitis is sometimes caused by the use of topical glucocorticoids on the face.

Seborrheic dermatitis causes white, scaling macules and papules that are sharply demarcated on yellowish-red skin and may be greasy or dry. Sticky crusts and fissures often develop behind the ears, and significant dandruff or scaling of the scalp frequently occurs. Seborrheic dermatitis may develop in a "butterfly"-shaped pattern but also may involve the nasolabial folds, eyebrows, and forehead. This condition usually improves during the summer and worsens in the fall and winter.

KEY POINT

- Papulopustular rosacea is a chronic inflammatory condition characterized by central facial erythema with transient papules or pustules.

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Item 4 Answer: D

Educational Objective: Diagnose venous stasis ulcers.

The patient's skin findings are most consistent with a venous stasis ulcer. Venous stasis ulcers are commonly found on the lower extremities, particularly on or near the medial malleoli. They often occur in patients with recurrent bouts of stasis dermatitis, which is an eczematous rash on the lower legs associated with impaired venous drainage of the lower extremities caused by venous insufficiency, or by chronic peripheral edema of any cause. Venous stasis leads to changes in vascular permeability with stretching of the skin and loss of integrity of the dermal barrier. Initial changes involve development of dermatitis, seen as dark discoloration (postinflammatory hyperpigmentation) and "woody" induration known as lipodermatosclerosis. Impaired skin function in areas of venous stasis may also lead to breakdown of the dermal barrier with development of ulceration. Venous stasis ulcers tend to be shallow rather than deep. They may be asymptomatic or quite tender.

Arterial ulcers also occur on the lower extremities, but in contrast to venous stasis ulcers, they are not surrounded by stasis dermatitis changes or lipodermatosclerosis. They tend to be more demarcated than venous stasis ulcers and are often painful. The surrounding skin tends to be white or erythematous, and there is a loss of leg hair. These ulcers typically occur in the setting of peripheral atherosclerotic disease, with diminished pedal pulses and impaired capillary refill.

Neuropathic ulcers arise from repetitive trauma in patients with a history of sensory loss in the lower extremities. The ulcers are well-demarcated, often quite deep, and lack surrounding inflammation; they develop on pressure points or other areas where recurrent trauma may occur. They are most commonly seen in patients with peripheral neuropathy associated with diabetes mellitus.

Pyoderma gangrenosum is an uncommon inflammatory process that often occurs on the pretibial aspects of the lower legs and is often associated with an underlying systemic disease, such as inflammatory bowel disease or monoclonal gammopathy. The ulcers are well-demarcated, often very deep and painful, and show progression of the ulcer under the overlying skin (undermined borders). The ulcers tend to lack surrounding evidence of stasis, as is present in this patient.

KEY POINT

- Venous stasis ulcers appear on the distal lower leg, particularly the medial aspect of the ankle, and often occur in patients with recurrent bouts of stasis dermatitis.

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Item 5 Answer: C

Educational Objective: Manage black hairy tongue.

This patient has black hairy tongue, and the correct management is tongue brushing as part of aggressive oral hygiene. Black hairy tongue is a benign and self-limited disorder related to several predisposing factors such as alcohol and tobacco use, poor oral hygiene, and medications (including bismuth, tetracycline, and linezolid). The clinical appearance of black discoloration and a thickened tongue without other symptoms is characteristic. Treatment includes aggressive oral hygiene with tongue brushing and scraping and modification of any risk factors (smoking cessation, avoidance of alcohol or medications inducing the change).

Amoxicillin-clavulanate is an antibiotic that is often used to treat oral infections. Black hairy tongue is not an infection that requires antibiotic treatment. The clinical appearance and the absence of oral or systemic symptoms make an oral infection as a cause of his findings unlikely.

A biopsy of the lesion is not indicated as this is a benign and self-limited condition. If the lesion is recalcitrant to therapy or if there are concerning manifestations such as leukoplakia or erythroplakia, a biopsy may be considered. Management with aggressive oral hygiene before biopsy is recommended.

Oral fluconazole is used for candidiasis oral infections, whereas black hairy tongue is a keratin build-up related to risk factors and poor oral hygiene.

KEY POINT

- Management of black hairy tongue consists of tongue brushing as part of aggressive oral hygiene.

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Item 6 Answer: C

Educational Objective: Diagnose psoriatic nail disease.

This patient has the classic features of psoriatic nail dystrophy with onycholysis (lifting of nail off the nail bed) that appears as areas of white nail at the lateral edges of the nail plate. This patient also has pitting of the nails, which manifests as small indentations on the surface of the nail plate. Lastly this patient also has "oil spots," which are the areas of yellow-tan discoloration at the distal end of the nail plate. Psoriasis most commonly presents as long-standing, discrete, erythematous plaques with silvery-white scale. Other patterns include inverse (intertriginous), guttate, pustular, and erythrodermic types. Nail changes occur in about 75% of patients with psoriasis. The most common psoriatic nail abnormality is subungual hyperkeratosis. Pitting and ridging are more common on fingernails as compared with toenails. The "oil drop" sign, which is yellow-tan discoloration, is another typical manifestation. Multiple nails are generally affected, both on the hands and feet. Over time, a significant amount of nail dystrophy can occur, and the changes may be indistinguishable from onychomycosis. Patients with psoriatic nail dystrophy are more often affected by psoriatic arthritis, but nail findings do not necessarily correlate with the severity of disease.

Candidal infection can cause intertrigo, recognized as pink-red patches with satellite lesions in skin folds but is an uncommon cause of nail dystrophy.

The eczematous dermatoses are a diverse group of skin disorders that share clinical features of itching and a red, scaly, vesicular-to-crusted rash. Eczema can cause changes in the nail plate (nail dystrophy), but it is secondary to inflammation of the nearby skin of the proximal and lateral nail folds, which is not present in this patient.

Tinea manuum is a dermatophyte infection involving the hand. Dermatophytes are the most common fungi that infect skin. Tinea manuum characteristically involves only one hand (and two feet). The findings are characterized by a dry scale, and if chronic, the nails can be involved. The diagnosis of tinea manuum is unlikely if the feet are not involved.

KEY POINT

- Pitting, onycholysis, and the "oil drop" sign are typical manifestations of psoriatic nail dystrophy.

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Item 7 Answer: C

Educational Objective: Treat pitted keratolysis.

This patient has pitted keratolysis and should be treated with erythromycin lotion. Pitted keratolysis presents with small indented pits on a background of hyperkeratosis and results from increased sweating or perspiration (hyperhidrosis) of the feet. It is a superficial bacterial infection secondary to *Kytococcus sedentarius*, *Corynebacterium*, or *Actinomyces* spp. First-line treatment includes clindamycin lotion or erythromycin lotion in conjunction with keeping the feet dry. Oral therapy with clarithromycin or erythromycin also can be used.

Topical clotrimazole and other antifungal agents are effective for tinea pedis or candidal infections of the feet, which often have macerated web spaces with superficial scale and erythema. The patient's web spaces were not affected, and the clinical picture is consistent with pitted keratolysis, not tinea pedis.

Clotrimazole-betamethasone cream also is ineffective for pitted keratolysis. The combination of a topical antifungal and a topical glucocorticoid will not improve a superficial bacterial infection and will allow it to worsen. In addition, combination treatment can decrease diagnostic accuracy, as combined agents can treat an underlying entity (fungus), but the topical glucocorticoid may also cause the infection to worsen. Combination treatment may be associated with more side effects at an increased cost.

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Another topical glucocorticoid, hydrocortisone, may cause the superficial bacterial infection to worsen and will not treat the underlying infection. Topical glucocorticoids may be used for eczematous dermatitis, but not for pitted keratolysis.

KEY POINT

- Pitted keratolysis is a superficial bacterial infection, and first-line treatment is clindamycin lotion or erythromycin lotion in conjunction with keeping the feet dry.

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Item 8 Answer: D

Educational Objective: Treat inflammatory skin disease on an area of thin skin.

This patient has allergic contact dermatitis of her eyelids, and a low-potency hydrocortisone ointment such as hydrocortisone valerate is the most appropriate treatment. Treatment courses should be of limited duration (2 weeks or less), which can be controlled by dispensing a small size tube (15 g) when treating areas of thin, sensitive skin such as the face or skin folds. There are multiple formulations of hydrocortisone that range in potency (hydrocortisone valerate, fumarate, and more); not all are low potency, and it is important when selecting a topical hydrocortisone to consider the anatomic site to be treated. The eyelids are very thin skin and are exposed to multiple irritants and allergens. Cosmetics, including nail products, shampoo, and fragrances, frequently result in an allergy on the eyelids, even when not directly applied to that location, because of the thin eyelid skin. This patient has mild allergic contact dermatitis; she should avoid the trigger, and topical glucocorticoids will relieve her symptoms.

The other three medications are all very potent topical glucocorticoids. The potencies of topical glucocorticoids in the United States are designated by classification into one of seven groups, with group 7 (1% and 2.5% hydrocortisone) being the least potent and group 1 being the most potent (up to 600 times more potent than the group 7 agents). Higher-potency glucocorticoids can rapidly lead to adverse effects, including lightening of the skin, atrophy, and telangiectasias, when used on areas of thin skin such as the eyelids. In addition, patients are at risk of ocular exposure and eventual cataract formation if chronically exposed. Therefore, treatment of facial lesions is usually limited to low-potency (groups 6 and 7) glucocorticoids.

KEY POINT

- Hydrocortisone valerate is a very-low-potency topical glucocorticoid that is safe to use on the eyelids.

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Item 9 Answer: A

Educational Objective: Diagnose allergic contact dermatitis.

This patient most likely has allergic contact dermatitis from the neomycin. Neomycin is a commonly used over-the-counter topical aminoglycoside antibiotic (often used either alone or as part of combination topical antibiotic preparations). With repeated use, especially on abraded or lacerated skin, neomycin can lead to contact sensitization, which is a T-cell mediated hypersensitivity reaction. Patients and clinicians often mistake this for a wound infection, but if the area is pruritic and there is a geometric, well-defined pattern generally corresponding with the contact area, a contact allergy should be suspected. Discontinuation of the medication and future avoidance are generally recommended.

Group A streptococcal infections would cause skin infections such as impetigo, cellulitis, or erysipelas. None of these infections tend to present with a well-demarcated pattern of involvement, as seen in this patient. This patient has no pain, wound drainage, or discharge that could be associated with bacterial impetigo. There is no pain or lymphangitic streaking typical of cellulitis. Erysipelas would appear as violaceous-red, edematous, well-demarcated plaques on the face or lower extremities, unlike this patient's presentation.

The classic presentation of herpes simplex virus infection is a group of painful, small vesicles on an erythematous base, transitioning to pustules and subsequent crusting of the lesions over time. Herpetic infection would be painful with no pruritus.

Staphylococcus aureus infection would present with eczematous plaques and open erosions on the flexural folds with pustules in those areas, not in a geometric pattern on a compromised skin barrier typical of allergic contact dermatitis.

KEY POINT

- Use of neomycin on abraded or lacerated skin can lead to contact sensitization, which is often mistaken for a wound infection; a contact allergy should be suspected if the area is pruritic and there is a geometric, sharply bordered pattern.

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Item 10 Answer: B

Educational Objective: Diagnose androgenetic alopecia in a woman.

This woman has androgenetic alopecia, which can affect both men and women. Hair loss (alopecia) is generally divided into two categories: scarring and nonscarring. Distinguishing between the two types is important because hair loss that occurs with scarring alopecia is permanent, whereas the hair

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loss that occurs with nonscarring alopecia is usually reversible, although the hair does not always completely regrow.

Androgenetic alopecia is categorized as a nonscarring alopecia. The prevalence of androgenetic alopecia in white men is 50% at age 50 years and over 70% at age 70 years. The prevalence is lower for women. In men, the temples and vertex are often affected. In contrast, in women the top of the head is affected, and balding is not complete. Androgenetic alopecia results in hair follicles that are thinner in caliber or "miniaturized" and, ultimately, the loss of hair follicles; however, androgenetic alopecia causes a decreased density of hair but not areas of complete loss of hair as seen in alopecia areata. A classic examination finding is "widening" of central part compared with the occipital part as a result of the decreased density of hairs. On examination, there is generalized rather than localized hair loss and decreased density of hair rather than complete smooth patch of hair.

Alopecia areata is an autoimmune disease characterized by well-demarcated areas of nonscarring total alopecia. The involved areas are often circular or oval but may coalesce to form more extensive areas of involvement. The affected areas are devoid of erythema or scale and are asymptomatic. Tapered "exclamation point" hairs may be seen at the periphery; these hairs have shafts that are thicker at the distal portion and narrower near the scalp. This patient's diffuse hair loss is not consistent with alopecia areata.

Frontal fibrosing alopecia is a scarring alopecia and is considered a variant of lichen planopilaris. The frontal scalp shows a band pattern of hair loss associated with follicular hyperkeratosis and perifollicular erythema. This patient's distribution of hair loss is not consistent with frontal fibrosing alopecia.

Telogen effluvium is a form of diffuse, nonscarring alopecia that is usually triggered by a systemically stressful event such as a serious illness, surgery, or childbirth. It is most commonly seen in women in the postpartum period. It is caused by the realignment of a higher-than-average number of hair follicles into the telogen, or final, phase of hair development. Approximately 3 to 5 months after the inciting event, numerous hairs are shed, leading to noticeably thinned hair. A small hair bulb may be visible at the scalp end of the shed hair. The hair loss tends to be patchy and diffuse; foci of total alopecia are not seen, and inflammation is absent. In most patients, the follicular maturation cycling returns to normal after a few months. This patient's history of gradual hair loss over 2 years is not consistent with telogen effluvium.

KEY POINT

- Female pattern androgenetic alopecia results in a decreased density of hair on top of the head but not complete loss of hair as seen in alopecia areata.

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Item 11 Answer: A

Educational Objective: Manage recalcitrant condylomata acuminata.

This patient has condylomata acuminata, and his lesions should be biopsied. This is especially important in a patient with underlying HIV infection. These lesions have been refractory to therapy, and the incidence is continuing to grow. Condyloma acuminatum is a form of human papillomavirus (HPV) infection in the genital area, most often secondary to HPV 6 and HPV 11. Therapy for condylomata acuminata includes destructive techniques such as cryotherapy, cantharidin, podophyllin, laser therapy, and topical application of salicylic acid. Immune modulators such as imiquimod also can be used. When these lesions are recalcitrant to therapy or large and atypical in appearance, biopsy is essential to establish the diagnosis and rule out verrucous carcinoma or squamous cell carcinoma.

Although use of cryotherapy for condylomata acuminata and other verruca vulgaris is standard care, repeat cryotherapy is not appropriate in this setting since the lesion has been previously treated multiple times without improvement and with worsening.

HPV vaccination is currently recommended for routine vaccination in males and females at 11 to 12 years of age, with catch-up vaccination up to age 21 years in men and up to age 26 years in women and men who have sex with men or are immunocompromised or have HIV infection. However, its use outside of these risk groups, and particularly in those who already have the infection, is unknown at this time. This vaccine is used to help prevent cervical and anal cancer, and whether the vaccine prevents development of condylomata is not known yet. The quadrivalent vaccine against four types of HPV is currently recommended for men and provides additional protection; a bivalent vaccine also is available.

Topical triamcinolone can be effective in the treatment of dermatitis and multiple inflammatory disorders but does not have a role in the treatment of condylomata or potential cancers.

KEY POINT

- Condylomata acuminata that is recalcitrant to therapy should be biopsied to rule out premalignant or malignant transformation of lesions.

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Item 12 Answer: B

Educational Objective: Diagnose neuropathic ulcers.

This patient has a neuropathic ulcer. Neuropathic ulcers often occur on the lower extremities in patients with peripheral neuropathy and other disorders of sensation. They result from repetitive trauma; patients are often unaware of the

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injury because of the lack of pain or other discomfort. The asymptomatic nature of most neuropathic ulcers highlights the need for clinical testing for neuropathy (by monofilament testing) and routine surveillance for ulcers in patients at high risk, such as this woman with long-standing diabetes mellitus. Neuropathic ulcers are usually noninflamed, have well-demarcated borders, and are often surrounded by signs of recurrent friction such as callus. The ulcers may be quite deep and occasionally extend to bone, increasing the risk for osteomyelitis. They typically occur over pressure points on the feet. Treatment consists of debridement of devitalized tissue, removal of friction, protection of the area, and treatment of any co-existing infection.

Arterial ulcers may also occur over bony prominences in patients with diabetes (since many patients with diabetes mellitus have peripheral vascular disease), but they are usually quite tender and have significant surrounding erythema. They may also occur on the pretibial aspects of the lower legs.

Squamous cell carcinomas may occur on the lower extremities and appear as nonhealing ulcers. They typically occur in sun-exposed areas such as the pretibial lower legs rather than the plantar feet. They are usually inflamed and are not surrounded by callus or other signs of chronic friction.

Venous stasis ulcers generally occur on the medial aspects of the lower legs and are surrounded by dyspigmentation and induration consistent with lipodermatosclerosis. Intermittent stasis dermatitis flares are also commonly seen.

KEY POINT

- Neuropathic ulcers occur on the lower extremities in patients with peripheral neuropathy and other disorders of sensation and often result from repetitive trauma.

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Item 13 Answer: C

Educational Objective: Recognize hirsutism associated with polycystic ovary syndrome.

This woman has hirsutism, and polycystic ovary syndrome (PCOS) is the most likely cause. PCOS is the cause of hirsutism in 50% to 70% of premenopausal women with excess hair growth. Hirsutism is defined as the excessive growth of thick, pigmented hair (terminal hairs) in androgen-responsive areas (a "male pattern") and affects about 8% of women. In androgen-dependent sites such as the jawline, the fine vellus hairs can be converted to thicker, courser terminal hairs like those on the underarms. The most to least common sites are the lower abdomen and areola, the chin and upper lip, between the breasts, and on the lower back.

The most important goal of the evaluation of a patient with hirsutism is to exclude the most serious causes, including androgen-secreting tumors (ovarian or adrenal). The patient must first be assessed for virilization, which is commonly due to an ovarian or adrenal tumor. Signs and symptoms of virilization include a deepening of the voice, severe acne, clitoromegaly, a decrease in breast size, and male-pattern balding. Other concerning features are rapid onset and progressive hirsutism over a short period of time (such as 1 year) or hirsutism that develops after 30 years of age. The diagnosis of PCOS is confirmed if two of the three following criteria are met: (1) oligo-ovulation or anovulation, (2) clinical or biochemical evidence of hyperandrogenism, and (3) polycystic ovarian morphology on an ultrasound when other endocrine disorders are excluded. In this patient, a transvaginal ultrasound will not be necessary to establish the diagnosis of PCOS.

Women in some family groups are predisposed to having more terminal hair growth in androgen-responsive areas. These women often develop the hairs slowly around the time of puberty and have normal menses. There is often a history of similar findings in other women in the family; however, this patient does not have a history of similar hair growth affecting the women in her family.

Hyperthyroidism may be associated with hypertrichosis, which is an excessive growth of hair but, as opposed to hirsutism, is not limited to androgen-responsive areas. The hairs often do not get as dark or thick as the terminal hairs that develop in hirsutism. Patients with hyperthyroidism may develop longer and more prominent hair growth all over their bodies, rather than in androgen-responsive sites. The hair growth is usually associated with other symptoms such as weight loss, anxiety, tachycardia, or hyperhidrosis.

Similarly, patients with porphyria can develop longer, thicker hairs in areas of sun exposure. Patients with porphyria are likely to have some skin blistering, fragility, or scarring in areas of sun exposure.

KEY POINT

- Polycystic ovary syndrome is the cause of hirsutism in 50% to 70% of premenopausal women with excess hair growth, and the evaluation begins with a medical and family history as well as examination for breast discharge and findings associated with androgen excess.

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Item 14 Answer: C

Educational Objective: Treat rhus dermatitis.

This patient should be treated with high-potency glucocorticoid ointment. She has pruritic linear red papules and plaques concentrated on exposed areas 1 day after exposure to a vine,

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which is typical of rhus dermatitis. Rhus dermatitis is caused by urushiol resin in poison ivy, oak, or sumac.

A topical antibiotic such as bacitracin would be indicated for impetigo, a highly contagious bacterial skin infection, but not for rhus dermatitis.

Diphenyhydramine is an antihistamine. Contact dermatitis is a type IV hypersensitivity reaction that is mediated by lymphocytes and not a primary histamine process. Therefore, an antihistamine would be ineffective.

Because this is an intensely pruritic eruption with localization on the hands and arms, a low-potency topical glucocorticoid cream would be unlikely to control her symptoms. In addition, ointments, which are preparations made up of approximately 80% oil and 20% water, would be less likely to cause a burning sensation in a patient with open skin compared with a cream, which is a preparation consisting of approximately half oil and half water.

KEY POINT

- Topical high-potency glucocorticoid ointment will reduce the redness and pruritus of rhus dermatitis.

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Item 15 Answer: A

Educational Objective: Treat stasis dermatitis.

This patient has stasis dermatitis, and compression stockings should be used. Stasis dermatitis is characterized by red, inflamed, pitted skin on the lower legs. It occurs in patients with venous stasis disease or other causes of chronic lower extremity edema. Decreased venous drainage causes an increase in extravascular tissue fluid that results in stretching of the skin and a subsequent propensity for loss of barrier integrity. Also, because the shins are often one of the driest parts of the body and are easily excoriated, dermatitis in this area is common. Compression stockings help to increase the venous return, decrease the stretching of the skin, and reduce the risk of ulceration.

Stasis dermatitis is frequently confused with cellulitis. The four cardinal signs of cellulitis are erythema, pain, warmth, and swelling; associated lymphadenopathy can occur. Systemic symptoms, including fever, chills, and malaise, also may be present. This patient does not have fever, pain, or clinical findings consistent with cellulitis, and it is unlikely for cellulitis to present on both legs simultaneously. Compared with cellulitis, the redness on the anterior shins in patients with stasis dermatitis is often bilateral and warm to the touch but typically is not tender. Therefore oral cephalexin is not indicated.

This patient has edema related to the venous stasis but has no jugular venous distension, no crackles, and no S_3. Given the absence of volume overload, furosemide would not be indicated.

Topical mupirocin would be indicated for impetigo, but this patient has no bullae, crusts, or erosions that would be seen in impetigo.

KEY POINT

- Stasis dermatitis is typically characterized by red, inflamed, pitted skin on the lower legs and occurs in patients with venous stasis disease or other causes of chronic lower extremity edema.

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Item 16 Answer: C

Educational Objective: Diagnose hidradenitis suppurativa.

This patient has hidradenitis suppurativa (HS) or "acne inversa," a chronic inflammatory disease that predominantly affects the apocrine gland-bearing areas of the skin. HS is a disease of follicular occlusion. The common sites are the axillae, breasts and inframammary creases, inguinal folds, and gluteal cleft. HS is marked by comedones, inflammatory papules, nodules, cysts, and scarring. The lesions are painful, and the drainage is often foul smelling. The distribution and severity of disease can range from minor to debilitating.

HS is estimated to affect 1% to 4% of the general population and frequently begins in the second to third decade. It is more common in women. Almost 40% of patients with HS report a family history of the disease. About half of patients with HS have breast and armpit involvement and hypertrophic scars.

Smoking is strongly associated with worsening of the disease. Antibacterial soaps and topical antibiotics provide minimal benefit. Oral tetracyclines are used long term for their anti-inflammatory properties, and bacterial cultures may be helpful. Intralesional injections of triamcinolone may hasten resolution of particularly tender areas. Counseling regarding weight loss and smoking cessation should be provided if applicable.

An abscess is a soft-tissue infection with a collection of pus that is walled off from adjacent tissue. Abscesses are warm, tender, fluctuant red-to-purple nodules, which may have an overlying collarette of scale. Bacterial abscesses tend to occur singly and do not typically recur repeatedly in the same general area.

Folliculitis results from infection of the hair follicle. Bacteria, fungi, and even herpes simplex virus can cause folliculitis; however, *Staphylococcus aureus* is the most common cause. Folliculitis appears as erythematous papules and pustules around a follicle on the face, chest, back, and buttocks. The lesions do not cause large painful nodules about the genitals, axillae, or breasts.

Ruptured epidermal cysts appear as red subcutaneous nodules, much like an abscess. These also tend to be solitary and also do not chronically recur.

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KEY POINT

- Hidradenitis suppurativa is a chronic inflammatory disease characterized by comedones, inflammatory papules, nodules, cysts, draining sinuses, and scarring of the axillae, breasts and inframammary creases, inguinal folds, and gluteal cleft.

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Item 17 Answer: D

Educational Objective: Diagnose squamous cell carcinoma.

The patient likely has a squamous cell carcinoma (SCC), which is the second most common type of skin cancer, and skin biopsy is the appropriate next step in management. Risk factors for SCC are smoking and sun exposure, as in this patient; other risk factors include human papillomavirus infection, immunosuppression, and arsenic exposure. Prompt recognition of SCCs is crucial for optimizing patient outcomes since these lesions can grow rapidly and occasionally metastasize. Lesions on the lip are particularly aggressive and are associated with worse outcomes. The relatively large size of this patient's lesion and tenderness both suggest a malignancy rather than a precancerous lesion. SCCs can sometimes resemble infectious processes such as furuncles, mycobacterial infections, or fungal infections; however, the patient's clinical presentation is most consistent with an SCC, and thus a skin biopsy would be crucial for diagnosis.

Tissue culture for bacteria would not yield useful diagnostic information and may confuse the diagnosis since SCCs are often colonized by bacteria.

Cryotherapy and topical 5-fluorouracil are used for the treatment of precancerous lesions (actinic keratoses) and occasionally SCC in situ, but would not be an appropriate choice for this patient since the lesion appears to be an invasive SCC in a high-risk site.

Similarly, electrodesiccation and curettage may be used for SCC in situ and in certain settings for low-risk well-differentiated SCCs, but would not be an appropriate choice for this location, particularly prior to obtaining a tissue diagnosis.

KEY POINT

- The diagnosis of squamous cell carcinoma of the lip is best established by skin biopsy since these lesions are particularly aggressive and are likely to metastasize.

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Item 18 Answer: D

Educational Objective: Diagnose interstitial lung disease associated with dermatomyositis.

This patient has a clinical picture consistent with dermatomyositis, and she is at increased risk for developing interstitial lung disease. Polymyositis and dermatomyositis are idiopathic inflammatory myopathies. Dermatomyositis also has various characteristic cutaneous manifestations. There are two forms of dermatomyositis: the classic form with both skin and muscle inflammation and either hypomyopathic or amyopathic dermatomyositis with skin findings but minimal or absent muscle inflammation. Patients with polymyositis and those with any form of dermatomyositis (classic, hypomyopathic, or amyopathic) are at increased risk for malignancy, with patients with dermatomyositis at higher risk than those with polymyositis. Similarly, patients with polymyositis or dermatomyositis (regardless of subtype) are at risk for developing interstitial lung disease. Several histopathologic patterns of interstitial lung disease are associated with polymyositis and dermatomyositis. Patients with certain serologic abnormalities may be at higher risks for interstitial lung disease, such as those with anti-Jo-1 antibody positivity. Current screening recommendations include performing pulmonary function tests with measurement of DLCO. Patients often require additional testing, including high-resolution chest CT scans. In patients with mild disease, observation may be appropriate. Increasing levels of immunosuppression may be required for patients with more severe interstitial lung disease.

Bronchiectasis is an acquired disorder characterized by permanent abnormal dilatation and destruction of the bronchial walls and requires an infectious insult plus impaired bronchial drainage to develop. Bronchiectasis is an uncommon finding in patients with dermatomyositis, and this patient has no clinical findings consistent with this diagnosis, including existing pulmonary disease, cough, or sputum production.

Diffuse alveolar hemorrhage may occur in a variety of settings, including in patients with active pulmonary vasculitis. Diffuse alveolar hemorrhage is a rare complication in patients with dermatomyositis and is inconsistent with this patient's clinical features.

Hilar lymphadenopathy is often seen in patients with sarcoidosis; the skin manifestations of sarcoidosis, if present, include violaceous infiltrated papules around the nasal ala and periorbitally or periorally or within scars or tattoos. This patient's skin findings are not consistent with a diagnosis of sarcoidosis.

Pleuritis is an uncommon pulmonary complication of systemic lupus erythematosus (SLE). Generally this will occur in patients with true SLE, as opposed to the cutaneous forms of lupus such as chronic cutaneous lupus erythematosus (discoid lupus). Patients with SLE will generally have a bright red patch symmetrically over their cheeks, the so-called butterfly or malar rash.

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KEY POINT

- Dermatomyositis is associated with an increased risk of interstitial lung disease.

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Item 19 Answer: C

Educational Objective: Treat basal cell carcinoma.

Mohs micrographic surgery is the most appropriate treatment for this patient's basal cell carcinoma (BCC). Many modalities are available for the treatment of BCCs. Selection of the most appropriate technique depends on a number of factors, including the size of the lesion, the location, the patient's age and comorbidities, the histologic subtype of the tumor, and the cost of the procedure. Although standard surgical therapy is appropriate treatment with high cure rates (>95%) for tumors and a low risk of recurrence, micrographic surgery (Mohs) is preferred for tumors with high-risk pathology (micronodular, infiltrative, or sclerosing) or lesions in sites where a cosmetic outcome is important. For this patient, the size of the lesion and location on the temple indicate that a tissue-sparing procedure would be desirable because of cosmetic considerations. The histologic subtype indicates that this lesion has a relatively high risk of recurrence, and given the patient's age, she will presumably live long enough for recurrence to be likely. Mohs micrographic surgery offers a very high cure rate (>98%) coupled with the likelihood of a good cosmetic result. It is also a cost-effective choice in this setting. The fact that the patient is on anticoagulation therapy is not a contraindication to surgery.

Cryotherapy may be used to treat superficial BCCs and some nodular BCCs, but it is not generally used for other histologic subtypes because of an unacceptably high risk of recurrence. It also has an unpredictable cosmetic result and is not generally used for tumors on the head and neck.

Electrodesiccation and curettage is a reasonable treatment for nodular and superficial BCCs that occur on the trunk and extremities. It is not appropriate for more infiltrative subtypes since the recurrence rate is quite high. It is rarely used for tumors on the face because of a relatively high recurrence rate and an unpredictable cosmetic result.

Radiation therapy is a reasonable choice for BCCs in patients who are either not surgical candidates or who refuse surgery. It carries the risk of chronic radiation skin changes in subsequent years, and given the patient's age, this makes it a less desirable option. Radiation therapy is also less cost-effective and less convenient for the patient, since it requires multiple treatments over the course of several weeks.

Topical imiquimod treatment is often used for superficial BCCs and sometimes used off-label for nodular BCCs, but it is generally not used for other subtypes of BCC because of an unacceptably high risk of recurrence. This is particularly true for lesions on the head and neck.

KEY POINT

- For basal cell carcinoma, Mohs micrographic surgery offers a very high cure rate coupled with good cosmetic results.

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Item 20 Answer: D

Educational Objective: Recommend appropriate sun protection.

This patient should use sunscreen with SPF 15 or greater plus UVA protection. Ultraviolet light is divided into categories based on wavelength: UVA (long wavelength) is the most deeply penetrating and can cause photoaging, tanning, and skin cancer, and UVB (shorter wavelength) penetrates less deeply but can cause both sunburns and skin cancer. The sun protection factor (SPF) measures the ability of a sunscreen to block UVB radiation and produce skin erythema determined under laboratory conditions. The SPF refers to the ratio of the dose of solar radiation needed to cause erythema on sunscreen-protected skin to the dose needed to cause erythema on unprotected skin, indicating the degree of protection. However, the relationship between SPF and degree of protection is not linear, such that an SPF of 30 is not twice as protective as an SPF of 15. SPF of 15 or more is required for adequate UVB protection; sunscreens with values lower than this can only be labeled to help decrease the risk of sunburn. To be considered "broad spectrum" sunscreens, the FDA mandates that products also provide protection against UVA. Only sunscreens that have SPF 15 or higher and broad spectrum protection are known to reduce the risk of both skin cancer and signs of photoaging. Additionally, sunscreens may not be labeled as "waterproof" or "sweatproof" because they have not been proved to be effective for more than 2 hours, at which point they should be reapplied.

Although tanning is a natural defense mechanism in response to chronic sun exposure, it requires exposure to ultraviolet light, which increases the risk of photoaging and both melanoma and nonmelanoma skin cancers. Additionally, some patients are unable to tan and may simply burn with ultraviolet light exposure. Therefore, tanning should be discouraged.

Although randomized controlled data are lacking and there is no consensus U.S. Preventive Services Task Force guideline, mathematical modeling and small-scale studies note benefits in populations in which patients perform skin self examinations. All patients at risk for skin cancer may

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benefit from performing monthly skin self-examinations, as many suspicious lesions, including melanomas, are detected initially by attentive patients. Although the sensitivity of skin self-examination is low, it has fair specificity, and patients who engage in skin self-examinations often detect skin cancers at an earlier stage when they are easier to treat and cure.

KEY POINT

- Only sunscreens that have SPF 15 or higher and broad spectrum protection are known to reduce the risk of both skin cancer and signs of photoaging.

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FDA announces changes to better inform consumers about sunscreen [press release]. Silver Spring MD: Food and Drug Administration (FDA). http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm258940. Published June 14, 2011. Accessed June 23, 2014.

Item 21 Answer: D

Educational Objective: Diagnose intertrigo.

This patient has intertrigo, a chronic, recurrent skin condition often seen in obese patients. It is caused by moist conditions in skin fold (intertriginous) areas and is exacerbated by heat and exercise. The rash is confined to the intertriginous area and does not extend beyond these boundaries. Secondary infection with *Candida* may occur, as in this patient; a clinical clue to this situation is the appearance of multiple small red papules on the periphery of the rash, referred to as "satellitosis." Treatment consists of keeping the areas dry and well ventilated, with avoidance of occlusive clothing and possibly the use of drying agents (such as powders). Low-potency topical glucocorticoids and antifungal creams may be used to relieve acute flares by reducing the inflammation and treating secondary yeast infection, respectively.

Allergic contact dermatitis in these areas is a diagnostic possibility; however, the multifocal recurrent nature of the rash and its limitation to areas under the breasts and groin make this less likely.

Atopic dermatitis is a red scaly eruption that arises in childhood and presents with periodic flares throughout life. It may occur on flexor surfaces of the arms and legs but does not typically appear under the breasts or in the groin. Atopic dermatitis is extremely pruritic and is frequently associated with allergic rhinitis and asthma.

Cellulitis may often cause an erythematous rash in various parts of the body; however, the findings would be unilateral rather than bilateral or multifocal. It tends to be painful; lack scale, maceration, or other surface changes; and not be accompanied by satellitosis/candidal infection. Also, the recurrent nature of the patient's rash is not typical of cellulitis.

KEY POINT

- Intertrigo is an inflammatory process found in intertriginous areas; the rash consists of confluent, well-demarcated erythema, generally symmetrically distributed.

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Item 22 Answer: A

Educational Objective: Manage generalized pruritus without a primary skin rash.

The next step in managing this patient's pruritus is to obtain a chest radiograph for possible Hodgkin lymphoma, which is the malignant disease most strongly associated with pruritus. When primary skin lesions are absent, especially when pruritus is generalized, systemic causes of pruritus are suspected. A systemic disease or medication reaction is found in 14% to 24% of patients with generalized pruritus without a primary skin rash. The investigation begins with the history, including a medication history, since medications can cause pruritus. A review of systems should be performed to investigate for thyroid disorders, lymphoma, kidney and liver diseases, and diabetes mellitus. Initial laboratory evaluation for occult systemic disease includes a complete blood count with differential, thyroid function studies, and measurement of serum alkaline phosphatase, bilirubin, creatinine, and blood urea nitrogen levels. A CT scan of the chest, abdomen, and pelvis is not recommended without earlier studies that indicate the need for widespread imaging.

A skin biopsy of normal appearing skin is unlikely to contribute useful information; however, a biopsy would be indicated if the patient had pruritus and primary skin changes.

No further testing is not an appropriate choice since the patient has an impaired quality of life from the pruritus, and up to a 25% of patients with diffuse pruritus without a rash can have an indolent metabolic or malignant process.

KEY POINT

- When pruritus is generalized and primary skin lesions are absent, systemic causes of pruritus should be sought.

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Item 23 Answer: C

Educational Objective: Diagnose scabies.

The most common cause of skin problems in the homeless is infections and infestations, and this patient has a scabies infection. Scabies usually involves the hands (including the palms and interdigital spaces) and feet as well as "folds" of the body (neck, axillary folds, waist, and upper thighs). Scabies also has a predilection for the areola/breast in women and the male genitals (glans, penile shaft, and scrotum). Head involvement is rare

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except in young children. The rash associated with scabies consists of pink papules and macules, some with scale or serous crust, as well as some linear macules that are the burrows of the mites. The patient likely became infested when he stayed with the friend with a rash. After infestation, the rash may take up to a month to become clinically obvious.

Allergic contact dermatitis may involve the dorsal hands, finger web spaces, and skin on the volar wrists, particularly when the palms are spared, but more commonly presents with erythema, edema, and papulovesicles, which are not present in this patient. Lesions are frequently geometric and have sharp cut-offs and a linear component to the morphology. There is typically a delayed onset of 1 to 3 days after exposure.

Bedbugs (genus *Cimex*) are another parasite of humans, but while the scabies mite lives on the human host, the bedbug lives off the human body. The bedbug is active during the night and typically bites areas of skin that are not covered by nightclothes. The face (including the eyelid), neck, hands, arms, and waist may have evidence of bites in the morning or may be delayed by 7 to 10 days. The bites are itchy and may be small pink-red papules or urticarial plaques 1 to 2 cm in diameter. Bedbugs live in crevices of mattresses, furniture cushions, suitcases, and walls.

Tinea manuum is a dermatophyte infection involving the hands and feet. Tinea manuum characteristically involves only one hand (and two feet). The findings are characterized by a dry scale, and if chronic, nails can be involved. The diagnosis of tinea manuum is unlikely if the feet are not involved.

KEY POINT

- The rash associated with scabies consists of pink papules and macules, some with scale or serous crust as well as some linear macules that are the burrows of the mites.

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Heukelbach J, Feldmeier H. Scabies. Lancet. 2006 May 27;367(9524):1767-74. [PMID: 16731272]

Item 24 Answer: A

Educational Objective: Diagnose allergic contact dermatitis.

A pruritic geometric patch typical of allergic contact dermatitis, and in this patient, the clonidine patch is the likely cause. Contact dermatitis is an example of an "outside job" when a rash is in linear or geometric patterns because the rash corresponds exactly to where the allergen touches the skin from the outside. Allergic contact dermatitis is a hypersensitivity reaction to a specific chemical. With repeated exposure to the chemical, a pruritic eczematous dermatitis develops on the area that was exposed. In exuberant cases, pinpoint flesh-colored to red papules develop in the vicinity of exposure or diffusely over the body. The clonidine patch has been associated with allergic contact dermatitis. Although many transdermal drug delivery systems may cause allergic contact dermatitis, the clonidine patch tends to have a higher incidence, possibly owing to its formulation that allows the patch to be left in place for up to 7 days. The patient's adjacent areas of hyperpigmentation likely represent resolving inflammation from prior applications of the patch.

A fixed drug eruption is typically a purple patch that is painful and is not localized to the area underneath a patch. Fixed drug eruptions occur in the same location (fixed) each time a patient is exposed to the same medication. Lips, genitals, and hands are commonly involved. Common drug culprits include over-the-counter medications such as pseudoephedrine, NSAIDs, sulfonamide medications, and other antibiotics.

Irritant contact dermatitis is a direct toxic effect on the epidermis from exposure to a chemical such as a cleaning agent, other caustic substance, or repeated wetting and drying and is not mediated by the immune system. Irritant contact dermatitis would present with a generalized dermatitis in all of the exposed areas but not in a geometric pattern.

Tinea corporis is a dermatophyte infection that may occur in healthy people, although patients with compromised immune systems (such as with diabetes mellitus) may be more susceptible. The classic findings are a pruritic, circular or oval, erythematous, scaling patch or plaque that spreads centrifugally with central clearing. This patient's skin findings are not consistent with this diagnosis.

KEY POINT

- Allergic contact dermatitis is a hypersensitivity reaction to a specific chemical, and with repeated contact with the chemical, a geometric pruritic eczematous dermatitis develops on the area that was exposed.

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Item 25 Answer: D

Educational Objective: Treat toxic epidermal necrolysis.

This patient has toxic epidermal necrolysis (TEN), and he should be admitted to the hospital and any medications that are possible triggers (minocycline) should be stopped immediately. The most commonly implicated medications are antiepileptic agents, especially carbamazepine, lamotrigine, and phenytoin. Sulfonamides, fluoroquinolones, β-lactam antibiotics, minocycline, pantoprazole, sertraline, NSAIDs (oxicam and acetic acid type), tramadol, and allopurinol are also frequent causes. The treatment of TEN begins with drug cessation and aggressive ICU or burn center care.

Stevens-Johnson syndrome (SJS) and TEN are related clinical syndromes that are characterized by acute epidermal necrosis. The classification of SJS and TEN is determined by the percentage of body surface area with epidermal detachment: SJS involves less than 10%, SJS-TEN overlap involves

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CONT.

10% to 30%, and TEN involves greater than 30%. TEN is a rare disease, with a prevalence of 1:1,000,000. TEN is almost exclusively caused by medications, whereas erythema multiforme and SJS can also be triggered by vaccines or infection. SJS and TEN occur within 8 weeks of drug initiation, often between 4 and 28 days. Patients may have flu-like symptoms for 1 to 3 days prior to the skin eruption. Initially, red-purple macules or patches develop on the trunk and extremities, which enlarge and coalesce. Skin pain is prominent, in contrast to the pruritus associated with a common drug exanthema. Vesicles, bullae, and erosions reflect the epidermal necrosis seen on biopsy. Nikolsky sign (the shearing off of the epidermis with lateral pressure on the skin) is present. Two or more mucosal surfaces, such as the eyes, nasopharynx, mouth, and genitals, are involved in more than 80% of patients. Systemic inflammation can result in pneumonia, hepatitis, nephritis, arthralgia, and myocarditis.

Infliximab is a monoclonal antibody that is used for several conditions including psoriasis; however, it has no role in the management of TEN. There is evidence to show that treatment with systemic glucocorticoids, such as intravenous methylprednisolone, can increase mortality rates in patients with TEN. Infection is a risk for patients with SJS or TEN because of the extensive damage to the skin barrier; however, antibiotics, such as vancomycin and ceftriaxone, are not started without signs or symptoms of infection.

KEY POINT

- The treatment of toxic epidermal necrolysis begins with discontinuing the offending drug and providing aggressive supportive care, such as that received in an ICU or burn center.

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Item 26 Answer: D

Educational Objective: Diagnose subacute cutaneous lupus erythematosus.

This patient has a typical eruption of subacute cutaneous lupus erythematosus (SCLE). Although associated with systemic lupus erythematosus (SLE), it is a distinct disorder that may present with different cutaneous findings than those usually associated with SLE. There are two presentations of SCLE: annular scaly patches on the upper back and sun-exposed areas or a more psoriasiform eruption that can have less distinctive morphology but also occurs in sun-exposed areas. SCLE is associated with a number of medications believed to trigger the disorder, including hydrochlorothiazide, calcium channel blockers, ACE inhibitors, terbinafine, and the tumor necrosis factor α (TNF-α) inhibitors. This patient is taking hydrochlorothiazide, which was the first drug reported in association with SCLE and remains a common cause of drug-induced SCLE. Patients with SCLE tend to be very photosensitive, may have antinuclear antibody positivity, and are often positive for anti-Ro/SSA antibodies (and may be positive for anti-La/SSB antibodies). Patients with drug-induced SCLE may be antihistone antibody positive (about one third to one half of patients), but antihistone antibody positivity is not necessary to make the diagnosis. Compared patients with SLE, those with SCLE tend to have fewer systemic findings, although a subset of patients may have kidney involvement. Notably, all women with anti-ro/SSA and anti-La/SSB antibodies are at risk for having newborns with neonatal lupus, and pregnant patients or mothers of newborns with this pattern of skin eruption or serologic antibody profiles should be counseled and their babies screened accordingly. For drug-induced SCLE, discontinuing the inciting medication is essential to treatment.

Dermatomyositis may present without muscle inflammation, but this patient's skin eruption is characteristic of SCLE. The rash of dermatomyositis is accentuated around the eyes (heliotrope rash), around the lateral shoulders ("shawl sign"), and involves the knuckles of the metacarpal and interphalangeal joints (Gottron sign).

Pemphigus foliaceus is an autoimmune blistering disease in which the autoantigen is in the upper regions of the epidermis, leading to superficial blisters that rapidly rupture and cause dried crusts over inflamed skin, which have been described as looking like "cornflakes." The morphology and distribution of the eruption described in this patient would be atypical, and patients with pemphigus foliaceus are not often positive for anti-Ro/SSA antibodies or high-titer antinuclear antibodies.

Psoriasis generally occurs over joints or at areas of trauma or friction, is not generally annular, and should not be photodistributed. Classic plaque psoriasis is characterized by pink plaques with silvery scale over the knees, elbows, and often around the umbilicus and gluteal cleft.

KEY POINT

- Patients with subacute cutaneous lupus erythematosus have annular scaly patches that are typically drug or sunlight induced.

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Item 27 Answer: D

Educational Objective: Treat a hospital-acquired skin infection.

This patient should be treated with vancomycin. Hospital-acquired skin and soft-tissue infections should be treated as a methicillin-resistant *Staphylococcus aureus* (MRSA) infection until culture results are received and therapy can be tailored appropriately. Hospital-acquired skin infections are increasingly caused by MRSA, and coverage against this organism in the hospital setting is important to prevent

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further morbidity and mortality, particularly in high-risk patients. Once culture and sensitivity results are known, antibiotic therapy can be focused toward a specific organism. In the patient described here, a local abscess and surrounding cellulitis with corresponding fever and leukocytosis suggests the potential for systemic involvement.

Amoxicillin-clavulanate should not be used because these antibiotics do not provide coverage against MRSA organisms.

Similarly, cephalexin is often effective against multiple skin and soft-tissue infections and may be considered first-line therapy for an abscess and cellulitis in the ambulatory setting; however, it too is ineffective against MRSA.

Although meropenem is a potent antibiotic with broader antimicrobial coverage, it is not effective against MRSA infection and thus would not be an appropriate choice for this patient.

Several strategies may be used to attempt to reduce rates of MRSA infection in hospitalized patients. Routine screening and active surveillance cultures for MRSA colonization are obtained in some institutions to identify carriers and to guide use of contact precautions and possibly attempted decontamination with intranasal mupirocin. However, the efficacy of this practice is not clear except in the setting of an acute outbreak. Daily chlorhexidine bathing has been shown to decrease the risk of colonization and infection with drug-resistant and other organisms in ICU settings.

KEY POINT

- Vancomycin, an empiric antibiotic therapy against methicillin-resistant *Staphylococcus aureus*, is the treatment of choice for most hospitalized patients with skin and soft-tissue infections until culture results are available.

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Item 28 Answer: A

Educational Objective: Diagnose localized alopecia areata.

This patient has alopecia areata, a chronic autoimmune disease that results in smooth, hairless patches of skin. Tapered "exclamation point" hairs may be seen at the periphery; these hairs have shafts that are thicker at the distal portion and narrower near the scalp. Older patients may demonstrate sparing of white/gray hairs, and in some patients the hair regrowth in existing patches begins with fine, white/fair hairs. The scalp is the most common site. Individual patches can spontaneously resolve within 12 months; however, new patches may develop. An autoimmune mechanism is supported by the increased rate of other autoimmune diseases, such as type 1 diabetes mellitus and autoimmune thyroid disease, in patients with alopecia areata as well in their family members.

Androgenetic alopecia is a type of diffuse nonscarring alopecia that can affect both men and women. In men, the bilateral temples and vertex are often affected. Androgenetic alopecia results in hair follicles that are thinner in caliber or "miniaturized" and loss of the hair follicle; however, androgenetic alopecia causes a decreased density of hair but not areas of complete loss of hair as seen in alopecia areata.

Discoid lupus erythematosus is the most common type of chronic cutaneous lupus. On the scalp, discoid lupus erythematosus manifests as scaling, erythematous, and hyper- and hypopigmented patches with alopecia. Multiple lesions are more likely than a single lesion.

Telogen effluvium is a diffuse nonscarring form of hair loss that is usually triggered by a systemically stressful event such as a serious illness, surgery, or childbirth. Approximately 3 to 5 months after the inciting event, numerous hairs are shed, leading to noticeably thinned hair. A small hair bulb may be visible at the scalp end of the shed hair. The hair loss tends to be patchy and diffuse; foci of total alopecia are not seen as in alopecia areata.

Tinea capitis causes scaling, inflammation, pustules, and pruritus, none of which are present in alopecia areata.

KEY POINT

- Alopecia areata is a chronic autoimmune disease that results in smooth, hairless patches of skin, most commonly appearing on the scalp.

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Item 29 Answer: A

Educational Objective: Diagnose calciphylaxis.

This painful black eschar with slight surrounding angulated purpura in a patient on dialysis is consistent with calciphylaxis. Calciphylaxis is an uncommon syndrome that typically occurs in patients with advanced kidney dysfunction and an elevated calcium-phosphorus product (>60-70 mg^2/dL^2), which may be present in this patient who has difficulty with medication adherence. Calciphylaxis results from abnormal deposition of calcium within the lumen of the arterial vasculature, compromising blood flow with distal ischemia resulting in painful tissue necrosis. It has a poor prognosis with a 60% to 80% 1-year mortality rate, with patients often succumbing to infectious complications. Management requires pain control, meticulous skin care, and surveillance for associated infection due to increased risk of tissue ischemia. Directed therapy is preferably multi-interventional and typically includes aggressive lowering of the calcium-phosphorus product (by dialysis and non-calcium phosphate binders) to less than 55 mg^2/dL^2, administration of sodium thiosulfate (mechanism unclear), and lowering of the parathyroid hormone level (by surgery or cinacalcet). Hyperbaric oxygen, careful debridement, and bisphosphonates may also be helpful.

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Vasculitis is inflammation of the blood vessels and can affect any size vessels. The most common cutaneous vasculitis is a small vessel vasculitis, which manifests as palpable purpura (nonblanching red papules). Medium vessel vasculitis (such as polyarteritis or granulomatosis with polyangiitis) can lead to ulcers in the skin, but the lesions are often strikingly inflamed with an active erythematous-to-red border and often surrounding livedo-like changes. A single, thick black eschar, as seen in this patient, would be uncommon.

Spider bites are exceedingly rare and overdiagnosed in clinical practice. Bites that do occur usually follow an exposure to secluded, dark, neglected areas such as a woodshed. Many patients living in environments rich in brown recluse spiders never receive a bite, and most patients diagnosed with bites have alternative diagnoses. Additionally, only a small percentage of brown recluse spider bites become necrotic. In those that do, the bite is usually exquisitely painful, rapidly progressing with deep tissue necrosis and accompanying systemic symptoms. Most necrotic bites are smaller than the lesion seen in this patient and usually stop expanding and start healing within about 10 days.

Pyoderma gangrenosum is a neutrophilic dermatosis in which the host's neutrophils cause autoinflammation in the skin, leading to painful, exudative, rapidly progressive ulcers. The ulcers typically start as a pustule or shallow erosion in response to minor trauma and rapidly expand. Classic PG ulcers will have a rim of violaceous erythema and edema; an overhanging lip; thin, anastomosing strands of intact epidermis hanging over the ulcer base; and excessive serous exudates that can lead to fibrinous "slough" over the ulcer base. This patient's skin findings are not consistent with pyoderma gangrenosum.

KEY POINT

- A painful black eschar with slight surrounding angulated purpura in a patient on dialysis who has calcium and phosphorus abnormalities is consistent with calciphylaxis.

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Item 30 Answer: C

Educational Objective: Treat impetiginized insect bite.

The most appropriate treatment for this patient is mupirocin ointment for localized impetigo. Impetigo is a superficial bacterial infection most commonly caused by *Staphylococcus aureus* and, to a lesser extent, β-hemolytic streptococci. The patient initially had an insect bite that became secondarily infected, likely due to the skin trauma associated with scratching the bite. Because there are no signs of systemic illness and the patient has a localized infection, treatment with topical antibacterial agents, such as mupirocin, is considered first-line therapy. Bleach baths may be a treatment option (put 1/4 to 1/2 cup of common liquid bleach into the bath water to create a chlorinated bath), which decreases colonization of *S. aureus*). Topical retapamulin cream also has been demonstrated to have effective antimicrobial properties against *Staphylococcus* and *Streptococcus* spp. and can be effective in patients with mupirocin-resistant organisms.

Although cephalexin can be effective for impetigo, localized infections should be treated with topical antibiotics whenever possible to avoid systemic side effects and potential resistance with overuse of oral antibiotics. If the infection was systemic or more severe, cephalexin would be appropriate. In addition, if topical mupirocin failed to resolve the infection, oral therapy can be considered.

Doxycycline is effective against methicillin-resistant *Staphylococcus aureus* but provides poor coverage against *Streptococcus*, which is another organism that can lead to impetigo. In addition, topical therapy is considered first-line therapy for localized impetigo.

Triamcinolone ointment is not effective against impetigo. Triamcinolone ointment can be used for symptomatic treatment of insect bites; however, when pain and honey-colored crust is present, impetigo needs to be considered and treated.

KEY POINT

- A topical antibacterial agent, such as mupirocin, is the first-line therapy for localized impetigo.

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Item 31 Answer: C

Educational Objective: Manage pityriasis rosea in a patient at risk for syphilis.

This patient should have a rapid plasma reagin test. He has scaling plaques on the trunk and proximal extremities after a recent upper respiratory tract infection, which is most typical of pityriasis rosea. The clinical appearance of scaling papules and plaques is similar to that of secondary syphilis, although pityriasis rosea typically spares the face, palms, and soles, whereas syphilis often affects the palms and soles. In a sexually active patient who is not consistently using protection and has palm involvement, secondary syphilis must be ruled out. The primary chancre is typically painless in syphilis and therefore may go unnoticed.

Hepatitis C virus testing is indicated for patients with lichen planus (LP), especially if oral. LP is an acute eruption of purple, pruritic, polygonal papules that most commonly presents on the flexural surfaces, especially the wrists and ankles. LP can also present in the mucous membranes (mouth, vaginal vault, and penis) with white plaques that, if uncontrolled, may ulcerate. This patient's physical findings are not consistent with LP.

Herpes simplex virus infection presents with grouped vesicles and erosions and no scaling plaques, and so polymerase chain reaction test is not necessary.

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Because testing should be performed if there is any clinical concern for syphilis, not doing a work-up is not an acceptable treatment option.

KEY POINT

- The clinical appearance of pityriasis rosea is similar to that of secondary syphilis, and rapid plasma reagin testing should be performed if there is any clinical concern for syphilis.

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Item 32 Answer: A

Educational Objective: Manage dysplastic nevus syndrome.

The patient has dysplastic nevi, and he should be taught how to perform monthly self-examinations and should be referred to a dermatologist for close clinical monitoring. Dysplastic nevi are benign melanocytic lesions most commonly found on the trunk and extremities. In contrast to common nevi, they have one or more atypical clinical features that may make them difficult to distinguish from malignant melanoma. Histologically, they possess varying degrees of cytologic atypia and architectural disorder. Although benign, they often serve as a marker for persons who have a higher than average risk of developing melanoma. Any lesions suspicious for melanoma should be removed and sent for histologic evaluation.

Partial biopsy of multiple pigmented lesions is not recommended since it leaves room for sampling error and the possibility of nevus recurrence. If a given pigmented lesion is worrisome for melanoma, it should be removed in its entirety whenever possible and sent for pathologic analysis.

Patients with dysplastic nevus syndrome often have large numbers of nevi. Removal of either the largest lesions or nevi en masse has not been shown to reduce the risk of developing melanoma, is often not practical, and is not cost effective; therefore, neither procedure is recommended. In patients with numerous dysplastic nevi who develop melanoma, approximately two thirds of the time the melanoma will arise on normal appearing skin rather than within a preexisting nevus. Thus, even if all of a patient's nevi were removed, the overall risk would only be partially reduced.

KEY POINT

- Dysplastic nevi are benign melanocytic lesions most commonly found on the trunk and extremities that have atypical clinical and histologic features that may make them difficult to distinguish from malignant melanoma.

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Item 33 Answer: D

Educational Objective: Treat pyoderma gangrenosum.

This patient has peristomal pyoderma gangrenosum (PG), and a topical potent glucocorticoid, such as clobetasol, is the preferred treatment. PG is an autoimmune ulcerative process that may occur idiopathically or in conjunction with an underlying disease; the most common disease association is inflammatory bowel disease (IBD). This patient has IBD and had recent surgery; 20% to 30% of patients with PG may exhibit "pathergy" or induction of lesions in response to trauma, such as surgery. Peristomal PG is a common manifestation, and early recognition is essential to avoid expansion, thereby limiting ostomy appliance adherence and devastating patients' quality of life. PG ulcers are typically painful, may rapidly expand, and are often exudative. When appropriate therapy is instituted, the lesions often dry out and become less painful over 1 to 2 weeks. Even when the PG inflammation is controlled, patients are left with a large ulcer that must then heal, and local care is critical. PG is treated with glucocorticoids (oral, topical, or intralesional), cyclosporine, or infliximab (a tumor necrosis factor α inhibitor) as first-line therapy for most patients. Active IBD should be treated as well.

Replacing the ostomy to the opposite side would entail major surgery, which, in the setting of active PG, could worsen the problem and may lead to PG at the new site. Removing the ostomy would not address the PG ulcer.

Rituximab is not indicated for PG, as rituximab targets CD20+ cells (B cells), which have little role in the pathogenesis of PG.

Because of the nature of the disease, PG lesions should not be debrided. PG lesions will worsen after debridement. It is not uncommon for PG to be diagnosed after repeated, unsuccessful debridements for a presumed infection result in dramatic worsening of the initial ulcer. Regardless, there is no necrotic tissue here to debride.

KEY POINT

- Glucocorticoids (oral, topical, intralesional) are first-line therapy for peristomal pyoderma gangrenosum.

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Item 34 Answer: C

Educational Objective: Diagnose pretibial myxedema.

This patient has clinical features of pretibial myxedema, generally seen in patients with Graves hyperthyroidism. Also termed thyroid dermopathy, pretibial myxedema results from the accumulation of glycosaminoglycans in the dermis that leads to the characteristic thickening and development of firm but compressible plaques described in this patient. The pretibial thickening generally occurs 1 to 2 years after the onset of Graves hyperthyroidism. The mechanisms of

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development of both pretibial myxedema and Graves ophthalmopathy are similar, and the findings often develop within a year of one another. The mechanisms of pretibial myxedema are not well understood but may be related to the interaction of thyrotropin-receptor antibodies with antigen-specific T cells and dermal fibroblasts causing inflammation and increased glycosaminoglycan production. Similar to increasing the risk for ocular disease, tobacco use may also increase the risk for pretibial myxedema in patients with Graves disease; almost all patients with pretibial myxedema have evidence of ophthalmopathy. The skin lesions typically occur on the shins, but rarely may occur elsewhere. Some patients may develop elephantiasis and severe leg deformity from the extent of myxedema. Once the lesions occur, they tend to persist regardless of the status of the thyroid disease. Skin-directed therapy may be required for improvement, although the lesions are generally of cosmetic concern and do not pose health risks.

Lipodermatosclerosis is a severe form of stasis in which the skin becomes thickened and may develop an "inverted champagne bottle" appearance with the skin on the distal legs being very tight and "woody."

Necrobiosis lipoidica (NL) is another skin manifestation of an endocrine condition that can occur on the anterior shins. NL presents as atrophic, orange-colored patches often associated with visible vasculature from skin thinning; the lesions may ulcerate. NL may develop in patients with diabetes mellitus, and when present may be a sign of end-organ damage, as patients with NL are more likely to have retinopathy or nephropathy.

Stasis dermatitis occurs in the setting of lower extremity edema. It is characterized by a ruddy-brown complexion in the setting of chronic venous backup and fluid filling the legs in response to proximal compression. This is typically seen in patients with heart failure.

KEY POINT

- Pretibial myxedema is generally seen in patients with Graves hyperthyroidism; dermal-based mucinous deposits in the skin of the anterior shins leads to the characteristic thickening and other skin changes.

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Fatourechi V. Pretibial myxedema: pathophysiology and treatment options. Am J Clin Dermatol. 2005;6(5):295-309. [PMID: 16252929]

Item 35 Answer: A

Educational Objective: Diagnose bedbug infestation.

This patient has bedbug bites, and the most appropriate treatment is topical glucocorticoids. Bedbugs (*Cimex lectularius*) are parasites that feed on human blood, often producing pruritic papules in a characteristic grouped pattern ("breakfast, lunch, and dinner"). Bites occur in exposed skin areas and are more pronounced in the morning because bedbugs are nocturnal and feed at night, usually without being noticed. Bedbugs are about the size of a dog tick and are brownish in color with flat bodies. They frequently inhabit spaces in furniture such as mattresses and cushions. Bedbug bites can be extremely pruritic, and topical glucocorticoids provide anti-inflammatory and symptomatic relief. However, the lesions will self-resolve, so treatment is not mandatory. Professional exterminators are required for evaluation and removal of the bedbugs with pesticides, and eradication can be difficult, making their infestation a significant public health concern. Travel is a risk factor for bedbug infestation, and often multiple family members, if they share the same sleeping quarters, can be affected.

Body lice (pediculosis) also can lead to pruritic papules, but do not occur in a characteristic grouped pattern. Pruritic lesions can occur diffusely, as body lice usually live within the seams of clothing and not on the skin.

Flea bites also result in pruritic papules, but these lesions are not typically grouped. Additionally, because fleas are external parasites and do not live on humans, bites are more commonly present on the lower extremities because fleas typically jump from another location (such as a dog or cat) and bite the legs.

Scabies is an infestation of a mite that lives on the human skin and results in intensely pruritic papules and eruptions involving the waistline, genitals, finger web spaces, wrists, and axillae. A hypersensitivity reaction also can occur. The distribution of lesions in the patient described here is uncommon for scabies infestation.

Spider bites can result in pruritic lesions, but they typically occur as an isolated finding without evidence of multiple or recurrent bites. The number of bites and frequency in which the patient is developing lesions would be atypical for spider bites.

KEY POINT

- Bedbug bites can be recognized by their characteristic grouping in a linear series pattern ("breakfast, lunch, and dinner"); the lesions are painless, pruritic, urticaria-like papules.

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Item 36 Answer: C

Educational Objective: Diagnose erythroderma.

This patient has erythroderma, which is a term used to describe erythematous inflammation of at least 80% to 90% of the skin surface and is a dermatologic urgency. Erythroderma is most often due to an uncontrolled existing dermatosis such as cutaneous T-cell lymphoma, graft-versus-host disease, psoriasis, or pityriasis rubra pilaris. Medications are the second most common cause; thus, taking a history of current and recently discontinued medications is also important. Men are affected more often than women, and the average age of onset is 55 years. Although the diagnosis of erythroderma is usually straightforward, in some patients it may be difficult

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to determine the cause, particularly in patients without a known preexisting condition that may be responsible. In these patients, a combination of clinical evaluation and careful clinicopathologic correlation is needed. Owing to compromise of the skin barrier, affected patients are at risk for dehydration, electrolyte abnormalities, protein loss, heat loss, and infection. Peripheral edema, erosions from severe pruritus, scaling, and lymphadenopathy are common findings.

Angioedema is soft-tissue swelling that may be mast cell or bradykinin mediated. It may occur independently, with urticaria, or may be associated with anaphylaxis. Angioedema tends to affect less dense connective tissue, including the face, lips, throat, and extremities, but is not associated with erythroderma. This patient's presentation is therefore not consistent with angioedema.

Drug-induced subacute cutaneous lupus erythematosus (SCLE) can be triggered by hydrochlorothiazide. Other medications that can cause this eruption are calcium channel blockers, ACE inhibitors, statins, proton-pump inhibitors, and tumor necrosis factor α inhibitors. Although this patient is taking hydrochlorothiazide, the appearance of his rash is not consistent with SCLE. Drug-induced SCLE typically presents as annular pink-red patches with fine scale, predominantly affecting the photodistributed areas of the upper chest, back, and shoulders.

Pityriasis refers to flaking of the skin, and a number of cutaneous conditions incorporate this descriptive term into their name. Pityriasis rosea (PR) is a relatively common inflammatory reaction of the skin and may be caused by a viral infection; however, a specific virus causing this condition has not been identified. It generally occurs in patients younger than 30 years old and does not cause an erythrodermic eruption. Typically, PR begins as a single annular patch or plaque with fine scaling (the so-called herald patch). About 1 week later many smaller pink macules, patches, and papules erupt over the trunk and proximal extremities.

KEY POINT

- Erythroderma is characterized by erythema of at least 80% to 90% of the skin surface and is a dermatologic urgency.

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Item 37 Answer: C

Educational Objective: Manage potential complications of herpes zoster infection.

This patient has herpes zoster infection involving the forehead and has a vesicular lesion on the tip of the nose (Hutchinson sign) suggesting the possibility of ocular involvement, and she should be referred for urgent ophthalmologic evaluation. This clinical scenario is consistent with herpes zoster infection involving the V1 distribution of the trigeminal nerve, which can result in eye involvement (herpes zoster ophthalmicus) and ophthalmologic complications including keratitis, scleritis, uveitis, and acute retinal necrosis. When grouped vesicles on an erythematous base involve the V1 distribution or extend to the tip of the nose, concurrent management with an ophthalmologist is indicated to help treat and prevent any of these complications. Management of these patients usually involves antiviral therapy and topical glucocorticoid eye drops to reduce inflammation.

The herpes zoster vaccine is recommended for persons 60 years or older to prevent herpes zoster and its complications. The administration of the vaccine after an episode of zoster is debated. The Centers for Disease Control recommends providing the vaccine even after an initial herpes zoster infection. However, a recent article states that the cellular immune response to varicella zoster virus (VZV) during the first 3 years after vaccination is similar to that after an episode of herpes zoster. As a result, deferring vaccination for up to 3 years in patients who are immunocompetent, such as this patient, is recommended, as vaccination during the episode will not be as effective.

Mupirocin is an antibiotic used for the treatment of bacterial skin infections such as impetigo, furuncles, or methicillin-resistant *Staphylococcus aureus*. Herpes zoster is a viral infection, and mupirocin would not be appropriate.

Otolaryngology consultation is not necessary. The distribution of the vesicles in the central face is not concerning for underlying hearing or other otolaryngologic involvement. Herpes virus infection may involve the ear canal and hearing may be affected and a facial nerve palsy or vertigo also can result. This complex of findings is known as Ramsay Hunt syndrome, and systemic glucocorticoids and antiviral agents may be necessary to treat this complication, usually with co-management with an otolaryngologist.

KEY POINT

- Herpes zoster infection involving the V1 distribution of the trigeminal nerve can result in ophthalmologic complications including keratitis, scleritis, uveitis, and acute retinal necrosis.

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Item 38 Answer: A

Educational Objective: Diagnose drug reaction with eosinophilia and systemic symptoms.

This patient should discontinue the trimethoprim-sulfamethoxazole, and a complete blood count and liver chemistry tests should be ordered. She has a widespread morbilliform eruption with fever, facial edema, and lymphadenopathy that started 6 days after taking trimethoprim-sulfamethoxazole. This is typical of a systemic drug hypersensitivity syndrome, otherwise known as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. It is a rare, potentially

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life-threatening drug-induced hypersensitivity reaction. The presentation of DRESS typically includes a skin eruption, hematologic abnormalities, lymphadenopathy, and internal organ involvement (including the liver, kidneys, and lungs). The presence of DRESS should be suspected in patients with a morbilliform rash, fever, facial swelling, and lymphadenopathy that occur 5 to 10 days after starting a potentially offending medication. The initial diagnostic approach in suspected DRESS is to assess for evidence of systemic organ involvement, and this is accomplished by obtaining a complete blood count, which may show atypical lymphocytosis and eosinophilia, and liver chemistry studies, which may show aminotransferase elevations. Patients with extensive cutaneous reactions or evidence of organ involvement may require hospitalization and possibly treatment with systemic glucocorticoids. Even if the rash fades, the patient can still progress to liver failure.

Lymph node biopsy may show a range of findings that may be suspicious for lymphoma. Lymph node biopsy is rarely required for the diagnosis or management of DRESS.

Skin biopsy may show lymphocytic infiltration and edema in DRESS and may confirm the diagnosis, although it is not helpful in assessing the severity of systemic organ involvement.

No further testing following discontinuation of the likely causative medication is appropriate in patients without evidence of significant organ involvement. However, exclusion of significant systemic involvement is necessary before a supportive approach is taken.

KEY POINT

- Patients with suspected drug hypersensitivity syndrome, also known as drug reaction with eosinophilia and systemic symptoms, should have a complete blood count with differential to evaluate for eosinophilia or atypical lymphocytosis and liver chemistry tests to assess for evidence of systemic organ involvement.

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Item 39 Answer: A

Educational Objective: Manage lichen sclerosus in a postmenopausal woman.

The patient should be treated with a topical high-potency glucocorticoid (class I or II), such as clobetasol, mometasone, or betamethasone. Her clinical presentation of white atrophic patches circumferentially involving the anus and vagina with associated pruritus and dyspareunia is consistent with lichen sclerosus. Lichen sclerosus is a benign, chronic, and progressive dermatologic condition of unclear etiology that tends to affect peri- and postmenopausal women. It manifests with marked inflammation and epithelial thinning that is pruritic; because of its usual location, lichen sclerosus is usually associated with pain during intercourse. Skin findings are characteristic, and the diagnosis is confirmed on biopsy showing epidermal thinning, scarring, and evidence of inflammation. The appropriate first-line therapy for this disease is a potent topical glucocorticoid, such as clobetasol, daily for 2 to 3 months (or until resolved) and then intermittently to prevent recurrence. Not treating lichen sclerosus will result in permanent scarring (including all anatomic structures such as the clitoris and vaginal opening), and there is evidence of early scarring with resorption of the labia minora in this patient. Close monitoring also is essential to evaluate for cutaneous squamous cell carcinomas that can occur with chronic inflammation.

A low-potency glucocorticoid, such as hydrocortisone 1% ointment, is not adequate to treat lichen sclerosus. Continued inflammation with this treatment will result in permanent scarring.

Vulvar lichen sclerosus is not caused by a bacterial infection; therefore systemic (cephalexin) or topical (mupirocin) antibiotics are not indicated.

Occasional co-infection with vaginal candidiasis can occur, which would present with foul-smelling and thick white discharge. Vulvar candidiasis can also occur, which would present with bright red patches and satellite pustules. These infections should be treated with intravaginal or oral antifungal agents. Topical nystatin is an antifungal agent used to treat candidiasis but would not be effective for treatment of vulvar lichen sclerosus.

KEY POINT

- The use of potent topical glucocorticoids is considered first-line treatment for lichen sclerosus.

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Item 40 Answer: B

Educational Objective: Diagnose fixed drug eruption.

This patient likely has a fixed drug eruption (FDE). A painful purple patch that occurs in the same location repeatedly is a classic sign of a FDE. Patients with an extensive eruption may have central bullae that occur in the same location (fixed) each time the patient is exposed to the same medication. Lips, genitals, and hands are commonly involved. There may be only one spot with the first exposure; but if reexposed, the lesion may recur along with new areas. Common drug culprits are over-the-counter medications such as NSAIDs, pseudoephedrine, sulfonamide medications, and other antibiotics. The patient's periodic recurrent lesion is likely associated with his periodic use of ibuprofen. Drug discontinuation is the appropriate treatment, with resolution of the rash expected to occur over days to weeks.

Contact dermatitis is a delayed hypersensitivity reaction to a specific chemical. With repeated exposure to the

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chemical, a diffuse, pruritic eczematous dermatitis develops on the area that was exposed. The characteristic rash is typically reddish, scaly, and crusting, and when occurring on the penis may be associated with condom use. However, this patient's rash is not typical for eczematous dermatitis.

Herpes simplex virus infection usually presents with a vesicular rash if acute or erosion if chronic, as may be seen in patients with HIV infection. Recurrent genital herpes is similar to oral herpes with a prodrome, followed by grouped vesicles on an erythematous base, erosions, and crusting. This patient's presentation is not consistent with recurrent herpes simplex virus infection.

Primary syphilis presents as a chancre, classically a shallow nonexudative ulcer with an indurated border that is not painful. This patient's lesion is not consistent with a chancre.

KEY POINT

- The classic sign of a fixed drug eruption is a painful purple patch that occurs in the same location repeatedly; the lips, genitals, and hands are commonly involved.

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Item 41 Answer: D

Educational Objective: Diagnose Sweet syndrome.

This patient has the typical skin findings characteristic of Sweet syndrome, also known as acute febrile neutrophilic dermatosis. The lesions are well demarcated with a sharp cut-off separating normal and inflamed skin. Because of the intense neutrophilic inflammatory infiltrate and accompanying papillary dermal edema, the lesions are often referred to as appearing "juicy." Patients often have a leukocytosis with a predominance of neutrophils and bands; there may be an accompanying, albeit nonspecific, elevation in inflammatory markers such as erythrocyte sedimentation rate. Patients with Sweet syndrome may have idiopathic disease (common in older white women) or paraneoplastic Sweet syndrome, most commonly seen in patients with hematologic malignancies, particularly acute myeloid leukemia or myelodysplastic syndrome. The sharply demarcated, indurated red papules, plaques, or nodules almost always develop in the setting of fever and are often mistaken for infection. Patients may develop these lesions at any time during their treatment course. Sweet syndrome may also occur as a reaction to certain medications, particularly granulocyte colony-stimulating factors. The condition is extraordinarily responsive to treatment with glucocorticoids, with the fever stopping immediately and the lesions fading within 1 to 2 days.

Candidiasis would not be expected to occur this early in this patient's neutropenic course, and the skin lesions of disseminated candidiasis are generally small red papules, sometimes with a prominent white or translucent center; plaques are not common in disseminated candidiasis.

Keratoacanthoma is a subtype of squamous cell carcinoma that often presents with an isolated, rapidly growing, red nodule with a central keratin-filled core, resembling a "volcano" with the center composed of crusted dried keratin. The "juicy" red nodule shown would be atypical for a keratoacanthoma.

Pyogenic granulomas are small, benign vascular papules that can occur almost anywhere but tend to be seen on the extremities around the nails and on the face. They tend to occur more commonly in patients treated with certain types of medications (such as certain acne medications and antiretroviral agents) and in pregnant women.

KEY POINT

- The lesions in Sweet syndrome are "juicy" red papules, plaques, or nodules with sharp borders, appearing on the upper trunk and proximal extremities in the setting of fevers.

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Dabade TS, Davis MD. Diagnosis and treatment of the neutrophilic dermatoses (pyoderma gangrenosum, Sweet's syndrome). Dermatol Ther. 2011 Mar-Apr;24(2):273-84. [PMID: 21410617]

Item 42 Answer: C

Educational Objective: Diagnose eosinophilic pustular folliculitis.

This patient has eosinophilic pustular folliculitis, a rash most commonly seen in patients with HIV infection, and usually in those with a CD4 cell count less than 300/μL. The lesions are typically intensely pruritic papules (and rarely pustules) clustered on the chest and face, generally in areas with a high concentration of sebaceous glands. Biopsy will reveal an eosinophilic infiltrate in the hair follicle, and peripheral eosinophilia may develop in up to 50% of patients. The exact etiology is unknown, but the condition is relatively common. Diagnosis is usually based on the presence of the typical skin rash in an appropriate clinical context. The rash usually responds to antiretroviral therapy, although high-potency glucocorticoids and systemic antihistamines may be used for symptomatic treatment.

Acne is characterized by comedonal lesions (plugged pores, blackheads) and, when drug induced, often involves the shoulders and back; this patient is not taking any drugs typically associated with drug-induced acne (glucocorticoids, bromides, lithium, certain oncologic agents [particularly epidermal growth factor-receptor antagonists], and more).

Drug reaction with eosinophilia and systemic symptoms (DRESS), also referred to as drug-induced hypersensitivity syndrome, would appear within 2 to 8 weeks of starting a new drug and would include fevers, a widespread morbilliform eruption often involving the face accompanied by facial edema, complete blood count abnormalities (eosinophilia or

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atypical lymphocytosis), and systemic inflammation (generally lymphadenopathy and hepatitis, although nephritis, pneumonitis, and myocarditis can occur). This patient lacks the fever and systemic symptoms of DRESS, and the rash would be atypical for this diagnosis.

Scabies can also cause intense pruritus and eosinophilia. However, patients rarely have lesions above the neck and generally have involvement of the finger web spaces, umbilicus, and, in men, the genitals.

KEY POINT

- Eosinophilic pustular folliculitis causes intensely pruritic papules on the face and chest and is most commonly seen in patients with HIV infection, generally with a CD4 cell count less than 300/μL.

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Nervi SJ, Schwartz RA, Dmochowski M. Eosinophilic pustular folliculitis: a 40 year retrospect. J Am Acad Dermatol. 2006 Aug;55(2):285-9. [PMID: 16844513]

Item 43 Answer: A

Educational Objective: Manage a superficial skin infection.

The most appropriate first step in management is to culture a pustule to identify the causative organism prior to institution of antibiotic therapy. Bacterial skin infections are most commonly caused by *Staphylococcus* and *Streptococcus* spp. and may present in a variety of ways. This patient has recurrent folliculitis and furunculosis but is otherwise healthy. The history of recurrent infections and being part of a wrestling team would suggest that infection may be secondary to community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). Community-acquired MRSA, defined as MRSA infections that occurs in the absence of health care exposure, tends to have enhanced virulence compared with other strains and is currently the most common organism causing skin infection requiring medical therapy. However, because of the recurrent nature of the patient's skin infections and his exposure to previous courses of antibiotics, a culture to identify the causative organism and its susceptibility pattern would be the most appropriate next step to guide further management.

In addition to systemic therapy, topical antibiotic therapies, including benzoyl peroxide wash, chlorhexidine, or topical mupirocin, can be used. Bleach baths may be a treatment option (put 1/4 to 1/2 cup of common liquid bleach into the bath water to create a chlorinated bath), which decreases colonization of *S. aureus*).

A Tzanck smear can be performed if a herpes simplex virus or varicella infection is suspected. Both infections can occur in wrestlers but would typically present as painful vesicles or punched-out erosions as opposed to furuncles or folliculitis.

Linezolid is effective against many strains of MRSA and streptococci. However, its use should be limited to patients with a documented infection who have not benefitted from sensitive antibiotics because of potential toxicities or cost. Oral cephalexin (or other cephalosporins or penicillins) should not be used because these antibiotics would not be effective against MRSA if used empirically. In addition, antimicrobial therapy in this patient would more appropriately be guided by culture and sensitivity results.

Parenteral therapy for skin and soft-tissue infections should be considered in patients with extensive involvement, in patients with evidence of systemic involvement, or patients who are immunocompromised. Although vancomycin is effective against possible MRSA, parenteral therapy would not be appropriate in a stable, otherwise healthy man without any signs of systemic infection, particularly without a confirmed MRSA infection.

KEY POINT

- In managing a superficial skin infection, a culture of the pustule is important to determine both the causative organism and the antibiotic susceptibility pattern.

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Item 44 Answer: B

Educational Objective: Recognize livedo reticularis.

The patient has livedo reticularis, and her clinical presentation is consistent with the antiphospholipid antibody syndrome. Livedo reticularis is a subtle, lacy network of faintly blue or purple vessels, usually seen on the lower legs, caused by the prominence of the vasculature under the skin. It is a very nonspecific finding and is most often seen in patients without an underlying condition. Livedo reticularis can sometimes be elicited by keeping a leg in the dependent position; if livedo resolves when the leg is straightened horizontally, it is likely not a pathologic process. However, it can also be a component of a variety of systemic diseases, typically those that cause a slow-flow or hypercoagulable state. Associated conditions include autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis), vasculitis (polyarteritis nodosa, giant cell arteritis), paraproteinemias (multiple myeloma, cryoglobulinemia), hematologic diseases (polycythemia vera, thrombocytosis), and infections. Livedo reticularis also has a strong association with the antiphospholipid antibody syndrome, and there is evidence that its presence suggests increased risk of cerebral or ocular ischemia. This patient's livedo reticularis and history of prior miscarriages are suggestive of antiphospholipid antibody syndrome. According to the revised Sapporo criterion, a diagnosis of antiphospholipid antibody syndrome requires at least one clinical criteria (vascular thrombosis excluding superficial venous thrombosis or pregnancy morbidity) and at least one laboratory criterion (the presence of antiphospholipid antibodies on two or more occasions at least 12 weeks apart).

Amyloidosis is an infiltrative disease that causes skin thickening and is more often associated with development

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of petechiae and ecchymoses than with changes consistent with livedo reticularis.

Autoimmune thyroid disease, particularly Graves disease, may uncommonly be associated with pretibial myxedema, an accumulation of glycosaminoglycans in the dermis, usually over the lower legs. This patient's clinical findings are not consistent with this diagnosis.

Systemic sclerosis involves excessive production of extracellular matrix with increased collagen production resulting in skin thickening. Livedo reticularis is not a common manifestation of this disorder.

KEY POINT

- Antiphospholipid antibody testing should be performed in persons with fixed livedo reticularis that persists despite position and temperature changes, or those with signs, symptoms, or history suggestive of thromboses.

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Item 45 Answer: D

Educational Objective: Diagnose seborrheic keratosis.

This patient's lesion is a seborrheic keratosis. Seborrheic keratoses are benign skin lesions that commonly occur in older persons. They typically have a waxy or scaly texture and often have a "stuck-on" appearance. They are usually oval and brown and may occasionally itch or bleed.

Dermatofibromas are benign firm brown or reddish papules that most commonly occur on the lower extremities. They generally lack the scale seen with seborrheic keratoses. They extend deeper into the skin than seborrheic keratoses and exhibit the "dimple sign" when squeezed.

Malignant melanomas may occasionally resemble seborrheic keratoses, and thus lesions that are questionable should be removed and sent for histologic evaluation. Although some features of seborrheic keratoses may be suggestive of malignant melanoma, such as elevations above the skin and inconsistent coloration, melanomas tend to progress more rapidly, are darker in color, have more blurred borders, and lack the scaly "stuck-on" appearance characteristic of seborrheic keratoses.

Pigmented basal cell carcinomas may mimic seborrheic keratoses, but they tend to be more translucent and less scaly.

Solar lentigines ("liver spots") are flat brown macules that occur on sun-exposed skin of older persons, particularly the face and dorsal hands rather than the trunk. They resemble large freckles.

KEY POINT

- Seborrheic keratoses are benign skin lesions commonly occurring in older persons; they typically have a waxy or scaly texture with a "stuck-on" appearance.

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Noiles K, Vender R. Are all seborrheic keratoses benign? Review of the typical lesion and its variants. J Cutan Med Surg. 2008 Sep-Oct;12(5):203-10. [PMID: 18845088]

Item 46 Answer: B

Educational Objective: Manage a patient with acute urticaria.

The most appropriate therapy for this patient is a second-generation H_1 antihistamine, such as cetirizine. He has acute urticaria, characterized by evanescent red, pruritic plaques and wheals that last less than 24 hours after a probable viral upper respiratory tract infection. Newer-generation H_1 antihistamines are preferred to first-generation agents (diphenhydramine, hydroxyzine) primarily because they are long-acting and are more likely to suppress the urticaria consistently. They also do not readily cross the blood-brain barrier and therefore have less sedating and anticholinergic side effects that may be dose-limiting in some patients.

Amoxicillin can be used if there is concern for a bacterial infection, but the clinical history of nonpurulent cough, rhinitis, and self-resolution is not consistent with a bacterial infection.

Glucocorticoids, such as prednisone, are effective therapy for urticaria, but have considerable systemic side effects. Although their use may be appropriate in patients with angioedema, antihistamines are the preferred initial treatment option owing to their effectiveness and safer side-effect profile.

Ranitidine is an H_2 antihistamine used primarily for gastric acid suppression and would not be appropriate antihistamine monotherapy for this patient. The combination of an H_1 and H_2 antihistamine is often used, particularly in patients with severe urticaria, although there is limited evidence of effectiveness of this practice.

KEY POINT

- Treatment of urticaria is most effective with long-acting antihistamines since they help treat active disease and prevent new flares.

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Item 47 Answer: B

Educational Objective: Treat seborrheic dermatitis.

This patient should be treated with ketoconazole cream. Scaling and redness, specifically on the eyebrows, nasolabial folds, and sides of the chin, are characteristic of seborrheic dermatitis. The redness and scaling are a response to commensal yeasts in the skin, and topical ketoconazole targets these yeasts. Patients may believe that their skin findings are due to dry skin on the face. However, the redness of the eyebrows and nasolabial folds extending onto the cheeks and chin with

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scaling is typical of seborrhea and often does not respond to moisturization only.

Benzoyl peroxide is approved for treatment of acne vulgaris, which is characterized by open and closed comedones and inflammatory lesions, but not the redness and scaling associated with seborrheic dermatitis.

Metronidazole is used to treat rosacea, which usually presents with flushing and central facial erythema, telangiectasias, papules, and pustules but not typically with scaling.

Mupirocin is a topical antibiotic that targets gram-positive organisms, but there are no pustules, crusting, bullae, or erosions that would be diagnostic of impetigo in this patient.

Triamcinolone would decrease the inflammatory response and redness of seborrheic dermatitis but is too potent to be used consistently on the face.

KEY POINT

- The redness and scaling of seborrheic dermatitis are a response to commensal yeasts in the skin, and topical ketoconazole targets these yeasts.

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Item 48 Answer: B

Educational Objective: Diagnose basal cell carcinoma.

This patient has basal cell carcinoma (BCC), the most common type of skin cancer. BCC typically presents as translucent ("pearly") telangiectatic papules on sun-exposed areas in fair-skinned persons with a history of extensive sun exposure. It is usually asymptomatic and enlarges slowly over time. Although it rarely metastasizes, BCC can cause significant local tissue destruction if not removed in a timely fashion. BCC has a wide variety of morphologies, some of which can be challenging diagnostically.

Angiofibromas (fibrous papules of the nose) are common solitary lesions that are often seen in patients with rosacea. They tend to be flesh colored, lack pearliness or telangiectasias, and are stable in size and appearance over time.

Sebaceous hyperplasia present as small papules found on the face in patients with rosacea. They often have a central umbilication, which is a characteristic feature. They lack the pearliness seen in BCC, have less prominent telangiectasias, and often have a yellowish color.

Squamous cell carcinoma (SCC) may resemble BCC in many aspects; however, SCC tends to be much scalier, lack the pearliness seen in BCC, and have less prominent telangiectasias. It also tends to grow more rapidly than BCC.

KEY POINT

- Basal cell carcinoma presents as asymptomatic translucent telangiectatic papules on sun-exposed areas in fair-skinned patients; extensive tissue damage may occur if not removed.

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Rubin AI, Chen EH, Ratner D. Basal cell carcinoma. N Engl J Med 2005 Nov 24;353(21):2262-9. [PMID: 16306523]

Item 49 Answer: A

Educational Objective: Treat mild acne in a pregnant woman.

This woman should be treated with azelaic acid cream. Women of childbearing age need special consideration, as treatment of some of the most common diseases, including acne, involves the use of teratogenic medications. The FDA pregnancy safety category of all medications should be considered when prescribing to women who are pregnant, breastfeeding, or trying to conceive. Several commonly used systemic and some topical dermatologic drugs are contraindicated for use in pregnancy. Azelaic acid cream is rated pregnancy category B and is the safest of the listed acne therapies. Acne is a chronic inflammatory skin condition characterized by open and closed comedones (blackheads and whiteheads, respectively) and inflammatory lesions, including papules, pustules, or nodules. Androgens stimulate increased sebum production, so pregnancy-associated hyperactivity of the hypothalamic–pituitary–gonadal axis can trigger acne exacerbations. This patient has mild comedonal and inflammatory acne, and topical treatment is preferred; however, it is important to consider the safety of topical acne treatments during pregnancy. Topical erythromycin can also be used to manage acne, since it is a pregnancy category B medication.

Doxycycline is rated pregnancy category D and can cause defects in the formation of teeth and bone in the fetus. Both tazarotene and tretinoin are topical retinoids and have been rated as pregnancy category X and D, respectively. They should not be used during pregnancy.

KEY POINT

- Azelaic acid cream is rated FDA pregnancy category B and is safe to use for mild comedonal and inflammatory acne during pregnancy.

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Item 50 Answer: B

Educational Objective: Diagnose herpes simplex virus infection.

This patient has a herpes simplex virus (HSV) infection, and direct-fluorescent antibody testing (DFA) should be performed. The patient is immunocompromised due to HIV infection, and establishing the diagnosis is important in these patients. Although the diagnosis of HSV infection can often be made clinically, ancillary tests are available to confirm the diagnosis. Of these, DFA and polymerase chain

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reaction (PCR) are tests that can be rapidly completed (in less than 24 hours). They are also able differentiate between the various types of herpesvirus infections: HSV1, HSV2, and varicella infection. DFA and PCR are done by unroofing a vesicle and swabbing the base of the vesicle to provide an adequate sample.

Bacterial culture is incorrect as the lips are often contaminated with bacteria, given the presence of multiple bacteria in oral flora. In addition, the patient's lesions do not have honey-colored crust, suggesting that these are not impetiginized. Performing serologic testing (HSV IgG) is not recommended to diagnose herpes virus infections, as the seroprevalence for both HSV1 and HSV2 is high, and a positive result is not indicative of active infection.

Viral culture had been considered the gold standard in the past, but it can take over 48 hours (sometimes up to 1 week) for results to return. Culture is useful if resistance testing is necessary for recalcitrant infections. However, the recommended initial tests are now DFA and PCR to help establish or confirm the diagnosis.

KEY POINT

- Although diagnosis of herpes simplex virus (HSV) infections can be made clinically, direct-fluorescent antibody and polymerase chain reaction testing can provide results in less than 24 hours and can differentiate between HSV1, HSV2, and varicella infections, which is important when treating immunocompromised patients.

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Item 51 Answer: C

Educational Objective: Diagnose miliaria.

This patient's rash is consistent with a diagnosis of miliaria crystallina. Miliaria, or "heat rash," is characterized by the eruption of fine red papules and pustules specifically located on the back, typically after immobilization in the supine position. Miliaria is caused by superficial clogging of the eccrine sweat glands, which leads to the development of minute pustules that rupture easily and can be wiped off. The clogging may be partially due to overgrowth of *Staphylococcus epidermidis*. Treatment involves implementing measures to decrease sweating and topical measures such cool baths and the use of loose clothing.

Allergic contact dermatitis on the back would appear as an eczematous dermatitis with pruritus on the area exposed to the allergen. This patient does not have pruritus or clinical findings consistent with an allergic contact dermatitis.

Candida albicans infections occur in hot, moist occluded areas, such as the armpits, groin, and beneath the breasts. The rash is not usually diffuse and will typically have some desquamation at the edges. The papules cannot be wiped off as with miliaria crystallina.

Staphylococcal folliculitis will cause more deep-seated follicular pustules, and the area would be red, swollen, and painful. Although *Staphylococcus aureus* is responsible for a wide range of skin infections such as folliculitis, abscesses, furuncles, carbuncles, impetigo, cellulitis, ecthyma, staphylococcal scalded skin syndrome, and erysipelas, this patient's clinical presentation is not consistent with an infection with this organism.

KEY POINT

- Miliaria, or "heat rash," is characterized by the eruption of fine red papules and pustules specifically located on the back, typically after immobilization in the supine position.

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Haas N, Martens F, Henz BM. Miliaria crystallina in an intensive care setting. Clin Exp Dermatol. 2004 Jan;29(1):32-4. [PMID: 14723716]

Item 52 Answer: C

Educational Objective: Manage arterial ulcers.

This patient has an arterial ulcer, and determination of the ankle-brachial index would be the next appropriate step in management. Arterial ulcers occur in the setting of significant peripheral vascular disease and result from inadequate perfusion of the lower extremities. Ulceration tends to occur at the distal aspects of the arterial supply (such as the distal toes) or in areas of trauma (such as overlying the metatarsal heads or shins and ankles). The ulcers are usually tender, have a well-demarcated border with a "punched out" appearance, and are surrounded by erythematous, tight skin. Dry, shiny skin is often present, and elevation of the legs often results in worsening pain. Changes consistent with venous stasis, such as stasis dermatitis and lipodermatosclerosis, are usually lacking. The presence of peripheral vascular disease may be suggested by a decreased ankle-brachial index, with a value less than or equal to 0.9 suggestive of significant arterial occlusion. If the ankle-brachial index is decreased in this patient, lower extremity Doppler ultrasound arterial studies are indicated to confirm impaired arterial flow as a cause of the ulceration. If significant arterial compromise is found, referral to a vascular surgeon is indicated for consideration of a revascularization procedure.

Biopsy is not useful for distinguishing between venous stasis ulcers and arterial ulcers, although it can be useful to rule out other causes of ulceration such as infection or malignancy. Skin biopsy in the setting of arterial insufficiency can lead to an enlargement of the ulcer and thus should be performed with caution.

External compression, a mainstay of treatment for venous stasis ulcers, is contraindicated for arterial ulcers as it may further interfere with perfusion. As venous stasis and arterial insufficiency may sometimes coexist, vascular studies should be considered prior to starting compression

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therapy for venous stasis if there is significant concern for the presence of arterial disease.

Oral antibiotics are useful when overt signs of infection are present; however, they are not indicated otherwise. Common signs of infection include purulent discharge, swelling, and increasing tenderness. Overuse of antibiotics has been shown to lead to the development of resistant bacteria, a situation that is particularly problematic in the setting of chronic wounds.

KEY POINT

- Determination of the ankle-brachial index (ABI) is helpful in diagnosing suspected arterial insufficiency.

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Item 53 Answer: B

Educational Objective: Treat cutaneous larva migrans.

This patient has cutaneous larva migrans, and the most appropriate treatment is oral ivermectin. Cutaneous larva migrans (creeping eruption) is a parasitic skin disease caused by migration of the hookworm larvae within the superficial layers of the skin. It presents as a pruritic serpiginous, linear, or arciform red plaque that migrates at a rate of a few millimeters to centimeters per day and represents a hypersensitivity reaction to the hookworm, most commonly *Ancylostoma braziliense*. The clinical appearance of a migratory pruritic plaque after exposure to a beach is characteristic of cutaneous larva migrans. Although cutaneous larva migrans can be self-limited, treatment with oral ivermectin (or albendazole) is the medication of choice.

Oral cephalexin is an antibiotic that is used for bacterial skin infections, which may occur secondarily in patients with cutaneous larva migrans at times, but the lack of honey- or yellow-colored crust and surrounding erythema in this patient make a bacterial infection unlikely.

Oral prednisone may be helpful for the symptoms associated with cutaneous larva migrans, but it is not necessary or first-line treatment (topical glucocorticoids can be used for severe pruritus); oral prednisone would be the treatment of choice for allergic contact dermatitis, which can be geometric (rectangular, circular, even serpiginous) in shape, but should not migrate.

Terbinafine is the treatment of choice for dermatophyte infections, such as tinea pedis, which presents on the feet and ankles. Dermatophyte infections can be annular in appearance but differ from the clinical picture here in that it usually has superficial scale in a "moccasin" distribution or annular configuration, maceration between the web spaces and does not migrate. It would not be effective against this parasitic infection.

KEY POINT

- Although cutaneous larva migrans can be self-limited, oral antiparasitic agents (ivermectin as the preferred agent or albendazole as an alternative) can help resolve the eruption.

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Item 54 Answer: A

Educational Objective: Recognize the prognostic features of malignant melanoma.

The depth of invasion (Breslow depth) of a melanoma is the most important prognostic feature and correlates most strongly with the risk of recurrence and metastasis. The 2009 American Joint Committee on Cancer (AJCC) staging system defines the primary tumor stage based on the Breslow depth, with 10-year survival rate decreasing progressively with increasing depth.

Other features have also been identified as secondary negative prognostic indicators, including an elevated mitotic rate (defined as more that 1 mitotic figure per mm^2) and the presence of ulceration. The presence or absence of these two factors are used to subdivide the tumor stages based on depth into further prognostic categories

The radial diameter of the lesion has not been found to correlate with prognosis; many melanomas are quite wide, and yet if they have not developed an invasion component, the risk of metastasis is very small.

KEY POINT

- The Breslow depth (or depth of invasion) of a melanoma is the most important prognostic feature and correlates most strongly with the risk of recurrence and metastasis.

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Item 55 Answer: E

Educational Objective: Manage a patient with acute urticaria.

No further diagnostic evaluation is indicated for this patient. This patient has urticaria, which affects up to 20% of the adult population at some point in time. She presents with red wheals and urticarial plaques on the trunk that appear and disappear. In addition to the rings, urticarial lesions are often in arcuate forms with "C" and "S" shapes. The lesions also last less than 24 hours, which is typical for urticaria. Common causes include infections, allergic reactions to medications,

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foods, or insect exposure (stings and bites), and nonallergic responses to medications (such as opioids or NSAIDs). Skin lesions in urticaria are characterized by erythematous papules and plaques that are pruritic and transient with no associated systemic symptoms. Acute urticaria is defined as being of less than 6 weeks' duration. The history should focus on the severity of the reaction (such as the presence of angioedema or anaphylaxis), identification of a potential trigger, and whether there is evidence of an underlying systemic disorder associated with urticaria. The physical examination should confirm the presence of urticaria and evaluate for evidence of angioedema or other systemic involvement. In patients with uncomplicated acute urticaria, laboratory studies are almost always normal, and no further diagnostic evaluation is required in most patients before initiating therapy, if needed.

Although infections, liver or kidney disease, thyroid dysfunction, and lymphoma have been associated with urticaria, in a healthy patient with a negative review of systems and normal physical examination, further diagnostic evaluation for an underlying cause is not generally indicated.

Food allergies can present with urticaria, but unless there is consistent ingestion of the food on a daily basis, the urticaria should not be consistent for 1 week. Testing for other allergic causes may be appropriate for confirmation if there is a clearly identifiable trigger or for refractory urticaria believed to be allergic in nature; however, allergy testing is not indicated for acute, uncomplicated urticaria.

KEY POINT

- In patients with uncomplicated acute urticaria, laboratory studies are almost always normal, and no further diagnostic evaluation is required in most patients before initiating therapy, if needed.

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Item 56 Answer: C

Educational Objective: Diagnose subungual melanoma.

This patient has melanonychia, and she requires a nail matrix biopsy. Melanonychia refers to a brown or black discoloration of the nail plate. It is a common normal variant in persons with darker skin types, but it may also occur as a result of systemic disease, medication, infection, or an underlying melanocytic lesion. Typically, multiple nails are affected. A single nail with longitudinal melanonychia is suggestive of an underlying melanocytic lesion. In this setting, it is important to rule out subungual melanoma. Clinical signs of subungual melanoma include Hutchinson sign (pigmentation expanding onto the proximal nail fold) and a wider diameter of the longitudinal pigment stripe proximally as compared with distally (indicative of an expanding underlying pigmented lesion in the nail matrix). Subungual melanoma may also present as diffuse nail discoloration and is often initially misdiagnosed as onychomycosis or subungual hematoma. Although rare in patients with fair skin, subungual acral lentiginous melanoma is the most common type of melanoma in Asian and black patients.

Onychomycosis is the result of dermatophytes invading the nail plate and causing thickening and discoloration. The diagnosis of onychomycosis can be confirmed by potassium hydroxide (KOH) examination of the nail, a fungal culture, or by histologic examination of the nail clippings. The finding of a pigmented linear streak is not consistent with the diagnosis of onychomycosis, and these studies are not indicated.

A culture of the nail clipping is not appropriate because the nail plate changes are not consistent with an infection such as onychomycosis.

Histopathologic examination of the nail clipping is not sufficient to determine the presence or absence of a melanoma since other disorders can cause pigment deposition in the nail plate. Observation is not appropriate in this situation, since a delay in diagnosis can have potentially serious consequences.

KEY POINT

- A single nail with longitudinal melanonychia is suggestive of an underlying melanocytic lesion that should be evaluated with a nail matrix biopsy.

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Item 57 Answer: A

Educational Objective: Diagnose bullous pemphigoid.

This patient has bullous pemphigoid. Bullous pemphigoid is a chronic autoimmune blistering disease that predominantly affects older patients and presents with urticarial plaques with tense bullae often on the trunk and upper legs. Mucosal involvement can occur in 10% to 40% of patients. Associated peripheral eosinophilia also is common. Microscopic examination of a blistering lesion usually reveals the presence of eosinophils with the separation of tissue layers subepidermally causing tense bullae (as opposed to an intraepidermal blister that causes more flaccid bullae seen in pemphigus). Bullous pemphigoid is caused by autoantibodies directed against collagen XVII, which is bullous pemphigoid antigen 180 (BP180); direct immunofluorescence shows linear IgG deposition at the basement membrane zone.

Pemphigus foliaceus is a chronic autoimmune blistering disorder with autoantibodies against desmoglein 1. It results in very superficial intraepidermal, flaccid bullae, which are often easily ruptured, as opposed to the tense bullae in bullous pemphigoid. The lesions in pemphigus foliaceus often present as superficial erosions with a "corn flake"-like crust, as opposed to bullae. Mucosal involvement is also uncommon.

Pemphigus vulgaris is a chronic autoimmune blistering disorder that has autoantibodies predominantly against desmoglein 3, also resulting in flaccid bullae with mucous membrane involvement.

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Toxic epidermal necrolysis is a severe medication reaction that results in fever, painful skin desquamation, and more than two mucosal surfaces that slough. It is not an autoimmune blistering disorder and would be unusual to present with pruritic edematous plaques.

KEY POINT

- Bullous pemphigoid is a chronic autoimmune blistering disease that predominantly affects elderly patients and presents with urticarial plaques with tense bullae often on the trunk and upper legs.

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Item 58 Answer: C

Educational Objective: Recognize striae and atrophy from potent topical glucocorticoids.

This patient has striae distensae or stretch marks. The groin is a common area for developing stretch marks, and one of the main risks of topical glucocorticoids is the development of striae. Potential cutaneous complications associated with the use of topical glucocorticoids include thinning of the skin, development of striae, development of purpura, pigmentary changes (hypo- or hyperpigmentation), acneiform eruptions, and increased risk of infections. The risk increases when glucocorticoids are used for prolonged periods, are applied under occlusion or in skin folds where there is natural occlusion, or when high-potency glucocorticoids are applied to areas of thin skin, as in this patient. This patient was appropriately prescribed potent topical glucocorticoids for the control of his plaque psoriasis on his elbows and knees, but potent glucocorticoids are too strong for the groin and can rapidly lead to striae and atrophy.

Contact dermatitis typically has a geometric pattern in response to the area of contact with an allergen, and not along lines of stress as in this patient. Additionally, the skin is more edematous and often weeps serous fluid, and the area is intensely pruritic.

Inverse psoriasis refers to psoriatic changes occurring in intertriginous areas (as opposed to its more usual presence on extensor surfaces) where it can appear somewhat atypical, often lacking the characteristic surface scale because of the moistness of the skin creases. Inverse psoriasis results in broad areas of erythema confluent through the skin folds.

Tinea cruris presents as broad patches of erythema with fine scale (most often at the edges) and usually has a macerated appearance deep in the skin creases.

KEY POINT

- Prolonged use of topical glucocorticoids in areas of thin, moist, occluded skin can lead to striae and atrophy.

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Item 59 Answer: D

Educational Objective: Manage severe, recalcitrant acne vulgaris.

This patient has recalcitrant nodulocystic acne, and the most appropriate next step in therapy is to discontinue his current medications and start oral isotretinoin. Acne is a chronic inflammatory skin condition characterized by open and closed comedones (blackheads and whiteheads, respectively) and inflammatory lesions, including papules, pustules, or nodules. Patients with severe acne can develop large, painful cysts; nodules; and interconnecting sinus tracts on the face, neck, and trunk. It is important to treat this disease aggressively as it can cause permanent scarring that can be disfiguring. Isotretinoin is an oral retinoid that is extremely effective in treating severe nodular acne. However, it is associated with significant side effects, including teratogenicity, mucocutaneous effects (cheilitis, pruritus, photosensitivity, or desquamation), skin thinning, myalgia, liver toxicity, and hyperlipidemia. Because of this, its use is limited to patients with recalcitrant disease. When used in women of childbearing age, prescribers and patients must participate in an FDA-mandated risk management program to minimize the risk of possible fetal exposure to isotretinoin. This patient has severe nodular acne that has been recalcitrant to oral antibiotic treatment; therefore, isotretinoin is an appropriate next step in treatment. In some patients, isotretinoin may be used as first-line treatment for severe, nodulocystic acne, and may also be appropriate for treatment of less severe inflammatory acne that is recalcitrant to multimodality therapy with topical retinoids and oral antibiotics.

Topical metronidazole is first-line therapy for rosacea; however severe nodular acne is usually treated initially with systemic antibiotics. It is important to educate patients that antibiotic treatments often take 6 to 8 weeks to demonstrate an effect. This patient has been on an oral antibiotic for 6 months and continues to have severe acne on his face and neck.

A change to an alternative topical retinoid (such as tazarotene) or another oral antibiotic (such as minocycline) is not expected to dramatically improve his acne. In addition, guidelines recommend that the duration of oral antibiotic therapy be limited; specifically, oral antibiotics should be used for 3 months and the patient reassessed for response. For patients who respond, antibiotics are discontinued.

KEY POINT

- Isotretinoin is first-line treatment for severe, nodulocystic acne and for inflammatory acne that is recalcitrant to multimodality therapy with topical retinoids and oral antibiotics.

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Item 60 Answer: D

Educational Objective: Diagnose porphyria cutanea tarda.

This patient has porphyria cutanea tarda (PCT). PCT is a rare skin disease that typically occurs in the setting of underlying liver disease, which in this patient is likely due to heavy alcohol use. It may also develop in patients with chronic hepatitis C infection and hemochromatosis. PCT is caused by decreased activity of hepatic uroporphyrinogen decarboxylase, an enzyme in the heme biosynthesis pathway that leads to accumulation of porphyrins in the tissues. Only 20% of cases of PCT are due to inherited enzyme mutations, the remainder is acquired. The acquired forms appear to be related to increased oxidative stress in hepatocytes, possibly associated with iron deposition, although the exact mechanisms of decreased enzyme activity have not been elucidated. Patients with PCT often have darkening of the skin, hypertrichosis, and fragility of the skin, particularly in sun-exposed and frequently traumatized areas, such as the dorsal hands. Numerous scars and small milia (tiny proteinaceous cysts) are often seen on the dorsal hands; intact blisters are rare, but often exist transiently before being spontaneously ruptured following mild trauma.

Allergic contact dermatitis may lead to blisters, but not scarring or milia, and there is no history to suggest an environmental trigger in this patient. The lesions of contact dermatitis typically will be sharply demarcated and geometric in appearance, corresponding to the area affected by the causative agent.

Bullous lupus erythematosus is a rare form of cutaneus lupus in which patients develop small blisters within and in addition to their other cutaneous lupus lesions; the blisters are generally small and often rupture with some residual dyspigmentation and scarring. Signs of systemic lupus erythematosus should be present when making a diagnosis of bullous lupus erythematosus.

Bullous pemphigoid is an autoimmune blistering disease common in the elderly that presents with urticarial plaques and tense, intact bullae; there is no association with liver disease.

KEY POINT

- Porphyria cutanea tarda, which may develop from extensive alcohol use, hemochromatosis, or hepatitis C virus infection, presents with skin fragility and small, transient, easily ruptured vesicles in sun-exposed areas such as on the hands.

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Item 61 Answer: C

Educational Objective: Manage urticarial vasculitis.

This patient's presentation is suggestive of urticarial vasculitis, and a skin biopsy is indicated. He has an urticarial eruption with joint pain and low-grade fevers suggesting systemic inflammation. Typical urticarial wheals last for less than 24 hours (with individual lesions lasting only a few hours), resolve without cutaneous sequelae, and are pruritic and not painful. In contrast, this patient has painful wheals that last for more than 24 hours and leave bruise-like changes when they resolve, which is atypical for usual urticaria, and is characteristic of urticarial vasculitis. Patients with urticarial vasculitis may have an underlying autoimmune disease, most often lupus erythematosus, but even in the absence of an associated autoimmune disease, patients with urticarial vasculitis (particularly hypocomplementemic urticarial vasculitis) are at risk of multisystem disease, including nephritis. A skin biopsy is important in making the diagnosis, and guiding further work-up and treatment.

A gluten-free diet is unlikely to have any impact on urticarial vasculitis, and only rarely will gluten intake impact urticarial skin conditions. Gluten avoidance is important in patients with dermatitis herpetiformis, which is often associated with insensitivity to gluten.

Radioallergosorbent testing (RAST) may be appropriate in patients with a typical urticarial eruption from a likely food or environmental trigger; however, this patient is presenting with atypical urticarial lesions with signs and symptoms concerning for urticarial vasculitis. RAST plays no role in the diagnosis of urticarial vasculitis.

Thyroid function testing is indicated in the evaluation of chronic urticaria in which patients have regular episodes of typical urticaria over a period of more than 6 weeks. Because of the atypical presentation of this patient's wheals and the lack of clinical findings suggestive of thyroid disease, testing would not be the most appropriate next step.

KEY POINT

- In contrast to typical urticaria, urticarial vasculitis presents with painful wheals that last for more than 24 hours and leave bruise-like changes behind.

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Item 62 Answer: D

Educational Objective: Diagnose stasis dermatitis.

This patient has stasis dermatitis. Stasis dermatitis, especially in the acute setting, can present with brightly erythematous, edematous plaques, as shown in the figure, that are tender to palpation and can be slightly warm to touch. Overlying scale and serum crust also can develop as a consequence of fluctuating edema (as seen in the figure). Differentiating

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stasis dermatitis from cellulitis can be difficult; however, the presence of similar-appearing erythematous plaques bilaterally in an afebrile patient with no lymphadenopathy or other symptoms or signs of infection would be unusual for cellulitis. Because stasis dermatitis usually results from decreased venous drainage or excess fluid in dependent areas causing increased vascular permeability and stretching of the skin, the clinical scenario of a patient with heart failure who has recently stopped taking a diuretic also is supportive of a diagnosis of stasis dermatitis. Chronic stasis dermatitis will cause more brown discoloration, suggesting a longer term process, but acute stasis dermatitis can present as bright red patches/plaques. Treatment typically includes optimization of volume status or external compression stockings to decrease fluid volume and skin stretching in dependent areas.

Cellulitis presents as a painful, erythematous, well-demarcated patch that is warm to touch. The presence of fever, lymphadenopathy, or other evidence of infection, such as an elevated leukocyte count, also would suggest this diagnosis. It is important to consider alternative diagnoses when there are erythematous patches on both legs.

Contact dermatitis may present with localized inflammation at the site of exposure to an irritant and may cause erythema and edema. However, it is often pruritic and may be accompanied by bullae and oozing. Contact dermatitis may also be preceded by a history of application of a sensitizing agent in the area.

Deep venous thrombosis can present as a swollen, erythematous leg. Although bilateral deep venous thromboses can occur, this is a less likely cause in this patient.

KEY POINT

- Stasis dermatitis is sometimes confused with cellulitis; however, patients with stasis dermatitis will have no leukocytosis or lymphadenopathy and will be afebrile.

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Item 63 Answer: C

Educational Objective: Diagnose *Staphylococcus aureus* infection of atopic dermatitis.

This patient has atopic dermatitis with new pustules typical for a *Staphylococcus aureus* infection. Staphylococcal colonization is very common, being present at the site of skin involvement in almost all patients with atopic dermatitis. Scratching of the skin and breakdown of the skin barrier are conducive to infection, and this is a common occurrence in patients with atopic dermatitis. However, efforts to identify or eradicate the organisms causing the colonization have not been shown to decrease the risk of infection. Therefore, routine skin or nasal swab testing or decolonization procedures for *S. aureus* are not recommended in these patients, although these procedures may be helpful in selected patients in whom there is recurrent infection or failure of an infection to respond to antimicrobial therapy. Most *S. aureus* infections may be treated with a topical antibiotic such as mupirocin, with more extensive infections requiring systemic antibiotic therapy.

Herpes simplex virus can superinfect atopic dermatitis (eczema herpeticum), but typically presents with painful groups of vesicles on an erythematous base, "punched-out" erosions, and hemorrhagic crusting. Intact herpetic vesicles may transition to pustules and may be difficult to distinguish from a staphylococcal infection. A viral cause should be suspected in a patient with superinfected atopic dermatitis who does not respond to appropriate antibiotic therapy.

Soap allergy can lead to widespread eczematous dermatitis with pruritus and edema. It would appear on the exposed area and would not be localized just to the areas of atopic dermatitis. Soap allergy also presents with vesicles or bullae, not pustules.

Although topical glucocorticoids are associated with multiple potential side effects, including skin thinning, purpura, and changes in pigmentation, their use is not directly associated with the occurrence of staphylococcal infection. Glucocorticoids may help reestablish the skin barrier by decreasing the inflammatory response of atopic dermatitis but would not directly cause staphylococcal infection.

KEY POINT

- Atopic dermatitis with new pustules in addition to breakdown of the skin barrier is indicative of *Staphylococcus aureus* infection.

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Item 64 Answer: D

Educational Objective: Treat postinflammatory hyperpigmentation due to acne in a patient with darker skin.

This patient has postinflammatory hyperpigmentation (PIH) resulting from her inflammatory acne papules, and she should be treated with a topical retinoid. The first step in management is to treat her acne, which is the source of the discoloration, rather than initially treating the discoloration with a bleaching cream such as hydroquinone. After any injury to the skin such as inflammation or trauma, dark skin may become hypo- or hyperpigmented. For this reason it is important to advise patients not to pick at their acne, as this can contribute to postinflammatory discoloration. Patients often report "scarring," when in fact there are only postinflammatory changes. The duration of postinflammatory pigmentary changes varies, depending on the location and degree of inflammation. Hyperpigmentation on the lower legs can take several years to fade. Some postinflammatory pigment changes are permanent. Treatment of postinflammatory pigment changes includes treatment of any underlying skin

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inflammation, sun avoidance or sun protection, and consideration of a bleaching cream, such as hydroquinone. Topical retinoids are the standard of care for acne therapy, as they can prevent acne. They should be applied to the entire area affected by acne, not used as a "spot treatment."

This patient has moderate acne with more than a dozen inflammatory papules distributed over her face. A topical antimicrobial agent would not be the first choice in acne management since it has no preventive properties and there are no clinical signs of infection, such as impetiginization of the acne lesions. Topical glucocorticoids would not be a treatment for this patient because they can exacerbate acne.

KEY POINT

- Topical retinoids are the standard therapy for acne and postinflammatory hyperpigmentation, especially when paired with depigmenting agents.

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Item 65 Answer: B

Educational Objective: Treat superficial dermatophyte infections (tinea).

This patient has tinea pedis, which is characterized by superficial scaling in a "moccasin" distribution on the feet, maceration in the toe webs spaces, and often dystrophic toenails corresponding to onychomycosis. The recommended treatment is a topical antifungal agent such as clotrimazole. Other azole-based agents or topical terbinafine (squalene epoxidase inhibitors) may also be used. Over-the-counter and prescription preparations are equally effective in treating tinea pedis. A 2- to 4-week course in conjunction with washing footwear to help remove any fomites also is necessary. Other associated management may include use of foot powder as a drying agent to prevent maceration, avoidance of occlusive footwear, and treating shoes with antifungal powders before being worn.

Topical betamethasone is a topical glucocorticoid that is beneficial in treated eczematous dermatitis. Although it may initially help with the inflammation of tinea pedis, it may result in a florid infection and potentially a pustular eruption known as Majocchi granuloma.

Although FDA approved, clotrimazole-betamethasone combination cream also is not the preferred treatment for dermatophyte infections as it can lead to increased side effects because of the potent topical glucocorticoid. Although this combination of a glucocorticoid and an antifungal agent is commonly prescribed, the combined agents can partially suppress a superficial dermatophyte infection but may ultimately make the infection more severe and deeper, requiring systemic antifungal agents to treat the disease. The use of this combination cream should be avoided because it can lead to treatment failures and skin atrophy related to prolonged topical glucocorticoid use, and has an increased cost compared with topical antifungal agents alone. It can be effective in treating chronic paronychia.

Although topical nystatin is an antifungal medication, it is effective only against *Candida* spp. and is ineffective against other dermatophytes. Tinea pedis is secondary to dermatophytes, not *Candida*, so nystatin should not be used in this patient.

KEY POINT

- Treatment of most superficial dermatophyte infections includes topical antifungal agents such as azole-based preparations or squalene epoxidase inhibitors (terbinafine); over-the-counter preparations are cost-effective options and have good efficacy.

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Item 66 Answer: D

Educational Objective: Diagnose cutaneous vasculitis.

This patient's skin findings are most likely caused by vasculitis of the cutaneous blood vessels. Inflammation of the blood vessels may lead to vascular injury with hemorrhage into the skin. The resulting clinical lesions are described by their size. Petechiae are pinpoint macules (<3 mm in diameter), which are seen most commonly in platelet disorders, while purpura causes more widespread areas of involvement (up to 1 cm in diameter). Ecchymoses are confluent purpuric areas larger than 1 cm in diameter. Vasculitic lesions are nonblanchable, and when vasculitis involves the small cutaneous vessels, they may be palpable, resulting in the characteristic diagnostic finding in cutaneous vasculitis of palpable purpura. Small vessel vasculitis may be idiopathic but may also occur in association with systemic diseases, including infection, sepsis, a more diffuse vasculitic process or autoimmune disorder, medication reactions, or rarely malignancy. Because vasculitic skin findings may reflect a significant underlying disease process, a thorough evaluation is required, particularly in this patient with fever, joint and muscle pain, and possible focal weakness.

Erythema multiforme (EM) is believed to be a cell-mediated immune process that occurs in response to a specific trigger, which is most commonly infectious (and particularly associated with herpes simplex virus infection). EM often manifests as a three-ring target on the palms, and the center of the target can have a dark red or purple appearance; the dusky center may become necrotic and can form a discrete blister or eschar. Lesions range in size from several millimeters to several centimeters. Few to hundreds of lesions develop within several days and are most commonly located on the extensor surfaces of the extremities, particularly the hands and feet. EM, however, does not cause widespread purpura.

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Lichen planus (LP) is an inflammatory skin disorder of unclear etiology that can affect the skin, mucous membranes, scalp, and/or nails. The hallmark lesion of LP is the pruritic, purple, polygonal papule; these papules are usually distributed symmetrically on the wrists, flexural aspects of the arms and legs, lower back, and genitals. A reticulated network of gray-white lines (Wickham striae) may be visible on the surface of the papules. LP does not cause purpura.

Traumatic ecchymosis can cause extensive purpura, especially in older patients who have age-related thinning of the skin and vascular structures and are more likely to take antiplatelet or anticoagulant medications; however, traumatic bruising is more often localized and may have a pattern that suggests the external cause of injury.

KEY POINT

- Purpura and ecchymosis are signs of vascular injury and may be associated with systemic disease including more widespread vasculitis.

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Item 67 Answer: A

Educational Objective: Treat hand dermatitis.

Less frequent washing and application of a thick emollient such as petrolatum are the treatments of choice for this patient. Irritant hand dermatitis often occurs through friction, removal of the protective skin barrier, and irritation from the surfactant properties of the soap in persons who overwash their hands. Overwashing is common in patients with obsessive-compulsive disorder. Irritant dermatitis will be especially marked on the dorsal hands where the stratum corneum is thinner than that of the palms. Topical petrolatum moisturizer is an inexpensive and effective way of repairing the damaged skin barrier by softening the stratum corneum, reducing skin water loss, and helping maintain a barrier to decrease further irritation. The petrolatum moisturizer should be applied several times daily, particularly after hand washing when it is most necessary.

Topical diphenhydramine is an antihistamine but irritant dermatitis is not driven by histamine. Therefore, an antihistamine will not be effective.

Although topical lidocaine may relieve the pain, it will not heal the skin barrier and it should not be applied repeatedly to fissured skin because of possible absorption.

Neomycin is not indicated since this patient does not have an infection. There is no purulence or crusting, and there are no pustules or erosions to indicate bacterial infection.

KEY POINT

- Less frequent handwashing and application of a thick emollient such as petrolatum are the treatments of choice for irritant hand dermatitis caused by overwashing.

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Item 68 Answer: A

Educational Objective: Diagnose drug hypersensitivity syndrome.

This patient most likely has systemic drug hypersensitivity syndrome, otherwise known as drug reaction with eosinophilia and systemic symptoms (DRESS). DRESS is a severe and potentially life-threatening type IV hypersensitivity reaction. Similar to most type IV reactions, onset of the syndrome is delayed, usually occurring 10 days to several weeks after the start of the causative medication. The most common medications that trigger this reaction are sulfonamide antibiotics, allopurinol, and anticonvulsants, but many others have been implicated. In DRESS, patients develop an exanthem rash on the face, trunk, and extremities, and they often have facial edema. Due to systemic inflammation, patients may have fever, lymphadenopathy, and, in severe reactions, hypotension. When these findings occur in a patient being treated with antibiotics, the systemic inflammatory nature of the reaction may make it difficult to differentiate between a response to an antimicrobial agent or inadequate control of the underlying infection, as in this patient. The treatment of DRESS is to stop the suspected medication immediately, switch to another medication that is unlikely to cross-react, and start systemic glucocorticoids, which can reduce systemic inflammation and lower the risk of end-organ damage.

Morbilliform (meaning measles-like) drug exanthems are the most common pattern of a cutaneous drug reaction. This reaction occurs in up to 8% of hospitalized patients and appears 5 to 15 days after exposure to the causative drug. The characteristic findings include erythematous papules coalescing into plaques, often with some pruritus, and no accompanying systemic symptoms. Facial edema, fever, and laboratory abnormalities are not expected.

Stevens-Johnson syndrome (SJS) is an inflammatory reaction with prominent skin findings that is more commonly triggered by medications than infections. Patients may also have flu-like symptoms, and these may precede the onset of the rash. SJS can be differentiated by the presence of mucosal erosions. Patients with SJS have two or more mucosal sites involved, associated with erythema, pain, and often bloody discharge, none of which this patient has. SJS also has different cutaneous findings including annular erythematous plaques that may have purpuric and eroded centers. These are found on the face, trunk, and extremities including the palms and soles, and involve no more than 10% of the body surface area.

Medications can cause a cutaneous or systemic vasculitis; however, the appearance of this patient's skin findings is not consistent with vasculitis. Purpuric or nonblanching

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CONT. erythematous macules, papules, or plaques are indicative of vasculitis.

KEY POINT

- Drug reaction with eosinophilia and systemic symptoms is a systemic drug hypersensitivity reaction that presents with new rash and flu-like symptoms.

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Item 69 Answer: D

Educational Objective: Diagnose psychogenic itch.

This patient has psychogenic itch, which is localized pruritus associated with a concomitant diagnosis (or symptoms of) depression, anxiety, or somatoform disorders. Self-reported depression is present in about 40% of persons with psychogenic pruritus. Most patients are able to identify a precipitating psychological trigger. Patients with psychogenic pruritus excessively pick and scratch normal skin and report constant pruritus. Physical examination findings include linear crusted lesions and hypopigmented scars. It is important to examine patients carefully and completely to avoid missing a dermatologic or systemic cause of itch in those with concomitant psychiatric disorders.

Morbilliform drug eruptions can be pruritic; however, this patient has only secondary skin changes (linear erosions) and does not have a primary finding that would be expected with a drug eruption.

Localized itching with less prominent skin lesions suggests neuropathic pruritus, which results from inflammation or damage to sensory nerves. The most common forms are notalgia paresthetica and brachioradial pruritus. With notalgia paresthetica, there is recurrent and persistent itching on the medial back, usually around the scapula. Brachioradial pruritus causes itching on the extensor forearms, arms, or upper back. The itch in these conditions is often described as burning or stinging, and some patients experience a crawling sensation. The skin is initially normal but may become excoriated, lichenified, and hyperpigmented from recurrent rubbing and scratching. Patients often obtain relief with application of ice, and this may be a distinguishing characteristic.

Patients with generalized pruritus who lack primary skin lesions may have an associated medical condition or internal malignancy. However, hematologic or hepatobiliary malignancies are more likely diagnoses than colorectal adenocarcinomas.

KEY POINT

- Psychogenic itch is localized pruritus associated with a concomitant diagnosis (or symptoms) of depression, anxiety, or somatoform disorders and is typically associated with linear cutaneous lesions and scars.

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Item 70 Answer: A

Educational Objective: Recognize the association of dermatitis herpetiformis with celiac disease.

This patient has dermatitis herpetiformis, which is associated with celiac disease. Dermatitis herpetiformis is a chronic, extremely pruritic autoimmune disorder associated with gluten-sensitive enteropathy, or celiac disease. Although not all patients have gastrointestinal symptoms, nearly 100% of patients will have some underlying abnormality associated with celiac disease. Dermatitis herpetiformis classically presents as extremely pruritic vesicles and papules in a symmetric distribution involving the elbows, knees, buttocks, and scalp. At times, excoriations predominate, and intact vesicles may not be visualized. Although dermatitis herpetiformis is an uncommon skin finding, the association with celiac disease is very high, and the diagnosis should be suspected if the characteristic skin findings are present. Patients with dermatitis herpetiformis are also at risk for other autoimmune conditions, including autoimmune thyroid disease, type 1 diabetes mellitus, and pernicious anemia. There is also a potential association of dermatitis herpetiformis with lymphoma. Treatment is gluten avoidance, although improvement of the rash may occur very slowly over months to years. Dapsone can be used to treat dermatitis herpetiformis and is very effective; however, it can allow persistence of celiac disease, which can result in small bowel lymphoma with chronic inflammation. As a result, dapsone should be used in conjunction with gluten-free diets as first line treatment.

Hepatitis C can occur in association with porphyria cutanea tarda, which presents as vesicles in sun-exposed areas such as the dorsal hands, and resultant milia (small white cysts). Associated hypertrichosis also can be seen.

Non-Hodgkin lymphoma is associated with paraneoplastic pemphigus, which presents as painful oral, conjunctival, or esophageal erosions with associated erythema and blistering on the skin. Paraneoplastic pemphigus always has mucosal involvement, which was absent in this patient's presentation.

Inflammatory bowel disease, including ulcerative colitis, can occur in association with epidermolysis bullosa acquisita, which presents as painful bullae and erosions in areas of trauma, often on extensor surfaces; these lesions heal with scarring and milia. This patient's extreme pruritus makes epidermolysis bullosa acquisita unlikely.

KEY POINT

- Dermatitis herpetiformis is a chronic, extremely pruritic autoimmune disorder associated with gluten-sensitive enteropathy, or celiac disease.

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Item 71 Answer: D

Educational Objective: Diagnose sarcoidosis.

This patient has sarcoidosis. Sarcoidosis is a granulomatous, infiltrating disease that is more common in black persons and may be incidentally discovered by detection of lymphadenopathy, often in the chest. A chronic, nonproductive cough is the most common pulmonary symptom of sarcoidosis, as occurs in this patient. The cutaneous manifestations of sarcoidosis result from granulomatous infiltration in the skin with papule formation at the site of disease. Lesions tend to be grouped around the nose and are sometimes seen around the eyes or mouth. Sarcoidal involvement of tattoos and scars is not uncommon. Smoking may alter the pulmonary immune milieu, and smokers tend to have a lower incidence of sarcoidosis, with some patients occasionally developing sarcoidosis after smoking cessation. However, smoking is not recommended as a preventive or therapeutic measure. Medium-potency topical glucocorticoids are the usual first-line therapy for cutaneous sarcoidosis on the face, with high-potency agents used in other lower risk sites. Intralesional glucocorticoids are also a treatment option.

Dermatomyositis presents with cutaneous findings of erythema over skin folds or flexures, such as the metacarpal and proximal and distal interphalangeal joints, the elbows, the shoulders and back ("shawl sign"), posterior neck, the upper chest ("V sign"), lateral hips, and around the eyes. Patients may have an interstitial lung disease; however, the skin lesions described in this patient are not characteristic of dermatomyositis.

Hodgkin lymphoma can cause hilar lymphadenopathy and may cause severe pruritus. The resulting pruritus can lead to extensive skin excoriations; these lesions are usually elongated, jagged, angled erosions and scars due to self-induced scratching. The pruritus from Hodgkin lymphoma may be striking and severe, and lymphoma is one of the potential culprits to consider as an internal source of pruritus in select patients.

Limited systemic sclerosis, or CREST syndrome, is characterized by cutaneous calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly or tapering of the digits, and telangiectasias. None of these features are present in this patient.

Systemic lupus erythematosus often presents with skin findings. The classic acute rash of systemic lupus is a bright red symmetric patch over the cheeks and central face, the "butterfly" malar rash. Subacute cutaneous lupus presents with annular red scaly patches in photodistributed areas, especially prominent on the upper back, chest, and arms. Chronic cutaneous lupus lesions are generally the characteristic "discoid lupus" lesions with pink-to-violaceous erythema, scaling, and dyspigmentation and atrophic scarring. While pleuritis can occur with lupus, the combination of papular skin lesions and dry cough is characteristic of sarcoidosis.

KEY POINT

- Classic cutaneous sarcoidosis appears as violaceous papules around the nose including the ala, or periorbitally and periorificially; lesions may also develop in sites of trauma, such as scars or tattoos.

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Item 72 Answer: B

Educational Objective: Treat chronic cutaneous lupus erythematosus.

Hydroxychloroquine is first-line systemic treatment for patients with chronic cutaneous lupus erythematosus, such as discoid lupus. The cutaneous manifestations of lupus may present focally, as with the classic "butterfly" malar rash, or with more diffuse findings. A unique form of lupus-associated skin disease is discoid lupus. Discoid lupus may occur in patients with clearly defined lupus but may also present in other patients with few other clinical manifestations of lupus. This patient has had chronic lesions for 3 years limited to a relatively small area on the head and neck. She lacks other symptoms of systemic lupus erythematosus (SLE). Low titer antinuclear antibody positivity may occur in patients with skin-limited chronic cutaneous lupus. Topical therapy with glucocorticoids and calcineurin inhibitors is the usual initial treatment approach. For patients who fail to improve, systemic antimalarial therapy such as hydroxychloroquine, which is the systemic treatment of choice for most manifestations of cutaneous lupus, is indicated. There is some evidence that treatment with hydroxychloroquine can diminish the risk of progression to overt SLE in some patients.

Dapsone is a sulfonamide that has efficacy in treating specific types of lupus-associated skin disease. However, along with methotrexate, mycophenolate mofetil, and systemic retinoids, dapsone is considered second-line therapy for cutaneous lupus.

Although systemic glucocorticoids such as prednisone are sometimes used in systemic lupus, this patient does not have SLE (negative titers for anti-Smith and antidouble-stranded DNA, normal complete blood count and urinalysis, and no extracutaneous signs or symptoms). Because of this and the potential associated adverse effects of systemic glucocorticoids, they are not routinely used in the management of lupus skin disease.

Vitamin D supplementation, even in high dosages, has not shown efficacy in preventing or treating the cutaneous manifestations of lupus.

KEY POINT

- Hydroxychloroquine is the first-line systemic treatment for patients with chronic cutaneous lupus erythematosus, such as discoid lupus.

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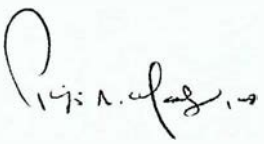

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Production/Systems: Dan Hoffmann (Director, Web Services & Systems Development), Neil Kohl (Senior Architect),

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The MKSAP Resource Site (mksap.acponline.org) is a continually updated site that provides links to MKSAP 17 online answer sheets for print subscribers; the latest details on Continuing Medical Education (CME) and Maintenance of Certification (MOC) in the United States, Canada, and Australia; errata; and other new information.

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The learning objectives of MKSAP 17 are to:

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- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
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- Subspecialists who need to remain up-to-date in internal medicine and in areas outside of their own subspecialty area

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Hospital-Based Medicine

For the convenience of subscribers who provide care in hospital settings, content that is specific to the hospital setting has been highlighted in blue. Hospital icons (H) highlight where the hospital-based content begins, continues over more than one page, and ends.

High Value Care Key Points

Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon (HVC).

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Errata

Errata for MKSAP 17 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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Endocrinology and Metabolism High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 17 in several important ways. MKSAP 17 now includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Endocrinology and Metabolism section of MKSAP 17.

- Lifestyle modifications are a cost-effective intervention that has been proven to decrease the risk of patients with prediabetes developing type 2 diabetes by 41% to 58%.
- The data for the role and cost-effectiveness of self-monitoring of blood glucose levels are less clear for regimens without multiple daily insulin injections and noninsulin regimens; generally this should be avoided.
- For noncritically ill patients who are eating, the use of basal and prandial subcutaneous insulin is the preferred and safest choice for achieving inpatient glycemic control; oral agents and noninsulin injectable agents do not have proven safety or efficacy data in the hospital setting.
- Isolated adult-onset growth hormone deficiency is extremely rare, and its clinical significance is debated; evaluation for growth hormone deficiency should be reserved for adults with at least one known pituitary hormone deficiency.
- Microprolactinomas in asymptomatic patients do not require treatment; however, surveillance is recommended (see Item 65).
- If the thyroid-stimulating hormone level is frankly abnormal, additional evaluation of thyroid function should be considered to determine the extent of the dysfunction; measure thyroxine (T_4) when the thyroid-stimulating hormone is elevated and measure both thyroxine (T_4) and triiodothyronine (T_3) when the thyroid-stimulating hormone is suppressed.
- There is no clinical indication for serial measurement of thyroid antibody titers to determine the need for or to guide therapy except to monitor for residual disease in patients treated for thyroid cancer
- Radioactive iodine uptake is a measure of iodine uptake by the thyroid over 24 hours; it is used to evaluate the cause of hyperthyroidism and is not indicated in patients with normal or elevated thyroid-stimulating hormone levels.
- In patients with subclinical hyperthyroidism, repeat assessment of thyroid function should be performed 6 to 12 weeks after the initial tests, as the values will normalize in up to 30% of patients.
- An elevated serum thyroid-stimulating hormone level indicates the diagnosis of primary hypothyroidism; thyroid imaging is not indicated unless there is concern for a nodule on physical examination.
- The typical pattern of euthyroid sick syndrome, nonthyroidal illness syndrome, or low triiodothyronine (T_3) syndrome is a mildly elevated thyroid-stimulating hormone level and slightly low thyroxine (T_4) and triiodothyronine (T_3) levels; this pattern should not prompt further testing in the hospital.
- After patients with euthyroid sick syndrome are discharged from the hospital, thyroid function abnormalities may persist for several weeks so follow-up thyroid function tests should not be repeated until 6 weeks after discharge.
- A serum thyroid-stimulating hormone measurement is the initial laboratory test in a patient with a thyroid nodule; if the thyroid-stimulating hormone is suppressed, then measurement of thyroxine (T_4) and triiodothyronine (T_3) should be performed, and a radionuclide scan should be considered to identify "hot" or functioning nodules, which have a very low likelihood of malignancy and typically do not require fine-needle aspiration.

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- If the thyroid-stimulating hormone level is high or normal, the radionuclide scan is unnecessary as it is unlikely to reveal a hot nodule and ultrasonography is an inexpensive and highly effective method for stratification of malignancy risk for nonfunctioning thyroid nodules.
- Measurement of testosterone levels is not recommended if a patient is having regular morning erections, does not have true gynecomastia on examination, and has a normal testicular examination, as it is highly unlikely that he has testosterone deficiency.
- Mild, chronic, asymptomatic gynecomastia in the male patient does not warrant evaluation.
- 25-Hydroxyvitamin D has a relatively long half-life of several weeks, is the best indicator of whole body vitamin D status, and is the recommended test for vitamin D deficiency.
- A 25-hydroxyvitamin D level between 30 and 40 ng/mL (75-100 nmol/L) is deemed sufficient for bone health; most expert groups recommend screening all groups at least once for evidence of deficiency since U.S. incidence is 30% to 60% of the population, however, it should not be a serial, recurring screening test.
- Treatment for low bone mass in postmenopausal women involves lifestyle modification (maximizing weight-bearing exercise and avoidance of tobacco or excessive alcohol) and vitamin D and calcium supplementation; the need for pharmacologic therapy is based on the 10-year estimated fracture risk (≥20% for a major osteoporotic fracture or ≥3% for hip fracture) (see Item 12).

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Endocrinology and Metabolism

Disorders of Glucose Metabolism

Diabetes Mellitus

Diabetes mellitus is a chronic metabolic disease characterized by elevated plasma glucose levels as a consequence of insulin deficiency, impaired action of insulin secondary to insulin resistance, or a combination of both abnormalities. Prediabetes is defined as elevated plasma glucose levels below the diagnostic criteria for diabetes, but above the normal range.

Screening for Diabetes Mellitus

Patients with diabetes mellitus may exhibit classic symptoms (polyuria, polydipsia, polyphagia), or more commonly, they can be asymptomatic. Diabetes screening may detect an early asymptomatic phase. Current guidelines do not recommend routine screening for type 1 diabetes as there is no consistent evidence that early treatment during the asymptomatic stage prevents progression of the disease. Similarly, it has not been firmly established that screening improves clinical outcomes in type 2 diabetes. However, microvascular and macrovascular disease can be present at the time of diagnosis of type 2 diabetes, which is indicative of ongoing organ damage during the asymptomatic phase. Furthermore, there is evidence that the microvascular and macrovascular disease associated with type 2 diabetes may be reduced with improved glucose control early in the disease course and that treatment of prediabetes may delay the onset of type 2 diabetes. In 2008, the U.S. Preventive Services Task Force (USPSTF) recommended screening for type 2 diabetes only in asymptomatic adults with a sustained blood pressure level (treated or untreated) greater than 135/80 mm Hg. Updated USPSTF draft guidelines from 2014 have expanded screening recommendations to all adults in primary care settings with risk factors for the development of diabetes (**Table 1**). In contrast, the American Diabetes Association (ADA) recommends screening for type 2 diabetes based on BMI (≥25) with additional risk factors, including a history of gestational diabetes, or age (≥45 years).

Diagnostic Criteria for Diabetes Mellitus

Prediabetes and diabetes can be diagnosed based on the elevated results from one of the following screening tests repeated on two separate occasions: fasting plasma glucose (FPG), 2-hour postprandial glucose during an oral glucose tolerance test (OGTT), or hemoglobin A_{1c} (**Table 2**). A random plasma glucose level greater than or equal to 200 mg/dL (11.1 mmol/L) with classic hyperglycemic symptoms is diagnostic of diabetes and does not warrant repeat measurement. The diabetes screening tests have several advantages and disadvantages to consider. FPG is cheaper and more readily available in most countries compared with hemoglobin A_{1c}, but the requirement for overnight fasting can be problematic. OGTT best reflects the pathophysiology of diabetes by identifying postprandial hyperglycemia secondary to pancreatic beta-cell deficiency; however, the test is time-intensive. Hemoglobin A_{1c} testing is more convenient with no fasting requirement, is unaffected by acute stress or illness, and provides an accurate reflection of the average plasma glucose over the previous 3 months. By contrast, hemoglobin A_{1c} testing can miss early glucose abnormalities, such as postprandial hyperglycemia. Another disadvantage is its decreased reliability in the setting of anemia, hemoglobinopathies, or kidney or liver disease. Furthermore, conditions that affect the turnover of erythrocytes, such as anemias/hemoglobinopathies and pregnancy, can affect the reliability of hemoglobin A_{1c}.

Classification of Diabetes Mellitus

Categories for classification of diabetes encompass a range of insulin abnormalities, including absolute or relative insulin deficiency, insulin resistance, or a combination of these abnormalities (**Table 3**).

Insulin Deficiency

Type 1 Diabetes Mellitus

Type 1 diabetes occurs in the setting of insulin deficiency. It accounts for 5% of diagnosed diabetes cases. The underlying mechanism is destruction of insulin-producing pancreatic beta cells, which can be autoimmune-mediated, idiopathic, or acquired.

Autoimmune-mediated type 1 diabetes mellitus can result from a combination of genetic, environmental, and autoimmune factors. There is a strong association between type 1 diabetes and specific HLA antigens. One or more precipitating events, such as viral infections, can trigger the autoimmune process of beta-cell destruction in genetically susceptible persons. Autoantibodies (one or more) can be present at the time of diagnosis, including antibodies to the following: islet cells, glutamic acid decarboxylase (GAD65), tyrosine phosphatases IA-2 and IA-2β, insulin, and zinc transporter autoantibodies. Measurements of autoantibodies to GAD65 and IA-2 are recommended for initial confirmation as both of these assays are highly automated. In addition, autoantibodies to GAD65 persist longer than those to islet cells after the development of diabetes.

Autoimmune-mediated type 1 diabetes has classically been considered a disease of children and young, thin adults,

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TABLE 1. Screening Guidelines for Type 2 Diabetes Mellitus in Asymptomatic Adults

	ADA	USPSTF
Screening criteria	BMI ≥25[a] and at least one additional risk factor: Physical inactivity First-degree relative with diabetes High-risk race/ethnicity (black, Latino, Native American, Asian American, Pacific Islander) Delivery of a baby weighing >4.1 kg (9 lb) History of GDM Hypertension (≥140/90 mm Hg or on antihypertensive medication) HDL cholesterol <35 mg/dL (0.90 mmol/L) and/or triglyceride level >250 mg/dL (2.82 mmol/L) Polycystic ovary syndrome Hemoglobin A_{1c} ≥5.7%, IGT, or IFG on previous testing Other conditions associated with insulin resistance (severe obesity, acanthosis nigricans) History of CVD	2008 guidelines: Sustained BP >135/80 mm Hg treated or untreated 2014 updated draft: Screening of adults in primary care settings with at least one of the following risk factors for IFG, IGT, or type 2 diabetes mellitus: Age ≥45 years Overweight or obese First-degree relative with diabetes History of GDM History of polycystic ovary syndrome High-risk race/ethnicity (black, American Indian/Alaska Native, Asian American, Hispanic/Latino, and Native Hawaiian/Pacific Islander)
Additional screening criteria	All patients age 45 years or older	Patients age 45 years or younger with any of the other risk factors in the screening criteria
Additional screening considerations	Use of glucocorticoids or antipsychotics	—
Screening intervals	3-year intervals if results are normal. Yearly testing if prediabetes (hemoglobin A_{1c} between 5.7% and 6.5%, IGT, IFG) is diagnosed.	3-year intervals if low-risk and normal plasma glucose values. In high-risk adults or those with near abnormal test values, yearly testing may be beneficial.

[a]At-risk BMI may be lower in some ethnic groups.

ADA = American Diabetes Association; BP = blood pressure; CVD = cardiovascular disease; GDM = gestational diabetes mellitus; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; USPSTF = U.S. Preventive Services Task Force.

Data from American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. *In* Standards of Medical Care in Diabetes-2015. Diabetes Care 2015;38 Suppl 1:S8-16. [PMID: 25537714]

TABLE 2. Diagnostic Criteria for Diabetes Mellitus[a]

Test	Normal Range	Increased Risk for Diabetes (Prediabetes)	Diabetes
Random plasma glucose	—	—	Classic hyperglycemic symptoms plus a random plasma glucose ≥200 mg/dL (11.1 mmol/L)
Fasting plasma glucose[b]	<100 mg/dL (5.6 mmol/L)	100-125 mg/dL (5.6-6.9 mmol/L)	≥126 mg/dL (7.0 mmol/L)
Plasma glucose during a 2-hour 75-g OGTT	<140 mg/dL (7.8 mmol/L)	140-199 mg/dL (7.8-11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)
Hemoglobin A_{1c}	<5.7%	5.7%-6.4%	≥6.5%

OGTT = oral glucose tolerance test.

[a]In the absence of hyperglycemic symptoms, an abnormal fasting plasma glucose, OGTT, or hemoglobin A_{1c} should be confirmed by repeat testing. The same test should be used when repeating the measurement for confirmation. If two different tests are performed and only one has abnormal results, the American Diabetes Association recommends repeating the test with the abnormal results.

[b]Fasting for at least 8 hours.

Data from American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care 2015 Jan;38 Suppl:S8-S16. [PMID: 25537714]

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TABLE 3. Classification of Diabetes Mellitus

Insulin Deficiency[a]
Immune-mediated
Type 1 diabetes
LADA
Rare forms: "stiff man" syndrome, anti-insulin receptor antibodies
Idiopathic (seronegative)
Acquired
Diseases of the exocrine pancreas: pancreatitis, trauma/pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous, pancreatopathy
Infections: congenital rubella
Drug-related: Vacor (rat poison), intravenous pentamidine
Insulin Resistance
Type 2 Diabetes[b]
Ketosis prone[c]
Other or Rare Types
Genetic defects in beta-cell function (including six distinct MODY syndromes)
Genetic defects in insulin action
Endocrinopathies:
(acromegaly, Cushing syndrome, glucagonoma, pheochromocytoma, hyperthyroidism)[d]
(somatostatinoma, aldosteronoma)[e]
Drug-related:
(glucocorticoids, thiazides, β-blockers, diazoxide, tacrolimus, cyclosporine, niacin, HIV protease inhibitors, atypical antipsychotics [clozapine, olanzapine])[f]
Genetic syndromes:
Down syndrome[g]
Wolfram syndrome (DIDMOAD)[h]
(Klinefelter, Turner, and Prader-Willi syndromes; myotonic dystrophy)[d]

DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, and deafness; LADA = late autoimmune diabetes in adults; MODY = maturity-onset diabetes of the young.

[a]Beta-cell destruction usually leading to absolute insulin deficiency.

[b]Insulin resistance with progressive relative insulin deficiency.

[c]More common in nonwhite patients who present with diabetic ketoacidosis but become non-insulin dependent over time.

[d]Impaired insulin action.

[e]Impaired insulin secretion.

[f]Impaired insulin secretion, impaired insulin action or altered hepatic glucose metabolism.

[g]Insulin deficiency, immune-mediated.

[h]Insulin deficiency.

although it can occur at any age or BMI range. The initial presentation can range from modest elevations in plasma glucose levels to diabetic ketoacidosis (DKA). The time course for beta-cell destruction is also variable, although it is frequently more rapid in children compared with adults. Upon initiation of insulin therapy for type 1 diabetes, the remaining functioning pancreatic beta cells may temporarily regain the ability to produce some insulin during a "honeymoon" phase lasting several weeks to many months, although this is not an adequate or sustained effect. Insulin therapy is therefore recommended during the honeymoon phase to reduce the metabolic stress on the functioning beta cells to preserve any residual function for as long as possible. Late autoimmune diabetes in adults (LADA) presents in patients with autoantibodies to pancreatic beta-cell antigens and beta-cell destruction who did not require insulin initially but eventually progressed to an insulin requirement. Patients with autoimmune-mediated type 1 diabetes are at an increased risk to develop other autoimmune diseases, such as thyroiditis and celiac disease most commonly. Thus, screening for associated autoimmune diseases should be considered at the time of diagnosis and/or the development of signs and symptoms. Consensus on the frequency and effectiveness of repeat screening for associated autoimmune diseases is lacking.

Idiopathic type 1 diabetes can present with relative insulin deficiency and episodic DKA without evidence for autoimmunity. There is a strong genetic history of diabetes, and Asian and African ancestry appears to be a predisposing factor.

Acquired type 1 diabetes can be caused by diseases affecting the exocrine pancreas, infections, or drugs. Diffuse damage to the pancreas and beta cells or impaired insulin secretion with subsequent insulin deficiency occurs in these scenarios.

KEY POINTS

- Prediabetes and diabetes mellitus can be diagnosed based on the elevated results from one of the following screening tests repeated on two separate occasions: fasting plasma glucose, 2-hour postprandial glucose during an oral glucose tolerance test, or hemoglobin A_{1c}.
- Measurements of autoantibodies to GAD65 and IA-2 are recommended for initial confirmation of autoimmune-mediated type 1 diabetes mellitus.

Insulin Resistance

Insulin resistance is characterized by the inability of the peripheral cells to utilize insulin effectively, with a compensatory increase in the amount of insulin secreted by the pancreatic beta cells in response to hyperglycemia. The pancreas exhibits a relative insulin deficiency when it cannot produce enough insulin to overcome the hyperglycemia. Obesity predisposes to the development of insulin resistance.

Metabolic Syndrome

Metabolic syndrome is the coexistence of a group of risk factors that increases a person's probability for the development of type 2 diabetes mellitus and cardiovascular disease (CVD). In addition to impaired glucose metabolism, these risk factors include central body obesity, hypertension, and hyperlipidemia (**Table 4**). Metabolic syndrome increases the relative risk of developing CVD by twofold and diabetes by fivefold, although it is not clear whether the combination of factors associated with metabolic syndrome imparts a greater risk than that attributable to each individual risk factor present. In the presence of one

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TABLE 4. AHA/NHLBI Criteria for the Definition of the Metabolic Syndrome

Clinical Criteria (Must meet at least 3 of the 5 criteria)	Qualifying Measurements
Waist circumference[a]	Men 40 in (102 cm)[b]
	Women 35 in (89 cm)[c]
Fasting TG	≥150 mg/dL (1.7 mmol/L) or
	Drug therapy targeting increased TG
HDL cholesterol	Men <40 mg/dL (1.0 mmol/L)
	Women <50 mg/dL (1.3 mmol/L) or
	Drug therapy targeting decreased HDL
Blood pressure	Systolic ≥130 mm Hg or
	Diastolic ≥85 mm Hg or
Fasting glucose	Drug therapy for hypertension
	Blood glucose ≥100 mg/dL (5.6 mmol/L) or
	Drug therapy for increased glucose

AHA = American Heart Association; HDL = high-density lipoprotein cholesterol; NHLBI = National Heart, Lung, and Blood Institute; TG = triglycerides.

[a]Some individuals with minimally elevated waist circumference measurements [e.g., (men 37-39 in or 94-99 cm) or (women 31-34 in or 79-86 cm)] may still be at risk for type 2 diabetes or cardiovascular disease and will benefit from lifestyle interventions.

[b]A lower waist circumference of 35 in (89 cm) should be used for Asian American men.

[c]A lower waist circumference of 31 in (79 cm) should be used for Asian American women.

Data from Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement: Executive Summary. Circulation. 2005 Oct 25;112(17):2735-52. [PMID: 16157765]

or more risk factors for metabolic syndrome, the Endocrine Society recommends a 3-year screening interval for the metabolic syndrome components including waist circumference, fasting lipid profile, fasting plasma glucose, and blood pressure. Calculation of the 10-year CVD risk is recommended in persons with metabolic syndrome to determine the need for lifestyle modifications and therapeutic interventions to prevent or delay progression to type 2 diabetes or CVD. The Framingham Risk Score and the new Pooled Cohort Equation from the American College of Cardiology/American Heart Association are frequently used within the United States to assess CVD risk.

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus accounts for most (90%-95%) diagnosed diabetes cases. It affects 10.9 million (26.9%) of adults in the United States aged 65 years or older. Asian Americans, American Indians, Alaska Natives, Hispanics, and non-Hispanic black persons are at an increased risk for developing diabetes compared with non-Hispanic white persons. The etiology of type 2 diabetes is likely multifactorial. There is often a strong family history of type 2 diabetes among first-degree relatives, although the specific genes responsible for the glucose abnormalities remain unidentified.

Insulin resistance from obesity in the setting of relative insulin deficiency contributes to the development of type 2 diabetes in the majority of patients. The degree of hyperglycemia depends on the extent of beta-cell function, which can decline over time.

Type 2 diabetes generally has an insidious onset of prolonged asymptomatic hyperglycemia. Most patients do not present with the classic symptoms of polydipsia, polyphagia, or polyuria. Patients with type 2 diabetes may present first with macrovascular or microvascular changes. Although type 2 diabetes is often considered an adult disease, the incidence is increasing along with obesity rates in children and adolescents.

Residual insulin production from the beta cells is insufficient to control glucose adequately, but it is able to suppress lipolysis for most persons with type 2 diabetes. Under extreme metabolic stress, such as an illness, some patients with type 2 diabetes cannot suppress lipolysis and present with DKA. Ketosis-prone patients with type 2 diabetes are more likely to be overweight or obese, middle-aged, male, and of black or Latino ethnicity. Insulin use during the time of metabolic stress can often restore the beta cells from the glucose toxicity with a return to diet, exercise, and oral hypoglycemic agents for glucose control. Prior to switching from insulin to oral therapy, pancreatic beta-cell function should be assessed with fasting C-peptide and glucose measurements.

Lifestyle modifications alone or combined with therapeutic interventions can prevent or delay the development of type 2 diabetes in high-risk persons. Lifestyle modifications are a cost-effective intervention. Several randomized controlled trials provide evidence that diet changes, increased daily exercise, and weight loss targets of 5% to 7% can significantly decrease the risk of developing type 2 diabetes in persons with prediabetes by 41% to 58%. Additionally, metformin has been shown to reduce the risk of diabetes in patients with prediabetes, although this effect was not as robust as lifestyle interventions. In the setting of impaired glucose tolerance, impaired fasting glucose values, or hemoglobin A_{1c} values between 5.7% and 6.4%, the ADA recommends considering metformin for prevention of type 2 diabetes.

Additional therapeutic agents, such as lipase inhibitors, α-glucosidase inhibitors, and thiazolidinediones, have been evaluated to delay or prevent type 2 diabetes; however, the effectiveness, cost, and potential side effects must be considered before implementation (**Table 5**).

KEY POINTS

- Lifestyle modifications are a cost-effective intervention that has been proven to decrease the risk of patients with prediabetes developing type 2 diabetes by 41% to 58%. **HVC**
- In high-risk persons, the American Diabetes Association recommends considering metformin for prevention of type 2 diabetes, particularly in patients who are younger than 60 years of age, have a BMI greater than 35, or have a history of gestational diabetes.

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TABLE 5. Strategies to Prevent or Delay Onset of Type 2 Diabetes Mellitus

Intervention	Effectiveness
Diet and exercise	Sustained weight loss of 7%, with at least 150 minutes of moderate exercise per week, shown to delay onset of diabetes by up to 3 years
Smoking cessation	Modestly effective as long as it does not cause weight gain, but is always recommended
Bariatric surgery	Effective if used in morbidly obese persons (BMI >40)
Metformin[a]	Shown to delay onset of diabetes by up to 3 years
Lipase inhibitors (orlistat)	Shown to delay onset of diabetes by up to 3 years
α-Glucosidase inhibitors (acarbose, voglibose)	Shown to delay onset of diabetes by up to 3 years
Thiazolidinediones (troglitazone, rosiglitazone, pioglitazone)	Shown to delay onset of diabetes by up to 3 years
Insulin and insulin secretagogues (sulfonylureas, meglitinides)	Ineffective
ACE inhibitors and angiotensin receptor blockers	Ineffective
Estrogen-progestin	Modest effect only

[a]Preferred.

Gestational Diabetes Mellitus

Relative insulin deficiency during the increased insulin resistance associated with pregnancy can result in the development of gestational diabetes mellitus. Pregnant women at high risk for developing gestational diabetes include those from certain racial or ethnic groups (Hispanic/Latino Americans, blacks, and American Indians), overweight or obese women, women older than 25 years of age, and women with a strong family history of type 2 diabetes. An estimated 2% to 10% of pregnant women have gestational diabetes. Complications related to gestational diabetes include miscarriage, fetal deformities, large for gestational age infants, macrosomia, preeclampsia, complications during labor and delivery, increased perinatal complications, and mortality. Complication risk is on a continuum with increasing hyperglycemia.

Disagreement exists among consensus groups regarding the definition, screening methods, and diagnostic criteria for gestational diabetes. High-risk pregnant women should be screened for overt diabetes at the initial prenatal visit using criteria for nonpregnant women, according to the International Association of Diabetes and Pregnancy Study Group (IADPSG) and the ADA. In the absence of overt diabetes at the initial office visit, diabetes screening should occur between 24 and 28 weeks' gestation. Once a diagnosis of gestational diabetes is made, glucose monitoring should be performed at least four times daily initially, to include fasting and 1-hour or 2-hour postprandial values. Postprandial hyperglycemia in pregnancy may predict worse fetal outcomes and complications.

Lifestyle interventions and/or pharmacologic agents should be implemented when glucose goals for gestational diabetes are not met. Nutrition requirements for gestational diabetes should allow for appropriate maternal weight gain for normal fetal growth while obtaining goal glucose values. A moderate exercise program is recommended for glycemic control.

Insulin has traditionally been the mainstay of therapy for gestational diabetes when glycemic goals are not met with diet and exercise. Off-label use of metformin and glyburide in pregnancy has been studied and there appears to be equivalence in efficacy with insulin; however, long-term safety data are lacking.

Gestational diabetes resolves after pregnancy for most women; however, the risk of developing type 2 diabetes is 5% to 10% after delivery and 35% to 60% in the subsequent 10 to 20 years. The ADA recommends diabetes screening for women with a history of gestational diabetes using standard criteria at 6 to 12 weeks postpartum and every 3 years thereafter.

KEY POINTS

- Lifestyle interventions should be implemented to meet glycemic goals in women with gestational diabetes; however, when these are not met, insulin should be initiated.
- For women with a history of gestational diabetes, diabetes screening using standard criteria should occur at 6 to 12 weeks postpartum and every 3 years thereafter.

Uncommon Types of Diabetes Mellitus

Genetic defects in beta-cell function and insulin action cause some uncommon forms of diabetes (see Table 3). Maturity-onset diabetes of the young (MODY) is an autosomal dominant monogenetic defect that affects beta-cell function but not insulin action. MODY should be suspected in non-obese patients with a strong family history for diabetes when the onset of diabetes occurs before 25 years of age in the absence of autoantibodies. Genetic defects in insulin action cause insulin resistance with varying degrees of hyperglycemia, as seen with congenital lipodystrophy.

Several endocrinopathies can impair insulin action or secretion as a consequence of excess hormone production. Conditions such as Cushing syndrome and pheochromocytoma decrease the action of insulin secondary to excess cortisol and epinephrine, respectively. The hypokalemia induced by hyperaldosteronism can inhibit the secretion of insulin.

Management of Diabetes Mellitus

The most effective management of diabetes mellitus includes a multidisciplinary approach, including patient education and support, engaging patients in their care and decision making,

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lifestyle modifications with diet and exercise, reduced caloric intake for overweight and obese patients, and pharmacologic therapies when necessary to meet individualized glycemic goals (**Table 6**).

Patient Education

Diabetes self-management education (DSME) and diabetes self-management support (DSMS) are recommended at the time of diagnosis of prediabetes or diabetes and throughout

TABLE 6. American Diabetes Association Recommended Outpatient Glycemic Goals for Adults with Diabetes Mellitus

State of Health	Characteristics of Patients	Hemoglobin A_{1c}[a]	Preprandial Capillary Glucose[a]	Postprandial Capillary Glucose (1-2 hours after meal)[a]
Healthy	Early in disease course Few comorbidities Preconception Patient preference Life expectancy >10 years	<7.0% without severe recurrent hypoglycemia (<6.5% for select patients)[b]	70-130 mg/dL (3.9-7.2 mmol/L)	<180 mg/dL (10.0 mmol/L)
Complex health issues	Significant comorbidities, including advanced atherosclerosis or microvascular complications Longer duration of diabetes Frequent hypoglycemia Hypoglycemia unawareness Life expectancy <10 years	<8.0% without severe recurrent hypoglycemia		
Older adults	Few comorbidities Extended life expectancy No impairment of cognition or function	<7.0%-7.5% without severe recurrent hypoglycemia	90-130 mg/dL (5.0-7.2 mmol/L)	
	Multiple comorbidities Hypoglycemic risk Fall risk Mild impairments in cognition and function	<8.0% without severe recurrent hypoglycemia	90-150 mg/dL (5.0-8.3 mmol/L)	
	Poor health Chronic comorbidities with end-stage disease Long-term care placement Moderate-to-severe impairment in cognition and function Limited life expectancy	<8.5% without severe recurrent hypoglycemia	100-180 mg/dL (5.6-10.0 mmol/L)	
Pregnant women	Preexisting type 1 or type 2 diabetes	<6.0% without severe recurrent hypoglycemia	60-99 mg/dL (3.3-5.5 mmol/L)	100-129 mg/dL (5.6-7.1 mmol/L)
	Gestational diabetes		≤95 mg/dL (5.3 mmol/L)	1-hour after meal: ≤140 mg/dL (7.8 mmol/L) 2-hours after meal: ≤120 mg/dL (6.7 mmol/L)

[a]Recommended if goal can be met without severe recurrent hypoglycemia. If severe recurrent hypoglycemia is present, there is no recommended hemoglobin A_{1c} goal, as modification of the patient's diabetes mellitus regimen to resolve severe recurrent hypoglycemia should take precedence. When severe recurrent hypoglycemia is resolved, an hemoglobin A_{1c} goal can be chosen, and treatment decisions can again be made based on that individualized hemoglobin A_{1c} goal without frequent hypoglycemia.

[b]This can be considered for patients with an early diagnosis of diabetes mellitus, no significant cardiovascular disease, or managed with lifestyle modifications or metformin.

Data from American Diabetes Association. Glycemic targets. Sec. 6. In Standards of Medical Care in Diabetes-2015. Diabetes Care. 2015;38(Suppl 1):S33-S40. [PMID: 25537705]. (Modification of Table 6.2 (p. S37).

Data from American Diabetes Association. Older adults. Sec. 10. In Standards of Medical Care in Diabetes-2015. Diabetes Care. 2015;38(Suppl 1):S67-S69. [PMID: 25537711]. (Modification of Table 10.1 (p. S68).

Data from American Diabetes Association. Management of diabetes in pregnancy. Sec. 12. In Standards of Medical Care in Diabetes-2015. Diabetes Care. 2015;38(Suppl 1): S77-S79. [PMID: 25537713].

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the lifetime of the patient. DSMS is an individualized plan that provides opportunities for educational and motivational support for diabetes self-management. DSME and DSMS jointly provide an opportunity for collaboration between the patient and health care providers to assess educational needs and abilities, develop personal treatment goals, learn self-management skills, and provide ongoing psychosocial and clinical support. Improved outcomes and reduced costs have been associated with DSME and DSMS.

Self-Monitoring of Blood Glucose

Blood glucose monitoring can involve a variety of modalities, including self-monitoring of blood glucose (SMBG), hemoglobin A_{1c}, or continuous glucose monitoring (CGM).

SMBG is recommended for patients on multiple daily injection (MDI) insulin therapy or continuous subcutaneous insulin infusion (CSII) therapy. SMBG should be performed frequently during several critical time periods: preprandial, bedtime, before and after exercise, periods of symptomatic hypoglycemia or hyperglycemia, and before important activities such as operating dangerous machinery. Monitoring blood glucose levels 1 to 2 hours after food consumption (postprandial) can be useful to assess prandial insulin coverage in patients with at-goal preprandial readings but with hemoglobin A_{1c} not at goal. Overnight blood glucose monitoring can help detect hypoglycemia or dawn phenomenon. Success with SMBG requires the physician and patient to act upon the information that it provides. This can include insulin dose adjustments, changes in meal content, or changes in activity level to reach individualized glycemic goals. The data for the role and cost-effectiveness of SMBG are less clear for regimens without multiple daily insulin injections and non-insulin regimens.

It is often necessary to combine both SMBG and hemoglobin A_{1c} to determine if adequate control of glucose has been achieved. There is a strong correlation between hemoglobin A_{1c} and the average 3-month plasma glucose value. Therefore, the ADA and the American Association for Clinical Chemistry advocate reporting both the hemoglobin A_{1c} and the estimated plasma glucose levels (**Table 7**). Hemoglobin A_{1c} monitoring should be measured at the time of diagnosis and every 3 months while making changes to achieve glycemic goals. Testing intervals can be decreased to twice yearly after glycemic goals have been met.

CGM technology measures real-time glucose values from the interstitial fluid every few seconds through the temporary placement of a sensor subcutaneously for 3 to 7 days. The sensor is connected to a transmitter that sends the data through wireless radiofrequency to a display device. CGM glucose values average +/- 15% from a laboratory glucose measurement. CGM may be useful in persons with frequent hypoglycemia, hypoglycemic unawareness, or extreme fluctuations in glucose levels. CGM systems can rapidly identify hypo- or hyperglycemia that is not always detected with SMBG or hemoglobin A_{1c} measurements. Additionally, the ADA endorses the use of CGM combined with intensive insulin therapy in adults (≥25 years of age) with type 1 diabetes as a successful modality to lower hemoglobin A_{1c} levels. The greatest improvements in glycemic control are associated with longer periods of CGM use. In patients using a CGM system, it is important to note that it does not replace SMBG. Calibration with SMBG is required at least twice daily with CGM systems. All CGM glucose values that warrant an immediate intervention should be confirmed with SMBG prior to action due to a lag time ranging from 5 to 21 minutes for several CGM brands between capillary blood glucose and interstitial glucose. Rapid glucose fluctuations further increase the lag time.

TABLE 7. Comparison of Hemoglobin A_{1c} Value and Estimated Plasma Glucose Level

Hemoglobin A_{1c} (%)	Estimated Average Plasma Glucose Level
	mg/dL(mmol/L)
6	126 (7.0)
7	154 (8.6)
8	183 (10.2)
9	212 (11.8)
10	240 (13.4)
11	269 (14.9)
12	298 (16.5)

Adapted with permission of American Diabetes Association, from Translating the A1C assay into estimated average glucose values. Nathan DM, Kuenen J, Borg R, Zheng H, Shoenfeld D, Heine RJ; A1C-derived average glucose study group. [erratum in Diabetes Care. 2009;32(1):207]. Diabetes Care. 2008;31(8):1476. [PMID: 18540046]

KEY POINTS

- Blood glucose monitoring, including self-monitoring of blood glucose levels, hemoglobin A_{1c} levels, or continuous glucose monitoring, is recommended for patients with diabetes mellitus requiring multiple daily insulin injections or continuous intravenous insulin injection therapy.
- The data for the role and cost-effectiveness of self-monitoring of blood glucose levels are less clear for regimens without multiple daily insulin injections and noninsulin regimens; generally this should be avoided. HVC

Nonpharmacologic Approaches

Nonpharmacologic approaches to diabetes management should be implemented throughout the lifespan of the patient. These approaches can be used alone or as adjunct therapy in type 2 diabetes to improve the success rate of pharmacologic agents. Medical nutrition therapy and exercise can be used in conjunction with insulin therapy for patients with type 1 diabetes.

Medical nutrition therapy is an essential component of any successful management plan for patients with prediabetes or diabetes. Modest weight loss (2.0-8.0 kg [4.4-17.6 lb] or 7%)

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through caloric reduction can benefit some overweight or obese adults with type 2 diabetes.

Consistent exercise provides beneficial effects on glucose control, weight, and cardiovascular status. For persons with diabetes in whom no contraindications exist, aerobic exercise should consist of at least 150 minutes/week at a moderate intensity level, 75 minutes/week at a vigorous activity level, or a combination of these two. Resistance training should be incorporated into the exercise routine at least 2 days per week. Hypoglycemia and extreme hyperglycemia can worsen if present at the time of exercise and should be corrected before proceeding with increased physical activity.

Bariatric surgical procedures (restrictive and bypass) can be considered in obese patients with type 2 diabetes. Weight loss and diabetes remission rates are significant with these procedures, but the long-term benefits require additional studies. See MKSAP 17 Gastroenterology and Hepatology and MKSAP 17 General Internal Medicine for more information.

Depression, anxiety, and diabetes-related stress are common among patients with diabetes and may impair their ability to achieve success with a diabetes management plan. Screening should occur continuously during the course of diabetes treatment.

Pharmacologic Therapy

An individualized treatment goal will help guide the selection of the optimal treatment regimen. For many persons with diabetes, a reasonable goal for hemoglobin A_{1c} is less than 7.0% (or less than 6.5%, if this can be achieved without significant hypoglycemia). If severe recurrent hypoglycemia is present, there is no recommended hemoglobin A_{1c} goal, as modification of the patient's diabetes regimen to resolve severe recurrent hypoglycemia should take precedence. The increased risks of hypoglycemia outweigh the risks of diabetes complications in older patients with longer disease duration, which necessitates consideration of a less-stringent glycemic goal. The recommended goals from the ADA for blood glucose and hemoglobin A_{1c} levels are located in Table 6.

Therapy for Type 1 Diabetes Mellitus

Lifelong insulin therapy is the first-line treatment for type 1 diabetes. Physiologic insulin therapy, also known as intensive insulin therapy, is the ideal insulin regimen as it attempts to mimic the actions of normal pancreatic beta cells. Intensive insulin therapy includes multiple daily injections (MDI) (≥3 per day) with an intermediate or long-acting insulin for basal coverage and multiple preprandial injections throughout the day with analogue or regular insulin. Intensive insulin therapy can also include continuous subcutaneous insulin infusion (CSII) and meal-time boluses with an insulin pump. Data support targeting normal glycemic levels with a goal hemoglobin A_{1c} of less than 7% for most persons with type 1 diabetes to reduce long-term complications. Long-term physiologic insulin therapy reduces early microvascular disease by 34% to 76% and reduces cardiovascular events by 42% to 57%. Intensive insulin therapy has risks, including significant increases in hypoglycemia and weight gain. Therapy should therefore be individually tailored for each patient's preferences, lifestyle, education level, financial resources, and comorbidities.

Available insulin preparations and their activity profiles are indicated in **Table 8**. Most persons with type 1 diabetes are sensitive to the effects of exogenous insulin therapy, with initial total daily doses of insulin typically ranging from 0.3 to 1 U/kg/d. A basal insulin dose should account for half of the total daily dose of insulin, while the remaining insulin should be divided to cover the number of meals consumed during the day. Basal insulin coverage can be provided with one to two daily injections of insulin detemir, glargine, or neutral protamine Hagedorn (NPH) insulin. CSII can also provide basal coverage with analogue insulin. For prandial coverage, analogue or regular insulin is injected prior to meal consumption or analogue insulin is bolused with CSII prior to meals. Insulin dosing immediately after a meal is appropriate in certain situations, particularly when food intake is unpredictable. Postprandial insulin dosing allows for a reduction in the insulin dose that is commensurate with the amount of food ingested to avoid hypoglycemia that could have resulted from the full insulin dose. For example, the postprandial insulin dose is reduced by 50% if only half of the meal is consumed.

TABLE 8. Pharmacokinetic Properties of Insulin Products[a]

Insulin Type	Onset	Peak	Duration
Rapid-acting or analogue (lispro, aspart, glulisine)	5-15 min	45-90 min	2-4 h
Short-acting (regular)	0.5-1h	2-4 h	4-8 h
NPH insulin	1-3 h	4-10 h	10-18 h
Detemir	1-2 h	None[b]	12-24 h[c]
Glargine	2-3 h	None[b]	20-24+ h
Pre-mixed insulins			
70% NPH/30% regular	0.5-1 h	2-10 h	10-18 h
50% NPH/50% regular	0.5-1 h	2-10 h[d]	10-18 h
75% NPL/25% lispro	10-20 min	1-6 h	10-18 h
50% NPL/50% lispro	10-20 min	1-6 h[d]	10-18 h
70% NPA/30% aspart	10-20 min	1-6 h	10-18 h

NPA = neutral protamine aspart; NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro.

[a]The time course of each insulin varies significantly between persons and within the same person on different days. Therefore, the time periods listed should be considered general guidelines only.

[b]Both insulin detemir and insulin glargine can produce a peak effect in some persons, especially at higher doses.

[c]The duration of action for insulin detemir varies depending on the dose given.

[d]Premixed insulins containing a larger proportion of rapid- or short-acting insulin tend to have larger peaks occurring at an earlier time than mixtures containing smaller proportions of rapid and short-acting insulin.

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Regular insulin requires a longer time interval between prandial injection and food consumption compared with analogue insulin due to its longer onset of action. Classic carbohydrate counting with prandial analogue insulin allows flexibility and variety in the types and sizes of meals consumed by adjusting the dose based on the number of carbohydrates ingested. Typically, 1 U of analogue insulin is used to cover every 10 to 20 g of carbohydrate in the meal. Modified carbohydrate counting for patients who are unwilling or cannot count carbohydrates includes fixed prandial doses of regular or analogue insulin that can be adjusted by 50% based upon the size of the meal: regular (100% dose), small (50% dose), or large (150% dose). In the setting of pre-meal hyperglycemia, the prandial dose of insulin determined by the classic or modified carbohydrate counting methods can be combined with a supplemental insulin dose to correct the hyperglycemia. There are a variety of methods to determine the supplemental insulin dose needed for correction; however, an additional 1 U of analogue or regular insulin for every 50 mg/dL (2.8 mmol/L) above the target blood glucose at the pre-meal measurement is a reasonable starting point. For example, an additional 2 U of regular or analogue insulin would be administered for a patient with a blood glucose level of 210 mg/dL (11.7 mmol/L) if the target blood glucose is 150 mg/dL (8.3 mmol/L) or less. When administering any prandial or supplemental insulin doses, the duration of action of previous analogue or regular insulin injections must be considered, as the risk of insulin-stacking and subsequent hypoglycemia increases if the dosing is too frequent. Allowing at least 3 to 4 hours between injections can decrease this risk. Premixed insulins containing a fixed percentage of a long-acting and regular or analogue insulin are given twice daily, particularly in patients who are unable to comply with more frequent daily injections, although greater glycemic variability and hypoglycemia are concerns when utilizing a nonphysiologic regimen.

CSII should be considered for select patients with type 1 diabetes if adequate glycemic control is not achieved with adherence to MDI therapy. CSII may be beneficial in several scenarios, including significant early morning hyperglycemia ("dawn phenomenon"), labile plasma glucose values and frequent DKA, frequent severe hypoglycemia or hypoglycemic unawareness, preconception and pregnancy, or active lifestyles/patient preference. If a patient is not adherent with insulin injections and blood glucose monitoring, adherence is unlikely to increase because a pump is prescribed; therefore, pump therapy is not recommended in the nonadherent patient.

Cost of the insulin regimen chosen should be weighed against potential benefits. MDI regimens require more insulin supplies and glucose monitoring. Insulin analogues demonstrate fewer hypoglycemic events, but cost more than regular human insulin. Insulin pens increase both convenience and cost when compared with insulin in vials. Insulin pump supplies are expensive compared with other insulin therapies; however, data from several analyses indicate that overall CSII is a cost-effective treatment modality.

KEY POINTS

- Lifelong insulin therapy is the first-line treatment for type 1 diabetes; physiologic insulin therapy reduces early microvascular disease by 34% to 76% in patients with type 1 diabetes mellitus compared with nonphysiologic regimens.
- Continuous subcutaneous insulin infusion is a cost-effective treatment modality and should be considered for select patients with type 1 diabetes mellitus if adequate glycemic control is not achieved with adherence to multiple daily injection therapy.

Therapy for Type 2 Diabetes Mellitus

Lifestyle modifications must often be combined with oral pharmacologic agents for optimal glycemic control, particularly as type 2 diabetes progresses with continued loss of pancreatic beta-cell function and insulin production. Multiple oral agents may be required or used in conjunction with noninsulin injectable agents or insulin as glycemic control worsens. There are many options for oral agents, with major differences in cost, timing of administration, mechanism of action, and side-effect profiles (**Table 9**).

Metformin is the recommended first-line therapy to be initiated either in conjunction with lifestyle modifications at the time of diagnosis or within 6 weeks of failing to obtain glycemic control with lifestyle changes alone. Metformin has a lower incidence of hypoglycemia and weight gain compared with some of the other oral agents and insulin. Gastrointestinal side effects (such as abdominal cramping or diarrhea) are common with metformin; initial low doses with gradual increases and administration of the tablet following a substantial meal can improve tolerance to the medication. Due to the potential risk of lactic acidosis, contraindications to metformin therapy include serum creatinine greater than 1.5 mg/dL (133 μmol/L) in men and 1.4 mg/dL (124 μmol/L) in women, symptomatic heart failure or liver disease, and illness with hemodynamic instability. Metformin must be withheld for 48 hours in the setting of intravenous contrast dye. In a nonhospitalized patient, metformin should be withheld with any illness that may cause dehydration.

If lifestyle modifications and maximally tolerated doses of metformin fail to adequately control glucose, additional agents should be added every 3 months until glycemic goals have been met. Without strong comparative-effectiveness data to identify the best class of second-line drugs to be implemented, several factors must be considered. Patient preferences and financial resources are key components to developing an individualized treatment plan. Another important determining factor in selection of the second-line drug class is the patient's weight. Weight-neutral drug classes include α-glucosidase inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors. If weight loss is a desired effect, glucagon-like peptide 1 (GLP-1) mimetics, pramlintide, and sodium-glucose transporter-2 (SGLT2) inhibitors are

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TABLE 9. Pharmacologic Agents Used to Lower Blood Glucose Levels in Type 2 Diabetes Mellitus

Class	Mechanism of Action	Effect on Weight	Risks and Concerns	Long-Term Studies on Definitive Outcomes
Insulin[a]	Decreases hepatic glucose production, increases peripheral glucose uptake	Increase	Hypoglycemia; insulin allergy (rare)	Decrease in both microvascular and macrovascular events
Sulfonylureas (tolbutamide, chlorpropamide, glipizide, glyburide, gliclazide, glimepiride)[b]	Stimulate insulin secretion	Increase	Hypoglycemia (especially in drugs with long half-lives or in older populations); weight gain	Decrease in microvascular events but possible increase in macrovascular events with tolbutamide, chlopropamide, glyburide, and glipizide; not seen with gliclazide or glimepiride
Biguanides (metformin)[b]	Decrease hepatic glucose production, increase insulin-mediated uptake of glucose in muscles	Neutral	Diarrhea and abdominal discomfort; lactic acidosis (rare); contraindicated in presence of progressive liver, kidney or cardiac failure	Decrease in both microvascular and macrovascular events
α-Glucosidase inhibitors (acarbose, miglitol, voglibose)[b]	Inhibit polysaccharide absorption	Neutral	Flatulence; abdominal discomfort	May reduce CVD events
Thiazolidinediones (rosiglitazone, pioglitazone)[b]	Increase peripheral uptake of glucose, decrease hepatic glucose production	Increase	Fluid retention; heart failure; macular edema; osteoporosis (possible increased risk of bladder cancer with pioglitazone)	Unclear whether pioglitazone causes net harm or good
Meglitinides (repaglinide, nateglinide)[b]	Stimulate insulin release	Increase	Hypoglycemia	None
Amylinomimetics (pramlintide)[a]	Slow gastric emptying, suppress glucagon secretion, increase satiety	Decrease	Nausea; vomiting; increased hypoglycemic risk with insulin	None
GLP-1 mimetics (exenatide and liraglutide)[a]	Slow gastric emptying, suppress glucagon secretion, increase satiety	Decrease	Hypoglycemia when used in combination with sulfonylureas; nausea and vomiting; possible increased risk of pancreatitis and chronic kidney disease	None
DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin)[b]	Slow gastric emptying, suppress glucagon secretion	Neutral	Hypoglycemia when used in combination with sulfonylureas; nausea; increased risk of infections; possible increased risk of pancreatitis	No increase in ischemic cardiovascular events; increased rate of hospitalization for heart failure with saxagliptin
SGLT2 inhibitors (dapagliflozin and canagliflozin)[b]	Increases kidney excretion of glucose	Decrease	Hypoglycemia with insulin secretagogues and insulin; hypotension; kidney impairment; hypersensitivity reactions; increased candidal genital infections and urinary tract infections	None

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose co-transporter 2.

[a]Injection.

[b]Oral.

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candidates to consider. Weight gain is likely with the use of insulin, sulfonylureas, thiazolidinediones, and meglitinides. The risk of hypoglycemia must be considered with the selection of any therapeutic agent, particularly when it is combined with insulin secretagogues or insulin. Gastrointestinal side effects from GLP-1 mimetics and pramlintide may decrease tolerability for some patients and should not be used in patients with gastroparesis. Patients with frequent candidal genital infections would not be ideal candidates for SGLT2 inhibitor therapy.

Insulin therapy should be strongly considered in the setting of symptomatic hyperglycemia or markedly elevated hemoglobin A_{1c} (>8.5% to 9%) at the time of diagnosis or when lifestyle modifications and/or noninsulin therapies fail to achieve glycemic goals. The American Association of Clinical Endocrinologists (AACE) recommends weight-based initiation of basal insulin at initial doses of 0.1 to 0.3 U/kg. The dose should be increased several units every 2 to 3 days to reach fasting plasma glucose goals, based on the patient's SMBG readings. Reductions of insulin doses by 10% to 40% should be made in the setting of hypoglycemia with insulin titrations. If glycemic goals are not met with basal insulin, then prandial insulin should be added to the regimen with frequent titration of doses for optimal glucose control. When premeal glucose values are not at a patient-specific goal, the preceding prandial insulin dose should be increased or decreased by 10% to 20% in the setting of hyper- or hypoglycemia, respectively. (Also see section on Therapy for Type 1 Diabetes Mellitus.)

KEY POINTS

- For patients with type 2 diabetes mellitus, metformin is recommended first-line therapy and should be initiated in conjunction with lifestyle modifications; it has a lower incidence of hypoglycemia and weight gain compared with some of the other oral agents and insulin.
- In older patients with type 2 diabetes mellitus of longer disease duration, treatment of severe recurrent hypoglycemia should take precedence over controlling hemoglobin A_{1c} values; the increased risks of hypoglycemia outweigh the risks of diabetes complications.

Inpatient Management of Hyperglycemia

Inpatient hyperglycemia, defined as consistently elevated plasma glucose values above 140 mg/dL (7.8 mmol/L), is associated with poor outcomes. Attempts to decrease morbidity and mortality with tight glycemic control (80-110 mg/dL [4.4-6.1 mmol/L]) have not consistently demonstrated improvements in adverse outcomes and, in some settings, have shown increased rates of severe hypoglycemic events and mortality. As a result, revised inpatient glycemic targets are less stringent than outpatient glucose targets to avoid both hypoglycemia and severe hyperglycemia that can lead to volume depletion and electrolyte abnormalities.

Hospitalized Patients with Diabetes Mellitus

Critically ill patients with type 1 diabetes mellitus will require insulin therapy upon admission to the hospital. For critically ill patients with type 2 diabetes, intravenous insulin infusion therapy should be initiated when plasma glucose levels exceed 180 to 200 mg/dL (10-11.1 mmol/L). Glucose goals on intravenous insulin are 140 to 200 mg/dL (7.8-11.1 mmol/L) with frequent bedside point-of-care (POC) monitoring every 1 to 2 hours for insulin adjustments.

In noncritically ill patients, the ADA and AACE advocate a premeal glucose goal of less than 140 mg/dL (7.8 mmol/L) and random plasma glucose values less than 180 mg/dL (10 mmol/L). Therapy adjustments should be considered when plasma glucose levels are less than 100 mg/dL (5.6 mmol/L) and are necessary when glucose values fall below 70 mg/dL (3.9 mmol/L) to avoid continued hypoglycemia. In contrast, the American College of Physicians (ACP) recommends avoiding glucose levels less than 140 mg/dL (7.8 mmol/L) owing to the increased risk of hypoglycemia with tighter glycemic control.

Insulin is the preferred therapy and likely the safest choice for achieving inpatient glycemic control. Use of sliding scale insulin alone is not recommended, as it is not physiologic and frequently causes large glucose fluctuations owing to the inherent reactive nature of its dosing, coupled with the near universal lag time between measurement of glucose and injection of insulin that occurs in most hospitals. The recommended insulin regimen should incorporate both basal and prandial coverage. In the setting of preprandial hyperglycemia, prandial coverage can be supplemented with additional insulin (correction factor insulin). Prandial coverage should account for the carbohydrates consumed at each meal and be adjusted accordingly. POC glucose monitoring should coincide with insulin administration before meals and at bedtime, with overnight measurements to monitor for hypoglycemia only if fasting readings are elevated or the patient is symptomatic. This glucose monitoring regimen will simulate the patient's home routine after discharge. POC monitoring should occur every 6 hours when a patient is on insulin therapy and receives nothing by mouth.

Outpatient CSII therapy can be continued if the patient is physically and mentally able to safely administer this therapy under proper supervision from health care providers with CSII expertise. POC glucose monitoring, basal rates of insulin, and patient-initiated bolus amounts of insulin should be documented in the medical record.

Oral agents and noninsulin injectable agents do not have safety or efficacy data in the hospital setting. The safest recommendation is to discontinue these agents upon admission to the hospital, although continuation can be considered in a stable patient with glycemic control at goal and no anticipated changes in nutrition or hemodynamic status. These agents can be particularly dangerous in fasting states or when organ perfusion or

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CONT. function is compromised. Resumption of these medications may be considered once a patient is stable with regular activities and nutrition or at the time of hospital discharge.

KEY POINTS

- For critically ill patients with type 2 diabetes mellitus, intravenous insulin infusion therapy should be initiated when plasma glucose levels exceed 180 to 200 mg/dL (10-11.1 mmol/L); glucose goals on intravenous insulin are 140 to 200 mg/dL (7.8-11.1 mmol/L) with frequent bedside point-of-care monitoring every 1 to 2 hours.
- H/C For noncritically ill patients, basal and prandial subcutaneous insulin is the preferred and safest choice for achieving inpatient glycemic; oral agents and noninsulin injectable agents do not have proven safety or efficacy data in the hospital setting.

Hospitalized Patients Without Diabetes Mellitus

Hyperglycemia as a result of acute stress related to illness, concomitant medications, or enteral/parenteral nutrition can occur in patients without a previous history of glucose abnormalities. The glycemic goals and glucose-management strategies in this population should follow those for hospitalized patients with diabetes. Hyperglycemia in hospitalized patients may also indicate the presence of previously undiagnosed diabetes. Measurement of hemoglobin A_{1c} in hyperglycemic non-hospitalized patients, if feasible, can provide insight into the length of the hyperglycemia. A hemoglobin A_{1c} level greater than 6.5% suggests long-standing hyperglycemia. Follow-up diabetes screening and care should be implemented after discharge from the hospital.

Management of Hypoglycemia

Hypoglycemia in Patients with Diabetes Mellitus

Hypoglycemia is a common complication of intensive therapeutic regimens in patients with diabetes mellitus, often limiting the ability to safely reach glycemic goals for many patients. Avoidance of hypoglycemia prior to focusing on a patient's hemoglobin A_{1c} goal is of utmost importance because of the significant morbidity and mortality associated with low plasma glucose levels.

Hypoglycemia is defined as a plasma glucose level less than 70 mg/dL (3.9 mmol/L). Insulin secretion ceases when the glucose level falls below 80 mg/dL (4.4 mmol/L). Hyperadrenergic symptoms begin to alert the patient to hypoglycemia through an increase in heart rate, sweating, tremors, hunger, and anxiety when glucose levels decline. Typically, the body responds to hypoglycemia by secreting counterregulatory hormones, such as glucagon, epinephrine, norepinephrine, cortisol, and growth hormone, in succession based on the escalating degree of hypoglycemia. If the counterregulatory measures fail or the hypoglycemia is not corrected, cognitive function begins to decline and can be rapidly followed by loss of consciousness, seizures, and death. Relative hypoglycemia occurs when a patient has symptoms of hypoglycemia but the plasma glucose level is greater than 70 mg/dL (3.9 mmol/L). This can occur with rapid decreases in glucose or with correction of glucose to near-normal glycemic levels in a patient with a history of prolonged hyperglycemia (plasma glucose >200 mg/dL [11.1 mmol/L]). Relative hypoglycemia can be diminished if glucose levels are maintained closer to normal ranges and if treatment to goal glucose level is achieved over a longer period of time in patients with a history of prolonged uncontrolled diabetes.

The etiology of hypoglycemia can be quite variable. Exercise can lead to hypoglycemia if appropriate measures are not taken to avoid it. Prior to exercise, consumption of a snack with 15 to 30 g of carbohydrates can help reduce the risk of hypoglycemia, or a patient can reduce the dose of prandial insulin given at the meal prior to the planned exercise, if on an MDI regimen. A snack with complex carbohydrates is often required after prolonged exercise to replenish glycogen stores since glucose utilization can be prolonged in muscles and the liver. In overweight/obese patients, decreasing the insulin dose instead of ingesting snacks before exercise can avoid additional weight gain. Poor timing or skipping of meals or consumption of smaller amounts of food without an adjustment to insulin doses or oral hypoglycemic agents can cause hypoglycemia. Use of a nonphysiologic sliding scale insulin regimen or use of an aggressive supplemental insulin correction factor regimen is often the etiology of hypoglycemic events. A reduction in kidney function, particularly in elderly patients, can decrease clearance of insulin or insulin secretagogues and lead to prolonged hypoglycemia. Alcohol consumption can cause delayed hypoglycemia.

Treatment of hypoglycemia is twofold: immediate correction of hypoglycemia and prevention of future events. If a patient is conscious, 15 to 20 g of a carbohydrate with glucose should be consumed. Glucose tablets or glucose gel are ideal treatment regimens. The blood glucose level should be checked again after 15 minutes, and consumption of 15 to 20 g of glucose should occur again if the hypoglycemia does not improve to greater than 70 mg/dL (3.9 mmol/L). Since the effects of the insulin or oral hypoglycemic agents are likely still present, a meal or snack should be consumed after the glucose has been corrected to avoid continued hypoglycemia. Every patient with diabetes on medications associated with hypoglycemia should receive a prescription for a glucagon kit, which should be used when oral consumption of glucose is not possible or safe.

Relaxing the glycemic targets and hemoglobin A_{1c} goals and reducing doses of therapeutic agents will decrease the risk of future hypoglycemia. A review of a patient's diabetes self-management skills can also help identify recurring risk factors for hypoglycemia.

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KEY POINTS

- Hypoglycemia is defined as a plasma glucose level less than 70 mg/dL (3.9 mmol/L) and is associated with significant morbidity and mortality.
- Relaxing the glycemic targets and hemoglobin A_{1c} goals and reducing doses of therapeutic agents will decrease the risk of future hypoglycemia.

Hypoglycemia in Patients Without Diabetes Mellitus

CONT.

Hypoglycemia in patients without diabetes is rare, thus evaluation for pathologic hypoglycemia should only occur when Whipple triad is present: symptomatic hypoglycemia, documented hypoglycemia at 55 mg/dL (3.1 mmol/L) or lower, and prompt symptomatic relief with correction of hypoglycemia. Hypoglycemia should not be confirmed with POC glucose monitors, but instead with a more accurate established laboratory method. Hypoglycemia in patients without diabetes is usually related to drugs, illness, hormonal deficiency, nonislet cell tumor, endogenous hyperinsulinism/noninsulinoma, pancreatogenous hypoglycemia, depletion of hepatic glycogen stores, or alcohol ingestion. Diagnostic studies should be obtained during a spontaneous hypoglycemic episode or during an attempt to recreate a scenario known to cause hypoglycemia, such as prolonged fasting or after a mixed meal, which consists of the type of food that induces the hypoglycemia, typically a simple carbohydrate-rich meal, such as orange juice, pancakes, and syrup. Hypoglycemia has classically been categorized as occurring in the fasting versus postprandial state, although the etiologies of each of these classifications of hypoglycemia are not mutually exclusive. The differential diagnoses based on the laboratory test results are found in **Table 10**. Imaging studies should not occur unless biochemical evidence of endogenous hyperinsulinism is confirmed and is related to a tumor or pancreatic abnormality.

Fasting Hypoglycemia

Suspected hypoglycemia that is either spontaneous or begins after a fast should be evaluated by the following simultaneous laboratory measurements: glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate, and insulin secretagogue screen. C-peptide and proinsulin are measures of the endogenous production of insulin. β-Hydroxybutyrate is suppressed by endogenous and exogenous insulin, but would be unsuppressed in a normal physiologic state of hypoglycemia or in a non–insulin-mediated condition. If hypoglycemia is not present at the time of evaluation, a 72-hour fast is indicated, which is typically performed in consultation with an endocrinologist. This test involves measurement of the above-mentioned laboratory values every 6 hours until the plasma glucose level reaches 60 mg/dL (3.3 mmol/L) and subsequently every 1 to 2 hours until specific plasma glucose, symptom, or time criteria are met. This test also involves measuring the response to glucagon administration. Evaluation for anti-insulin antibodies can detect the rare condition of insulin autoimmune hypoglycemia as the underlying etiology for the hypoglycemia.

Postprandial Hypoglycemia

Postprandial hypoglycemia without a history of a prior bariatric procedure is rare. It typically occurs within 5 hours of food consumption. A mixed meal tolerance test is usually performed in consultation with an endocrinologist and measures the glucose level as symptoms occur. Glucose, insulin, proinsulin, and C-peptide levels are measured prior to the meal and repeated at 30-minute intervals or at the time of symptomatic hypoglycemia (blood glucose level <60 mg/dL [3.3 mmol/L]) within the 5 hours after meal consumption. If symptomatic hypoglycemia occurs, insulin antibodies are measured and an oral hypoglycemic agent screening test is obtained. Treatment, with or without the detection of pathologic hypoglycemia on the mixed meal test, often involves small, frequent complex

TABLE 10. Differential Diagnosis of Spontaneous Fasting Hypoglycemia[a] in a Patient Without Diabetes

Diagnosis	Serum Insulin	Plasma C-Peptide	Plasma Proinsulin	Serum β-hydroxybutyrate	Serum Insulin Antibodies	Urine or Blood Metabolites of Sulfonylureas or Meglitinides
Insulinoma	↑	↑	↑	↓	Negative	Negative
Surreptitious use of sulfonylureas of meglitinides	↑	↑	↑	↓	Negative	Positive
Surreptitious use of insulin	↑	↓	↓	↓	Negative	Negative
Insulin autoimmune hypoglycemia	↑	↑	↑	↓	Positive	Negative

[a]Symptomatic hypoglycemia, fasting plasma glucose 55 mg/dL (3.1 mmol/L) or lower, and prompt symptomatic relief with correction of hypoglycemia (Whipple triad).

Data from Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009 Mar;94(3):709-28. [PMID: 19088155]

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CONT.

meals composed of protein, fat, and carbohydrate to avoid the sensation of hypoglycemia.

Acute Complications of Diabetes Mellitus

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS) are acute complications of uncontrolled hyperglycemia with life-threatening consequences if not recognized and treated early. DKA typically occurs in the setting of hyperglycemia with relative or absolute insulin deficiency and an increase in counterregulatory hormones. Sufficient amounts of insulin are not present to suppress lipolysis and oxidation of free fatty acids, which results in ketone body production and subsequent metabolic acidosis. DKA occurs more frequently with type 1 diabetes, although 10% to 30% of cases occur in patients with type 2 diabetes. HHS occurs in the setting of partial insulin deficiency that is more typical of type 2 diabetes. There is sufficient insulin in patients with HHS to suppress lipolysis and production of ketone bodies, but inadequate amounts to prevent the hyperglycemia, dehydration, and hyperosmolality characteristic of HHS.

Several risk factors can precipitate the development of extreme hyperglycemia: infection, intentional or inadvertent insulin therapy nonadherence, myocardial infarction, stress, trauma, and confounding medications, such as glucocorticoids or atypical antipsychotic agents. In addition, DKA may be the initial clinical presentation in some patients with previously undiagnosed type 1 or type 2 diabetes. An illness or event that leads to dehydration will often precipitate the hyperglycemia associated with HHS.

Symptoms of extreme hyperglycemia in DKA and HHS include polyuria, polydipsia, unintentional weight loss, vomiting, weakness, and mentation changes. Dehydration and metabolic abnormalities worsen as hyperglycemia progresses, which can lead to respiratory failure, lethargy, obtundation, coma, and death. DKA can occur within several hours of the inciting event. The development of HHS is less acute than DKA and may take days to weeks to develop. HHS typically presents with more extreme hyperglycemia and mental status changes compared with DKA.

The initial evaluation of severe hyperglycemia includes serologic studies (plasma glucose, serum ketones, blood urea nitrogen, creatinine, electrolytes, calculated anion gap, arterial blood gases, osmolality, complete blood count with differential, blood cultures), urine studies (ketones, urinalysis, urine culture), chest radiograph, and an electrocardiogram.

Urine and serum ketones are elevated in DKA; however, a negative measurement initially does not exclude DKA. β-Hydroxybutyrate is the major ketone body in DKA, but ketone laboratory measurements often use the nitroprusside reaction, which only estimates acetoacetate and acetone levels that may not be elevated initially. Although hyperglycemia is the typical finding at presentation with DKA, patients can present with a range of plasma glucose values, including those in the normal range (**Figure 1**). The anion gap is elevated. Stress-related mild leukocytosis is often present. Higher levels of leukocytosis may indicate an infectious process as the etiology of the hyperglycemia. Serum sodium levels can be low due to osmotic shifts of water from the intracellular to extracellular spaces. Normal or elevated serum sodium levels are indicative of severe volume depletion. Serum potassium levels may be elevated due to shifts from the intracellular to extracellular spaces due to ketoacidosis and the absence of sufficient insulin. Normal or low potassium levels on presentation indicate low potassium stores in the body with need for correction prior to initiation of insulin therapy to avoid cardiac arrhythmias. Serum amylase and lipase levels also can be elevated in the absence of pancreatitis.

HHS typically presents with normal or small amounts of urine or serum ketones. Plasma glucose values in HHS are typically greater than in DKA and can exceed 1200 mg/dL (66.6 mmol/L). The serum osmolality is elevated greater than 320 mOsm/kg H_2O. The serum bicarbonate level is greater than 18 mEq/L (18 mmol/L), and the pH remains greater than 7.3.

Treatment of DKA and HHS requires correction of hyperglycemia with intravenous insulin infusions, frequent monitoring and replacement of electrolytes, correction of hypovolemia with intravenous fluids, and possible correction of acidosis (**Table 11**). The ICU is the best place for management of severe hyperglycemia because of the frequent monitoring required with intravenous insulin therapy, the need for monitoring for potential electrolyte-induced arrhythmias, and the potential for rapid decompensation. Plasma glucose levels should be monitored initially every hour while on insulin infusion therapy. Electrolytes should be monitored every 2 to 4 hours, depending on the initial electrolyte deficits and level of acidosis. H

KEY POINTS

- The development of hyperglycemic hyperosmolar syndrome is less acute than that of diabetic ketoacidosis and may take days to weeks to develop; however, hyperglycemic hyperosmolar syndrome typically presents with more extreme hyperglycemia and mental status changes compared with diabetic ketoacidosis.
- Treatment of diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome requires correction of hyperglycemia with intravenous insulin infusions, frequent monitoring and replacement of electrolytes, correction of hypovolemia with intravenous fluids, and possible correction of acidosis.

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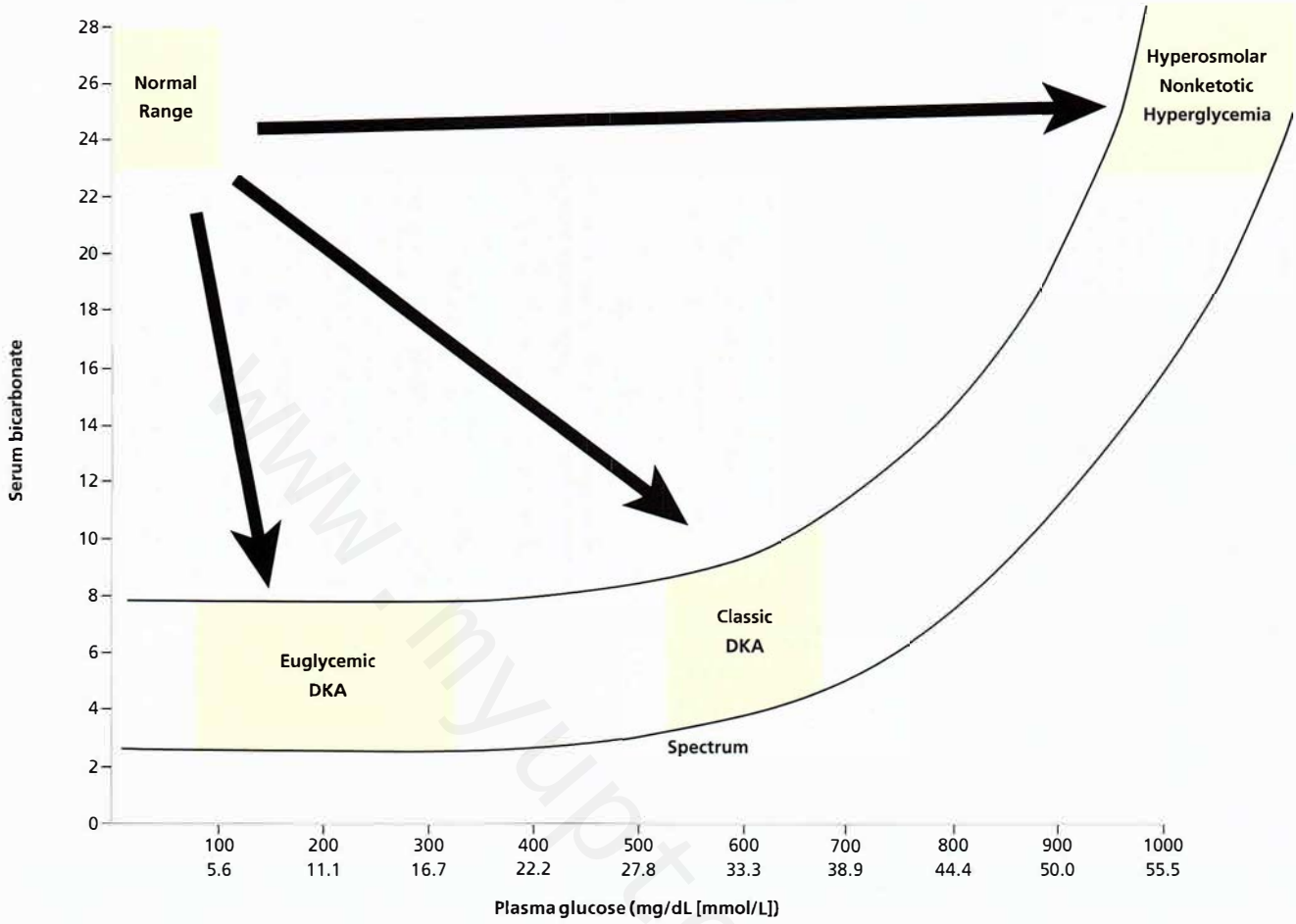

FIGURE 1. Spectrum of metabolic decompensation that occurs in diabetic ketoacidosis. DKA = diabetic ketoacidosis.

TABLE 11. Management of Hyperglycemic Crisis (DKA and HHS)

Fluids	Insulin (Regular)	Potassium	Correction of Acidosis
Assess for volume status, then give 0.9% saline at 1 L/h initially in all patients, and continue if patient is severely hypovolemic. Switch to 0.45% normal saline at 250-500 mL/h if corrected serum sodium level becomes normal or high. When the plasma glucose level reaches 200 mg/dL (11.1 mmol/L) in patients with DKA or 300 mg/dL (16.7 mmol/L) in HHS, switch to 5% dextrose with 0.45% normal saline at 150-250 mL/h.	Give regular insulin, 0.1 U/kg, as an intravenous bolus followed by 0.1 U/kg/h as an intravenous infusion; if the plasma glucose level does not decrease by 10% in the first hour, give an additional bolus of 0.14 U/kg and resume previous infusion rate; when the plasma glucose level reaches 200 mg/dL (11.1 mmol/L) in DKA and 300 mg/dL (16.7 mmol/L) in HHS, reduce to 0.02-0.05 U/kg/h, and maintain the plasma glucose level between 150-200 mg/dL (8.3-11.1 mmol/L) until anion gap acidosis is resolved in DKA.	Assess for adequate kidney function, with adequate urine output (approximately 50 mL/h). If serum potassium is <3.3 mEq/L (3.3 mmol/L), do not start insulin but instead give intravenous potassium chloride, 20-30 mEq/h, through a central line catheter until the serum potassium level is >3.3 mEq/L (3.3 mmol/L); then add 20-30 mEq of potassium chloride to each liter of intravenous fluids to keep the serum potassium level in the 4.0-5.0 mEq/L (4.0-5.0 mmol/L) range. If the serum potassium level is >5.2 mEq/L (5.2 mmol/L), do not give potassium chloride but instead start insulin and intravenous fluids and check the serum potassium level every 2 hours.	If pH is <6.9, give sodium bicarbonate, 100 mmol in 400 mL of water, and potassium chloride, 20 mEq, infused over 2 hours. If pH is 6.9 or greater, do not give sodium bicarbonate.

DKA = diabetic ketoacidosis; HHS = hyperglycemic hyperosmolar syndrome.

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Chronic Complications of Diabetes Mellitus

Cardiovascular Morbidity

Cardiovascular disease (CVD) is a major contributor to morbidity and mortality among patients with diabetes mellitus. Diabetes alone is an independent risk factor for CVD and is considered a CVD equivalent. Concomitant risk factors in patients with diabetes, such as hypertension, obesity, and dyslipidemia, also contribute to the development of CVD and should be identified early through screening (**Table 12**).

The 8th Joint National Committee (JNC-8) recently revised its recommended blood pressure goals for patients with diabetes to 140/90 mm Hg or less, citing a lack of data to support lower targets. In contrast, the American Diabetes Association (ADA) recommends a blood pressure goal of less than 140/80 mm Hg. The ADA advocates for a lower systolic blood pressure (<130 mm Hg) in select patients (young, long life expectancy, increased risk of stroke), if this can be accomplished safely. Although JNC-8 does not specify use of an ACE inhibitor or an angiotensin receptor blocker (ARB) as initial therapy for patients with diabetes and hypertension in the absence of chronic kidney disease, the ADA recommends preferential use of these agents in treating hypertension in these patients.

The most recent American College of Cardiology/American Heart Association guidelines base treatment recommendations for patients with diabetes on age, the presence of atherosclerotic cardiovascular disease (ASCVD), or estimated 10-year ASCVD risk using the Pooled Cohort Equations; a specific goal LDL cholesterol level is no longer used in these guidelines. Treat patients with diabetes and known cardiovascular or other vascular disease with high-intensity statin therapy. In the absence of known cardiovascular or vascular disease, provide high intensity statin therapy to patients with diabetes if the LDL cholesterol level is greater than 190 mg/dL (4.9 mmol/L) or the 10-year ASCVD risk is equal to or greater than 7.5%. Provide moderate-intensity statin therapy for patients with diabetes and a 10-year ASCVD risk less than 7.5%. Consider withholding statin therapy in patients with diabetes younger than 40 years without additional cardiovascular risk factors. In contrast, ADA guidelines continue to recommend an LDL cholesterol goal in patients with diabetes of less than 100 mg/dL (2.6 mmol/L), with the option of LDL cholesterol less than 70 mg/dL (1.8 mmol/L) in patients with clinical ASCVD. Therefore, it is recommended that statin therapy be added to lifestyle modifications in patients with diabetes who have clinical ASCVD, are older than 40 years of age with CVD risk factors, or are younger than 40 years of age with LDL cholesterol not at goal.

TABLE 12. Screening Recommendations for Chronic Complications of Diabetes Mellitus

Chronic Complication	Clinical Situation	When to Start Screening	Screening Frequency	Preferred Screening Test
Retinopathy	Type 1 diabetes	At 5 years after diagnosis	Annually[a]	Dilated and comprehensive eye examination
	Type 2 diabetes	At diagnosis	Annually[a]	Dilated and comprehensive eye examination
	In pregnant women with either type of diabetes	First trimester	Every trimester and then closely for 1 year postpartum	Dilated and comprehensive eye examination
	In women with either type of diabetes planning to conceive	During preconception planning	Same as recommendations for pregnant women once conception occurs	Dilated and comprehensive eye examination
Nephropathy	Type 1 diabetes	At 5 years after diagnosis	Annually[b]	Albumin-creatinine ratio on random spot urine
	Type 2 diabetes	At diagnosis	Annually[b]	Albumin-creatinine ratio on random spot urine
Neuropathy (distal symmetric polyneuropathy)	Type 1 diabetes	At 5 years after diagnosis	Annually	10-g monofilament, 128-Hz tuning fork, ankle reflexes
	Type 2 diabetes	At diagnosis	Annually	10-g monofilament, 128-Hz tuning fork, ankle reflexes
Cardiovascular disease	Hypertension	At diagnosis	Every visit	Blood pressure measurement
	Dyslipidemia	At diagnosis	Annually[c]	Fasting lipid profile

[a]It is reasonable to screen every 2 years if no diabetic retinopathy is present and to screen more often than annually if diabetic retinopathy is advanced or progressing rapidly.

[b]The American Diabetes Association guidelines state that it is reasonable to assess progression of disease and response to therapeutic interventions with continued monitoring of urine albumin excretion.

[c]It is reasonable to screen every 2 years if lipid parameters are at goal.

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KEY POINTS

- High-intensity statin therapy is indicated for patients with diabetes and known cardiovascular or vascular disease; LDH cholesterol greater than 190 mg/dL (4.9 mmol/L), or atherosclerotic cardiovascular disease 10-year risk of equal to or greater than 7.5%.
- Moderate intensity statin therapy is indicated for patients with diabetes 40 years of age and older and an atherosclerotic cardiovascular disease 10-year risk less than 7.5%.

Diabetic Retinopathy

Among adults aged 20 to 74 years, diabetic retinopathy is the leading preventable cause of blindness. Changes associated with nonproliferative retinopathy include retinal thickening from macular edema, infarcts (resulting in "cotton wool" spots or soft exudates), hard exudates, and hemorrhages. With proliferative retinopathy, neovascularization occurs secondary to chronic retinal ischemia. These new vessels may rupture, causing intraocular hemorrhage and subsequent fibrosis and retinal detachment.

Risk factors for diabetic retinopathy include long-term diabetes, poorly controlled diabetes, hypertension, and nephropathy. Retinopathy can be accelerated in pregnant women with type 1 diabetes. Rapid improvements in glycemic levels for pregnant women and nonpregnant patients can temporarily worsen preexisting retinopathy.

Screening guidelines vary depending on the type of diabetes, time of diagnosis, and pregnancy status (see Table 12).

Optimal blood glucose and blood pressure control can prevent or delay the progression of diabetic retinopathy. Laser photocoagulation is used to treat retinopathy as severity progresses. Focal laser photocoagulation of the retina can restore some vision and reduce the risk of further vision loss with macular edema. Panretinal laser photocoagulation reduces continued vision loss in proliferative diabetic retinopathy and severe nonproliferative diabetic retinopathy. Laser photocoagulation can also reduce the risk of retinopathy progression associated with pregnancy. Intravitreal injections of antiangiogenic agents, such as vascular endothelial growth factor inhibitors, may also be included in the management of proliferative retinopathy and macular edema.

KEY POINT

- Optimal blood glucose and blood pressure control can prevent or delay the progression of diabetic retinopathy; however, laser photocoagulation is used to treat diabetic retinopathy as the severity progresses.

Diabetic Nephropathy

Diabetic nephropathy not only increases the risk of progression to end-stage kidney disease, but is also a risk factor for CVD.

Measurement of increased protein excretion can be performed by two methods: albumin-creatinine ratio on a random spot urine collection or a 24-hour urine collection. Persistently elevated levels of urine albumin excretion are defined as greater than or equal to 30 mg/g in a spot urine measurement or 30 to 299 mg/24 h and greater than or equal to 300 mg/24 h. Urine albumin levels should be elevated on multiple samples over 3 to 6 months to diagnose albuminuria, as false-positive elevations can occur in the setting of illness, menstruation, recent exercise, extreme hyperglycemia or hypertension, and heart failure. Screening timelines for urine albumin excretion are found in Table 12. Annual measurements of serum creatinine and an estimated glomerular filtration rate (GFR) can be utilized in conjunction with the urine albumin measurement to determine the stage of chronic kidney disease. When the estimated GFR is less than 30 mL/min/1.73 m^2, a referral to a nephrologist is recommended.

Diabetic nephropathy can be prevented or delayed with optimal plasma glucose and blood pressure control. In nonpregnant normotensive patients with persistently elevated urine albumin excretion, an ACE inhibitor or angiotensin receptor blocker (ARB) is recommended to decrease progression of nephropathy. In nonpregnant hypertensive patients with persistently elevated urine albumin excretion and hypertension, the ACE inhibitor or ARB should be titrated to achieve a blood pressure goal of less than 130/80 mm Hg. Measurement of urine albumin annually after initiation of therapy with an ACE inhibitor or ARB is reasonable to assess disease progression and therapeutic response as evidenced by stabilization or reduction of urine albumin excretion. Data are conflicting regarding the ability of low-protein diets to slow the progression of kidney disease, but these diets may be considered if nephropathy progresses while using an ACE inhibitor or ARB or after achieving target plasma glucose and blood pressure goals. ACE inhibitor/ARB combination treatment is not recommended.

KEY POINTS

- Elevated urinary albumin excretion is defined as greater than or equal to 30 mg/g in a spot urine measurement; annual measurements of serum creatinine and an estimated glomerular filtration rate can be utilized in conjunction with the urine albumin measurement to determine the presence of diabetic nephropathy and, if present, the stage of chronic kidney disease.
- In nonpregnant normotensive patients with persistently increased urine albumin excretion, an ACE inhibitor or angiotensin receptor blocker is recommended to decrease progression of diabetic nephropathy.

Diabetic Neuropathy

There are several categories of diabetic neuropathy, which may present separately or in combination. Symptoms of diabetic neuropathy depend on the nerve(s) or nerve root that is affected and may present as focal or diffuse disease. Achieving optimal glycemic control early in the course of diabetes can

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prevent the development of neuropathy, and sustained optimal glucose levels can delay the progression of neuropathy.

Distal symmetric polyneuropathy (DPN) is the most common form of diabetic neuropathy. It is characterized by a "stocking-glove" distribution that ascends proximally. DPN frequently presents as a sensation of numbness, tingling, burning, heaviness, pain, or sensitivity to light touch. The pain may worsen at night and with walking. Muscle weakness may occur in severe cases. DPN is a risk factor for muscle and joint deformities, such as Charcot foot, and foot ulcers. DPN evaluation includes assessment of ankle reflexes, vibration sensation with a 128-Hz tuning fork, and touch with a 10-g monofilament and pinprick. Screening intervals are found in Table 12. Management of DPN symptoms may require one or more classes of drugs, including antidepressants (amitriptyline, venlafaxine, duloxetine, paroxetine), anticonvulsants (pregabalin, gabapentin, valproate), or capsaicin cream.

Autonomic neuropathy can affect a single organ or multiple organs. Symptoms may include gastroparesis, diarrhea, constipation, neurogenic bladder, abnormal hidrosis, and erectile dysfunction. Cardiac symptoms include resting sinus tachycardia, orthostatic or postprandial hypotension, exercise intolerance, and silent myocardial infarction. Cardiovascular autonomic neuropathy is an independent risk factor for mortality, which underscores the need to reduce other cardiovascular risk factors in these patients.

Diabetic amyotrophy occurs in older patients or those with type 2 diabetes, and may be due to infarcts in the major nerve trunks of the leg. It can present acutely with severe pain and asymmetric proximal weakness or pain in the leg, weight loss, and autonomic neuropathy. Partial remission may occur over many months. Without any approved treatments for diabetic amyotrophy, management consists of symptomatic therapy for neuropathic pain and ambulatory aids, if necessary.

Mononeuropathies can occur acutely with a cranial or peripheral distribution. There are no specific treatments for these mononeuropathies, as the symptoms usual resolve within a few months. Nerve compression syndromes, such as carpal tunnel syndrome or peroneal palsy, occur frequently in patients with diabetes. See MKSAP 17 Neurology for more information regarding diabetic neuropathy. Referral to a neurologist for electrodiagnostic testing or evaluation for nondiabetic-related etiologies should occur with severe, rapidly progressive, or atypical neuropathies.

Diabetic Foot Ulcers

Diabetic foot ulcers increase the risk for amputation and subsequent morbidity and disability. The etiology is often multifactorial. Loss of peripheral sensation can result in significant injuries that may be undetected by the patient. Peripheral arterial disease predisposes to the development of lower extremity ischemic ulcers and impairs healing. Altered leukocyte function from hyperglycemia can impede wound healing of injuries.

Clinicians should evaluate the feet at least annually to assess for pedal pulses, sensation, ulcers, skin or nail infections, pain, ankle reflexes, and foot deformities. Patients should inspect their feet daily for early detection of any abnormality and wear appropriate footwear. Although patients with diabetes have different footwear needs, the selection of shoes should take into account several important factors: intended use, plantar protection, shape and fit on the foot, and stability issues (see MKSAP 17 Infectious Disease).

Hypoglycemic Unawareness

Frequent severe hypoglycemia can diminish the ability to detect life-threatening hypoglycemia. This unawareness is caused by failure of the release of counterregulatory hormones to trigger an autonomic response to decreased glucose levels. Continual avoidance of hypoglycemia for several weeks or longer may help restore the body's ability to detect hypoglycemia. Plasma glucose levels should be kept greater than 150 mg/dL (8.3 mmol/L) during the time period when restoration of hypoglycemic symptoms is the goal to avoid unintended and unexpected hypoglycemia. Continuous glucose monitoring systems can be useful for hypoglycemia management by alerting the patient to rapid decreases in glucose levels to allow prompt correction and avoidance of hypoglycemia (see Self-Monitoring of Blood Glucose).

KEY POINT

- Distal symmetric polyneuropathy (DPN) is the most common form of diabetic neuropathy, and it presents as a sensation of numbness or burning pain in a stocking-glove distribution; management may require one or more classes of drugs, including antidepressants (amitriptyline, venlafaxine, duloxetine, paroxetine), anticonvulsants (pregabalin, gabapentin, valproate), or capsaicin cream

Disorders of the Pituitary Gland

Hypothalamic and Pituitary Anatomy and Physiology

The anterior pituitary is made up of glandular tissue that receives its blood supply from the hypothalamus through the hypothalamic-pituitary portal plexus, whereas the posterior pituitary consists of direct extension of neurons from the hypothalamus. Both the portal blood system and the hypothalamic neurons transverse from the hypothalamus to the pituitary by way of the pituitary stalk. The hypothalamus regulates anterior pituitary gland function by synthesizing specific stimulating and inhibiting hormones, which are released in the portal blood. Posterior pituitary hormones are synthesized in the hypothalamus and travel through hypothalamic neurons to be secreted by the posterior pituitary gland. The anterior and posterior lobes are joined by the Rathke pouch. **Table 13** lists the pituitary hormones and initial testing for suspected pituitary hormone excess or deficiency.

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TABLE 13. Initial Testing for Pituitary Hormone Deficiency and Excess

Pituitary Hormone Excess			
Pituitary Hormone	**Peripheral Hormone**	**Initial Test(s)**	
ACTH	Cortisol	24 hour urine free cortisol (×2) OR nocturnal salivary cortisol (×2) OR overnight low dose dexamethasone test	
ADH	ADH	Simultaneous serum, urine sodium, and urine osmolality	
GH	IGF-1	IGF-1	
TSH	Thyroxine, triiodothyronine	TSH, free (or total) thyroxine	
Pituitary Hormone Deficiency			
Pituitary Hormone	**Peripheral Hormone**	**Initial Test(s)**	**Confirmatory Test[a]**
ACTH	Cortisol	Simultaneous ACTH, cortisol	ACTH stimulation test
ADH	ADH	Simultaneous serum sodium, urine and serum osmolality	Water deprivation test
LH and FSH[b]	Sex hormones	Simultaneous LH, FSH, testosterone (male), estriol (female)	
TSH	Thyroxine, triiodothyronine	Simultaneous TSH, free (or total) thyroxine	

ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; FSH = follicle -stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.

[a]See Table 15 for additional information on confirmatory testing for pituitary dysfunction.

[b]Routine testing for deficiency is not recommended without specific signs of deficiency such as amenorrhea, gynecomastia, or impotence.

The anterior pituitary gland secretes and releases six hormones: adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), the gonadotropins–luteinizing hormone (LH) and follicle-stimulating hormone (FSH), growth hormone (GH), and prolactin. ACTH is released in response to corticotrophin-releasing hormone (CRH) and acts on the adrenal glands to promote the synthesis and secretion of cortisol. TSH is released in response to thyrotropin-releasing hormone (TRH) and acts on the thyroid to stimulate thyroid hormone production. LH and FSH are differentially released from the pituitary gland in response to pulses of gonadotropin-releasing hormone (GnRH). LH and FSH regulate normal male and female reproductive function. GH production is regulated by somatostatin. Prolactin controls lactation and is inhibited by dopamine.

The posterior pituitary gland secretes oxytocin, which is necessary for parturition, and antidiuretic hormone (ADH, also called vasopressin), which regulates water balance.

The pituitary gland is posterior and superior to the sphenoid sinus, which provides surgical access to the gland, and is adjacent to the optic chiasm, the carotid arteries, and the cavernous sinuses (**Figure 2**).

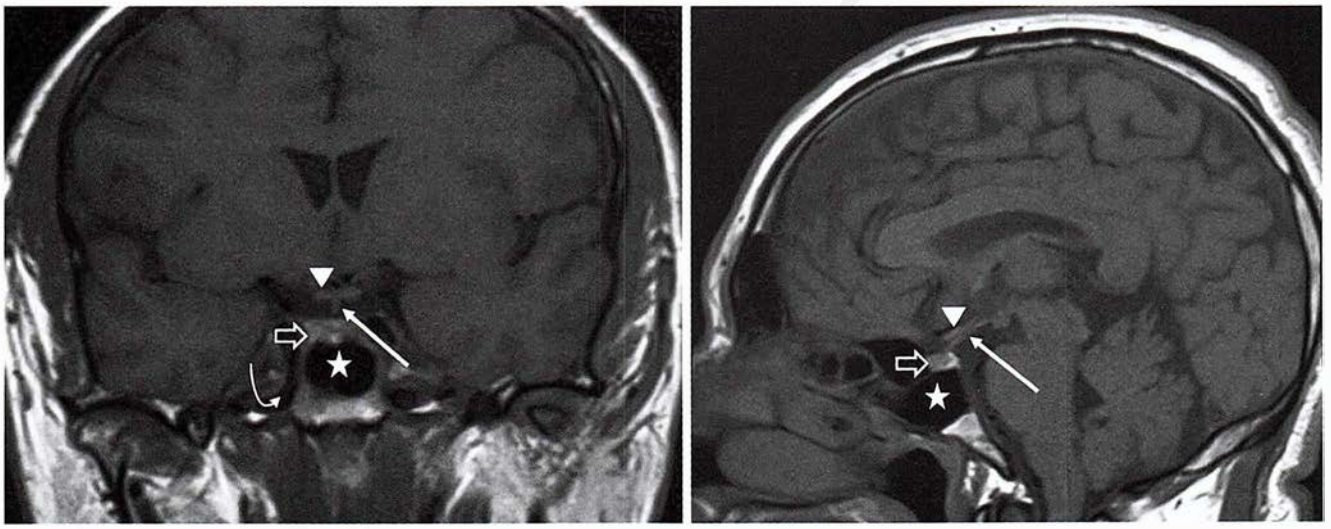

FIGURE 2. A coronal MRI (*left*) and sagittal MRI (*right*) showing the pituitary gland (*open arrow*), pituitary stalk (*thin arrow*), optic chiasm (*arrowhead*), sphenoid sinus (*star*), and carotid artery (*curved arrow*).

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The pituitary gland is best imaged using MRI with gadolinium. Because the normal pituitary is relatively small, a dedicated pituitary protocol that obtains thin MRI slices through the sella is used.

Pituitary Tumors

Pituitary adenomas, which are benign, are the most common tumor of the pituitary gland. A tumor less than 1 cm is defined as a microadenoma, and a tumor 1 cm or larger is termed a macroadenoma (**Figure 3**). Pituitary adenomas are common. Autopsy studies document that 10% of the general population had undiagnosed pituitary adenomas. Frequently, pituitary adenomas are incidental findings on imaging studies completed for other reasons. When patients undergo brain MRI, 10% to 38% are found to have incidental pituitary microadenomas and 0.2% have incidental pituitary macroadenomas. Certain genetic mutations increase the chance of developing a pituitary tumor.

Approach to a Sellar Mass

When a sellar mass is noted, pituitary adenomas are most likely; however, they need to be distinguished from other pituitary lesions and nonpathologic pituitary enlargement.

The pituitary gland is enlarged diffusely in untreated primary hypothyroidism and during pregnancy. When possible, imaging of the pituitary gland should be avoided or delayed in pregnancy and in untreated primary hypothyroidism because gland enlargement on imaging may prompt an expensive and unnecessary evaluation for pituitary hormone abnormality and tumor.

Pituitary tumors are almost always nonmalignant. Two exceptions are metastatic disease and the very rare pituitary carcinoma. Additional kinds of noncancerous pituitary lesions include craniopharyngiomas, meningiomas, and Rathke cleft cysts. Inflammatory and infiltrative disorders, including lymphocytic hypophysitis, sarcoidosis, hemochromatosis, amyloidosis, Langerhans cell histiocytosis, lymphoma, and tuberculosis, can affect the pituitary gland.

Lymphocytic hypophysitis is an inflammatory pituitary lymphocytic infiltration that most commonly occurs in pregnant and postpartum women. It may cause transient or permanent pituitary insufficiency. Lymphocytic hypophysitis is treated with glucocorticoids.

A sellar mass can compress normal surrounding tissue and impair normal neurologic and pituitary function. Pituitary adenomas may also be functional and secrete excess hormone.

Incidentally Noted Pituitary Masses

When a pituitary tumor is incidentally noted, investigation must determine (1) whether it is causing a mass effect, (2) whether it is secreting excess hormones, and (3) whether it has a propensity to grow and cause problems in the future. After a thorough history and physical examination, biochemical testing can be undertaken in a targeted fashion based on the patient's clinical signs and symptoms. Initial tests could include measurement of 8 AM cortisol, TSH, free (or total) thyroxine (T_4), prolactin, and insulin-like growth factor 1 (IGF-1).

If the tumor is not causing mass effect and there is no evidence of hormone excess, a pituitary MRI should be repeated in 6 months for a macroadenoma and 12 months for

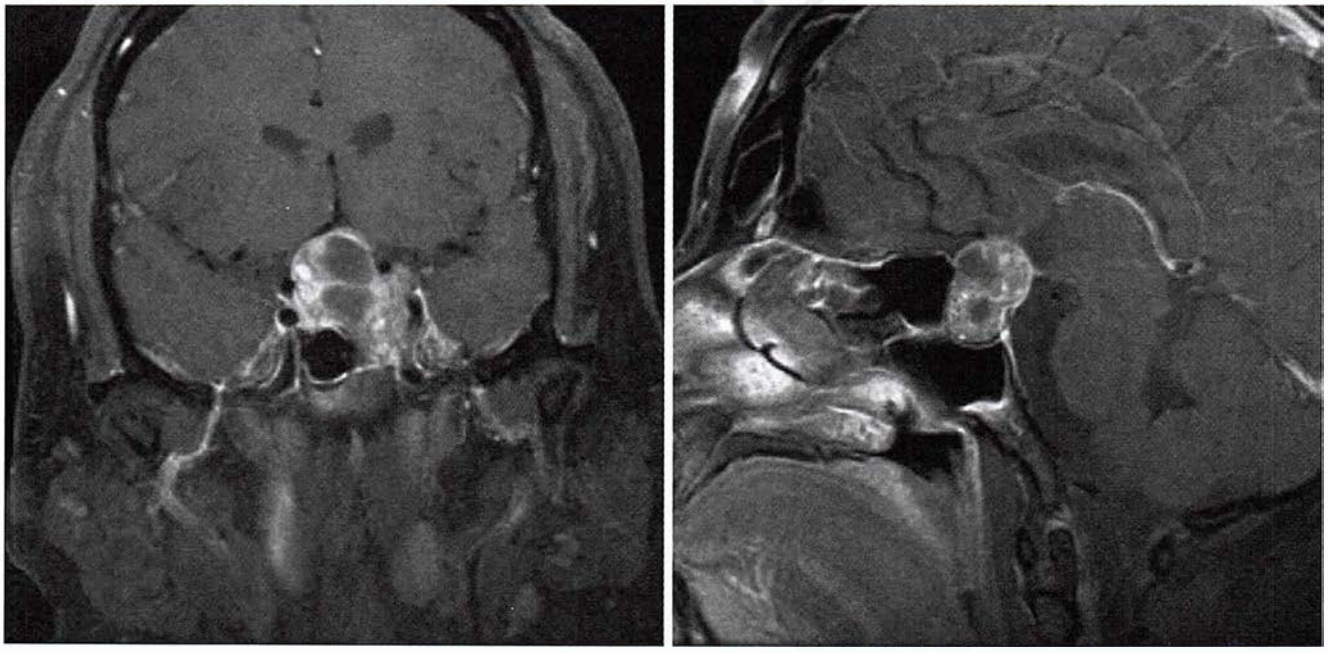

FIGURE 3. A coronal MRI (*left*) and sagittal MRI (*right*) showing a large pituitary macroadenoma. The normal pituitary gland and the optic chiasm cannot be seen because of compression from the tumor. The tumor is invasive into the left cavernous sinus. Likely, the tumor appears heterogeneous because of internal necrosis.

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CONT. a microadenoma to assess for growth. If no growth occurs, MRIs should be repeated every 1 to 2 years for the next 3 years and then intermittently thereafter. In a patient at risk for cancer or with a history of cancer, metastatic disease must be excluded.

Empty Sella

Empty sella is diagnosed when the normal pituitary gland is not visualized or is excessively small on MRI; it is a radiologic finding and not a distinct clinical condition. The pituitary sella is said to be "empty" because normal tissue is not seen. The finding may be primarily due to increased cerebrospinal fluid entering and enlarging the sella, or it may be secondary to a tumor, previous pituitary surgery, radiation, or infarction. Empty sella can also occur as a congenital abnormality when the sella is normal size, but the pituitary is small. When empty sella is found incidentally on imaging, an evaluation should be completed to determine if there is a known cause for secondary empty sella and if the patient has signs or symptoms of pituitary hormone deficiency. A patient without signs or symptoms should be screened for cortisol deficiency and hypothyroidism with 8 AM cortisol, TSH, and free (or total) T_4. A patient with signs of pituitary hormone deficiency should receive a more complete biochemical evaluation of the pituitary axes, based on the signs and symptoms found.

Repeat imaging is not necessary unless indicated as surveillance for the underlying pathology that resulted in the empty sella.

KEY POINTS

- Incidentally noted pituitary tumors are common, and biochemical testing is informed by findings on history and physical examination.
- Initial tests for pituitary incidentally noted masses include measurement of 8 AM cortisol, thyroid-stimulating hormone, free (or total) thyroxine (T_4), prolactin, and insulin-like growth factor 1.
- Empty sella is diagnosed when the normal pituitary gland is not visualized or is excessively small on MRI; it is a radiologic finding and not a distinct clinical condition.

Mass Effects of Pituitary Tumors

Pituitary tumors may cause headaches in some but not all patients; the size of the tumor does not always correlate with the presence and severity of headache.

Pituitary masses can compress the normal pituitary gland, causing hormone deficiencies. A large pituitary mass may cause panhypopituitarism in which there is impaired secretion of all pituitary hormones.

Because the optic chiasm is located superior to the pituitary gland, a large pituitary mass may compress the optic chiasm resulting in vision changes. Depending on the size of the tumor and severity of optic nerve damage, a pituitary tumor may cause minimal peripheral vision loss, bitemporal hemianopsia, or complete blindness. Visual field testing is a sensitive measure of optic nerve damage and should be evaluated by an ophthalmologist in patients who report a change in vision, who have a pituitary tumor that abuts or compresses the chiasm on MRI, or who have any evidence of gross peripheral vision loss on physical examination. Change in vision due to optic chiasm compression is an indication for treating a pituitary tumor.

Pituitary tumors can also invade surrounding brain tissue leading to seizures and neurologic manifestations. Pituitary tumors can invade the cavernous sinus, causing damage to cranial nerves III, IV, and VI that pass through the sinus causing diplopia and extraocular muscle palsies/paralysis.

KEY POINT

- Pituitary masses can compress the normal pituitary gland, causing hormone deficiencies; a large pituitary mass may cause panhypopituitarism in which there is impaired secretion of all pituitary hormones.

Treatment of Clinically Nonfunctioning Pituitary Tumors

Nonfunctioning pituitary tumors that are growing or causing mass effect are treated with neurosurgery. The most common surgical approach is transsphenoidal through the nares or the mouth. A very large or invasive tumor may require craniotomy for decompression. Indications for surgery include mass effect, particularly a visual field defect; tumor that abuts the optic chiasm; tumor growth; or an invasive tumor (invading the brain or cavernous sinus). Surgery should also be considered in a patient with a tumor close to the optic chiasm who plans to become pregnant (due to the physiologic enlargement of the pituitary associated with pregnancy).

Functional pituitary tumors will be discussed later in this chapter, based on the hormone in excess (see Pituitary Hormone Excess).

KEY POINT

- Nonfunctioning pituitary tumors that are growing or causing mass effect are treated with neurosurgery.

Hypopituitarism

Hypopituitarism is caused by one or more pituitary hormone deficiencies, usually resulting from damage to the normal pituitary gland by a tumor. Hypopituitarism can also occur as a complication from surgery if the normal gland or the pituitary stalk is damaged during tumor resection or radiation therapy. Additional causes of hypopituitarism are listed in **Table 14**.

Pituitary apoplexy is acute hemorrhage into the pituitary gland often at the site of a preexisting pituitary adenoma (typically a macroadenoma). Pituitary apoplexy can cause acute pituitary hormone deficiency or mass effect from rapid

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TABLE 14. Causes of Hypopituitarism
Pituitary adenoma
Pituitary surgery
Pituitary radiation
Pituitary apoplexy
Pituitary infarction
Craniopharyngioma
Metastatic tumor
Meningioma
Lymphocytic hypophysitis
Sarcoidosis
Langerhans cell histiocytosis
Lymphoma
Hemochromatosis
Congenital deficiencies
Hypothalamic disease

CONT

expansion of the sellar contents due to bleeding. It is an endocrine and neurosurgical emergency. Acute ACTH deficiency is common and can be life-threatening. If suspected, stress-dose glucocorticoid replacement should be initiated emergently. Patients with vision changes or loss associated with apoplexy require urgent surgical decompression. H

Hypopituitarism can occur due to postpartum pituitary infarction (Sheehan syndrome) because of excessive postpartum hemorrhage causing hypotension and hypoperfusion. Patients who may have Sheehan syndrome should be emergently tested and treated for secondary cortisol deficiency. A patient with Sheehan syndrome will not lactate because of prolactin deficiency; no treatment is available to induce lactation. Other hormone deficiencies can be evaluated 6 weeks after delivery.

GH and gonadotropin deficiencies often occur early when the pituitary gland is damaged by tumor, radiation, surgery, or hemorrhage because the cell lines that synthesize GH (somatotrophs) and LH and FSH (gonadotrophs) are most sensitive to injury. Secondary hypothyroidism (TSH deficiency) and secondary cortisol deficiency (ACTH deficiency) often occur later in the disease process. Pituitary adenomas can cause elevation in prolactin due to stalk compression, leading to a decrease in dopaminergic inhibition of prolactin secretion.

KEY POINTS

- Pituitary tumors and surgery for pituitary tumors are the most common causes of hypopituitarism.
- Stress-dose glucocorticoid replacement should be initiated emergently in patients with pituitary apoplexy or infarction, as well as emergent neurosurgical intervention; patients with vision loss associated with apoplexy require urgent surgical decompression.

Adrenocorticotropic Hormone Deficiency (Secondary Cortisol Deficiency) H

Although secondary cortisol deficiency may result from damage to the pituitary gland or pituitary stalk that impairs ACTH production, it is most commonly iatrogenic due to exogenous glucocorticoid use that suppresses pituitary ACTH secretion. Patients with secondary cortisol deficiency have only glucocorticoid deficiency. The remainder of the adrenal gland functions normally and the renin-angiotensin system is intact, so these patients do not have mineralocorticoid deficiency (see Disorders of the Adrenal Glands for a discussion of primary adrenal failure). Although patients with secondary cortisol deficiency do require stress-dose glucocorticoids, they are at less risk for hypotension, hyponatremia, and adrenal crisis than those with primary cortisol deficiency (failure of the adrenal glands) because the production of mineralocorticoid is retained. Also, unlike patients with primary cortisol deficiency, patients with secondary cortisol deficiency do not develop hyperpigmentation or bronzing of the skin because ACTH and its prohormone responsible for these changes, proopiomelanocortin (POMC), are not hypersecreted.

Oral, injectable (including joint injections), and even topical glucocorticoids are able to suppress ACTH secretion. Glucocorticoids prescribed at doses above physiologic replacement for longer than 3 weeks should be tapered when discontinued to allow recovery of the pituitary-adrenal axis; if therapy has lasted less than 3 weeks, no taper is required for pituitary-adrenal axis recovery.

When tapering glucocorticoids, the patient can be transitioned to a hydrocortisone dose that is 10% to 20% lower than the equivalent, current glucocorticoid dose. The dose can then be decreased by 2.5 to 5 mg of hydrocortisone every 1 to 2 weeks. When tapering with prednisone, taper large doses by 25% to 50% weekly until the patient is on a dose of 5 mg daily and then taper by 1 mg every 1 to 2 weeks. It is difficult to taper dexamethasone due to the limited mg tablets available. The taper can be slower if symptoms such as lightheadedness persist.

After prolonged glucocorticoid use, recovery of the pituitary-adrenal axis should be tested prior to discontinuing glucocorticoid replacement. Specifically, morning serum cortisol should normalize to greater than 11 µg/dL (303.6 nmol/L) when glucocorticoids are withheld for 36 to 48 hours following the taper. Even after endogenous ACTH production has returned, patients may require more time to mount an adequate ACTH response to stress. After discontinuing the glucocorticoid taper, the patient can undergo an ACTH stimulation test (Table 15) to document adequate glucocorticoid response to stress. The diagnosis relies on demonstrating a low basal serum cortisol level that does not increase appropriately after stimulation with the ACTH analogue cosyntropin. This is done by measuring early morning (8 AM) serum cortisol. A serum cortisol level less than 3 µg/dL (82.8 nmol/L) is consistent with cortisol deficiency. A normal response is a peak serum cortisol

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TABLE 15. Dynamic Testing for Pituitary Dysfunction

Indication	Test	Technique	Interpretation
ACTH (cortisol) deficiency	ACTH stimulation test	Measure baseline serum cortisol level. Administer 250 µg of synthetic ACTH. Measure cortisol levels at 30 and 60 minutes.	Serum cortisol level >18 µg/dL (496.8 nmol/L) indicates a normal response.
ADH deficiency (DI)	Water deprivation test, followed by desmopressin challenge if indicated	Patient empties bladder, and baseline weight is measured. Measure urine volume and osmolality hourly. Measure serum sodium, osmolality, and weight every 2 hours. The test is stopped when one of the following occurs: - Urine osmolality exceeds 600 mOsm/kg H_2O - Patient has lost 5% of body weight - Urine osmolality is stable for 2-3 h while serum osmolality rises - Plasma osmolality >295 mOsm/kg H_2O - Serum sodium >145 mEq/L (145 mmol/L) Desmopressin challenge if final urine osmolality <600 mOsm/kg H_2O, serum osmolality >295 mOsm/kg H_2O, or serum sodium >145 mEq/L (145 mmol/L): Give desmopressin 1 µg subcutaneously. Measure urine osmolality every 30 minutes for 2 hours.	*Water deprivation test interpretation:* Urine osmolality >600 mOsm/kg H_2O is a normal response to water deprivation, indicating ADH production and peripheral effect are intact. Urine osmolality <600 mOsm/kg H_2O, serum osmolality >295 mOsm/kg H_2O and/or serum sodium >145 mEq/L (145 mmol/L) are diagnostic of DI. *Desmopressin challenge interpretation:* >100% increase in urine osmolality is diagnostic of complete central DI. 0% increase in urine osmolality is diagnostic of complete nephrogenic DI. >50% increase in urine osmolality is diagnostic of partial central DI. <50% increase in urine osmolality is diagnostic of partial nephrogenic DI.
Growth hormone excess (acromegaly)	Glucose tolerance test	75 g oral glucose tolerance test. Measure glucose and GH at 0, 30, 60, 90, 120, and 150 minutes.	GH <0.2 ng/mL (0.2 µg/L) is a normal response. GH ≥1.0 ng/mL (1.0 µg/L) (or ≥0.3 ng/mL [0.3 µg/L] on an ultrasensitive assay) is diagnostic of acromegaly.

ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; DI = diabetes insipidus; GH = growth hormone.

CONT.

greater than 20 µg/dL (552 nmol/L). When the test result is normal, patients no longer require daily cortisol replacement, but should follow "sick day rules" (increasing cortisol replacement dose during illness) for up to a year after cessation of daily cortisol replacement.

Symptoms of secondary cortisol deficiency include weight loss, nausea, vomiting, lightheadedness, hypoglycemia, hypotension, and hyponatremia. Secondary cortisol deficiency is also diagnosed using an ACTH stimulation test. Secondary cortisol deficiency can be life threatening and must be treated with glucocorticoid replacement, often with hydrocortisone, although prednisone or dexamethasone may also be used. Hydrocortisone (15-30 mg/d) should be administered in 2 to 3 divided doses, or hydrocortisone should be dosed 10 to 20 mg in the morning and 5 to 10 mg in the early afternoon.

Patients require stress doses of glucocorticoids when acutely ill, hospitalized, or undergoing the stress of surgery. For moderate physiologic stress (minor or moderate surgery with general anesthesia), hydrocortisone should used (45-75 mg/d orally or intravenously in 3-4 divided doses for 2-3 days). Prednisone (10-20 mg or dexamethasone 2-3 mg/d in 1-2 divided doses) may be used alternatively. For major physiologic stress (major surgery, trauma, critical illness, or childbirth), hydrocortisone (150-200 mg/d intravenously in 3-4 divided doses; 100 mg/d the next day; taper to baseline in 3-5 days) may be used. An alternative would be dexamethasone (6-8 mg/d intravenously in 2-3 divided doses). If the patient has pituitary apoplexy and urgent/emergent neurosurgery is planned with no time for ACTH-stimulation testing, the patient should empirically be treated with glucocorticoids and then receive an ACTH stimulation test 4 to 8 weeks after surgery.

Thyroid-Stimulating Hormone Deficiency

Thyroid-stimulating hormone (TSH) deficiency leads to secondary or central hypothyroidism. Secondary hypothyroidism is clinically identical to primary hypothyroidism (see Disorders of the Thyroid Gland).

Secondary hypothyroidism is diagnosed by demonstrating a simultaneously inappropriately normal or low TSH and low T_4 (free or total). Patients are treated with levothyroxine replacement in the same manner as primary hypothyroidism; however, the serum TSH cannot be used to monitor and assess for adequacy of thyroid hormone replacement dosing. Instead,

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the levothyroxine dose is adjusted based on free T_4 levels with the goal of obtaining a value within the normal reference range.

KEY POINTS

- Patients with secondary cortisol deficiency have isolated glucocorticoid deficiency without mineralocorticoid deficiency; in addition, they do not develop hyperpigmentation or bronzing of the skin because adrenocorticotropic hormone and pro-opiomelanocortin are not hypersecreted.
- Secondary or central hypothyroidism is diagnosed by demonstrating a simultaneously inappropriately normal or low thyroid-stimulating hormone and low thyroxine (T_4) (free or total) level.

Gonadotropin Deficiency

The pituitary gland normally secretes LH and FSH in response to GnRH from the hypothalamus. LH and FSH stimulate the secretion of normal male and female sex hormones; LH and FSH deficiency causes hypogonadotropic hypogonadism (see Reproductive Disorders).

Hypogonadotropic hypogonadism may be caused by GnRH deficiency. The most common cause of GnRH deficiency in women is hypothalamic amenorrhea, which is associated with excess exercise, illness, or anorexia. Additional causes of GnRH deficiency include congenital GnRH deficiency and Kallmann syndrome, a condition in which hypothalamic neurons responsible for releasing GnRH fail to migrate into the hypothalamus during embryonic development.

Treatment of hypogonadotropic hypogonadism depends on the goals of therapy and whether the patient desires fertility. Fertility treatment requires replacement of the gonadotropins in men and women. Premenopausal women who do not desire fertility may be treated with estrogen- and progesterone-containing oral contraceptives (after assessment of risk of thromboembolic disease). Treatment of premenopausal hypogonadotropic hypogonadism is recommended to avoid loss of estrogen-dependent bone at a young age, which could lead to osteoporosis. Treatment of postmenopausal hypogonadotropic hypogonadism is not indicated. Men who do not desire fertility may be treated with testosterone replacement therapy (see Reproductive Disorders).

Growth Hormone Deficiency

Growth hormone (GH) is vital for normal linear growth, and deficiency prior to puberty will lead to short stature. At puberty, the epiphyses close, halting linear growth. In adulthood, GH production is necessary for normal physiology but is not as important for growth as during childhood. In adults, GH deficiency causes fatigue, loss of muscle mass, an increased ratio of fatty tissue to lean tissue, and increased risk for osteoporosis.

GH deficiency is often the first hormone deficiency to occur when a patient is developing pituitary insufficiency, but isolated adult-onset GH deficiency is extremely rare, and its clinical significance in adults is debated. Therefore, evaluation for GH deficiency is recommended in patients with at least one known pituitary hormone deficiency. Unfortunately, GH therapy has been used inappropriately as an alternative medication. GH naturally declines with age and does not require replacement. The use of GH does not promote longevity and when used inappropriately can be harmful. Specifically, GH therapy can encourage cancer growth, worsening the disease in a patient with cancer, or promoting growth of an occult, undiagnosed cancer.

Because GH secretion is pulsatile, testing random levels is not diagnostically useful. Therefore, GH deficiency is diagnosed by measurement of IGF-1. A GH deficiency is confirmed by measuring the response of serum GH on a stimulatory test, such as the insulin tolerance test. An insulin tolerance test carries a high risk of severe hypoglycemia, so referral to an endocrinologist for testing is appropriate.

A decision regarding replacement therapy should be made based on that patient's symptoms, goals, and risks in consultation with the patient's endocrinologist. When clinically indicated, GH deficiency is treated with daily subcutaneous GH injections. In an otherwise healthy adult, treatment of GH deficiency can improve quality of life and increase the percentage of lean muscle mass. Also, it can reduce the risk of osteoporosis. However, the risks and benefits of therapy must be carefully considered. Replacement of GH is cost prohibitive for some patients. It is contraindicated in patients with cancer and should not be used in patients with an untreated pituitary tumor due to potential stimulation of tumor growth.

KEY POINT

- Isolated adult-onset growth hormone deficiency is extremely rare, and its clinical significance is debated; evaluation for growth hormone deficiency should be reserved for adults with at least one known pituitary hormone deficiency.

HVC

Central Diabetes Insipidus

H

Central diabetes insipidus (DI) results from inadequate production of antidiuretic hormone (ADH) by the posterior pituitary gland. In the presence of ADH, aquaporin water channels are inserted in the collecting tubules and allow water to be reabsorbed. In the absence of ADH, excessive water is excreted by the kidneys. Excretion of more than 3 liters of urine per day is considered polyuric.

The severity of DI varies with the completeness of the deficiency. Patients describe mild to extreme polyuria and corresponding thirst; partial DI is common.

Frank hypernatremia is unusual because patients develop extreme thirst and polydipsia, and with free access to water, can maintain serum sodium in the high normal range. When patients do not drink enough to replace the water lost in the urine, due to poor or absent thirst drive or lack of free access to water, they develop hypernatremia.

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CONT.

In the patient with polyuria, DI is diagnosed with simultaneous laboratory evidence of inability to concentrate urine in the face of elevated serum sodium and osmolality, with inappropriately low urine osmolality. If necessary, a water deprivation test can confirm the diagnosis (see Table 15).

Patients with mild partial DI with an adequate thirst drive and access to water may choose to compensate without hormone replacement therapy, but highly symptomatic polyuria and nocturia that interferes with restful sleep and daily function necessitate treatment. In those requiring treatment, hormone replacement is with desmopressin (1-desamino-8-D-arginine vasopressin, or dDAVP) either intranasally, subcutaneously, or orally. Desmopressin is not absorbed well in the gastrointestinal tract, so oral doses are much higher than intranasal or subcutaneous doses. Most patients with DI require either evening dosing to aid in sleep or twice daily dosing of desmopressin. If ADH is overreplaced, patients will develop water intoxication, volume overload, and hyponatremia.

KEY POINTS

- In the patient with polyuria, diabetes insipidus is diagnosed by clinical symptoms with simultaneous laboratory evidence of inability to concentrate urine with elevated serum sodium and osmolality, and inappropriately low urine osmolality; a water deprivation test can confirm the diagnosis.
- Treatment of central diabetes insipidus is once or twice daily hormone replacement with desmopressin.

Panhypopituitarism

Panhypopituitarism occurs when patients lack all anterior and posterior pituitary hormone production. Panhypopituitarism may be caused by a large or aggressive pituitary tumor or as a complication of surgery. If the pituitary stalk is transected during surgery or as the result of trauma, panhypopituitarism will result acutely. Patients with panhypopituitarism require lifelong replacement of T_4, cortisol, and ADH because these deficiencies can be life-threatening. GH and sex hormones are replaced dependent on each patient's preference, coupled with a discussion of the risks and benefits of therapy. In addition to requiring exogenous gonadotropins to conceive, a reproductive-aged woman with panhypopituitarism will not go into spontaneous labor and will not lactate. These pregnancies are classified as high risk, and obstetric care should be provided by a maternal-fetal specialist.

Patients with panhypopituitarism should wear medical alert identification documenting their panhypopituitarism, specifically noting the need for stress-dose glucocorticoid therapy and desmopressin dosing in emergent situations.

KEY POINT

- Patients with panhypopituitarism require lifelong replacement of thyroxine (T_4), cortisol, and antidiuretic hormone because these deficiencies can be life-threatening.

Pituitary Hormone Excess

Pituitary tumors are called functional when they secrete excessive amounts of hormone. The most common functional pituitary tumor is a prolactinoma. GH and ACTH overproduction by pituitary tumors is important to recognize because the clinical consequences of oversecretion are potentially severe. TSH-secreting tumors cause hyperthyroidism but are extremely rare.

Occasionally, a pituitary tumor can oversecrete more than one hormone, most commonly GH and prolactin, or less commonly, TSH and GH or prolactin.

Hyperprolactinemia and Prolactinoma

Causes

Prolactinomas are pituitary tumors that secrete excessive amounts of prolactin; however, they are not the only cause of hyperprolactinemia (**Table 16**).

The most common cause of hyperprolactinemia is physiologic; prolactin is released during pregnancy and postpartum to cause lactation. Nipple stimulation such as during sex can cause mild hyperprolactinemia (serum prolactin <40 ng/mL [40 µg/L]). Physiologic stress, coitus, and exercise can also increase prolactin levels up to 40 ng/mL (40 µg/L). Nipple piercing can raise prolactin levels above 200 ng/mL (200 µg/L). Clinical breast examination should not raise prolactin levels above the reference range, unless evaluation for milk production is performed, but if desired, palpation of the breast can be deferred until after a serum prolactin level is measured.

Medications are a common cause of hyperprolactinemia (see Table 16). Antipsychotic agents cause hyperprolactinemia due to their antidopaminergic effect that interrupts the inhibition of prolactin by dopamine. Specific agents, such as risperidone or metoclopramide, may raise the prolactin level above 200 ng/mL (200 µg/L). Evaluation for pituitary hypersecretion when a patient is taking a medication known to raise the prolactin level is difficult. When the prolactin level is only mildly elevated (<50 ng/mL [50 µg/L]), it may be reasonable to assume that hyperprolactinemia is a medication side effect. When significantly elevated (>100 ng/mL [100 µg/L]), either the

TABLE 16. Causes of Hyperprolactinemia

Physiologic	Medications	Other
Pregnancy	Antipsychotic agents[a]	Prolactinoma
Lactation	Metoclopramide	Pituitary tumor—stalk compression
Nipple stimulation	Cimetidine	Hypothyroidism
	Verapamil	Cirrhosis
	Methyldopa	Chronic kidney disease
	Opiates	
	Cocaine	

[a]Including risperidone, olanzapine, haloperidol, chlorpromazine, and clomipramine.

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medication needs to be withheld to further assess or a pituitary MRI obtained to evaluate for prolactinoma. Caution is warranted when discontinuation of an antipsychotic agent is being considered, and consultation with a psychiatrist is recommended prior to discontinuation.

Another common cause of hyperprolactinemia is primary hypothyroidism. Hypothyroidism can cause diffuse swelling of the pituitary gland that may resemble enlargement due to a pituitary adenoma on imaging. Therefore, a patient with primary hypothyroidism and hyperprolactinemia should be treated with thyroid hormone replacement with retesting of the prolactin level once the TSH has normalized. Further evaluation is indicated if the hyperprolactinemia does not correct when hypothyroidism is treated. If pituitary imaging has noted pituitary enlargement prior to treatment of hypothyroidism, repeat MRI should be obtained when the TSH is normal.

Nonfunctioning pituitary adenomas can also cause hyperprolactinemia by compressing the pituitary stalk and decreasing dopamine inhibition of prolactin secretion. It is important to distinguish between prolactinomas and nonfunctioning pituitary adenomas as the cause of hyperprolactinemia because of different treatment approaches.

Clinical Features and Diagnosis

Physiologically, prolactin induces and regulates lactation. Hence, elevated levels of prolactin cause galactorrhea. Women are more likely to develop galactorrhea than men.

Hyperprolactinemia also causes hypogonadotropic hypogonadism because of negative feedback on GnRH, LH, and FSH by high levels of prolactin. Both men and women present with hypogonadism. Women of reproductive age often present earlier than men because of amenorrhea. They may also have early menopausal symptoms. Symptoms in men are insidious and may go unrecognized for years. Both men and women with hyperprolactinemia are likely to be infertile and are at risk for osteoporosis. Postmenopausal women are already hypogonadal because of ovarian failure; therefore, hyperprolactinemia may have minimal clinical implications in this population. However, the cause of postmenopausal hyperprolactinemia still requires diagnosis because it may be due to a pituitary tumor.

Diagnostic imaging is indicated in situations in which there is unexplained hyperprolactinemia.

The degree of hyperprolactinemia is useful in differentiating prolactinomas from nonfunctioning macroadenomas. In general, large nonfunctioning tumors cause mild serum prolactin elevations (<100 ng/mL [100 µg/L]) from stalk compression. Macroprolactinomas raise serum prolactin levels to greater than 250 ng/mL (250 µg/L). Very large macroprolactinomas may raise prolactin levels greater than 10,000 ng/mL (10,000 µg/L).

Therapy

Patients with microprolactinomas without symptoms of hypogonadism do not require treatment. Symptomatic women with microadenomas may be treated with either oral contraceptive pills (if fertility is not desired) or dopamine agonists. Postmenopausal women with microadenomas do not require treatment. Patients with hypogonadism from medication-induced hyperprolactinemia may be treated with hormone replacement.

Unlike other pituitary tumors, medication rather than surgery is first-line therapy for prolactinomas. Even patients with severe mass effect such as vision loss are treated with medical therapy initially. Rarely, very large tumors or more invasive prolactinomas do not shrink with medical therapy and, also rarely, continue to grow. In these patients, surgery should be considered, followed by radiotherapy if growth recurs or continues. After being debulked, the prolactinoma may respond better to medical therapy.

Prolactinomas are treated with dopamine agonists (DA). The two FDA-approved dopamine agonists are bromocriptine and cabergoline. Dopamine agonists typically decrease the size and hormone production of prolactinomas rapidly. Response to therapy can be monitored by checking serum prolactin levels 1 month after initiating therapy and then every 3 to 4 months. Decreasing serum prolactin usually correlates with decreasing size of the tumor. MRI should be repeated in 1 year for microprolactinomas if the prolactin level normalizes on dopamine agonists. After tumor shrinkage is confirmed, additional MRIs are not necessary unless the serum prolactin level rises. An MRI should be repeated after 3 months of medical therapy for macroprolactinomas, or if prolactin levels are rising on therapy with good medication adherence. MRI should be repeated every 6 to 12 months until the macroprolactinoma is stable on serial studies and the prolactin level is not rising.

Bromocriptine is dosed 1 to 3 times daily, so adherence can be challenging. When initiated, it is associated with orthostasis and lightheadedness, and patients can have dizziness, nausea, and headache during treatment. Cabergoline is much better tolerated and more effective at normalizing prolactin and tumor shrinkage, so it is typically the initial therapy chosen. It is dosed once or twice a week, but typically costs more than bromocriptine.

Therapy may be tapered after the prolactin level has been normal for 2 years, and there is no longer a visible tumor on pituitary MRI. After discontinuing the dopamine agonist, prolactin levels should be followed once a month for 3 months, then every 3 months for the first year, and then annually thereafter; a pituitary MRI should be repeated if the prolactin level rises above normal.

Prolactinomas and Pregnancy

Hyperprolactinemia is a frequent cause of infertility because of the effect on gonadotropin release. DA therapy lowers prolactin, normalizing gonadotropin regulation and allowing normal ovulation. DA therapy should be discontinued when the pregnancy is diagnosed. The pituitary increases in size during normal pregnancy, and prolactinomas can increase in size as well. The risk for significant tumor expansion is negligible in patients with microprolactinomas.

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Women with macroprolactinomas are at risk for clinically significant tumor growth or vision compromise during pregnancy. If the tumor is very large or abuts the optic chiasm, patients should be counseled on risk of tumor growth during pregnancy, as well as the risks and benefits of surgical resection of the tumor before pregnancy. DA therapy is sometimes continued during pregnancy if the patient has a history of visual field defect.

Pregnant women with macroprolactinomas should be assessed clinically at least once per trimester and have visual fields tested every trimester or more frequently for vision change. Changes in visual fields or severe headache are indications to proceed with pituitary MRI. If the macroprolactinoma causes mass effect during pregnancy, bromocriptine may be started. If the bromocriptine does not decrease tumor size and reduce symptoms of mass effect, surgical debulking may be necessary.

Normal pregnancy causes hyperprolactinemia, so hyperprolactinemia from prolactinoma does not require treatment during pregnancy. Prolactin levels should not be measured during pregnancy. Postpartum, prolactin levels return to normal within a few months, and lactation becomes nonprolactin mediated.

KEY POINTS

- Prolactinomas, pregnancy and lactation, or medications such as antipsychotic agents are frequent causes of hyperprolactinemia.
- A patient with primary hypothyroidism and hyperprolactinemia should be treated with thyroid hormone replacement with retesting of the prolactin level once the thyroid-stimulating hormone level has normalized.
- Dopamine agonists (bromocriptine and cabergoline) are first-line therapy for symptomatic patients with hyperprolactinemia and prolactinomas.

Acromegaly

Acromegaly is a rare diagnosis that is often missed for years because of the insidious onset and rare presentation in primary care; however, it has very serious implications for a patient's health and longevity and must be diagnosed and treated in as timely a manner as possible.

Causes

Acromegaly is the clinical syndrome that occurs when a pituitary tumor secretes excessive amounts of GH in an adult patient. Prior to puberty, patients with a GH-secreting tumor develop excessive longitudinal growth and gigantism, a term used to indicate excessive growth and height above normal for age. Because epiphyseal growth plates require sex hormones to close, patients with large pituitary tumors causing hypogonadism will not have closure of their growth plates and will continue growth into adulthood.

Clinical Features and Diagnosis in the Adult Patient with Acromegaly

Patients have changes in facial structure such as a prominent brow and jawline, an enlarged skull, a large nose, facial edema, excessive spacing between teeth, and macroglossia. The hands and feet may be disproportionately large. Other manifestations may include arthritis, skin tags, diabetes mellitus, hypertension, colon polyps, thickened skin, and excessive perspiration. Acromegaly can cause severe obstructive sleep apnea because of soft-tissue swelling and macroglossia. Additionally, it can result in heart disease, including left ventricular hypertrophy, cardiomyopathy, valvular heart disease, arrhythmia and diastolic heart failure. Increased rates of cancer are observed in acromegaly, including colon, esophageal, and gastric adenocarcinomas; thyroid cancer; and melanoma. Acromegaly increases mortality, likely due to cardiovascular disease, diabetes, sleep apnea, and cancer. Age-appropriate testing for these conditions should occur for the lifetime of the patient with acromegaly.

Acromegaly is diagnosed biochemically. Because GH is pulsatile throughout the day, it is not useful for diagnosis, so measurement of serum IGF-1 is used instead. Excess GH is confirmed with an oral glucose tolerance test (see Table 15) because glucose normally suppresses GH levels to less than 1 ng/mL (1 µg/L). GH levels greater than 1 ng/mL (1 µg/L) are diagnostic of GH excess. A pituitary MRI should be obtained once GH excess is confirmed biochemically. Consultation with an endocrinologist is recommended if IGF-1 is elevated.

Treatment

Treatment of acromegaly is transsphenoidal tumor resection; surgery is the only treatment that is potentially curative. In many instances, cure with surgery is not possible and additional therapy is necessary to treat the residual GH excess and tumor.

Remission is achieved when IGF-1 levels are within the normal reference range for age and the response of GH to a glucose tolerance test is normal. Patients not achieving remission require medication to decrease GH levels and the long-term effects of GH excess. The initial therapy of choice is injectable somatostatin analogues to inhibit GH secretion. If a patient fails to benefit from somatostatin analogue treatment, high-dose dopamine agonist therapy is marginally effective when the tumor co-secretes prolactin. If IGF-1 remains elevated, pegvisomant, a GH receptor blocker, is used. Pegvisomant effectively lowers IGF-1 levels, but patients on pegvisomant have risk of tumor growth because the medication works in the peripheral tissues as an antagonist to GH and does not decrease GH production by the tumor.

Stereotactic radiosurgery (gamma knife) may be offered to increase the chance of remission or cure. External beam radiation carries a high risk of causing pituitary insufficiency, but the risk is decreased when stereotactic radiosurgery is used.

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When acromegaly is in remission, MRI and hormone testing should be completed annually. When the pituitary tumor is stable but the IGF-1 level is elevated, MRI should be repeated annually and treatment should be altered until the IGF-1 declines.

KEY POINTS

- Acromegaly occurs when a pituitary tumor secretes excessive amounts of growth hormone in an adult patient resulting in changes in facial structure, an enlarged skull, a large nose, facial edema, excessive spacing between teeth, macroglossia, and disproportionately large hands and feet.
- Treatment of acromegaly is transsphenoidal tumor resection; however, in some patients, adjuvant radiation therapy or medical therapy, such as injectable somatostatin analogues, is needed for residual disease.

Gonadotropin-Producing Adenomas

Gonadotropin-producing pituitary adenomas are typically asymptomatic and are treated similarly to nonfunctioning adenomas because they either do not secrete functional gonadotropins or do not secrete enough FSH or LH to produce a clinical syndrome. Often, the diagnosis is made postoperatively, based on histopathologic staining of surgical pathology specimens.

Thyroid-Stimulating Hormone-Secreting Tumors

TSH-secreting tumors are extremely rare. These tumors may co-secrete TSH and prolactin or GH. TSH-secreting tumors cause hyperthyroidism. Patients with TSH-secreting tumors have either an inappropriately normal or a high TSH level with a simultaneous elevation of T_4 and T_3 levels. They present with identical symptoms associated with non-TSH-mediated thyrotoxicosis (see Disorders of the Thyroid Gland). After biochemical proof of TSH excess is obtained, pituitary imaging is recommended to confirm a pituitary mass. Neurosurgery is first-line therapy, but patients often require additional medical therapy with either somatostatin analogues or dopamine agonists.

Excess Antidiuretic Hormone Secretion

The syndrome of inappropriate ADH secretion (SIADH) causes water retention and hyponatremia. Central nervous system pathology such as stroke, hemorrhage, trauma, or infection can cause SIADH because of the excessive release of hypothalamic and pituitary ADH. Also, transient SIADH is a common complication of pituitary surgery, occurring in about one third of patients approximately 3 to 10 days after surgery (see MKSAP17 Nephrology).

Cushing Disease

Cushing disease is the term used to indicate excess cortisol production due to an ACTH-secreting pituitary adenoma. Cushing syndrome refers to hypercortisolism from any cause, exogenous or endogenous, ACTH-dependent or not. The most common cause of endogenous Cushing syndrome is Cushing disease. When undiagnosed, Cushing disease is associated with devastating long-term morbidity such as diabetes, morbid obesity, hypertension, infertility, and osteoporosis.

The initial step in evaluation for Cushing disease is to seek biochemical evidence of hypercortisolism (see Disorders of the Adrenal Glands).

Once ACTH-dependent Cushing syndrome is confirmed biochemically, a pituitary MRI should be obtained. If no pituitary tumor or a tumor less than 6 mm is visualized on MRI, an 8-mg dexamethasone suppression test is used to differentiate Cushing disease from an ectopic source of ACTH. Ectopic ACTH production from a nonpituitary tumor (most often lung, pancreas, or thymus carcinomas) is very uncommon.

Dexamethasone is administered at 11 PM, and cortisol is tested at 8 AM. A pituitary source of ACTH will respond to negative feedback from high doses of dexamethasone, suppressing cortisol to less than 5 μg/dL (138 nmol/L), while an ectopic source of ACTH will not have suppressible cortisol. However, this test has low sensitivity (88%) and specificity (57%) for Cushing disease, so intrapetrosal sinus sampling (IPSS) is often recommended before exploratory pituitary surgery. In IPSS, a catheter is threaded through the petrosal sinus, and ACTH levels in the sinus are compared with those in the periphery after the administration of corticotropin-releasing hormone (CRH). A central to peripheral gradient greater than 2.0 before CRH or greater than 3.0 after CRH is diagnostic of Cushing disease (95% sensitivity, 93% specificity). Imaging of the chest and abdomen is indicated in patients with a suspected ectopic source of ACTH.

Treatment

Cushing disease is treated by transsphenoidal pituitary tumor resection, which may be curative. Endogenous ACTH production in the remaining normal pituitary gland will be suppressed after removal of the tumor due to long-standing hypercortisolism, so patients with successful surgical treatment will have acute ACTH deficiency and require glucocorticoid replacement. It may take up to 1 year for endogenous ACTH production to return to normal, and sometimes the hypothalamic-pituitary-adrenal axis does not recover. After successful resection, Cushing disease can recur, and patients must be monitored annually for several years, and then less frequently, or sooner if symptoms of hypercortisolism recur.

If surgical cure is not achieved, patients may be offered pituitary radiation or medical therapy. Medical options include inhibitors of adrenal enzyme synthesis of cortisol, ketoconazole, or metyrapone; the dopamine agonist, cabergoline; or the somatostatin analogue, pasireotide. Medical cure of Cushing disease has a relatively low success rate, but hypercortisolism symptom control is an achievable goal in all patients with endogenous Cushing syndrome.

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CONT.

In patients who do not benefit from surgical treatment and who have an inadequate response to medical treatment, bilateral adrenalectomy to remove the target of ACTH stimulation is an option. However, these patients will require lifelong glucocorticoid and mineralocorticoid replacement.

KEY POINTS

- Cushing disease refers to excess cortisol production due to an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma; Cushing syndrome refers to hypercortisolism from any cause, exogenous or endogenous, ACTH-dependent or not.
- Cushing disease is treated by transsphenoidal pituitary tumor resection; after surgery glucocorticoid replacement therapy will be required at least transiently while the hypothalamic-pituitary-adrenal axis recovers endogenous function.

Disorders of the Adrenal Glands

Adrenal Anatomy and Physiology

Located just superior to each kidney, the paired adrenal glands consist of an outer cortex and an inner medulla that are distinct in embryologic origin and endocrine function. The adrenal cortex is composed of three zones: the zona (outer) glomerulosa, zona (middle) fasciculata, and zona (inner) reticularis. Within these zones corticosteroid hormones are synthesized from cholesterol by cytochrome P450 enzymes. Aldosterone, the principal mineralocorticoid hormone, is produced in the zona glomerulosa. Aldosterone production is triggered by an increase in the extracellular potassium concentration and by activation of aldosterone synthase through the renin-angiotensin-aldosterone pathway. Upon binding to type 1 mineralocorticoid receptors (MR) in the kidney, aldosterone promotes potassium wasting and sodium retention, which leads to an increase in intravascular volume and consequently blood pressure.

The zona fasciculata is the main site of glucocorticoid synthesis. Production of cortisol, the principal glucocorticoid, is stimulated by adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary. Cortisol secretion varies according to the circadian rhythm with relatively little secretion overnight, peak levels in the early morning, and smaller oscillations throughout the day. Cortisol attenuates inflammatory responses and contributes to glucose homeostasis by promoting lipolysis, hepatic gluconeogenesis, and insulin resistance. Physical stress (for example, critical illness) stimulates increased cortisol secretion, which enhances vascular smooth muscle tone and responsiveness to endogenous vasoconstrictors, thereby augmenting blood pressure.

Synthesis of adrenal androgens, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), and androstenedione, occurs primarily in the zona reticularis and is regulated by ACTH. Although the adrenal androgens themselves have minimal intrinsic androgenic activity, they are converted peripherally to testosterone and dihydrotestosterone. Unlike glucocorticoids and mineralocorticoids, deficiencies of adrenal androgens are not typically recognized due to parallel production of gonadal androgens.

The adrenal medulla and extra-adrenal sites of the sympathetic nervous system consist of chromaffin cells, which synthesize catecholamine hormones from the amino acid tyrosine (**Figure 4**). Catecholamines are stored within chromaffin granules, which release their contents in response to stress. Although catecholamine excess produces disease, hypofunction of the adrenal medulla does not because of redundancy of catecholamine production throughout the sympathetic nervous system. Norepinephrine is synthesized in the adrenal medulla and the extra-adrenal sites of the sympathetic nervous system. It causes vasoconstriction due to preferential binding to α-receptors. Epinephrine is almost exclusively produced in the adrenal medulla. It binds predominantly to β-receptors, and thus has positive effects on cardiac inotropy and chronotropy, produces peripheral vasodilation, and increases plasma glucose levels in response to hypoglycemia.

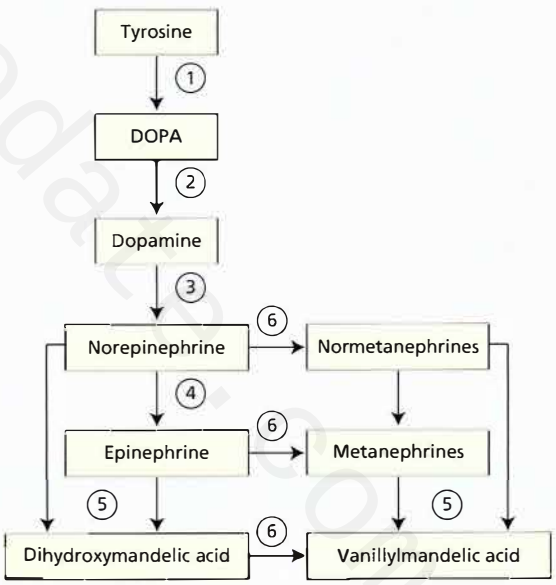

FIGURE 4. Catecholamine hormones are produced in the adrenal medulla and sympathetic ganglia. The pathways of synthesis and degradation are shown. Excessive catecholamine secretion can occur with pheochromocytomas and paraganglionomas.
1 = Tyrosine hydroxylase
2 = DOPA decarboxylase
3 = Dopamine β-hydroxylase
4 = Phenylethanolamine *N*-methyltransferase (PNMT)
5 = Monoamine oxidase (MAO)
6 = Catechol-*O*-methyltransferase (COMT)

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Adrenal Hormone Excess

Cushing Syndrome

Cushing syndrome (CS) is a rare disorder affecting two to three persons per million per year that results from elevated levels of cortisol. Poor suppressibility of cortisol with dexamethasone and loss of normal diurnal variation in cortisol secretion are seen. Without treatment, it is associated with high morbidity and mortality.

However, iatrogenic hypercortisolism from the administration of exogenous oral, inhaled, intra-articular, or topical glucocorticoids is often seen in clinical practice and is the most common cause of CS overall. The pharmacokinetics and relative potencies of synthetic oral glucocorticoids are shown in **Table 17**. The sustained administration of any synthetic glucocorticoid above the normal physiologic cortisol requirement can result in iatrogenic CS and hypothalamic-pituitary-adrenal (HPA) axis suppression, but is more likely to occur the longer the half-life of the drug. Doses equivalent to prednisone 5 mg/d or less are unlikely to cause clinically significant HPA axis suppression, while those in excess of 10 to 20 mg/d commonly do after 3 weeks or more of consecutive use.

Endogenous CS can result from ACTH-dependent and ACTH-independent causes. Cushing disease, which results from the autonomous secretion of ACTH by a corticotroph adenoma of the pituitary gland, is the cause of CS in more than two thirds of patients (see Disorders of the Pituitary Gland). Ectopic ACTH secretion by carcinomas and carcinoid tumors (usually bronchial origin) is less common, accounting for 10% to 15% of cases, while ectopic corticotropin-releasing hormone (CRH) production is rare. The most common ACTH-independent etiologies of CS are adrenal adenomas and carcinomas, which collectively account for approximately 20% of CS cases.

CS must be differentiated from other disorders and clinical states that are associated with physiologic hypercortisolism (pseudo-Cushing syndrome). Causes of pseudo-Cushing syndrome include severe obesity, polycystic ovary syndrome, pregnancy, anorexia nervosa, depression, alcoholism, and extreme physical stress, as in the setting of infection.

Clinical manifestations of CS are listed in **Table 18**. Clinical findings that are highly specific for CS include centripetal obesity, facial plethora, abnormal fat deposition in the supraclavicular or dorsocervical ("buffalo hump") areas, and wide (>1 cm) violaceous striae (**Figure 5**). It is important to initiate evaluation for CS in patients who have specific signs and symptoms of CS, rather than in patients who are diffusely obese, have nonpathologic striae, and are having trouble losing weight because endogenous CS is such a rare condition with a costly evaluation algorithm.

Biochemical testing is used to establish the diagnosis of CS. It is critical that the biochemical diagnosis is firmly established prior to any imaging studies due to the relatively high prevalence of clinically insignificant pituitary and adrenal nodules. At least two first-line tests should be diagnostically abnormal before the diagnosis is confirmed. Initial tests include the overnight low-dose dexamethasone suppression test (LDST), 24-hour urine free cortisol (UFC), and late-night (LN) salivary cortisol. All three tests have similar diagnostic utility, but the LDST or LN salivary cortisol tests are more convenient. The 24-hour UFC and LN salivary cortisol tests should be performed at least twice to ensure reproducibility of results. Because the secretion of cortisol is pulsatile, measurement of random serum cortisol is neither sensitive nor specific for the diagnosis of CS. An algorithm to establish the diagnosis of CS is shown in **Figure 6**. Referral to an endocrinologist is indicated if two initial tests are abnormal.



FIGURE 5. Wide violaceous striae are seen on the abdomen of a patient with Cushing syndrome. Striae larger than 1 cm in width are highly specific for hypercortisolism.

TABLE 17. Dose Equivalence and Relative Potencies of Common Synthetic Oral Glucocorticoids

Synthetic Glucocorticoid	Equivalent Replacement Dose (mg)[a]	Biologic Half-Life (hours)	Relative Anti-Inflammatory Potency[b]	Relative Mineralocorticoid Potency[c]
Hydrocortisone	20	8-12	1	1/125
Prednisolone/prednisone	5	18-36	4	1/156
Methylprednisolone	4	18-36	5	0
Dexamethasone	0.75	36-54	25-50	0

[a]Denotes common glucocorticoid dosing for primary adrenal failure equivalent to hydrocortisone, 20 mg.

[b]Anti-inflammatory potency relative to hydrocortisone.

[c]Mineralocorticoid potency relative to fludrocortisone.

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TABLE 18. Clinical Features of Cushing Syndrome

Specific Findings	Less Specific Findings	Associated Conditions[a]
Centripetal obesity	Easy bruising	Osteoporosis
Facial plethora	Excessive skin fragility	Hypertension
Supraclavicular fat pads	Proximal muscle weakness	Diabetes mellitus
Dorsocervical fat pads	Impaired memory	Obesity
Wide violaceous striae	Temporal balding[b]	Depression
	Hirsutism (in women)[b]	Hypokalemia
	Menstrual abnormalities[b]	Nephrolithiasis
		VTE/PE

PE = pulmonary embolism; VTE = venous thromboembolism.

[a]Medical disorders that may be seen in association with but are not specific for Cushing syndrome.

[b]Features of androgen excess seen with pituitary corticotroph adenoma or adrenocortical carcinoma.

In the standard LDST, dexamethasone (0.5 mg) is administered every 6 hours for 48 hours and serum cortisol is measured at 9 AM. In the overnight LDST, 1 mg of dexamethasone is administered at 11 PM or midnight, and serum cortisol is measured the next morning at 8 AM. With either test, serum cortisol will typically be suppressed to less than 2 µg/dL (55 nmol/L). Standard assays measure total serum cortisol, or that which is bound to cortisol-binding globulin (CBG) and other proteins. Therefore the LDST should not be performed when CBG is likely to be abnormal, such as with malnutrition, cirrhosis, the nephrotic syndrome, and hyperestrogenemia (oral contraceptive pills or pregnancy). There is no clear association between dexamethasone responses and BMI or weight, and therefore the LDST may be used similarly in the obese population. The LDST is best avoided in patients taking medications that could accelerate dexamethasone metabolism, such as antiepileptic drugs (phenytoin, phenobarbital, and carbamazepine), rifampin, or pioglitazone. Concomitant measurement of serum dexamethasone can confirm altered dexamethasone metabolism and patient adherence.

Measuring 24-hour UFC circumvents problems related to cortisol pulsatility and binding protein abnormalities. The test should be performed at least twice to ensure accuracy. To confirm adequate collection, 24-hour urine creatinine is also measured (normal range, 20-25 mg/kg/24 h [177-221 mmol/kg/24 h] in men; 15-20 mg/kg/24 h [133-177 mmol/L/24 h] in women). A test is considered abnormal when UFC exceeds the upper limit of the normal range of the assay (45 µg/24 h [124 nmol/24 h]), while values greater than 3 times normal are diagnostic of CS. Less marked elevations are seen with pseudo-Cushing syndrome and polyuria. A falsely low UFC can occur in chronic kidney disease and when CS is subclinical or mild.

The LN salivary cortisol test is performed between 11 PM and midnight. The normal evening nadir in cortisol secretion is lost in patients with CS, while it is preserved in patients with pseudo-Cushing syndrome. Both emotional and physical stress (for example, exercise) can cause a physiologic increase of salivary cortisol. False-positive results are seen with

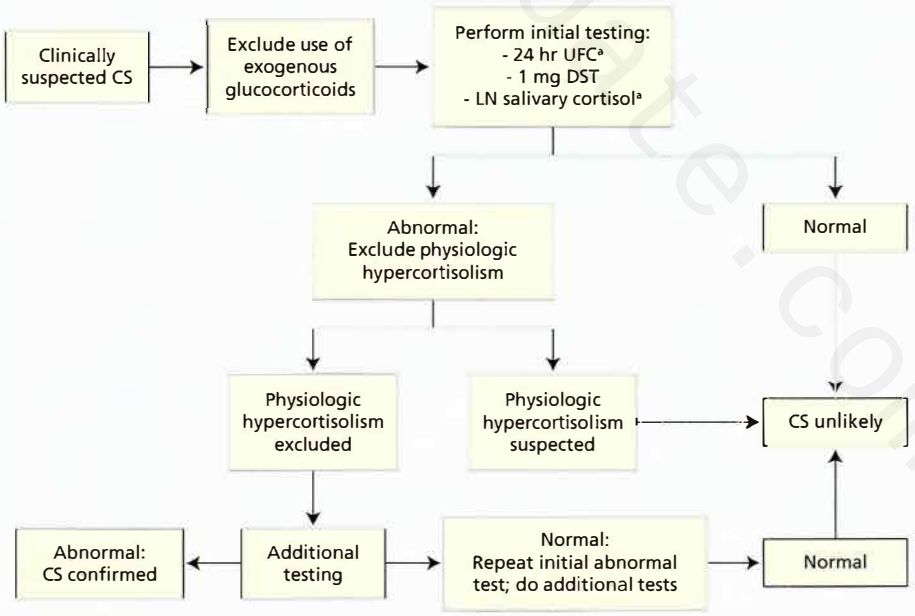

FIGURE 6. Algorithm to confirm or rule out the diagnosis of Cushing syndrome. CS = Cushing syndrome; DST = dexamethasone suppression test; LN salivary cortisol = late-night salivary cortisol; UFC = urine free cortisol.

[a]Must be performed at least twice.

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cigarette smoking or use of chewing tobacco. LN salivary cortisol testing should not be performed in patients with erratic sleep schedules (for example, shift-workers).

After CS has been confirmed biochemically, further testing is required to distinguish ACTH-dependent or -independent causes, and consultation with an endocrinologist is recommended. The first step is to measure plasma ACTH on two separate occasions. With adrenal (ACTH-independent) CS, plasma ACTH is usually less than 5 pg/mL (1.1 pmol/L), whereas values greater than 20 pg/mL (4.4 pmol/L) are typically seen with ACTH-dependent causes. Plasma ACTH values of 5 to 20 pg/mL (1.1-4.4 pmol/L) are nondiagnostic but are more likely to be seen with ACTH-dependent disorders. For a discussion of the evaluation and management of ACTH-dependent CS, see Disorders of the Pituitary Gland.

The next step in the evaluation of ACTH-independent CS is with imaging of the adrenal glands, such as dedicated adrenal imaging with thin-section CT or MRI. Both studies have equal sensitivity; however, MRI is more costly. Adrenal adenomas and carcinomas can usually be distinguished from one another radiographically (**Table 19**). Surgery is considered first-line treatment for adrenal adenomas and nonmetastatic adrenocortical carcinomas (ACCs). When surgery is delayed for patients with overt CS, adrenal enzyme inhibitors (metyrapone, ketoconazole, and etomidate) can be used to reduce cortisol levels and decrease the risk of complications, such as opportunistic infections and cardiovascular events. The management of ACC is discussed elsewhere (see Adrenocortical Carcinoma).

Following adrenalectomy, patients with adrenal CS will often develop acute adrenal insufficiency because of HPA axis suppression and contralateral adrenal atrophy from long-standing elevated cortisol levels. All patients should therefore be treated with stress-dose glucocorticoids during the perioperative period and continued on physiologic replacement until HPA axis recovery has been confirmed. Following successful surgery, the physical changes associated with CS can take up to 1 year to resolve.

KEY POINTS

- Cushing syndrome results from endogenous hypercortisolism or exogenous exposure to glucocorticoids; it is associated with poor suppressibility of endogenous cortisol production with oral dexamethasone.
- The most common cause of Cushing syndrome is the administration of exogenous glucocorticoid therapy for another medical condition.
- Initial tests for Cushing syndrome include the overnight low-dose dexamethasone suppression test, 24-hour urine free cortisol, and late-night salivary cortisol.

Pheochromocytomas and Paragangliomas

Paragangliomas are tumors composed of chromaffin cells. Approximately 80% are intra-adrenal (pheochromocytomas); the rest originate from extra-adrenal sympathetic or parasympathetic paraganglia. The most common location for extra-adrenal sympathetic paragangliomas is the abdomen, whereas parasympathetic paragangliomas are usually found in the head and neck. Pheochromocytomas and extra-adrenal sympathetic paragangliomas almost always secrete catecholamines (norepinephrine, epinephrine, dopamine); however, head and neck parasympathetic paragangliomas almost never do.

TABLE 19. Typical Imaging Characteristics of Adrenal Masses

Adrenal Mass	Overall	CT	MRI Signal Intensity[a]
Adrenal adenoma	Diameter <4 cm	Density <10 HU	Isointense on T2-weighted images
	Homogeneous enhancement[b]	Contrast washout >50% (10 min)	
	Round, clear margins		
Adrenocortical carcinoma	Usually >4 cm	Density >10 HU	Hyperintense on T2-weighted images
	Heterogeneous enhancement[b]	Contrast washout <50% (10 min)	
	Irregular margins		
	Calcifications, necrosis		
Pheochromocytoma	Variable size	Density >10 HU	Hyperintense on T2-weighted images
	Heterogeneous enhancement[b], cystic areas	Contrast washout <50% (10 min)	
	Round, clear margins		
	Can be bilateral		
Metastases	Variable margins	Density >10 HU	Hyperintense on T2-weighted images
	Can be bilateral	Contrast washout <50% (10 min)	

HU = Hounsfield units (measure of radiodensity compared with water).

[a]Signal intensity as compared with liver.

[b]Enhancement following intravenous contrast administration.

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Although catecholamine-secreting tumors are rare overall, they are found in 0.5% of patients with hypertension, and pheochromocytomas account for 5% of adrenal incidentalomas (see Incidentally Noted Adrenal Masses). Most pheochromocytomas secrete norepinephrine, resulting in episodic or sustained hypertension. Orthostatic hypotension can also be seen and likely reflects low plasma volume. In addition to the classic triad of diaphoresis, headache, and tachycardia, common symptoms include palpitations, tremor, pallor, and anxiety. Less common features are papilledema, diabetes mellitus, and cardiomyopathy. Approximately 10% of pheochromocytomas and 20% to 50% of paragangliomas are malignant.

One third of pheochromocytomas and paragangliomas occur in the context of a genetic disorder. Pheochromocytomas are seen with multiple endocrine neoplasia (MEN) syndromes type 2A and 2B (**Table 20**), neurofibromatosis type 1, and von Hippel-Lindau syndrome (VHL). Paragangliomas and, less frequently, pheochromocytomas can occur with familial paraganglioma syndrome mutations, some of which are associated with high rates of malignancy.

The diagnosis of pheochromocytoma and paraganglioma is based on confirmation of the excessive secretion of catecholamines or their metabolites, as measured in the plasma or urine. Evaluation is recommended, if clinically suspected, in the evaluation of an incidentally noted adrenal mass or in the setting of hereditary pheochromocytoma or paraganglioma syndromes. The sensitivity of plasma free metanephrines is the highest of any screening test (96%-100%); however, its specificity is relatively low (85%-89%). Therefore, plasma free metanephrines will reliably exclude a pheochromocytoma when negative, but further testing is needed to confirm the diagnosis unless the result is markedly abnormal (above 4 times the upper limit of normal). The sensitivity and specificity of 24-hour urine fractionated metanephrines and catecholamines are 91% to 98%. Due to the lower frequency of false-positive results, 24-hour urine measurements are recommended when the pre-test probability of disease is relatively low (adrenal mass without typical radiographic appearance), while measurement of plasma free metanephrines is preferred when clinical suspicion is higher (known hereditary syndrome). Referral to an endocrinologist is recommended when biochemical testing is abnormal.

Many medications and other substances cause falsely high levels of plasma and urine catecholamines or metanephrines (**Table 21**); therefore, discontinuation of these agents before testing is recommended. If a catecholamine-secreting tumor is strongly suspected in a critically ill hospitalized patient, CT or MRI of the abdomen is the preferred initial test because biochemical testing cannot be interpreted reliably in this setting.

Following the biochemical diagnosis of pheochromocytoma or catecholamine-secreting paraganglioma, radiographic localization is needed. Because most catecholamine-secreting tumors are located in the abdomen, CT or MRI of the abdomen and pelvis is the best initial study. If negative, iodine 123 (^{123}I)-metaiodobenzylguanidine (MIBG) scanning can be performed. Adjunctive diagnostic tests are CT or MRI of the chest or head and neck region.

When multiple tumors or malignant pheochromocytomas or paragangliomas are suspected, MIBG scanning should be performed preoperatively. However, for identification of metastatic disease, fluorine 18 (^{18}F)-fluorodeoxyglucose (FDG) PET scanning is superior to other diagnostic tests.

Preoperative pharmacologic treatment is mandatory for pheochromocytomas and paragangliomas to prevent life-threatening cardiovascular complications related to the massive release of catecholamines during surgery. Preoperative blockade of α-adrenoceptors, usually with phenoxybenzamine, is first-line medical therapy. The dosage is titrated to achieve a blood pressure below 130/80 mm Hg seated and greater than 90 mm Hg (systolic) standing. Commonly used but non-FDA approved alternatives include calcium channel blockers and selective α_1-blockers (terazosin or doxazosin). β-Adrenoceptor blockers (metoprolol or propranolol) are

TABLE 20. Multiple Endocrine Neoplasm Syndromes

Type	Mutation	Most Common Feature	Associated Features
1	*MEN1* (inheritance of one mutated allele with somatic mutation in other allele leads to neoplasia)	Parathyroid adenoma (often multiple)	Pancreatic islet cell and enteric tumors (gastrinoma, insulinoma most common) Pituitary adenoma Other (carcinoid tumors, adrenocortical adenoma)
2A	*RET* (exon 11, codon 634[a])	Medullary thyroid carcinoma	Pheochromocytoma (often multifocal) Parathyroid hyperplasia
2B	*RET* (exon 16, codon 918[a])	Medullary thyroid carcinoma	Pheochromocytoma (often multifocal) Mucosal neuroma Gastrointestinal ganglioneuroma Marfanoid body habitus

[a]Most common mutation observed.

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TABLE 21. Substances Associated with False-Positive Biochemical Testing for Pheochromocytoma

Drug Class	Medication/Substance
Analgesics	Acetaminophen
Antiemetics	Prochlorperazine
Antihypertensives	Phenoxybenzamine[a]
Psychiatric medications	Antipsychotics
	Buspirone
	Monoamine oxidase inhibitors
	Tricyclic antidepressants[a]
Stimulants	Amphetamines
	Cocaine
	Caffeine
Other agents	Levodopa
	Decongestants (pseudoephedrine)
	Reserpine
Withdrawal	Clonidine
	Ethanol
	Illicit drugs

[a]Most likely to cause false-positive results.

added later to treat reflex tachycardia, but should never be started before adequate α-blockade has been achieved due to the risk of hypertensive crisis from unopposed α-receptor stimulation. A heart rate of 60 to 70/min seated and 70 to 80/min standing can be targeted in most patients.

Because it is associated with fewer surgical complications and shorter postoperative hospital stays, laparoscopic adrenalectomy is preferred for pheochromocytoma except in the case of large or malignant tumors, when open adrenalectomy is required. Following the surgical removal of a catecholamine-secreting tumor, large-volume intravenous crystalloid is administered to counter hypotension. Vasopressors (for example, norepinephrine) are sometimes required. Long-term follow-up is needed for pheochromocytomas and paragangliomas due to difficulty distinguishing benign from malignant tumors. Metastases have been reported up to 20 years after diagnosis. In addition to routine clinical surveillance, annual measurement of plasma or urine metanephrines is indicated to assess for recurrent or metastatic disease. Metastatic disease is managed with additional surgery, iodine 131 (^{131}I)-labeled MIBG therapy, chemotherapy, and/or radiotherapy. Cure is not possible unless all disease can be surgically resected.

KEY POINTS

- Pheochromocytomas are seen with multiple endocrine neoplasia (MEN) syndromes type 2A and 2B, neurofibromatosis type 1, and von Hippel-Lindau syndrome.

(Continued)

KEY POINTS *(continued)*

- When clinical suspicion of pheochromocytoma or paraganglioma is low, measurement of 24-hour urine fractionated metanephrines and catecholamines are the tests of choice because of their high specificity (low false-positive rates); when clinical suspicion is high, measuring plasma free metanephrines is preferred due to its greater sensitivity.
- Preoperative α-adrenergic blockade is first-line medical therapy for pheochromocytomas and paragangliomas; β-adrenoceptor blockers (metoprolol or propranolol) are added after α-blockade to treat reflex tachycardia.
- Pheochromocytomas and paragangliomas require lifelong surveillance for recurrence with annual plasma free metanephrine measurement.

Primary Hyperaldosteronism

Primary hyperaldosteronism (PA) results from the autonomous secretion of excessive aldosterone. PA is relatively common, occurring in approximately 10% of patients with hypertension. Additional signs of PA include hypokalemia and metabolic alkalosis. Without treatment, excess cardiovascular morbidity and mortality are seen.

Aldosterone-producing adrenocortical adenomas (APA; aldosteronomas) cause approximately 40% of PA, whereas nearly all other cases are due to bilateral adrenal hyperplasia. Unilateral adrenal hyperplasia and aldosterone-secreting adrenocortical carcinomas (ACCs) are rare. Familial hyperaldosteronism is also uncommon.

Testing for PA should be considered in all patients with difficult to control hypertension. It should also be performed in patients with hypertension and an incidentally noted adrenal mass or spontaneous or diuretic-induced hypokalemia. A number of disorders can mimic PA clinically; however, the results of biochemical testing will differ. Examples include secondary hyperaldosteronism (renal artery stenosis or renin-secreting tumors), autosomal dominant pseudoaldosteronism (Liddle syndrome), CS, certain forms of congenital adrenal hyperplasia (CAH), and licorice-induced hypermineralocorticoidism.

Initial screening for PA is with the simultaneous measurement of midmorning ambulatory plasma renin activity (PRA) and plasma aldosterone concentration (PAC), in a volume replete normokalemic patient. Testing is positive if PAC is frankly elevated (>15 ng/dL [414 pmol/L]), PRA is suppressed, and PAC/PRA ratio is greater than 20. Many medications, including common antihypertensive agents, can affect measurements of PAC, PRA, or both (**Table 22**). However, because patients undergoing screening often have drug-resistant hypertension, discontinuing all potentially offending medications can be unsafe. Stopping mineralocorticoid receptor antagonists (spironolactone and eplerenone) for 4 to 6 weeks prior to testing is recommended. Diuretics should also be discontinued prior to testing to assure euvolemia. Most other medications

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TABLE 22. The Effect of Commonly Prescribed Medications on Measurements of Plasma Renin Activity and Plasma Aldosterone Concentration

Effect on Test Results	Medication Class	PRA	PAC	PAC/PRA
False-Positive	α-Adrenoceptor agonist	↓↓	↓	↑
	β-Adrenoceptor blocker	↓↓	↓	↑
	Direct renin inhibitor	↓	↓	↑
	NSAID	↓↓	↓	↑
False-Negative	ACE inhibitor/ARB	↑↑	↓	↓
	Dihydropyridine CCB	↑	↓	↓
	Diuretic[a]	↑↑	↑	↓
	Mineralocorticoid receptor antagonist	↑↑	↑	↓
	SSRI		↑	↓

ARB = angiotensin receptor antagonist; CCB = calcium channel blocker; PAC = plasma aldosterone concentration; PRA = plasma renin activity; SSRI = selective serotonin reuptake inhibitor.

[a]Both potassium-sparing (amiloride) and potassium-wasting (hydrochlorothiazide) diuretics.

CONT.

can be continued, but results must be interpreted in context. For example, if PRA is suppressed despite treatment with an ACE inhibitor or angiotensin receptor blocker, PA is likely. If results are difficult to interpret, repeat testing after eliminating potential interfering medications is advised. Verapamil, hydralazine, and α-blockers (doxazosin) can be substituted for blood pressure control if necessary. Referral to an endocrinologist is recommended when screening tests are abnormal.

Confirmatory testing is performed except when initial testing is diagnostic for PA, as in cases of spontaneous hypokalemia with undetectable PRA and PAC greater than 30 ng/dL (828 pmol/L). Confirmatory tests include oral and intravenous salt loading and the fludrocortisone suppression and captopril challenge tests (**Table 23**).

Once the diagnosis of PA has been confirmed biochemically, radiographic localization with abdominal CT is indicated. CT is recommended over MRI in most cases due to similar efficacy and lower cost. Adrenal hyperplasia and adenomas can often be visualized and adrenocortical carcinoma can be ruled out. Adrenal vein sampling (AVS) is needed in most patients to determine the source of aldosterone secretion when imaging is unrevealing and to confirm lateralization when imaging demonstrates an adrenal adenoma. AVS is especially important in older patients (40 years and older) because of a higher frequency of nonfunctioning adrenal incidentalomas. AVS should be performed at experienced centers only.

The goals of treatment include improvement in blood pressure (resolution of hypertension is unlikely), normalization of serum potassium (this is very likely), and reduction in plasma aldosterone because hyperaldosteronemia is associated with a blood pressure–independent increase in cardiovascular events. The treatment of choice for PA due to APA or unilateral adrenal hyperplasia is laparoscopic adrenalectomy.

For patients with bilateral adrenal hyperplasia or those with unilateral causes of PA who are not surgical candidates, medical therapy with a mineralocorticoid antagonist is indicated. Spironolactone is the most commonly used medication due to its proven efficacy and cost-effectiveness. Eplerenone is less likely to cause side effects (gynecomastia in men and menstrual irregularities in women) because of greater mineralocorticoid receptor selectivity. Amiloride is a potassium-sparing diuretic that blocks the aldosterone-sensitive sodium channel. Use of amiloride in PA is second-line therapy because of lower efficacy.

TABLE 23. Laboratory Testing Used in the Diagnosis of Hyperaldosteronism

Test	Details	Positive If...
Captopril challenge test	Administer: Captopril 25-50 mg orally after the patient has been seated for 1 hour Measure: PAC, PRA, and cortisol at 0 and 1 or 2 hours while seated	PAC remains elevated and PRA suppressed (Normal response is suppression of PAC by >30%)
Fludrocortisone suppression test	Administer: Fludrocortisone 0.5 mg orally every 6 hours for 4 days along with sodium and potassium supplementation Measure: Serum cortisol at 7 and 10 AM, and PAC and PRA at 10 AM on day 4	PAC >6 ng/dL (165. 6pmol/L) PRA <1 ng/mL/h (1 µg/L/h) (Cortisol at 10 AM lower than 7 AM)
Oral salt loading test	Administer: Sodium chloride 6 g orally daily (in divided doses) for 3 days Measure: 24-hour urine aldosterone and urine Na on the third day	24-hour urine aldosterone >12 µg (Urine Na >200 mEq [220 mmol/L])
Intravenous salt loading test	Administer: 2 L 0.9% saline intravenously over 4 hours while supine Measure: PAC, PRA, cortisol, and serum K at 0 and 4 hours	PAC >10 ng/dL (276.0 pmol/L)

IM = intramuscular; IV = intravenous; K = potassium; Na = sodium; PAC = plasma aldosterone concentration; PRA = plasma renin activity.

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KEY POINTS

- Testing for primary hyperaldosteronism is with the simultaneous measurement of midmorning ambulatory plasma renin activity and plasma aldosterone levels; testing is positive if plasma aldosterone concentration is frankly elevated (>15 ng/dL [414 pmol/L]), plasma renin activity is suppressed, and a ratio of the former over the latter is greater than 20.
- The treatment of choice for primary hyperaldosteronism due to an aldosteronoma or unilateral adrenal hyperplasia is laparoscopic adrenalectomy; for patients with bilateral adrenal hyperplasia or those with unilateral causes of primary hyperaldosteronism who are not candidates for surgery, medical therapy with a mineralocorticoid antagonist such as spironolactone is indicated.

Androgen-Producing Adrenal Tumors

Pure androgen-secreting adrenal neoplasms are very rare. These tumors usually secrete DHEA and DHEAS and/or androstenedione, which are converted peripherally to testosterone. Approximately half of androgen-producing tumors are benign and half are malignant. Manifestations of androgen-producing adrenal tumors are usually absent in adult men, although decreased testicular volume can occur. In women, rapid onset of hirsutism, menstrual irregularities, and virilization can be seen and, if present, should raise suspicion for tumoral hyperandrogenism. Signs of virilization are deepening of the voice, clitoromegaly, and temporal hair loss. The diagnosis of an androgen-producing adrenal tumor is based on demonstrating elevated levels of DHEA and its sulfate (usually greater than 800 µg/dL [21.6 µmol/L]) and/or androstenedione. Although adrenal androgen excess can be seen in 30% to 40% of women with polycystic ovary syndrome, mild elevation of DHEAS (approximately 300 µg/dL [8.1 µmol/L) is typical. Adrenal imaging with CT or MRI is indicated following biochemical diagnosis of disease to locate the tumor. Treatment is surgical removal of the tumor.

Adrenal Insufficiency

Adrenal insufficiency may be due to failure of the adrenal glands (primary adrenal failure), or there may be inadequate secretion of cortisol from the adrenals due to other causes, including critical illness and pituitary ACTH deficiency (secondary cortisol deficiency). For a discussion of secondary cortisol deficiency, see Disorders of the Pituitary Gland.

Primary Adrenal Failure

Causes and Clinical Features

Primary adrenal failure is a rare disorder resulting from a failure in production of all the hormones of the adrenal cortex. The overall prevalence is 10 to 15 per 100,000 persons. Autoimmune adrenalitis is the most common etiology accounting for 70% to 80% of cases. Up to two thirds of patients have at least one other autoimmune endocrine disorder, and more than 80% have adrenal autoantibodies (21-hydroxylase antibodies). Infiltration of the adrenal glands by tuberculosis (Addison disease) was formerly the most common etiology of primary adrenal failure; now it is responsible for only 7% to 20%. Replacement of the adrenal glands can also occur with metastatic cancer. Genetic causes include autoimmune polyglandular syndromes (APS) type 1 and 2, congenital adrenal hyperplasia, and X-linked adrenoleukodystrophy. Adrenal crisis resulting from bilateral adrenal hemorrhage can occur with the antiphospholipid syndrome, disseminated intravascular coagulation, or systemic anticoagulation.

The clinical presentation of primary adrenal failure depends on disease chronicity and the presence of physical stressors. In autoimmune adrenalitis, the zona glomerulosa is usually affected first, which is manifest by an increase in PRA. With involvement of the zona fasciculata, a diminished cortisol response to ACTH is seen, followed by an increase in basal plasma ACTH, and lastly a decrease in serum cortisol. Patients typically do not have symptoms until hypocortisolemia occurs. **Table 24** shows the clinical and laboratory manifestations of primary adrenal failure. Hyperpigmentation is a clinical hallmark of this disorder that is not seen with secondary cortisol deficiency (see Disorders of the Pituitary Gland for discussion of secondary cortisol deficiency).

Adrenal crisis may occur when onset of adrenal failure is abrupt (bilateral adrenal hemorrhage) or when increased stress occurs in the setting of chronic adrenal failure. Manifestations of adrenal crisis include shock, hypotension, fever, nausea, vomiting, abdominal pain, tachycardia, and even death. Aldosterone is critical to the maintenance of intravascular volume and blood pressure, while cortisol contributes to augmentation of blood pressure mostly during times of increased physical stress (see Adrenal Anatomy and Physiology). Aldosterone deficiency is the major impetus for the development of hypotension and shock in patients with untreated primary adrenal failure. Adrenal crisis is rare in the setting of secondary cortisol deficiency because the renin-angiotensin-aldosterone pathway is intact.

Diagnosis

The diagnosis of primary adrenal failure is based on demonstrating inappropriately low serum cortisol levels. Because most assays measure total cortisol, abnormalities in cortisol-binding protein or albumin can trigger spurious results. An early morning (8 AM) serum cortisol of less than 3 µg/dL (82.8 nmol/L) is consistent with cortisol deficiency, whereas values greater than 15 to 18 µg/dL (414.0-496.8 nmol/L) exclude the diagnosis when binding protein abnormalities and synthetic glucocorticoid exposure are excluded. For patients with nondiagnostic basal cortisol values (5-12 µg/dL [138-331.2 nmol/L), stimulation testing with synthetic ACTH (cosyntropin) is indicated (see Disorders of the Pituitary Gland). A normal response is a peak serum cortisol level greater than 20 µg/dL (552 nmol/L). ACTH stimulation testing should not be used

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TABLE 24. Clinical and Laboratory Manifestations of Primary Adrenal Failure

Hormone Deficiency	Symptoms	Signs	Laboratory Findings
Cortisol	Fatigue Weakness Low-grade fever Weight loss Anorexia Nausea/vomiting Abdominal pain Arthralgia Myalgia	Hyperpigmentation[b] (palmar creases, extensor surfaces, buccal mucosa) Decrease in BP	↓ Serum cortisol ↑ Plasma ACTH ↓ Serum sodium[c] ↓ Plasma glucose[d]
Aldosterone	Salt craving Dizziness	Orthostasis Hypotension	↑ PRA ↓ Serum sodium ↑ Serum potassium
DHEAS	Reduced libido[a]	Decreased axillary or pubic hair[a]	↓ Serum DHEAS

ACTH = adrenocorticotropic hormone; BP = blood pressure; DHEAS = dehydroepiandrosterone sulfate; PRA = plasma renin activity.

[a]Women only.

[b]Occurs exclusively in primary adrenal failure.

[c]Cortisol inhibits the secretion of antidiuretic hormone (ADH), so hypocortisolemia will lead to increased secretion of ADH and hyponatremia.

[d]Rare in adults.

for diagnosis in the critical care setting (see Adrenal Function During Critical Illness).

Once the diagnosis of cortisol deficiency has been established, measurement of 8 AM plasma ACTH will differentiate primary and secondary causes. In primary adrenal failure, ACTH is typically greater than 200 pg/mL (44 pmol/L), whereas it will be low or inappropriately normal in secondary cortisol deficiency. Although not specific for the diagnosis, hyponatremia and hyperkalemia are characteristic of primary adrenal failure and principally result from aldosterone deficiency.

Treatment

Without appropriate treatment, primary adrenal failure is uniformly fatal. Even when treated, the mortality of patients is twice that of the general population. Normal adrenal physiology cannot be reproduced exactly by the administration of exogenous glucocorticoids and mineralocorticoids. Moreover, the administration of doses of glucocorticoid in excess of physiologic replacement can be associated with decreased bone mineral density and features of CS, with increased risk of metabolic syndrome, type 2 diabetes mellitus, hypertension, hyperlipidemia, obesity, and cardiovascular disease. Avoidance of chronic overreplacement is paramount.

Table 25 shows the medical treatment for primary adrenal failure. Most patients require glucocorticoid doses equivalent to 12.5 to 25 mg of hydrocortisone daily. Hydrocortisone is administered 2 to 3 times daily, while once daily dosing of longer-acting glucocorticoids (prednisone or dexamethasone) is acceptable. All patients with cortisol deficiency need to receive instructions for increasing their cortisol replacement dose during illness ("sick day rules"). Patients should always wear a medical alert identification.

In contrast to patients with secondary cortisol deficiency (see Disorders of the Pituitary Gland), those with primary adrenal failure also require mineralocorticoid replacement. Usual doses are 0.05 to 0.2 mg per day of fludrocortisone. Measurements of serum sodium and potassium help guide dosing. Replacement of DHEA is controversial. It is not indicated for men but can be considered for some women with primary adrenal failure. However, the objective benefit is minimal, and there are concerns regarding the quality and safety of U.S. preparations where DHEA is considered a supplement rather than a pharmaceutical.

Patients who present emergently with suspected adrenal crisis should be treated empirically prior to confirmation of the diagnosis. A blood sample should be drawn for serum cortisol, plasma ACTH, and routine chemistries. The patient should receive immediate treatment with 100 mg of hydrocortisone intravenously and aggressive fluid resuscitation. Hydrocortisone is continued at 100 to 200 mg per day in divided doses (every 6–8 hours) and then tapered to physiologic replacement if cortisol deficiency is confirmed with the above testing. Other synthetic glucocorticoids can also be used for the treatment of adrenal crisis; however, only hydrocortisone in supraphysiologic doses has clinically relevant

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TABLE 25. Chronic Medical Treatment of Primary Adrenal Failure

Medication	Basal Dose	Considerations
Glucocorticoid[a] Hydrocortisone Prednisone Prednisolone Dexamethasone	Hydrocortisone Usually 12.5-25 mg/d, divided into 2-3 doses over the day *Alternatives to hydrocortisone:* Prednisone 2.5-5 mg once daily Dexamethasone 0.25-0.75 mg once daily *How to dose:* Titrate to clinical response with goal of no signs or symptoms of cortisol deficiency or excess (increase dose if symptoms of cortisol deficiency remain; decrease if CS signs and symptoms are present)	*"Sick Day Rules":* patient follows at home For minor physiologic stress (upper respiratory infection, fever, minor surgery under local anesthesia) 2-3 times basal dose for 2-3 days *Stress Dosing:* health care providers follow while patient is in the hospital For moderate physiologic stress (minor or moderate surgery with general anesthesia) Hydrocortisone 45-75 mg/d orally or IV in 3-4 divided doses for 2-3 days *Alternatives:* Prednisone 10-20 mg or dexamethasone 2-3 mg/d in 1-2 divided doses For major physiologic stress (major surgery, trauma, critical illness, or childbirth) Hydrocortisone 150-200 mg/day IV in 3-4 divided doses; 100 mg/day the next day; taper to baseline in 3-5 days *Alternative:* Dexamethasone 6-8 mg/d IV in 2-3 divided doses
Mineralocorticoid Fludrocortisone	0.05-0.2 mg once daily in the morning *How to dose:* Titrate to 1. Normal BP 2. Normal serum Na, K	Fludrocortisone is not required if hydrocortisone dose >50 mg/d
Adrenal androgen DHEA	25-50 mg once daily	Consider DHEA for women with impaired mood or sense of well-being when glucocorticoid replacement has been optimized.

BP = blood pressure; CS = Cushing syndrome; DHEA = dehydroepiandrosterone; IV = intravenous; Na = sodium; K = potassium.

[a]Shorter acting glucocorticoids may be preferred over longer acting agents due to lower risk of glucocorticoid excess. Longer-acting preparations have the advantage of once daily dosing (see Table 17).

CONT.

mineralocorticoid activity. If present, electrolyte abnormalities and hypoglycemia should be treated, and precipitants of adrenal crisis (for example, infection) should be sought and treated.

It is critical that patients with suspected primary or secondary cortisol deficiency and concomitant hypothyroidism be treated with glucocorticoids first because correcting thyroid hormone deficiency will accelerate the clearance of cortisol and can precipitate acute adrenal crisis.

In the nonmedical literature, the term "adrenal fatigue" has been used to describe a constellation of symptoms, including difficulty sleeping, fatigue, and salt and sugar craving, hypothetically from long-term emotional or physical stress having a deleterious effect on the adrenal glands, resulting in a simultaneous excess and deficiency of cortisol. However, there is no scientific evidence to support this claim, and the term "adrenal fatigue" should not be used. Proponents of adrenal fatigue prescribe synthetic glucocorticoids and supplements containing adrenal, pituitary, or hypothalamic extracts that can cause iatrogenic CS, as well as mineralocorticoid supplements that can lead to hypertension. Patients should receive appropriate evaluation for their symptoms and be educated to avoid taking hormonal replacements for which there has not been a demonstrated biochemical need.

Adrenal Function During Critical Illness

Glucocorticoid deficiency related to critical illness is an entity that has not been well characterized. It has been postulated that critical illness may lead to transient primary or secondary cortisol deficiency (ACTH deficiency) or an increase in tissue resistance to cortisol. The American College of Critical Care Medicine recommends considering this diagnosis in patients with hypotension who have responded insufficiently to fluids and vasopressor therapy. A maximum increase in serum cortisol of 9 µg/dL (248.4 nmol/L) or less following the administration of synthetic ACTH has been associated with increased mortality from septic shock; however, results of testing do predict benefit from glucocorticoid therapy. In the setting of critical illness, both CBG and albumin concentrations decrease resulting in lower total cortisol. Free cortisol levels, either directly measured or calculated based on total cortisol and CBG, may be more reliable in critically ill patients with hypoalbuminemia. It is not known if free cortisol levels provide useful prognostic information. The administration of glucocorticoids has not been shown to benefit critically ill patients who do not have shock, and the

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CONT. results of placebo-controlled randomized trials in patients with septic shock are conflicting. Further research is needed to clarify if there is a population of critically ill patients who can objectively benefit from glucocorticoid therapy.

Adrenal Masses

Incidentally Noted Adrenal Masses

Adrenal masses are often discovered incidentally when abdominal imaging is performed for another reason. These adrenal incidentalomas are seen on 4% of all CT scans and 7% of those performed in patients 70 years of age and older. The differential diagnosis includes benign and malignant neoplasia of adrenal cortex or medulla, adrenal cysts, adrenal hyperplasia, metastatic tumors of nonadrenal origin, and infections and infiltrative disorders. The most common cause of an adrenal mass is an adrenal adenoma, and adrenal metastasis is the next most common. The two main goals in the evaluation of an incidentally noted adrenal mass are to identify adrenal masses that are likely to be malignant and those that are associated with hormonal hypersecretion so that targeted treatment can be undertaken promptly. An algorithm for the evaluation and follow up of an adrenal mass is shown in **Figure 7**.

The risk of malignancy varies according to size. Only 2% of adrenal masses smaller than 4 cm are cancerous; however, 25% of those larger than 6 cm are malignant. An adrenal mass's risk of malignancy can be clarified based on its appearance on CT or MRI (see Table 19 for the typical radiographic features of adrenal masses).

Adrenal metastases account for about half of adrenal masses in patients with known nonadrenal malignancies. Cancers that metastasize to the adrenal glands include lymphomas, carcinomas, and melanomas. Percutaneous biopsy is indicated to confirm the diagnosis of adrenal metastasis; however, this should never be performed prior to ruling out pheochromocytoma biochemically. Biopsy is not recommended when adrenocortical carcinoma (ACC) is suspected because it cannot reliably distinguish benign from malignant adrenocortical neoplasia. The evaluation and management of ACC are covered in the Adrenocortical Carcinoma section.

One quarter of incidentally noted adrenal masses autonomously secrete hormones (cortisol 6%-10%; catecholamines

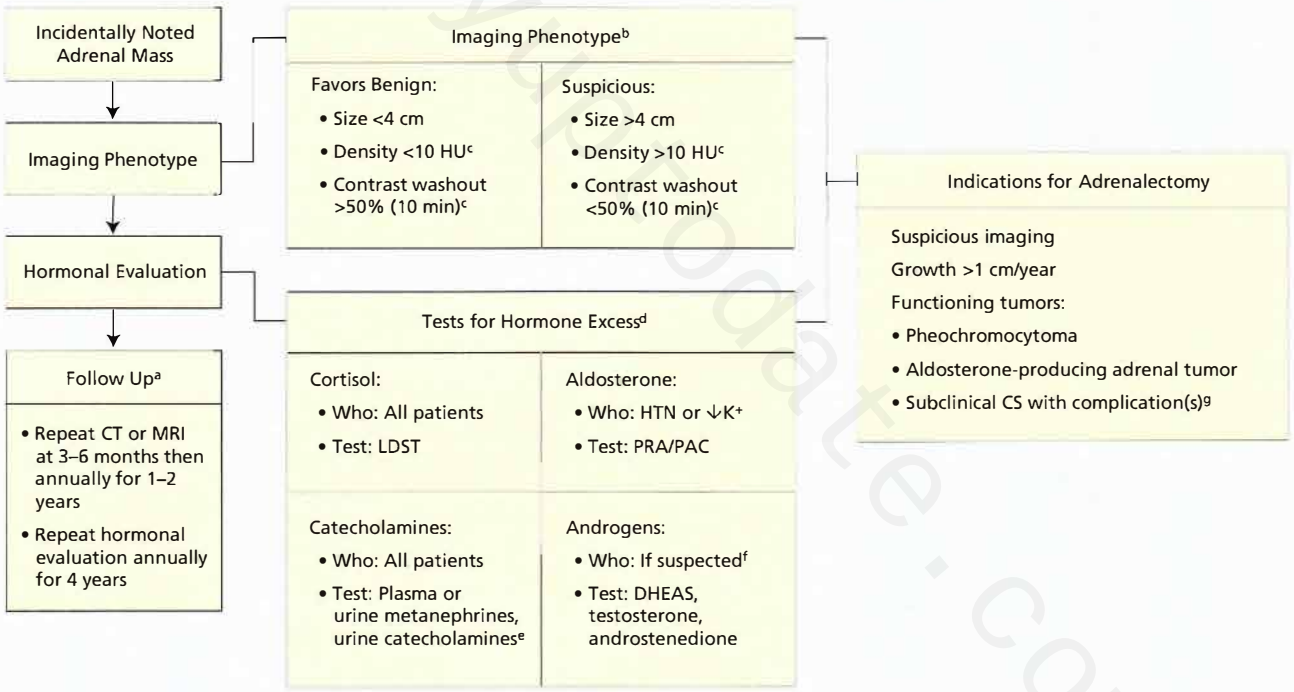

FIGURE 7. Algorithm for the initial diagnostic evaluation and follow up of an incidentally noted adrenal mass. CS = Cushing syndrome; DHEAS = dehydroepiandrosterone sulfate; HTN = hypertension; HU = Hounsfield units; K = potassium; LDST = low-dose (1-mg) dexamethasone suppression test; PAC = plasma aldosterone concentration; PRA = plasma renin activity.

[a]Repeat imaging and hormone testing are indicated for adrenal masses not meeting criteria for surgery at initial diagnosis.

[b]Refer to Table 19 for more CT and MRI findings. If imaging is suspicious in a patient with known malignancy, biopsy should be considered to confirm adrenal metastasis after screening for pheochromocytoma is completed.

[c]CT scan findings.

[d]Positive screening tests usually require further biochemical evaluation to confirm the diagnosis (see text).

[e]Measure plasma metanephrines if radiographic appearance is typical for a pheochromocytoma; otherwise measure 24-hour urine metanephrines and catecholamines.

[f]Hormonal evaluation for an androgen-producing adrenal tumor is indicated only if clinically suspected based on the presence of hirsutism, virilization, or menstrual irregularities in women.

[g]Adrenalectomy is considered for confirmed cases of subclinical CS associated with recent onset of diabetes, hypertension, obesity, or low bone mass.

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CONT.

5%; aldosterone 1%). Excess cortisol secretion is most common; however, the majority of patients have subclinical disease without classic stigmata of CS. Despite this, important complications may be seen, including osteoporosis, hypertension, diabetes mellitus, and cardiovascular events. The LDST is the initial screening test of choice. A serum cortisol value greater than 5 µg/dL (138 nmol/L) is considered positive; however, some advocate using a cut-off of 1.8 µg/dL (49.7 nmol/L) to increase diagnostic sensitivity if CS is suggested by history or physical examination. Because the specificity of the LDST is only approximately 90%, the diagnosis of subclinical CS should be confirmed with additional testing. For a review, see the Cushing Syndrome section.

Aldosteronomas are usually smaller than 2 cm. Case detection for PA is performed in all patients with hypertension or those on antihypertensive medications. Testing for autonomous secretion of adrenal androgens is performed if clinically suspected following careful history and physical examination. All patients with an incidental adrenal mass should be tested for pheochromocytoma. Measurement of 24-hour urine metanephrines and catecholamines is the preferred first test in most asymptomatic patients, due to the lower incidence of false-positive test results. However, if the radiographic appearance of the adrenal mass is suspicious for a pheochromocytoma (see Table 19) or the patient is symptomatic, then plasma free metanephrines should be measured (see Primary Hyperaldosteronism, Androgen-Producing Adrenal Tumors, and Pheochromocytomas and Paragangliomas).

Adrenal masses that are larger than 4 cm, those with worrisome radiographic findings, and pheochromocytomas should be removed surgically. Surgery is also indicated for unilateral aldosteronomas and is considered for patients with subclinical CS associated with the recent onset of diabetes, hypertension, obesity, or low bone mass. For nonfunctioning adrenal masses, if imaging favors a benign lesion, repeat radiographic evaluation is recommended in 3 to 6 months, and then annually for 1 to 2 years. Adenomas usually will not grow more than 1 cm over 12 months. More rapid growth should prompt adrenalectomy. Screening for hormonal hypersecretion is repeated annually for 4 years, as in the rare instance that the mass becomes functional, it is likely to occur in the first 4 years following its discovery. A recent study documented subclinical CS on follow-up testing in approximately 8% of patients who were thought to have nonfunctioning adenomas at initial screening.

KEY POINTS

- The two main goals of evaluation of adrenal incidentalomas are to identify adrenal masses that are likely to be malignant and those that are associated with hormonal hypersecretion so that targeted treatment can be undertaken promptly.
- Adrenal masses that are larger than 4 cm, those with worrisome radiographic findings, and pheochromocytomas should be removed surgically.

Adrenocortical Carcinoma

ACC is a rare malignancy affecting 0.5 to 2 persons per million per year that is often associated with the excessive production of adrenal hormones. Patients with ACC most frequently present with signs and symptoms related to hormonal excess. They may also experience symptoms related to local tumor growth (abdominal fullness, nausea, or back pain) or metastasis. ACC is sometimes detected incidentally when abdominal imaging is performed for another reason (see Incidentally Noted Adrenal Masses).

Autonomous secretion of adrenal hormones or their biologically inactive precursors is seen in more than 80% of patients with ACC (cortisol 50%; multiple hormones 20%; androgens 5% to 10%; aldosterone rarely). The pathologic diagnosis of ACC is challenging, such that with low-risk pathology but large tumor size or concerning imaging findings (see Table 19) close interval radiographic follow up is needed after surgery.

The prognosis of ACC is very poor with an overall mortality rate of 67% to 94%. Management depends on the extent of disease at presentation. Open surgical resection is first-line treatment for early disease. Adjuvant radiotherapy to the tumor bed is used when resection is incomplete. Adjuvant medical therapy with mitotane, an adrenolytic drug, is recommended for patients with known or suspected residual or metastatic disease. Cytotoxic chemotherapy has poor efficacy. In addition to mitotane, inhibitors of adrenal steroidogenesis (metyrapone, ketoconazole, and etomidate) are used to treat CS, if present. Surgery for metastatic ACC is indicated if symptoms related to hormonal hypersecretion cannot be controlled with medical therapy alone. Percutaneous radiofrequency ablation may also be used to treat unresectable primary tumors or metastases when needed.

KEY POINT

- Adrenocortical carcinoma is marked by signs and symptoms related to hormonal excess as well as symptoms related to local tumor growth (abdominal fullness, nausea, or back pain) or metastasis.

Disorders of the Thyroid Gland

Thyroid Anatomy and Physiology

In healthy adults in the United States, each thyroid lobe normally measures up to 5 cm in length, 2 cm in width, and 2 cm in depth; the entire gland weighs 10 to 20 grams. The isthmus, a thin band of thyroid tissue that connects the two lobes, is 1 to 4 mm in thickness and is typically not palpable. Diffuse thyroid disorders, such as lymphocytic thyroiditis, may result in enlargement of the isthmus to 5 mm or more, which may be palpable and give the clinician the false sense that the entire thyroid is enlarged.

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There are two forms of active thyroid hormone: thyroxine (T_4) and triiodothyronine (T_3). Iodine is necessary for the formation of thyroid hormone. Deficiency may result in hypothyroidism. The hypothalamic-pituitary-thyroid axis responds to the subsequent hormone deficiency by increasing thyroid-stimulating hormone (TSH) secretion, resulting in development of a goiter. Iodine is typically obtained through diet; it is present in seafood, dairy products, and iodized salt. Although iodine deficiency is a worldwide health problem, it is relatively rare in the United States with the incorporation of iodine into salt.

Thyroid hormone production is controlled by two main forces: secretion of TSH (thyrotropin) and regulation of peripheral conversion of T_4 to T_3. TSH release from the anterior pituitary is stimulated by decreases in concentrations of serum T_4 and T_3 and secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus. The T_3 and T_4, in turn, decrease secretion of TSH from the anterior pituitary as part of a negative feedback loop. Additionally, T_3 inhibits further secretion of TRH from the hypothalamus.

Although the thyroid gland produces both T_3 and T_4, the ratio of T_4 to T_3 secretion is nearly 20:1, with most T_3 (80%) resulting from 5′-deiodination of T_4 in peripheral tissues.

The vast majority of both hormones are bound to circulating proteins, including thyroxine-binding globulin, transthyretin, albumin, and lipoproteins. The function of these proteins is to increase the circulating pool of hormone by delaying clearance and maintaining a reservoir of hormone available for use. Only a small percentage of total circulating thyroid hormone is free (unbound); this fraction is readily available for cellular uptake and determines the biologic activity of the hormone.

KEY POINT

- Thyroid hormone production is controlled by two main forces: secretion of thyroid-stimulating hormone (thyrotropin) and regulation of peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3).

Evaluation of Thyroid Function

In patients with an intact hypothalamic-pituitary axis, the initial laboratory test of thyroid activity is TSH measurement, which is exquisitely sensitive for detection of disorders of thyroid dysfunction. In patients for whom there is a high suspicion of thyroid or pituitary dysfunction, a concomitant thyroid hormone (T_4) level should be assessed with the TSH level to evaluate for central hypothyroidism. The TSH level may reflect hypofunction (high TSH), hyperfunction (low TSH), or a normal range.

The normal reference range for TSH is variable among laboratories but is generally between 0.5 and 5 μU/mL (0.5-5 mU/L), and determinations of normal TSH levels should be made based on the reference range of the laboratory being used. There are three very important exceptions to this general range. During pregnancy, the range shifts lower and varies by trimester (see Thyroid Function and Disease in Pregnancy). The second important exception is in the elderly. With aging, the reference range shifts higher; the upper limit of normal extends to 7 μU/mL (7 mU/L) in patients older than 70 years. The third exception is in patients with known pituitary dysfunction or a risk of pituitary dysfunction (history of cranial irradiation, pituitary surgery, or massive head trauma).

If the serum TSH level is frankly abnormal, additional evaluation of thyroid function should be considered to determine the extent of the dysfunction. This is accomplished by measuring T_4 when the TSH is elevated and by measuring T_4 and T_3 when the TSH is suppressed.

When indicated by an abnormal TSH, the circulating level of thyroid hormone should be assessed using total or free T_4 levels. Total T_4 is a reflection of the bound and unbound fractions of the hormone and is a reasonable method of assessing overall thyroid hormone levels in most patients. However, in patients with disorders of protein metabolism, such as kidney or liver disease, measurement of free T_4 ensures a more accurate representation of the hormone concentrations. Additionally, conditions that raise serum total protein level, such as in patients taking estrogen or during pregnancy, may result in a higher total T_4 concentration, and measuring the free T_4 is indicated. The same rules apply to T_3 as to T_4 regarding protein levels, but free T_3 has a very short half-life and levels fluctuate more and are less reliable; therefore, it is controversial whether total or free T_3 should be measured in patients at risk for protein abnormalities.

Measurement of serum T_3 is necessary if the patient has a suppressed TSH level because, in some patients with thyrotoxicosis, T_3 may be preferentially secreted over T_4 (T_3 toxicosis). In patients with an elevated TSH level, indicating hypothyroidism, measurement of serum T_3 is not helpful because it will be maintained in the normal range even in those with significant disease.

Thyroid autoantibody measurement may be helpful under certain clinical circumstances. In patients with a personal history of autoimmune disease (such as type 1 diabetes mellitus, systemic lupus erythematosus, or celiac disease) or a strong family history of thyroid dysfunction, measuring thyroid autoantibodies may indicate the cause of the thyroid dysfunction or whether a patient is at risk for developing thyroid autoimmune disease if the TSH is normal. There is no clinical indication for serial measurement of thyroid antibody titers to determine the need for or to guide therapy. There are three forms of thyroid autoantibodies: thyroid peroxidase (TPO), thyrotropin receptor (TRAb), and thyroglobulin (TgAb). Elevated titers of TPO antibodies are associated with autoimmune hypothyroidism, or Hashimoto disease. Patients with TPO antibodies and normal thyroid function tests are at an increased risk of developing overt thyroid failure (2%-4% per year). Thyrotropin receptor antibodies (TRAb) are divided into three types: blocking (also called thyrotropin-binding

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inhibitory immunoglobulins), stimulating (also called thyroid-stimulating immunoglobulins or TSI), and neutral. The presence of TSI autoantibodies is responsible for the development of Graves disease. TSI autoantibodies should be measured if autoimmune hyperthyroidism is suspected. Thyroglobulin (Tg) is a glycoprotein located within the colloid on which thyroid hormones are synthesized and stored. Serum Tg and TgAb measurements are used to monitor patients with thyroid cancer; serum Tg is a highly sensitive and specific marker of residual thyroid tissue. After total thyroidectomy and radioactive iodine ablation, the persistence of a detectable serum Tg is a possible indicator of residual or recurrent disease. Thyroglobulin antibodies are present in up to 30% of patients. Their presence in the serum is only significant in patients with thyroid cancer, as they can falsely lower the serum Tg. Therefore, TgAb titers should always be assessed simultaneously with the Tg; if antibodies are present, the Tg level may not be reliable.

Calcitonin, secreted by the C cells of the thyroid, is most frequently used as a tumor marker in patients with a history of medullary thyroid carcinoma. Serum calcitonin levels can help increase the sensitivity of detection of medullary thyroid carcinoma when used in conjunction with fine-needle aspiration (FNA). However, it is not recommended as a screening test in all patients with thyroid nodules because it lacks the requisite specificity. Instead, measurement of calcitonin should be considered if a patient with thyroid nodular disease has a history of hyperparathyroidism or a family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, or if there is clinical suspicion for these disorders.

Radioactive iodine uptake (RAIU) is a measure of iodine uptake by the thyroid over a pre-specified time frame, typically 24 hours. RAIU is used to evaluate the cause of hyperthyroidism; it is not indicated in patients with normal or elevated TSH levels. The degree of uptake is useful for distinguishing the various causes of hyperthyroidism. RAIU percentage is typically very high in patients with Graves disease (diffusely increased uptake) and only moderately elevated in those with toxic multinodular goiter (patchy uptake in areas of nodules with relative suppression of normal tissue). In contrast, the RAIU is very low in those with thyroiditis or exposure to exogenous thyroid hormone. The presence of a "cold" nodule on isotope scanning is an indication for ultrasonography to help determine if FNA is indicated. RAIU is contraindicated during pregnancy and while breastfeeding.

KEY POINTS

- The initial laboratory test of thyroid activity is thyroid-stimulating hormone measurement; in patients with an intact anterior pituitary, measurement of thyroid-stimulating hormone is exquisitely sensitive for detection of disorders of thyroid hypofunction (high thyroid-stimulating hormone) and hyperfunction (low thyroid-stimulating hormone).

(Continued)

KEY POINTS *(continued)*

- If central hypothyroidism is suspected, a concomitant thyroid hormone (thyroxine [T_4]) level should be assessed in conjunction with the thyroid-stimulating hormone level.
- If the thyroid-stimulating hormone level is frankly abnormal, additional evaluation of thyroid function should be considered to determine the extent of the dysfunction; measure thyroxine (T_4) when the thyroid-stimulating hormone is elevated and measure both thyroxine (T_4) and triiodothyronine (T_3) when the thyroid-stimulating hormone is suppressed. **HVC**
- There is no clinical indication for serial measurement of thyroid antibody titers to determine the need for or to guide therapy except to monitor for residual disease in patients treated for thyroid cancer. **HVC**
- Radioactive iodine uptake is a measure of iodine uptake by the thyroid over 24 hours; it is used to evaluate the cause of hyperthyroidism and is not indicated in patients with normal or elevated thyroid-stimulating hormone levels. **HVC**

Functional Thyroid Disorders

Thyrotoxicosis

Evaluation

Thyrotoxicosis is a term used to describe thyroid hormone excess from all sources, whereas hyperthyroidism is the more specific term to describe thyroid gland overactivity. Thyrotoxicosis may result from endogenous thyroid disorders, pituitary tumors, and exogenous levothyroxine. The most common causes of hyperthyroidism are Graves disease and toxic adenoma(s).

The symptoms of thyrotoxicosis include heat intolerance, palpitations, dyspnea, tremulousness, menstrual irregularities, hyperdefecation, weight loss, increased appetite, proximal muscle weakness, fatigue, insomnia, and mood disturbances. The severity of symptoms may not correlate with the level of thyroid hormone derangement. In older patients, many of the classic symptoms of thyroid hormone excess may be absent, and the only presenting symptom may be atrial fibrillation or heart failure; this is known as apathetic hyperthyroidism.

The initial evaluation based on clinical signs and/or symptoms of thyrotoxicosis should be measurement of serum TSH alone, followed by measurement of T_4 and T_3 levels if TSH is suppressed. The typical pattern of hyperthyroidism is TSH suppression with an elevated T_4 and/or T_3. A normal serum TSH in the setting of an elevated T_4 and/or T_3 concentration suggests the presence of a TSH-secreting pituitary adenoma; these tumors are extremely rare and are managed differently from other causes of thyrotoxicosis (see later discussion).

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KEY POINT

- The typical pattern of laboratory studies in hyperthyroidism is thyroid-stimulating hormone suppression with an elevated thyroxine (T_4) and/or triiodothyronine (T_3) level.

Management

Although the specific intervention used is usually determined by the underlying cause and patient and physician preference, control of the thyrotoxic state may be achieved by one of three treatment modalities: thionamides, radioactive iodine ablation, or surgery.

Rapid control of adrenergic symptoms with a β-blocker is indicated in most patients with thyrotoxicosis. Although propranolol is frequently used for its added effect of inhibition of peripheral conversion of T_4 to T_3, cardioselective β-blockers, such as atenolol, are preferred owing to the additional benefits of decreased central nervous system side effects and improved adherence with once-daily dosing.

Methimazole and propylthiouracil (PTU) are the two thionamides available in the United States. Methimazole is the preferred agent because it has a higher intrathyroidal retention (potency), a preferable dosing regimen (typically once daily), and a reduced side-effect profile. Antithyroid medications reduce T_3 and T_4 levels within a few days of initiation, but the full effect may take several weeks. Normalization of a previously suppressed TSH level may take several months. It is critical, therefore, to monitor T_4 and T_3 levels during treatment of hyperthyroidism because the TSH may not be an accurate reflection of the thyroidal status.

Thionamides may be used to prepare patients for thyroidectomy or radioiodine treatment, or they may be used as the primary therapy. Thionamides may be used for 1 to 2 years in patients with Graves disease in the hope of achieving remission; more definitive therapy with radioactive iodine or surgery may then be sought after that timeframe if hyperthyroidism persists. Although thionamides are generally well tolerated, it is important to be familiar with their side-effect profile. The most common reaction to antithyroid medications is a rash, seen in up to 10% of patients. Additionally, PTU may cause elevations of aminotransferase levels. Rare cases of fatal hepatotoxicity have been described with PTU. Therefore, its use is reserved for patients who cannot tolerate methimazole and during the first trimester of pregnancy, when methimazole has a possible teratogenic effect. A cholestatic pattern of liver test abnormalities may also be seen with methimazole, but it is typically temporary and milder than that seen with PTU. Both drugs may be associated with reversible agranulocytosis in approximately 1 in 500 patients. Baseline liver chemistry studies and complete blood count with differential are recommended before initiation of antithyroid medications, with serial monitoring of the complete blood count during therapy. If patients taking a thionamide develop a fever, rash, severe sore throat, jaundice, or other symptoms of serious illness, they should be assessed promptly for an adverse reaction to the medication.

The goal of radioactive iodine ablation is to render the patient hypothyroid, which can typically be accomplished in 90% of patients with the first treatment. Although a minority of patients may develop acute anterior neck pain from radiation thyroiditis, radioactive iodine ablation is typically well tolerated. It may take several months for the development of hypothyroidism, so it is important to monitor thyroid function tests monthly after therapy. In a patient with severe thyrotoxicosis, radioactive iodine may provide additional substrate to the hyperfunctioning gland, resulting in exacerbation of the hyperthyroid state. Consequently, it may be reasonable to initiate a thionamide prior to ablation to lower the thyroid hormone levels.

Surgery is rarely first-line therapy, given the inherent risks with any surgery. Patients in whom control cannot be achieved with thionamides and those who are not comfortable with radioiodine therapy are typically referred for surgery. Because of the increased intrathyroidal vascularity, the procedure can be technically more difficult than a typical thyroidectomy. Additionally, restoration of the euthyroid state before surgery with thionamides is important to improve hemodynamics during general anesthesia and decrease the patient's risk of thyroid storm.

KEY POINT

- Control of hyperthyroidism may be achieved by one of three treatment modalities: thionamides, radioactive iodine ablation, or surgery; modality choice depends on the underlying cause and patient preference.

Graves Disease

Graves disease is a multiorgan system autoimmune disorder that can affect the thyroid, eyes, and skin. It is frequently seen in women between the ages of 20 and 50 years and is the most common cause of hyperthyroidism in the United States. Antibodies against the TSH receptor (TSI or TRAb) stimulate autonomous production of T_4 and T_3. Patients frequently report a family history of Graves disease, Hashimoto thyroiditis, or other autoimmune conditions.

On physical examination, patients have elevated systolic blood pressure with a widened pulse pressure, tachycardia, and a diffusely enlarged thyroid. Further inspection of the thyroid may reveal a bruit. Careful examination of the skin may reveal pretibial myxedema, an infiltrative process that is typically patchy with a peau d'orange appearance to the skin.

Diagnosis of Graves disease is made clinically in most instances, and measurement of TSI antibodies is reserved for patients who are not markedly thyrotoxic on examination and do not have a classic smooth, rubbery, diffuse goiter. In those patients, TSI antibodies may help determine the cause of the hyperthyroidism. RAIU and scan will show markedly increased uptake with diffuse activity on the scan.

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If ophthalmopathy is present, the patient may exhibit lid retraction (lid lag), whereby contraction of the levator palpebrae muscles of the eyelids results in immobility of the upper eyelid with downward rotation of the eye. Additionally, patients may have proptosis, scleral injection, and periorbital edema.

Because thionamide drugs also have an immunomodulatory effect that reduces autoantibody titers, antithyroid drugs are often first-line treatment for Graves disease. Up to 50% of patients may go into remission within 24 months, and some may maintain a euthyroid state without further therapy after an initial treatment with thionamides. If the patient does not go into remission or if disease recurs, definitive therapy with radioactive iodine ablation or surgery is recommended. However, in patients with Graves ophthalmopathy, there is an acute escalation of thyroid autoantibody titers following radioiodine therapy that may exacerbate ocular symptoms. Such patients may be better treated with thionamides and/or surgery.

Toxic Adenoma and Multinodular Goiter

Activating mutations in the TSH receptor gene are responsible for the autonomous production of thyroid hormone in a toxic nodule (adenoma) or in multiple hyperfunctioning nodules in a toxic multinodular goiter. Because of this loss of normal regulation of thyroid hormone production, patients are at risk for developing acute thyrotoxicosis when exposed to iodine excess, particularly after a contrast load for medical testing (Jod-Basedow phenomenon), such as in cardiac catheterization and contrast-enhanced CT scans. Although patients with a toxic adenoma or multinodular goiter may exhibit the typical symptoms of thyrotoxicosis, they can be relatively asymptomatic. On physical examination, a nodule may be palpable or there may be a diffusely enlarged goiter with a nodular contour but no discrete palpable nodules.

If a patient is suspected of having a toxic nodule, thyroid scintigraphy should be performed to determine if the nodule is autonomous. The thyroid uptake scan will reveal increased activity in the "hot" nodule with relative suppression of the remaining thyroid tissue. These results should then be correlated with the ultrasonographic findings to determine if any additional nodules exist, which will require further investigation with FNA.

Radioactive iodine ablation or surgery is the most common treatment for toxic nodules. Thionamides can be used to decrease hormone production in the short term, but unlike Graves disease, this condition has no chance of spontaneous remission and would require lifelong medical therapy, which is not recommended. Radioiodine therapy will ideally ablate only the autonomous areas. In elderly patients, those with coronary disease, those who are highly symptomatic, and those with severe thyrotoxicosis, thionamides are recommended to normalize thyroid hormone levels prior to radioactive iodine; this is done to avoid exacerbation of the thyrotoxicosis due to release of preformed hormone from the gland acutely after radioactive iodine ablation. Thionamides should be withheld for 5 to 7 days before the administration of radioactive iodine therapy. If a patient has a particularly large goiter with compressive symptoms or if there is concern for malignancy, surgery is recommended as first-line therapy.

KEY POINT

- Radioactive iodine ablation or surgery is the most common treatment for toxic thyroid nodules; indications for surgery include a large goiter with compression symptoms or concern for malignancy.

Destructive Thyroiditis

Thyroiditis is a self-limited inflammatory condition of the thyroid resulting in the release of preformed thyroid hormone into the circulation. The duration of the thyrotoxic phase is typically 2 to 6 weeks, during which patients may exhibit classic symptoms of thyrotoxicosis. Following the release of preformed hormone, the damaged thyroid ceases production of T_3 and T_4 during the recovery phase; consequently, administration of thionamides will not be effective in treating elevated hormone levels. The patient may then become clinically hypothyroid, a condition that may require temporary levothyroxine therapy. The length of the hypothyroid phase can vary but classically is 6 to 12 weeks.

There are two categories of thyroiditis: painful and painless. The causes of painful thyroiditis are inflammatory (de Quervain or subacute granulomatous thyroiditis), infectious (suppurative), and radiation-induced. The pain, typically only present during the thyrotoxic phase, can be quite intense. Treatment is aimed at controlling inflammation with NSAIDs or systemic glucocorticoids if severe. Subacute thyroiditis is the most common form and is presumably caused by a postviral inflammatory process; many patients report a recent history of upper respiratory illness preceding the thyroiditis. Radiation thyroiditis may occur 5 to 10 days after treatment with radioactive iodine. This may be associated with transient exacerbation of the hyperthyroidism. The accompanying pain is usually mild and lasts for up to 1 week. Infectious thyroiditis is rare but may be seen in an immunocompromised patient; the most common causative organisms are *Staphylococcus* and *Streptococcus* species.

Painless thyroiditis is more commonly seen than painful thyroiditis and has several causes, including postpartum thyroiditis, silent thyroiditis, and drug-induced thyroiditis. Postpartum thyroiditis may occur up to 1 year after delivery; the frequency is variably reported but may occur in up to 10% of pregnancies. The presence of TPO antibodies is nearly universal, and the likelihood of subsequent permanent hypothyroidism is very high. Thyroiditis is also likely to recur in later pregnancies.

KEY POINT

- Thyroiditis is a self-limited inflammatory condition of the thyroid resulting in the release of preformed thyroid hormone into the circulation; the duration of the thyrotoxic phase is typically 2 to 6 weeks, which is followed by a hypothyroid phase typically lasting 6 to 12 weeks.

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Central Hyperthyroidism

TSH-secreting pituitary adenomas are extremely rare. In this condition, serum TSH is detectable or normal in the setting of an elevated T_4 and/or T_3 concentration. A dedicated pituitary MRI will demonstrate an adenoma. Treatment should focus on removal of the pituitary tumor; thyroid-targeted therapy is ineffective (see Disorders of the Pituitary Gland).

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is a laboratory-based diagnosis, defined as the presence of a suppressed TSH level with normal T_3 and T_4 levels. Repeat assessment of thyroid function should be performed 6 to 12 weeks after the initial tests, as the values will normalize in up to 30% of patients. Symptoms of thyrotoxicosis are typically mild; most patients are asymptomatic.

Which patients will benefit most from normalization of the TSH level is not universally agreed on, but consensus opinion recommends treatment for patients with a TSH level below 0.1 μU/mL (0.1 mU/L). The benefits of treatment for asymptomatic patients with a TSH level between 0.1 μU/mL (0.1 mU/L) and the lower limit of the normal reference range are less clear. Emerging data suggest that chronic subclinical hyperthyroidism has a negative effect on cardiac function, the central nervous system, and bone mass. The risk of atrial fibrillation is significantly increased when the TSH level is below 0.3 μU/mL (0.3 mU/L), so patients over the age of 65 years and those with a history of coronary artery disease or tachyarrhythmias, as well as patients with osteoporosis, may benefit from normalization of the TSH level. Radioiodine is the preferred treatment, but often the gland does not have sufficient iodine avidity and methimazole must be used.

KEY POINTS

HVC
- In patients with subclinical hyperthyroidism, repeat assessment of thyroid function should be performed 6 to 12 weeks after the initial tests, as the values will normalize in up to 30% of patients.
- Treatment for subclinical hyperthyroidism is recommended when the thyroid-stimulating hormone level is less than 0.1 μU/mL (0.1 mU/L).

Thyroid Hormone Deficiency

Hypothyroidism

Evaluation

Hypothyroidism refers to low circulating thyroid hormone levels. Hypothyroidism is more prevalent in women than men (2% versus 0.2%) and in those with other autoimmune diseases. The most frequent cause is Hashimoto thyroiditis, also known as chronic lymphocytic thyroiditis. Iatrogenic causes include surgery, radioiodine therapy, and external beam radiation therapy to the neck. Hypothyroidism may also be medication induced; the most common causative agents include lithium, amiodarone, interferons, interleukin-2, and tyrosine kinase inhibitors. Rarely, pituitary tumors, severe head trauma, pituitary surgery, or cranial radiation can cause central hypothyroidism.

The clinical manifestations of hypothyroidism include fatigue, cold intolerance, constipation, heavy menses, weight gain, impaired concentration, dry skin, edema, depression, mood changes, muscle cramps, myalgia, and reduced fertility. The physical examination findings may include reduction in basal temperature, diastolic hypertension, bradycardia, dry skin, brittle hair, hoarseness, delayed relaxation phase of the deep tendon reflexes, and an enlarged thyroid.

An elevated serum TSH level indicates the diagnosis of primary hypothyroidism. In patients with an elevated TSH that is less than 10 μU/mL (10 mU/L), a low serum T_4 measurement is helpful, as a frankly low value indicates that thyroid hormone replacement is necessary. The presence of TPO antibodies suggests that Hashimoto thyroiditis is the underlying cause. Thyroid imaging is not indicated unless there is concern for a nodule on physical examination.

KEY POINTS

- An elevated serum thyroid-stimulating hormone level indicates the diagnosis of primary hypothyroidism; thyroid imaging is not indicated unless there is concern for a nodule on physical examination. HVC
- The most frequent cause of primary hypothyroidism is Hashimoto thyroiditis (chronic lymphocytic thyroiditis); the presence of TPO antibodies is suggestive of Hashimoto thyroiditis.

Management

In patients with a TSH level greater than 10 μU/mL (10 mU/L), daily thyroid hormone replacement is recommended.

Thyroid hormone replacement with levothyroxine alone is recommended. The goal of thyroid hormone replacement therapy is normalization of the TSH. The starting dose can be weight-based at 1.67 μg/kg/d, using ideal body weight. In patients with prevalent cardiac disease, tachyarrhythmias, or multiple comorbidities, or in those who are older than 65 years, the dose should not be based on weight but rather should be 25 to 50 μg/d. The dose should be titrated based on TSH levels measured 6 to 8 weeks after any dose change. To improve gastrointestinal absorption, levothyroxine should be taken on an empty stomach, 1 hour before or 2 to 3 hours after ingestion of food or medications that would interfere with absorption, such as calcium- or iron-containing supplements. Patients with celiac disease may require higher levothyroxine doses because of impaired absorption.

There has been significant debate regarding the need for supplementation of T_3 (liothyronine) in patients with hypothyroidism. The short half-life of T_3 triggers acute spikes in serum T_3 levels, which are of significant concern for elderly patients or those with preexisting cardiac issues. Additionally, numerous studies have failed to show a clear benefit of a T_4/T_3 combination over T_4 alone; therefore, this is not generally recommended.

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KEY POINT

- In patients with a thyroid-stimulating hormone level greater than 10 μU/mL (10 mU/L), daily thyroid hormone replacement is recommended and should be taken on an empty stomach; the dose should be titrated based on thyroid-stimulating hormone levels measures 6 to 8 weeks after any dose change.

Subclinical Hypothyroidism

Subclinical hypothyroidism is defined as an elevated serum TSH level with a normal T_4 level. The potential causes are the same as for overt hypothyroidism. Repeat measurement of the TSH level is recommended, particularly in an asymptomatic patient, as it will normalize in up to 30% of patients by 6 weeks.

Patients typically have mild or no symptoms of hypothyroidism. Subclinical hypothyroidism may be associated with several laboratory abnormalities including elevated total cholesterol, LDL cholesterol, and C-reactive protein levels. Large studies suggest that these laboratory abnormalities translate into an increased risk of atherosclerosis and cardiac events. However, supplementation with levothyroxine has not been shown to mitigate this risk. Treatment is generally recommended for those with a TSH level greater than 10 μU/mL (10 mU/L), but levothyroxine treatment should be considered in patients who have positive TPO antibodies or a large goiter, as these patients are at risk for progression to overt hypothyroidism at rates of 3% to 8% per year. A goal TSH level less than or equal to 2.5 μU/mL (2.5 mU/L) is recommended for women with subclinical hypothyroidism and positive TPO antibody status who are planning to conceive.

KEY POINT

HVC
- In patients with suspected subclinical hypothyroidism, repeat measurement of the thyroid-stimulating hormone level is recommended, as it will normalize in up to 30% of patients by 6 weeks.

Drug-Induced Thyroid Dysfunction

Various medications can affect thyroid function and are listed in **Table 26** based on their mechanism of action.

Amiodarone may have a potentially toxic effect on the thyroid. The iodine content of amiodarone is 37% by weight. It is stored in fat, myocardium, liver, lung, and thyroid tissues, with a half-life exceeding 50 days. This long half-life, coupled with the high iodine content, renders it a potentially toxic compound to the thyroid. The two types of amiodarone thyroid toxicity are changes in thyroid function studies seen in all patients (obligatory effects), and those seen in only a subset of patients (facultative effects).

The obligatory effects result from the increased circulating iodine after initiation of the drug. Adaptation to the acute iodine excess causes a reduction in organification of iodine and reduced production of thyroid hormone (Wolff-Chaikoff effect). The result is a temporary reduction in circulating T_3 and T_4 levels with a minor rise in the TSH level; these changes typically reverse within the first 3 months of treatment and require no intervention.

Facultative effects, seen in up to 15% of patients, may cause either hypo- or hyperthyroidism. In areas of iodine sufficiency, hypothyroidism is the more common toxicity. Those at highest risk are women with preexisting TPO antibody positivity. Amiodarone-induced thyrotoxicosis (AIT) is more commonly seen in males and in those living in iodine-deficient areas. Type 1 AIT is the result of exposure to excess iodine and occurs in those with preexisting thyroid conditions, such as latent Graves disease or nodular goiter, in which the iodine increases unregulated thyroid hormone production. Type 2 AIT is the result of the cytotoxic effects of amiodarone on thyroid tissue, producing a clinical picture of painless thyroiditis, with abnormal release of thyroid hormone. The treatments differ with each type, but distinguishing between the two forms of AIT often can be challenging and may require the aid of an endocrinologist. The time to recovery of normal thyroid function may be several months, even with prompt diagnosis and treatment. Discontinuation of amiodarone is typically necessary, particularly in those patients with type 1 AIT.

KEY POINTS

- In the majority of patients, amiodarone causes a temporary reduction in circulating triiodothyronine (T_3) and thyroxine (T_4) and levels with a minor rise in the thyroid-stimulating hormone that reverses within first 3 months of treatment and requires no intervention.
- In 15% of patients, amiodarone may cause either hypo- or hyperthyroidism; those at highest risk for amiodarone-induced hypothyroidism are women with preexisting thyroid peroxidase antibody positivity.

Thyroid Function and Disease in Pregnancy

Significant changes in thyroid function occur during pregnancy; understanding the normal physiology during gestation is critical for a correct interpretation of thyroid laboratory studies. Abnormalities of thyroid function can have a dramatic effect on the health of the mother and the fetus. A diagram of the physiologic changes in thyroid function during each trimester is shown in **Figure 8**.

Increased estrogen levels cause a rise in thyroxine-binding globulin. To maintain a stable free T_4 and T_3, thyroid hormone production is increased and TSH remains within the normal reference range for the patient's trimester (see later discussion for trimester-specific ranges). Routine screening of TSH is not indicated for every pregnant woman. TSH screening is indicated in women with a risk of thyroid gland dysfunction, including those already on thyroid hormone replacement therapy; those with autoimmune disorders, goiter, previous

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TABLE 26. Medications that Affect Thyroid Function

Mechanism of Action	Drugs	Comments
Decreased absorption or enterohepatic circulation	Calcium Proton pump inhibitors Iron Cholestyramine Aluminum hydroxide Soybean oil Sucralfate Psyllium	It is recommended that levothyroxine ingestion be separated from these medications by several hours
Increased metabolism of levothyroxine	Phenytoin Carbamazepine Rifampin Phenobarbital Sertraline	Higher levothyroxine doses may be required to maintain levothyroxine in the normal range
Thyroiditis	Amiodarone Lithium Interferon alfa Interleukin-2 Tyrosine kinase inhibitors	May cause hypo- or hyperthyroidism
De novo development of antithyroid antibodies	Interferon alfa	May develop Hashimoto thyroiditis, Graves disease, or painless thyroiditis
Inhibition of TSH synthesis or release	Glucocorticoids Dopamine Dobutamine Octreotide	
Increased thyroxine-binding globulin	Estrogen Tamoxifen Methadone	False elevation of total T_3, total T_4 levels; free T_3, T_4 may be more accurate reflection of hormone levels
Decreased thyroxine-binding globulin	Androgen therapy Glucocorticoids Niacin	False lowering of total T_3, total T_4 levels; free T_3, T_4 may be more accurate reflection of hormone levels

T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

head/neck irradiation, previous thyroid surgery, known positive TPO antibodies or positive TSI antibodies, or a strong family history of thyroid dysfunction; those who live in iodine-deficient areas; or those older than 30 years. In patients on levothyroxine replacement, the dose of the medication may need to be increased, on average by 30% to 50%, and patients should have their TSH level checked as soon as a pregnancy test is positive.

Fetal thyroid tissue is not functional until 10 to 12 weeks' gestation, necessitating maternal thyroid hormone transfer through the placenta. Thyroid hormone deficiency can negatively affect fetal neurocognitive development. It is critical to maintain a euthyroid state during pregnancy in these patients. TSH testing should be performed every 6 weeks throughout pregnancy, with adjustments in thyroid hormone replacement dosing as needed to maintain the TSH within the trimester-specific normal range. The largest dose escalations typically occur in the first trimester, with more dose stability later in pregnancy.

Diagnosing possible hyperthyroidism during pregnancy may be challenging because some physiologic changes during gestation may overlap with symptoms of thyrotoxicosis, such as tachycardia, fatigue, and heat intolerance. Serum TSH and human chorionic gonadotropin have a common α-subunit, allowing cross-reactivity at the TSH receptor. Consequently, TSH declines during the first trimester; the reference range shifts down to 0.03 to 2.5 μU/mL (0.03-2.5 mU/L). During the second and third trimesters the upper limit of TSH rises to

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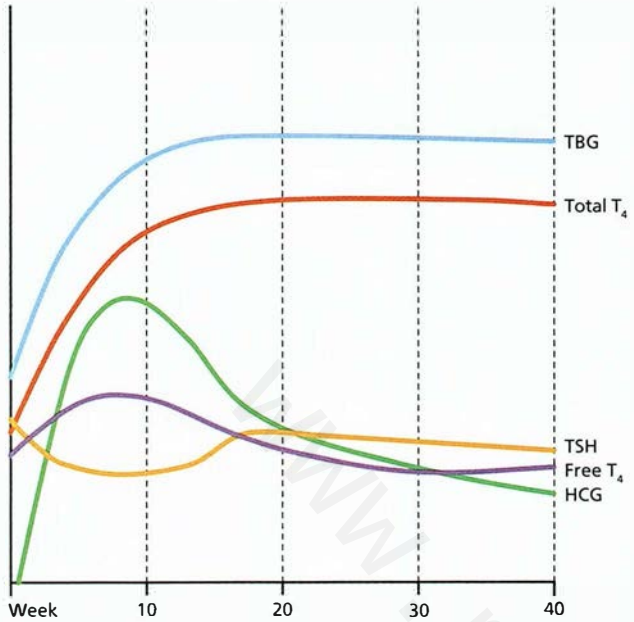

FIGURE 8. Thyroid function in pregnancy. HCG = human chorionic gonadotropin; T_4 = thyroxine; TBG = thyroid-binding globulin; TSH = thyroid-stimulating hormone.

3.0 µU/mL (3.0 mU/L). An additional complicating factor is that radioiodine scanning is contraindicated during pregnancy because of the risk for fetal thyroid exposure to radiation. Instead, several clinical clues may be used to help determine if the patient has thyrotoxicosis, including the presence of a goiter, ophthalmopathy, or TSI antibodies, all of which are suggestive of Graves disease.

The use of thionamides is considered safe during pregnancy, but PTU is preferred during the first trimester because of potential teratogenic effects from methimazole during organogenesis. Although rarely indicated, surgery may be performed during the second trimester. It should be reserved for those who are unable to tolerate thionamides or who have inadequate control on medical therapy. Radioiodine therapy is contraindicated during pregnancy and while breastfeeding. Treatment goals with thionamides are a detectable TSH in the lower end of the pregnancy reference range and a free T_4 in the upper end of the reference range.

KEY POINT

- In pregnant patients on levothyroxine replacement, the dose may need to be increased, on average by 30% to 50%; patients should have their thyroid-stimulating hormone level checked as soon as a pregnancy test is positive.

Euthyroid Sick Syndrome

Euthyroid sick syndrome (ESS), nonthyroidal illness syndrome, or low T_3 syndrome are various names that have been assigned to the changes seen in thyroid function test results during critical illness. Although not a true syndrome, there are significant perturbations of the hypothalamic-pituitary-thyroid (HPT) axis that occur in up to 75% of hospitalized patients. The underlying cause of the critical illness may influence the pattern of thyroid function abnormalities. Drugs that are frequently used in critically ill patients can have a significant effect on the HPT axis (see Table 26). The typical pattern is initially a low T_3 level, followed by a decline in the T_4 level. As the patient becomes more critically ill, the TSH level may also decline, creating a clinical picture that is difficult to discern from central hypothyroidism. Rarely, TSH can be elevated in ESS.

Two general guidelines are important in evaluating a critically ill patient. First, measurement of TSH alone should be obtained only if there is a high clinical suspicion of thyroid dysfunction. If TSH is abnormal, the previously described recommendations for additional laboratory studies should be followed. If the TSH is greater than 20 µU/mL (20 mU/L) or is undetectable, ESS is less likely to be the cause and overt thyroid dysfunction should be strongly considered. If the TSH falls between these two values, historical clues and examination findings are very important for identifying patients with true thyroid dysfunction.

After discharge from the hospital, thyroid function abnormalities may persist for several weeks. The typical pattern is a mildly elevated TSH level and slightly low T_4 and T_3 levels. In a clinically euthyroid patient, thyroid function tests should be repeated 6 weeks after hospitalization to confirm overt thyroid dysfunction with persistent TSH abnormality or confirm ESS with normalization of TSH. H

KEY POINTS

- Critical illness can cause changes in thyroid function tests in up to 75% of hospitalized patients, known as euthyroid sick syndrome; measurement of TSH should only be obtained in the hospital when there is a high clinical suspicion of thyroid dysfunction.
- The typical pattern of euthyroid sick syndrome, nonthyroidal illness syndrome, or low triiodothyronine (T_3) syndrome is a mildly elevated thyroid-stimulating hormone level and slightly low thyroxine (T_4) and triiodothyronine (T_3) levels. HVC
- After patients with euthyroid sick syndrome are discharged from the hospital, thyroid function abnormalities may persist for several weeks so follow-up thyroid function tests should not be repeated until 6 weeks after discharge. HVC

Thyroid Emergencies H

Although most thyroid conditions are not urgent, thyroid storm and myxedema coma represent true medical emergencies requiring critical care. Failure to make a timely diagnosis and institute treatment is associated with a high mortality rate.

Thyroid Storm

Thyroid storm is a severe manifestation of thyrotoxicosis with life-threatening secondary systemic decompensation (shock).

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CONT.

The cardinal features for diagnosis include elevated temperature, significant tachycardia, heart failure, gastrointestinal dysfunction (nausea, vomiting, diarrhea, and/or jaundice), and neurologic disturbances. The range of central nervous system manifestations includes increasing agitation, emotional lability, confusion, paranoia, psychosis, or coma. Although thyroid storm has been reported with many causes of thyrotoxicosis, it occurs most commonly with Graves disease. Thyroid storm may be precipitated by another event such as infection, surgery, myocardial infarction, trauma, or parturition. Administration of radioactive iodine therapy to a patient with untreated or uncontrolled hyperthyroidism can trigger thyroid storm.

The diagnosis is based on clinical presentation but can generally be ruled out if T_4 and T_3 levels are within normal limits.

Treatment of thyroid storm should be directed toward reduction of thyroid hormone production, decreasing peripheral conversion of T_4 to T_3, addressing adrenergic symptoms and thermoregulatory changes, searching for and treating precipitating factors, and reversing systemic decompensation. Thionamides and β-blockers are the mainstay of treatment to reduce thyroid hormone production and control adrenergic symptoms. PTU and propranolol are the preferred agents because they have the added benefit of blocking peripheral conversion of T_4 to T_3. Additionally, high-dose glucocorticoids reduce T_4 conversion to bioactive T_3. At least 1 hour after the first dose of a thionamide, iodine drops should be administered to inhibit further release of thyroid hormone from the gland. Acetaminophen and cooling blankets may be used to control the hyperthermia. However, even with aggressive therapy and supportive measures, mortality rates are as high as 15% to 20%.

KEY POINTS

- Thyroid storm is a severe manifestation of thyrotoxicosis with life-threatening secondary systemic decompensation (shock); it occurs most commonly with underlying Graves disease coupled with a precipitating factor such as infection, surgery, myocardial infarction, or parturition and mortality is 15% to 20%.
- In addition to supportive care and treating the participating cause, thionamides and β-blockers are the mainstay of treatment to reduce thyroid hormone production and are often combined with iodine drops and high-dose glucocorticoids to treat thyroid storm.

Myxedema Coma

Myxedema coma is an extreme but rare manifestation of hypothyroidism, resulting in life-threatening secondary systemic decompensation. Without a frankly low T_4 level, myxedema coma is unlikely, regardless of the degree of TSH elevation. It has a very high mortality rate if there is a delay in treatment. Myxedema coma is more common in elderly women; it may occur in those with a history of hypothyroidism or no antecedent illness. Precipitating events are frequent, such as myocardial infarction, infection, stroke, trauma, gastrointestinal bleeding, or metabolic derangements. Cold exposure appears to be a risk factor, as this condition is more commonly seen in the winter months.

Mental status changes and hypothermia are the most common clinical manifestations. The spectrum of mental status changes includes lethargy, stupor, coma, depression, or even psychosis. Hypothermia (temperature less than 34.4 °C [94.0 °F]) is present in nearly all patients; lower temperatures are associated with a worse prognosis. Ventilatory drive is decreased, resulting in hypoxemia and hypercapnia. Additional signs include bradycardia, hypoglycemia, hyponatremia, and/or hypotension. A significant percentage of patients experience seizures, which may be related to the coexisting metabolic derangements.

If myxedema coma is suspected, the serum TSH and T_4 levels should be tested immediately. Diagnosis is made based on the clinical presentation and the coexisting metabolic abnormalities. The serum cortisol level should be checked as soon as possible to evaluate for concomitant adrenal insufficiency prior to initiation of thyroid hormone replacement. While awaiting the results of the serum cortisol measurement, it is generally advisable to empirically initiate high-dose glucocorticoid therapy. This therapy may be discontinued if the serum cortisol level is found to be normal or high.

The treatment of myxedema coma is aimed at restoration of the euthyroid state with thyroid hormone therapy, supportive care (mechanical ventilation, vasopressors, and glucocorticoids), warmed intravenous fluids, warming blankets, and management of the underlying precipitating event. The exact dose and preparation of thyroid hormone to administer is controversial; minimal clinical trial information is available to ascertain the optimal treatment regimen. It is important to balance the need for rapid reinstatement of a euthyroid state with the risk of precipitating a fatal cardiac event due to increased cardiac work with administration of thyroid hormone. Generally, intravenous levothyroxine therapy is administered, initially as an intravenous bolus of 200 to 500 µg, followed by daily doses of 50 to 100 µg intravenously until transition to an oral formulation is feasible. Treatment with T_3 is not recommended.

Even with aggressive therapy, the mortality rate for myxedema coma is 20% to 25%.

KEY POINTS

- Myxedema coma is an extreme but rare manifestation of hypothyroidism, resulting in life-threatening secondary systemic decompensation and a mortality rate of 20% to 25%.
- The treatment of myxedema coma is aimed at restoration of the euthyroid state with thyroid hormone therapy, supportive care (mechanical ventilation, vasopressors, and glucocorticoids), warmed intravenous fluids, warming blankets, and management of the underlying precipitating event.

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Structural Disorders of the Thyroid Gland

Thyroid Nodules

Nodularity of the thyroid is extremely common; large population studies suggest that up to 5% of women and 1% of men have a clinically evident nodule. The prevalence increases with age. In autopsy series and screening ultrasound studies, nodules may be seen in up to 60%.

The differential diagnosis for a nodule in the thyroid is varied and includes both primary thyroid disorders and metastatic spread from other primary malignancies (**Table 27**). Most thyroid nodules are benign, with only approximately 10% harboring a malignancy. Ultrasonography is an inexpensive and highly effective method for stratification of malignancy risk. All patients with a suspected thyroid nodule should have a neck ultrasound that includes evaluation of the thyroid and cervical lymph nodes.

TABLE 27. Types of Thyroid Nodules

Benign	Malignant
Multinodular goiter (colloid adenoma)	Papillary thyroid cancer
Hashimoto (chronic lymphocytic) thyroiditis	Follicular thyroid cancer
Colloid cyst	Medullary thyroid cancer
Hemorrhagic cyst	Anaplastic thyroid cancer
Follicular adenoma	Primary thyroid lymphoma
Hürthle cell adenoma	Metastatic cancer
	Breast
	Melanoma
	Renal cell

Nodules are frequently detected incidentally on imaging studies performed for other reasons. The diagnostic evaluation of incidentally discovered thyroid nodules is identical to those that are clinically detected, with the same rate of malignancy. Nodules incidentally identified on fluorodeoxyglucose-PET (FDG-PET) scanning, however, have a malignancy rate of 30% to 50%. Consequently, FDG-avid nodules found on PET scans require heightened suspicion and a lower threshold for intervention or diagnostic evaluation.

A careful history should be performed in patients with a thyroid nodule. Increased risk of malignancy is found in patients with history of radiation exposure to the head or neck, a family history of thyroid cancer, or a personal history of thyroid cancer. Additional factors that increase the risk for malignancy in a nodule include male sex, extremes of age (<20 or >60 years), rapid nodule growth, and hoarseness. On physical examination, the nodule should be assessed for texture, mobility, and associated lymphadenopathy. If the nodule is hard, fixed to surrounding tissue (nonmobile with swallowing), and/or there is associated cervical lymphadenopathy, the risk of malignancy is greater. Pain is an uncommon finding with thyroid nodules, but when present it is usually associated with benign conditions.

A serum TSH measurement is the initial laboratory test in a patient with a thyroid nodule. If the TSH is suppressed, measurement of T_4 and T_3 should be performed, and a radionuclide scan should be considered (**Figure 9**). The objective of the scan is to identify "hot" or functioning nodules, which have a very low likelihood of malignancy and typically do not require FNA. In contrast, if the TSH is high or normal, the radionuclide scan is unnecessary as it is unlikely to reveal a hot

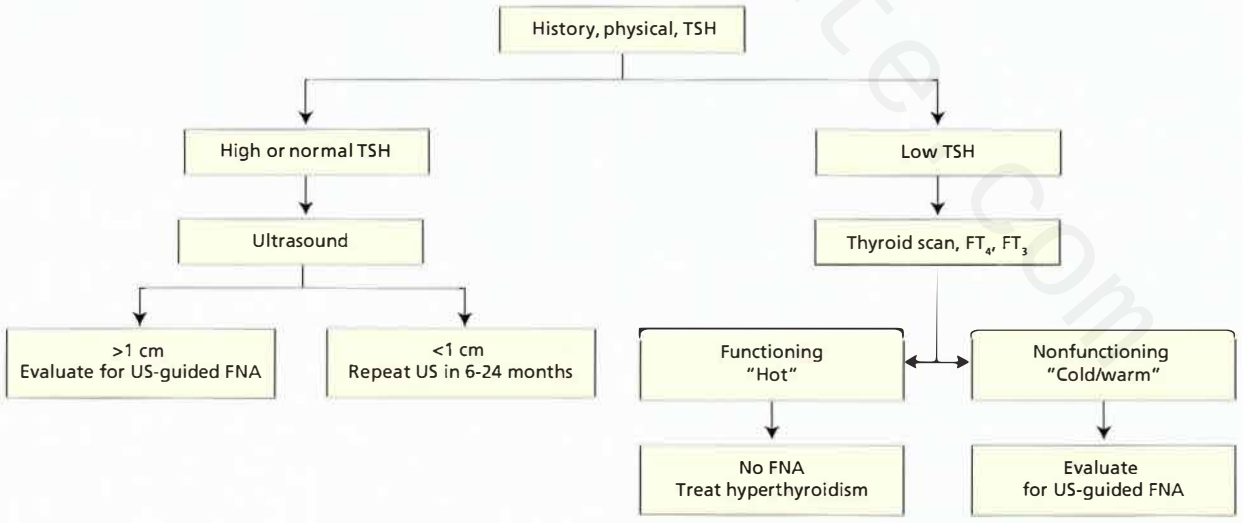

FIGURE 9. Initial evaluation of a thyroid nodule. There are size thresholds for FNA based on US appearance. A less suspicious lesion may not need FNA until it is larger than 2 cm, suspicious nodules if larger than 1 cm. FNA = fine-needle aspiration; FT_3 = free triiodothyronine; FT_4 = free thyroxine; TSH = thyroid-stimulating hormone; US = ultrasound.

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nodule; the evaluation should proceed with an ultrasound and possible FNA. As thyroid nodular disease can be altered by normalization of the TSH, ultrasound and FNA should be postponed in patients with elevated TSH until TSH is normal, unless there is marked concern for malignancy. One-time measurement of thyroid antibodies may be appropriate if autoimmune thyroid disease is suspected or if multinodular goiter is identified by ultrasound to stratify the patient's future risk of developing overt thyroid failure. Serum thyroglobulin measurement is not useful and is not recommended.

FNA, performed under ultrasound guidance, is the optimal test to determine whether a nodule is malignant. When performed by an experienced clinician, FNA is safe and relatively simple to perform. The sensitivity of FNA cytology is 90% to 95%, and the false-negative rate is 3% to 5%. FNA of a nodule is generally recommended for those nodules larger than 1 cm that are solid and hypoechoic. The threshold for FNA of nodules that are partially cystic and lacking suspicious ultrasound features is 2 cm in size or greater. Aspirating a nodule of 5 mm or more may be considered if a patient has risk factors such as a personal or family history of thyroid cancer or prior radiation exposure.

The sonographic appearance of a nodule may be used to assess the risk of malignancy and thereby guide the decision of which nodules require biopsy. Features concerning for malignancy include microcalcifications, marked hypoechogenicity, irregular borders, and taller-than-wide shape. Such findings are nearly 70% specific for cancer, but their poor sensitivity cannot exclude the presence of malignancy.

The various diagnoses obtained on FNA and the associated risks of malignancy are listed in **Table 28**.

TABLE 28. Diagnoses Obtained by Fine-Needle Aspiration of Thyroid Nodules and Risk for Malignancy

FNA Diagnosis	Risk for Malignancy	Management
Benign	<3%	Serial ultrasound examinations for growth
Atypia of uncertain significance/follicular lesion of uncertain significance	5%-10%	Repeat FNA
Suspicious for follicular lesion	20%-30%	Hemithyroidectomy
Suspicious for malignancy	50%-75%	Hemithyroidectomy or total thyroidectomy
Malignant	97%-100%	Total thyroidectomy
Nondiagnostic	0%-50%	Repeat FNA; if two nondiagnostic FNAs, surgery

Modified from: Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference. The Bethesda System For Reporting Thyroid Cytopathology. Am J Clin Pathol. 2009 Nov;132(5):658-65. [PMID: 19846805]

FNA = fine-needle aspiration.

Nodules that are benign by FNA should be followed with repeat ultrasound examination in 6 to 18 months to assess for significant changes. If the nodule is stable on repeat imaging and lacks suspicious features, clinical examination and repeat ultrasound can be extended to longer intervals, such as 3 to 5 years. Greater than 50% change in nodule volume or interval development of concerning ultrasound characteristics should prompt a repeat FNA to evaluate for a false-negative initial biopsy.

Malignant nodules and those that are suspicious for malignancy require prompt excision; this is typically done with total thyroidectomy, but hemithyroidectomy may be preferable for patients younger than 45 years of age with a tumor smaller than 4 cm. A nondiagnostic FNA warrants a repeat attempt. In a solid nodule with two unsatisfactory biopsies, diagnostic hemithyroidectomy is indicated. Surgical complications include hypoparathyroidism and recurrent laryngeal nerve paresis; although typically temporary, either complication may be permanent in up to 3% of patients.

KEY POINTS

- Thyroid nodules are found in 1% to 5% of the population; most thyroid nodules are benign, with only approximately 10% harboring a malignancy.
- A serum thyroid-stimulating hormone measurement is the initial laboratory test in a patient with a thyroid nodule; if the thyroid-stimulating hormone is suppressed, then measurement of thyroxine (T_4) and triiodothyronine (T_3) should be performed, and a radionuclide scan should be considered to identify "hot" or functioning nodules, which have a very low likelihood of malignancy and typically do not require fine-needle aspiration. HVC
- If the thyroid-stimulating hormone level is high or normal, the radionuclide scan is unnecessary as it is unlikely to reveal a hot nodule and ultrasonography is an inexpensive and highly effective method for stratification of malignancy risk for nonfunctioning thyroid nodules. HVC
- Fine-needle aspiration of a nodule is generally recommended for those nodules larger than 1 cm (0.4 in) that are solid and hypoechoic and is the optimal test to determine whether a nodule is malignant.

Goiters

Multinodular Goiter

Multinodular goiters occur more frequently with advancing age, low iodine intake, or Hashimoto disease. The risk for malignancy is the same for multiple nodules as it is for a solitary nodule; therefore, the evaluation and management are identical. Biopsy should be performed on the three or four nodules (larger than 1 cm) with the most suspicious ultrasound features. In the absence of suspicious features, the largest nodules should be chosen for aspiration.

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A large multinodular goiter may be associated with compressive symptoms such as dysphagia, hoarseness, or positional dyspnea. To assess the extent of mass effect, additional testing and imaging, including noncontrast CT of the neck/chest, barium swallow, direct laryngoscopy, and/or spirometry with flow-volume loops, may be indicated. Levothyroxine therapy to suppress TSH secretion and reduce goiter size is generally not helpful, poses a risk of thyrotoxicosis, and is not recommended. Radioactive iodine ablation is not an option for euthyroid and hypothyroid patients. Surgical removal is the treatment of choice if the compressive symptoms are significant, if malignancy is suspected, or if the patient desires cosmetic intervention.

KEY POINTS

- In patients with a multinodular goiter, the risk for malignancy is the same for multiple nodules as it is for a solitary nodule; therefore, the evaluation and management are identical.
- Surgical removal of a large multinodular goiter is the treatment of choice if the compressive symptoms are significant, if malignancy is suspected, or if the patient desires cosmetic intervention.

Simple Goiter

A simple goiter is defined as an enlargement of the thyroid gland without the presence of nodules. It may be seen in conditions of dyshormonogenesis, autoimmune thyroid disease, or primary thyroid lymphoma. Primary thyroid lymphoma is a rare condition that typically occurs in elderly women with a history of Hashimoto thyroiditis. The clinical presentation is a symptomatic, rapidly enlarging goiter with a very firm texture. Patients may also have systemic lymphoma symptoms and lateral cervical lymphadenopathy. The diagnosis can be made by FNA. Treatment typically involves chemotherapy and/or radiation therapy. Surgery generally is not indicated, but it can be used to aid in diagnosis when FNA is not informative.

Thyroid Cancer

The incidence of thyroid cancer is rising at a faster rate than any other type of malignancy; the incidence has more than doubled in the last 30 years. This increase is due solely to papillary cancers, with the highest rate of rise occurring in tumors measuring less than 2 cm. Meanwhile, the survival rate for thyroid cancer has remained stable or slightly improved. Autopsy series reveal that occult thyroid cancers measuring less than 1 cm may be identified in as many as 20% of dissected specimens. This finding, coupled with the improving survival rate, has led some investigators to conclude that the change in incidence of thyroid cancer is due solely to increased incidental detection of indolent tumors because of greater use of imaging modalities. Although there is little doubt that escalated detection of otherwise occult tumors has contributed to the trend, there is evidence that larger tumors are increasingly being discovered.

The vast majority of patients with thyroid cancer have well-differentiated thyroid cancer, with excellent long-term survival. The major forms and their relative frequency are listed in **Figure 10**. The most common well-differentiated thyroid cancers are papillary, papillary-follicular variant, and follicular. There are rare, less well-differentiated variants of papillary thyroid cancer (columnar, tall cell, insular, oxyphilic, clear cell, diffuse sclerosing) that are more aggressive and carry a worse prognosis. Anaplastic thyroid cancer is undifferentiated and is the most aggressive form of thyroid cancer; 1-year survival rates range from 20% to 30%.

Staging and prognosis of well-differentiated thyroid cancers (papillary and follicular) are based on the American Joint Committee on Cancer criteria, which include age (<45 or ≥45 years), primary tumor size, local and distant metastases, and capsular and lymphovascular invasion. However, because the majority of patients have excellent survival, T (tumor) N (node) M (metastasis) staging plays a minimal role in the management of thyroid cancers. Instead, decisions regarding treatment are aimed at lowering the likelihood of recurrent disease.

Treatment of well-differentiated thyroid cancer includes a combination of surgery, radioactive iodine, and levothyroxine suppression. The extent of surgery is largely based on the tumor size; solitary tumors smaller than 1 cm may be sufficiently managed with lobectomy alone. Patients with larger tumors, multifocal disease, nodal metastases, or a history of irradiation are best treated with total or near-total thyroidectomy. For patients younger than 45 years of age with a tumor smaller than 4 cm and no evidence of nodal or distant metastases, hemithyroidectomy may be a reasonable alternative to total thyroidectomy. The decision to administer radioactive iodine is based on two factors: improvement in mortality rates and/or reduction in recurrence risk. Patients with distant metastases have improved survival with successful radioiodine

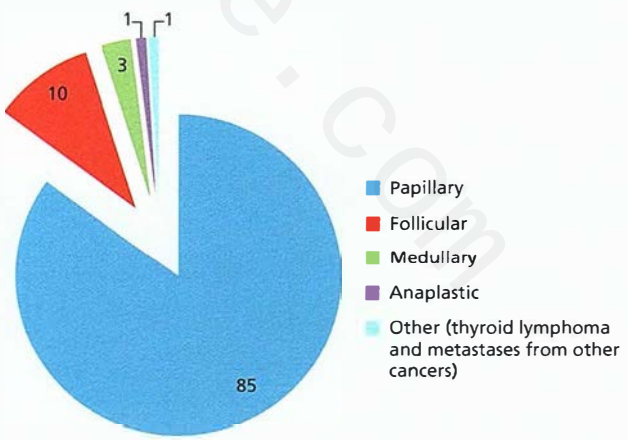

FIGURE 10. Relative frequency of the types of thyroid cancer.

Data from Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer. 1998 Dec 15;83(12):2638-48. [PMID: 9874472]

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therapy, whereas administration of radioactive iodine may decrease the likelihood of recurrent disease in those patients with nodal metastases. Suppression of TSH with levothyroxine therapy may also be used to improve morbidity and reduce mortality, particularly in patients with persistent disease or distant metastases. The necessary degree of TSH suppression varies according to the risk of cancer progression and comorbidities of the patient. Patients with persistent disease typically require lowering of their TSH level to less than 0.1 μU/mL (0.1 mU/L), whereas those who are free of disease but have a high risk for recurrence should have a target TSH level of 0.1 to 0.5 μU/mL (0.1-0.5 mU/L) for 5 to 10 years. Those patients who are disease-free with a low risk of recurrence should maintain a TSH level of 0.3 to 2.0 μU/mL (0.3-2.0 mU/L).

Medullary thyroid cancer represents less than 10% of all thyroid cancers. Approximately 25% of medullary thyroid cancers are hereditary; all patients with medullary thyroid cancer should be screened with *RET* proto-oncogene sequencing. Medullary thyroid cancer may be associated with several syndromes, including multiple endocrine neoplasia type 2A (MEN2A) (which may include pheochromocytoma and hyperparathyroidism), MEN2B (marfanoid habitus and mucosal ganglioneuromas), or familial medullary thyroid cancer (medullary thyroid cancer alone). Biochemical screening for pheochromocytoma with measurement of plasma fractionated metanephrine levels should be done in all patients with an *RET* mutation prior to thyroidectomy.

KEY POINTS

- The vast majority of patients with well-differentiated thyroid cancer have excellent long-term survival.
- Treatment of well-differentiated thyroid cancer includes a combination of surgery, radioactive iodine, and levothyroxine suppression of thyroid-stimulating hormone for patients with persistent disease or high risk of recurrence.

Reproductive Disorders

Physiology of Female Reproduction

A regular, predictable menstrual cycle requires coordination of inhibition and stimulation between the hypothalamus (secreting gonadotropin-releasing hormone [GnRH]), the pituitary (secreting follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), and the ovaries (secreting estradiol and progesterone). The coordination of these signals is referred to as the hypothalamic-pituitary-ovarian axis. The GnRH pulse frequency varies throughout the menstrual cycle to promote follicular development and ovulation (**Figure 11**). The phases of the menstrual cycle are referred to in reference to the activity of the ovary (follicular and luteal phases).

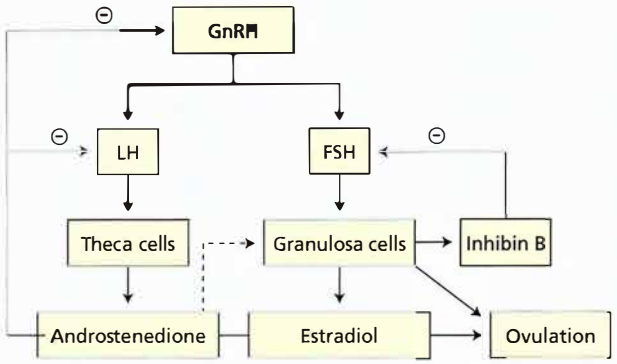

FIGURE 11. Female reproductive axis. Pulses of GnRH drive LH and FSH production. LH acts on theca cells to stimulate androgen (principally androstenedione) production. Androstenedione is metabolized to estradiol in granulosa cells. FSH acts on granulosa cells to enhance follicle maturation. Granulosa cells produce inhibin B as a feedback regulator of FSH production. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; – (circled) = negative feedback.

FSH, under control of pulsatile GnRH secretion, rises in the early menstrual cycle to promote recruitment and growth of a follicle containing a microscopic oocyte (follicular phase). Granulosa cells lining the follicle secrete estradiol, which contributes to negative feedback inhibition of FSH secretion and resultant monofollicular development in the majority of women. Estradiol also stimulates endometrial proliferation. Further into the follicular phase, estradiol levels peak and exert acute positive feedback on the pituitary gland, which elicits an LH surge. This LH surge results in ovulation and initiates the luteal phase of the menstrual cycle. LH stimulates androgen production by the theca cells, which also line the follicle; androgen is subsequently aromatized to estrogen in the granulosa cells via aromatase enzyme. After the LH surge and ovulation, the follicle develops into the corpus luteum, which secretes both estradiol and progesterone and causes the secretory phase of the endometrium in preparation for implantation of a fertilized oocyte. With implantation, the early embryo produces human chorionic gonadotropin, which maintains the corpus luteum. However, when a fertilized embryo is not present, progesterone levels decline, leading to the menstrual phase of the endometrium and menstrual bleeding.

An average menstrual cycle ranges from 25 to 35 days in length. The follicular phase may vary in each woman but is typically from 14 to 21 days. Variability in a menstrual cycle is typically the result of a shortened or lengthened follicular phase, more commonly seen during the first 5 years of menstruation. A decrease in follicular phase length occurs commonly in perimenopause. The luteal phase is usually 14 days and is constant. In women younger than 40 years of age, menstrual cycles less than 25 days or greater than 35 days are likely anovulatory.

KEY POINT

- In women younger than 40 years of age, menstrual cycles less than 25 days or greater than 35 days are likely anovulatory.

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Amenorrhea

Clinical Features

Primary Amenorrhea

Primary amenorrhea is the absence of menses by age 16 years accompanied by normal sexual hair pattern and normal breast development. Primary amenorrhea with absence of thelarche (breast development at the beginning of puberty) and/or adrenarche (androgen production increase that typically occurs at age 8 or 9 years) prior to 14 years of age should be evaluated. Pregnancy must be ruled out in any patient with primary amenorrhea before additional evaluation occurs. Causes of primary amenorrhea may be genetic, hormonal, or structural. Fifty percent of patients with primary amenorrhea have a chromosomal abnormality, such as Turner syndrome (45,XO) (gonadal dysgenesis), although some patients with Turner mosaicism may have secondary amenorrhea (see Secondary Amenorrhea).

Turner syndrome is commonly characterized by other clinical manifestations such as short stature, neck webbing, recurrent otitis media with hearing loss, aortic coarctation, and bicuspid aortic valve. The diagnosis of Turner syndrome may be made with a karyotype.

Approximately 15% of patients presenting with primary amenorrhea may have an anatomic abnormality of the uterus, cervix, or vagina such as müllerian agenesis, transverse vaginal septum, or imperforate hymen. Digital vaginal examination, transvaginal ultrasound, or MRI may help to identify outflow tract anomalies.

KEY POINT

- Fifty percent of patients with primary amenorrhea have a chromosomal abnormality, such as Turner syndrome (45,XO) (gonadal dysgenesis); 15% of patients presenting with primary amenorrhea may have an anatomic abnormality of the uterus, cervix, or vagina.

Secondary Amenorrhea

Secondary amenorrhea is the absence of a menstrual cycle for three cycles or 6 months in previously menstruating women. The most common cause of secondary amenorrhea is pregnancy. A potential structural cause of secondary amenorrhea, such as Asherman syndrome, should be considered. Asherman syndrome is an uncommon complication of dilation and curettage, intrauterine device placement, or surgical procedures such as hysteroscopic myomectomy; it is caused by lack of basal endometrium proliferation and formation of adhesions (synechiae). Diagnosis should be considered in any woman with amenorrhea and past exposure to uterine instrumentation. The classic presentation is amenorrhea or scant bleeding during periods (hypomenorrhea) with ovulatory symptoms (cervical mucous changes, adnexal tenderness associated with follicle formation) or premenstrual symptoms (mood changes or breast tenderness). Some patients will maintain small functional pockets of active endometrium with outflow obstruction by synechia closer to the cervix, resulting in cyclic pain and hematometrium identifiable on ultrasound.

After structural causes and pregnancy are excluded, the hormonal status should be assessed. Low estradiol and inappropriately normal FSH and LH levels indicate hypogonadotropic hypogonadism and point to a central cause (hypothalamic-pituitary). Low estradiol in the setting of elevated FSH and LH levels indicates hypergonadotropic hypogonadism and points to ovarian insufficiency.

The most common hormonal cause of secondary amenorrhea is polycystic ovary syndrome (PCOS) (see Hirsutism and Polycystic Ovary Syndrome), which accounts for 40% of cases. Additional hormonal causes of secondary amenorrhea include hypothalamic amenorrhea (hypogonadotropic hypogonadism), hyperprolactinemia, thyroid disease, and premature ovarian insufficiency (POI) (hypergonadotropic hypogonadism).

Hypogonadotropic hypogonadism caused by hypothalamic amenorrhea (HA) or functional hypothalamic amenorrhea (FHA) affects 3% of women between the ages of 18 and 40 years. Risk factors include low BMI and low body fat percentage, rapid and substantial weight loss or weight gain, eating disorders, excessive exercise, severe emotional stress, or acute and chronic illness. FSH and LH levels are inappropriately low in HA but may be inappropriately normal in FHA. Estradiol levels are typically low, and patients may experience vasomotor symptoms and sleep disturbance. If left untreated, patients are at increased risk for osteoporosis owing to this low-estrogen state. Recovery of menses may occur if BMI returns to normal. Cognitive-behavioral therapy for cases caused by emotional stress has been shown to be effective.

Hyperprolactinemia causes secondary amenorrhea through direct inhibition of GnRH secretion. Treatment of the cause of hyperprolactinemia typically results in restoration of menses. Hypothyroidism may cause secondary amenorrhea through increased thyrotropin-releasing hormone levels, which causes stimulation of prolactin secretion.

Hypergonadotropic hypogonadism as a result of POI is defined as amenorrhea before age 40 years in the setting of two elevated FSH levels (>40 mU/mL [40 U/L]) more than 1 month apart. Possible causes include Turner mosaicism (in which secondary amenorrhea may occur due to POI), fragile X premutation, chemotherapy or radiation, and autoimmune oophoritis. In patients in whom an autoimmune cause is diagnosed, evaluation of other endocrine organs (thyroid, parathyroid, pancreas, and adrenal) is recommended at the time of diagnosis and annually thereafter.

Estrogen replacement is necessary in patients with hypergonadotropic hypogonadism to prevent bone mass loss until the average age of natural menopause (50-51 years). Estrogen replacement preparations are available in oral, transdermal, subcutaneous, and vaginal routes of administration. The dose

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of estrogen required by young women is titrated to prevent vasomotor symptoms and vaginal dryness and may be higher than that used in an older age group. Because spontaneous ovulation may occur (although it is infrequent), counseling on contraceptive options should also be provided for sexually active women not desiring pregnancy. Cyclic progesterone exposure should be considered in patients with an intact uterus to prevent excessive unopposed endometrial proliferation. Oocyte donation may be considered for fertility options for this patient population.

KEY POINT

- The most common causes of secondary amenorrhea are pregnancy, structural abnormalities, and polycystic ovary syndrome.

Evaluation of Amenorrhea

A thorough history and physical examination, including a pelvic examination, are needed to evaluate both primary (no history of menstruation) and secondary amenorrhea (cessation of menstruation after menarche). Urine or serum human chorionic gonadotropin (HCG) testing should be done first to exclude pregnancy, as this is the most common cause of amenorrhea. In patients with primary amenorrhea, a karyotype is recommended if a pregnancy test is negative. Serum levels of prolactin, FSH, LH, estradiol, and thyroid-stimulating hormone (TSH) should then be obtained in the evaluation of primary and secondary amenorrhea. Abnormal levels of prolactin and/or TSH support a nonovarian cause of amenorrhea. Elevations of FSH and LH levels in the presence of a low estradiol level support the diagnosis of POI.

If no elevations in these hormones are found, a progesterone challenge test (oral medroxyprogesterone acetate, 10 mg for 7-10 days) may be used to determine if the amenorrhea is due to estrogen deficiency. If the patient has menstrual bleeding within 1 week of completing 7 to 10 days of medroxyprogesterone, estrogen deficiency is not the cause. In this case PCOS (or a similar diagnosis) should be considered. If no menstrual bleeding occurs, the patient has a low-estrogen state, and hypogonadotropic hypogonadism is the diagnosis (see Disorders of the Pituitary Gland).

Pelvic ultrasound is helpful to identify structural causes of amenorrhea such as müllerian agenesis and intrauterine synechiae. Saline-infusion sonohysterogram can identify intrauterine synechiae, and transvaginal or transabdominal ultrasound can identify absence of a uterus in patients with müllerian agenesis. Endocrinology consultation for further evaluation and testing of patients with findings suspicious for a genetic cause of amenorrhea may be appropriate. A pituitary MRI may be indicated to exclude other intracranial causes of hypogonadotropic hypogonadism when diagnosing HA or FHA, and consultation with an endocrinologist is recommended before imaging is pursued.

KEY POINTS

- After excluding pregnancy, the laboratory evaluation of primary and secondary amenorrhea includes measurements of prolactin, follicle-stimulating hormone, luteinizing hormone, estradiol, and thyroid-stimulating hormone.
- If hormonal evaluation for amenorrhea is negative, the next step is a progesterone challenge test; if the patient bleeds within 1 week of completing 7 to 10 days of progesterone, estrogen deficiency is not the cause and PCOS should be considered

Hyperandrogenism Syndromes

Hirsutism and Polycystic Ovary Syndrome

When hirsutism is present, the patient should be assessed for virilization, or development of male characteristics. Rapid onset and progression of deepening of the voice, severe acne, clitoromegaly, and male pattern balding are signs of virilization and are concerning for an ovarian or adrenal tumor. Age of onset after 30 years is also a risk factor for an androgen-secreting tumor.

In patients with hirsutism or virilization, recommended initial laboratory tests include measurement of plasma dehydroepiandrosterone sulfate (DHEAS) level and serum levels of TSH, prolactin, total testosterone, and follicular-phase 17-hydroxyprogesterone. Normal levels exclude adrenal tumors, hypothyroidism, hyperprolactinemia, and ovarian tumor. Common forms of late-onset congenital adrenal hyperplasia, often mistaken for PCOS, can be excluded with a normal 17-hydroxyprogesterone level. Pelvic ultrasound and adrenal CT should be performed to exclude an ovarian or adrenal neoplasm if the serum total testosterone level is greater than 200 ng/dL (6.9 nmol/L). Adrenal CT is necessary to exclude an adrenal cortisol-secreting and/or androgen-secreting neoplasm if the plasma DHEAS level is greater than 700 µg/mL (18.9 µmol/L). Hirsutism is typically a benign condition, most commonly from PCOS. A marked elevation of total testosterone or DHEAS is not compatible with a diagnosis of PCOS.

PCOS has a prevalence of 7% to 10% and is one of the most common endocrine disorders in young women. Two sets of diagnostic criteria are commonly used. The 2003 American Society for Reproductive Medicine and the European Society of Human Reproduction criteria for PCOS require two of the following three findings in the absence of other endocrine disorders: (1) oligo-ovulation or anovulation, (2) clinical or biochemical evidence of hyperandrogenism (such as hirsutism or acne), or (3) ultrasound findings of polycystic ovarian morphology in at least one ovary. The 1990 criteria from the National Institutes of Health and the National Institute of Child Health and Human Development require all of the following for diagnosis of PCOS: oligo-ovulation, signs of androgen excess (clinical or biochemical), exclusion of other disorders that can result in menstrual irregularity, and hyperandrogenism.

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A constant stagnant follicular stage is seen in PCOS, resulting in unopposed estradiol secretion from small ovarian follicles. Owing to disordered secretion of LH by the anterior pituitary, intraovarian androgen production is also increased in PCOS, resulting in the hyperandrogenism associated with the disorder. Women with PCOS typically have elevated resting LH levels. In patients trying to conceive, this can lead to false-positive indication of the ovulatory LH surge on home urinary LH kits for ovulation.

Estradiol secretion results in proliferation of the endometrium in the absence of progesterone secretion from a corpus luteum. This predisposes patients to endometrial hyperplasia and heavy menstrual bleeding as a result of anovulatory bleeding. Oligo-ovulation and anovulation result in infertility but are typically correctable with clomiphene citrate or letrozole for ovulation induction if fertility is desired. If fertility is not desired, oral contraceptives should be considered if not contraindicated. Addition of oral contraceptives will increase secretion of sex hormone–binding globulin (SHBG) and decrease circulating levels of free testosterone. If a patient has a contraindication to oral contraceptives, a progestin-secreting intrauterine device or cyclic oral or vaginal progesterone should be given to prevent prolonged unopposed estrogen exposure.

Hyperandrogenism may present as hirsutism, acne, or androgenic alopecia. In patients with hirsutism desiring treatment, existing terminal hairs will need to be removed with depilatory methods, but the rate of hair growth while on treatment will decrease. Spironolactone, an aldosterone and androgen inhibitor, may be added after 6 months if acne and hirsutism are still cosmetically bothersome. Before initiation of therapy, the patient should be counseled about teratogenic effects on a male fetus, and contraceptive counseling should be provided.

Both obese and lean women with PCOS also have insulin resistance, and studies have identified an increased incidence of metabolic syndrome, obesity, impaired glucose tolerance, and type 2 diabetes mellitus in these women. Although insulin resistance may improve with weight loss, the use of insulin-sensitizing agents such as metformin is associated with a decrease in serum androgens; however, it is not very effective as a single agent for ovulation induction.

Evaluation of patients with PCOS should include assessment for signs of sleep apnea, hypercholesterolemia, and fatty liver. In women with a thickened endometrium or menometrorrhagia, endometrial sampling with endometrial biopsy should be considered to evaluate for endometrial hyperplasia. Weight loss and exercise should be emphasized.

KEY POINTS

- Polycystic ovary syndrome has a prevalence of 7% to 10% and is one of the most common endocrine disorders in young women; it is often associated with insulin resistance, metabolic syndrome, obesity and type 2 diabetes mellitus.

(Continued)

KEY POINTS *(continued)*

- Polycystic ovary syndrome can be diagnosed if two of the following three findings are present: (1) oligo-ovulation or anovulation, (2) clinical or biochemical evidence of hyperandrogenism (such as hirsutism or acne), or (3) ultrasound findings of polycystic ovarian morphology in at least one ovary.
- The 1990 criteria from the National Institutes of Health and the National Institute of Child Health and Human Development require all of the following for diagnosis of PCOS: oligo-ovulation, signs of androgen excess (clinical or biochemical), exclusion of other disorders that can result in menstrual irregularity, and hyperandrogenism.

Androgen Abuse in Women

Anabolic steroids may be abused by some women to enhance their athletic performance or physique. Such exogenous administration may result in absence of GnRH pulsatility and resultant hypogonadotropic hypogonadism and amenorrhea. Adverse effects may include hirsutism, acne, deepening of the voice, decreased breast size, and clitoromegaly. Withdrawal of exogenous androgens does not result in severe hypogonadism as it does in men, and most women return to regular menstrual cycles.

Female Infertility

Infertility is defined as the absence of conception after 1 year of unprotected intercourse (on average twice weekly) in a woman younger than 35 years of age. Investigation should begin after 6 months if no conception has occurred in a woman 35 years of age or older. Infertility evaluation should include a careful medical history of both partners with special focus on menstrual history, previous exposure to sexually transmitted infections, pelvic surgery, and previous obstetric complications such as miscarriage or cesarean delivery. If a report of oligomenorrhea is elicited, measurement of serum TSH and prolactin levels is appropriate to exclude thyroid disease and hyperprolactinemia as causes of oligo-ovulation.

Further evaluation of infertility causes typically includes semen analysis of the male partner, confirmation of ovulation with measurement of midluteal progesterone level (>3 ng/mL [9.5 nmol/L]), and because Fallopian tubes may be obstructed due to infection such as pelvic inflammatory disease, tubal patency evaluation with hysterosalpingogram. A common cause of tubal occlusion and resultant infertility is past pelvic inflammatory disease. Laparoscopy for evaluation of pelvic adhesions or mild endometriosis may be warranted in patients with dysmenorrhea, previous exposure to sexually transmitted infections, or previous pelvic surgery.

If no abnormalities are found, treatment to enhance endogenous gonadotropin release and increase the numbers of oocytes ovulated monthly may be warranted. Some studies

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support moving directly to in vitro fertilization treatment for women with infertility at age 40 years. In women treated with ovarian stimulation, oral medications such as clomiphene citrate or letrozole are typically used. This therapy is not appropriate in patients with POI. Patients should be counseled about the 5% to 8% risk of multiple gestation with these therapies. Referral to a reproductive endocrinologist is recommended.

KEY POINT

- Infertility evaluation in women should include a medical history of both partners with special focus on menstrual history, previous exposure to sexually transmitted infections, pelvic surgery, and previous obstetric complications such as miscarriage or cesarean delivery.

Physiology of Male Reproduction

Control of spermatogenesis and testosterone production depends on the pulsatile secretion of GnRH from the hypothalamus as well as subsequent downstream stimulation of the anterior pituitary and male gonads. In the testicle, FSH stimulates Sertoli cell spermatogenesis, and LH stimulates Leydig cell testosterone production. Negative feedback from testosterone production inhibits FSH and LH secretion at the level of the anterior pituitary as well as pulsatile hypothalamic GnRH secretion. Inhibin B, produced by the Sertoli cells, also inhibits FSH (**Figure 12**).

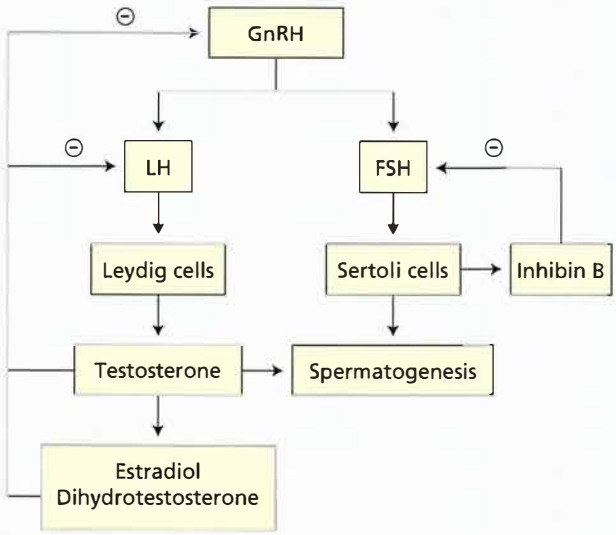

FIGURE 12. Male reproductive axis. Pulses of GnRH elicit pulses of LH and FSH. FSH acts on Sertoli cells, which assist sperm maturation and produce inhibin B, the major negative regulator of basal FSH production. The Leydig cells produce testosterone, which feeds back to inhibit GnRH and LH release. Some testosterone is irreversibly converted to dihydrotestosterone or estradiol, which are both more potent than testosterone in suppressing GnRH and LH. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; – (circled) = negative feedback.

Leydig cell production of testosterone occurs in a diurnal pattern, with the highest concentration observed in the morning. A large percentage of circulating testosterone is bound either to SHBG or albumin. A serum total testosterone level measured in the early morning is generally considered to be an accurate measurement of a patient's androgen status, but it does not account for decreased SHBG as seen in obesity (see Evaluation of Male Hypogonadism).

Hypogonadism

Primary Hypogonadism

Primary hypogonadism, or testicular failure, represents a decrease in testosterone or sperm production. Primary hypogonadism is uncommon and may have congenital or acquired causes. Klinefelter syndrome is the most common cause of congenital primary hypogonadism. Klinefelter syndrome is a common cause of hypergonadotropic hypogonadism and azoospermia, resulting in infertility. A 47,XXY karyotype is diagnostic of Klinefelter syndrome. Mosaic variants of this condition exist but typically present with oligoasthenospermia, testicular failure or hypogonadism. Concomitant symptoms often include sexual dysfunction and generalized fatigue. Tall stature is a common finding. Patients with Klinefelter syndrome may fail to achieve puberty or may present after sexual maturation with azoospermia. Exposure to chemotherapy or radiation may also result in primary testicular failure. Local injury as a result of torsion, orchitis, or trauma may result in ischemia and necrosis of testicular tissues.

Secondary Hypogonadism

Typically secondary hypogonadism is a result of insufficient GnRH production by the hypothalamus or deficient LH/FSH secretion by the anterior pituitary. Causes may be congenital or acquired. Idiopathic hypogonadotropic hypogonadism, with anosmia (Kallmann syndrome) or without anosmia, is the most common cause of congenital secondary hypogonadism. Acquired secondary hypogonadism is most commonly iatrogenic due to exogenous testosterone administration. Untreated sleep apnea and obesity are other common causes. Other acquired causes include hyperprolactinemia, chronic opioid use, glucocorticoid use, or infiltrative disease (lymphoma or hemochromatosis).

Androgen Deficiency in the Aging Male

The natural progression of male aging involves testosterone level decline. Most men will not become hypogonadal, and the decline in testosterone production is highly variable with each person. "Low T" has become a part of the popular vernacular, owing to aggressive direct-to-consumer marketing, and describes many symptoms that may or may not be associated with a low serum testosterone level in men. Both prescription and over-the-counter testosterone and derivative sales have surged in the United States and many other countries. With

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the increased sales of testosterone formulations to treat aging men, questions have emerged about the potential adverse effects of exogenous testosterone therapy, particularly in men who have no biochemical evidence of testosterone deficiency. Potential adverse effects include increased risk of cardiovascular disease and death, venous thromboembolism, and prostate cancer.

Evaluation of Male Hypogonadism

A thorough history and physical examination are essential in the evaluation of hypogonadism. A sleep history is especially helpful. A large constellation of nonspecific symptoms is associated with male hypogonadism, which makes diagnosis and treatment based on symptoms alone not advisable. Nonspecific symptoms include fatigue, decreased muscle strength, decreased libido, amotivational state, or decreased robustness or frequency of erections. Testosterone measurements are not recommended if only nonspecific symptoms are present; rather, investigation of other causes of the patient's symptoms is appropriate. More specific symptoms include gynecomastia, diminished testicular volumes, and absence of morning erections. Measurement of testosterone levels is not recommended if a patient is having regular morning erections, does not have true gynecomastia on examination, and has a normal testicular examination, as it is highly unlikely that he has testosterone deficiency.

Testosterone deficiency is diagnosed with two early morning serum total testosterone levels below the reference range. Because illness and strenuous activity can falsely lower testosterone levels, measurement should occur in healthy men who have avoided strenuous activity for several days. Measurements of the testosterone level occurring later in the morning or in the afternoon are not useful for interpretation. Consultation with an endocrinologist should be considered if two early morning total testosterone levels are low. In certain clinical scenarios, such as morbid obesity, total testosterone may be low but free testosterone may be normal. Free testosterone assays can be unreliable, and routine measurement of free testosterone is not recommended. Free testosterone by equilibrium dialysis is the gold-standard assay.

Once confirmed, the cause of hypogonadism (primary or secondary) should be further investigated prior to initiation of testosterone replacement. Serum LH, FSH, prolactin, and TSH levels should be measured. Primary testosterone deficiency (hypergonadotropic hypogonadism) is diagnosed when FSH and LH levels are frankly elevated in the presence of a simultaneously low testosterone level. Low or inappropriately normal FSH and LH levels in the presence of simultaneous low testosterone levels are diagnostic of secondary hypogonadism (hypogonadotropic hypogonadism).

A hypergonadotropic state (elevated LH and FSH levels) should be further investigated with a karyotype if no history of gonadotoxic therapy or testicular insult is elicited. If a hypogonadotropic state is revealed, transferrin saturation and ferritin levels should be evaluated to exclude hemochromatosis. MRI of the pituitary should be performed to evaluate for hypothalamic or pituitary masses as the cause of the hypogonadotropic state if no confounding medications or reversible secondary causes are discovered. **Figure 13** shows an algorithm for evaluating male hypogonadism.

KEY POINTS

- Measurement of testosterone levels is not recommended if a patient is having regular morning erections, does not have true gynecomastia on examination, and has a normal testicular examination, as it is highly unlikely that he has testosterone deficiency. **HVC**
- Testosterone deficiency is diagnosed with two early morning total testosterone levels below the reference range.
- Once testosterone deficiency is confirmed, the cause should be further investigated prior to initiation of testosterone replacement.

Testosterone Replacement Therapy

Testosterone replacement therapy is a widely used treatment for men with hypogonadism. Possible benefits seen with testosterone replacement therapy, such as improved libido, energy level, and bone density, have been described but remain controversial. Testosterone therapy has been associated with increased hemoglobin and hematocrit levels, worsened obstructive sleep apnea, and a decrease in HDL cholesterol levels. LDL cholesterol levels do not appear to be affected.

Although hypogonadism remains an independent risk factor for mortality, recent studies have examined the association between testosterone therapy and cardiovascular risk. The association between testosterone therapy and mortality has remained controversial. Physicians prescribing testosterone therapy to elderly men with biochemically proven testosterone deficiency and comorbidities should use it prudently with close follow-up. Cardiovascular disease risk as well as risk for thrombosis should be discussed with patients before pursuing therapy. Prescribing testosterone therapy in the absence of biochemically proven testosterone deficiency puts the patient at risk for iatrogenic hyperandrogenism with subsequent increased risk of myocardial infarction, stroke, death, venous thromboembolism, polycythemia, and obstructive sleep apnea. Prescribing testosterone therapy in the absence of a full evaluation may delay treatment for secondary causes such as prolactinoma, hemochromatosis, or intracranial mass.

Although implantable pellets and injectable testosterone preparations are available, the most popular testosterone preparations currently are topical (most commonly hydroalcoholic

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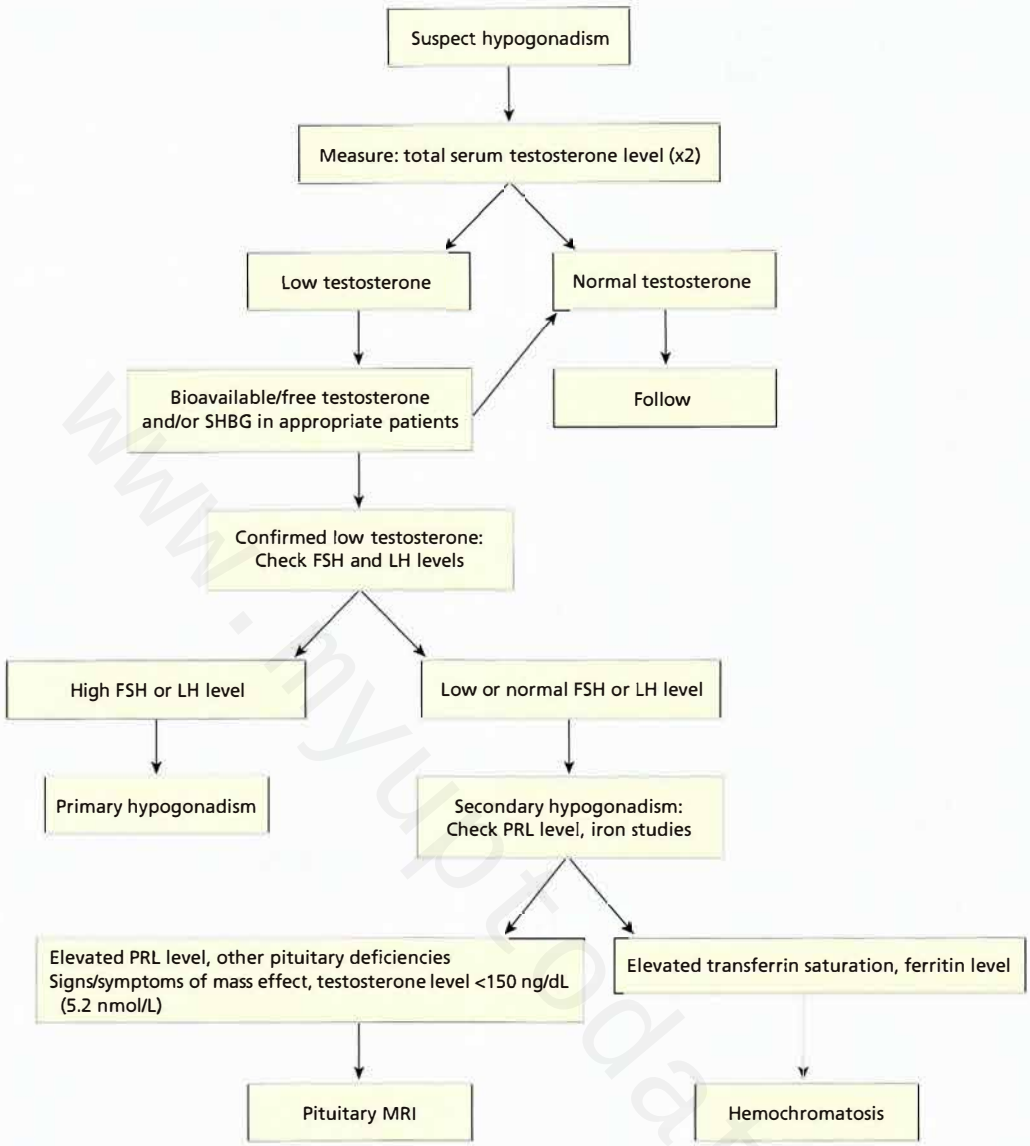

FIGURE 13. Algorithm for evaluating male hypogonadism. FSH = follicle-stimulating hormone; LH = luteinizing hormone; PRL = prolactin; SHBG = sex hormone-binding globulin; ×2 = two separate measurements.

gels). They require daily use and may incur significant cost to the patient, but the steady level of testosterone achieved within 30 minutes of application is an appealing feature. Inadvertent absorption by patient contacts may occur; users should be informed that virilization of contacts is not uncommon and premature puberty can occur in exposed children. The patient should also be counseled that decline in endogenous testosterone production and spermatogenesis may occur. If fertility is desired, testosterone therapy should be avoided, and consultation with a reproductive endocrinologist is recommended.

Patients requiring testosterone replacement therapy should have testosterone levels monitored at 3 and 6 months after initiation and annually thereafter; the goal total testosterone level should be in the mid-normal range. Monitoring of the prostate specific antigen and hematocrit level should follow Endocrine Society guidelines (**Table 29**).

KEY POINTS

- Testosterone deficiency should be diagnosed biochemically, and its cause should be definitively determined before initiation of testosterone replacement therapy.
- Patients requiring testosterone replacement therapy should have testosterone, prostate specific antigen, and hematocrit levels monitored.
- Goal total testosterone level should be in the mid-normal range for patients requiring testosterone therapy.

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TABLE 29. Endocrine Society Clinical Guidelines for Monitoring Adverse Effects of Testosterone Replacement Therapy

Parameter	Recommended Screening Schedule	Alerts
Hematocrit	Value obtained at baseline and then at 3 months and 6 months after therapy initiation, followed by yearly measurements	Value >54%
PSA level	For patients >40 years of age with a baseline value >0.6 ng/mL (0.6 µg/L), DRE and PSA level (determined at 3 and 6 months after therapy initiation followed by regular screening)	Increase >1.4 ng/mL (1.4 µg/L) in 1 year or >0.4 ng/mL (0.4 µg/L) after 6 months of use; abnormal results on DRE; AUA prostate symptoms score/ IPSS >19

AUA = American Urological Association; DRE = digital rectal examination; IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen.

Data from Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2010;95(6):2550. [PMID: 20525905]

Anabolic Steroid Abuse in Men

Testicular testosterone production is suppressed in the presence of exogenous testosterone administration. Many elite athletes abuse androgens in injectable form, and herbal preparations of oral testosterone are readily available. Commonly used androgens include injectable testosterone esters and oral alkylated testosterone preparations. HCG injections mimic LH stimulation to the Leydig cells and result in elevated testosterone levels. Although this therapy is appropriate in men with hypogonadotropic hypogonadism, it may also be abused. Aromatase inhibitors are frequently used concurrently with exogenous testosterone preparations to prevent adipose conversion of estrogens to androgens and development of gynecomastia. Androstenedione supplements are commonly abused.

Excessive muscle bulk, acne, gynecomastia, and decreased testicular volume may be found on physical examination in patients using anabolic steroids. Irreversible hypogonadism may result and often presents as male infertility with oligospermia or azoospermia on sperm analysis. Permanent inability to produce endogenous testosterone may occur. Extratesticular effects may also be noted, including low HDL cholesterol level, hepatotoxicity, erythrocytosis, and increased risk of obstructive sleep apnea. Mood disorders are common in anabolic steroid users.

Laboratory studies showing low or normal gonadotropin levels and a low testosterone level with clinical evidence of hyperandrogenism are consistent with use of a non-testosterone-containing product, such as one containing androstenedione, or cessation of long-standing (typically greater than 1 year) anabolic steroid use, with failure to recover endogenous testosterone function.

KEY POINTS

- Excessive muscle bulk, acne, gynecomastia, and decreased testicular volume may be seen on physical examination in male patients using anabolic steroids.
- Exogenous testosterone use may result in irreversible decline in spermatogenesis and resultant infertility, as well as permanent inability to produce endogenous testosterone.

Male Infertility

Physical examination should include assessment for the presence or absence of the vas deferens, evaluation for congenital bilateral absence of the vas deferens (as seen in cystic fibrosis), assessment of testicular volume, and evaluation for the presence of hernia, varicocele, or tumor. Semen analysis obtained after 48 to 72 hours of abstinence from sexual activity is the best test to assess male fertility. For accurate results, analysis of the sample should occur within 1 hour of ejaculation. Extended abstinence periods may diminish fructose in the ejaculate and artificially lower sperm motility. If the physical examination is abnormal, evaluation by a urologist may be appropriate. If semen analysis results are abnormal, the test should be repeated, and referral, if abnormal, to a reproductive endocrinologist is warranted.

KEY POINT

- Semen analysis obtained after 48 to 72 hours of abstinence from sexual activity is the best test to assess male fertility; if abnormal, the test should be repeated for confirmation.

Gynecomastia

Gynecomastia is glandular breast tissue enlargement in men due to imbalance in the levels or activity of testosterone and estrogen. This imbalance results in an increased estrogen-to-testosterone ratio, which in turn results in decreased inhibitory action of testosterone on the breast tissue. The less testosterone and/or more estrogen the breast tissue is exposed to, the more likely gynecomastia will develop. Although abnormal in the postpubertal man, it is usually benign. It is typically bilateral but not always symmetric. Unilateral gynecomastia is uncommon and should be evaluated with mammogram as soon as possible owing to risk of breast cancer.

There are many causes of gynecomastia, ranging from drug-induced (marijuana, alcohol, 5α-reductase inhibitors, H_2-receptor antagonists, spironolactone, digoxin, ketoconazole, calcium channel blockers, ACE inhibitors, antiretroviral agents, tricyclic antidepressants, selective serotonin reuptake inhibitors) and hypogonadism (primary, secondary) to chronic illness (hepatic cirrhosis, chronic kidney disease) and endocrine disorders (hyperprolactinemia, acromegaly, hyperthyroidism, Cushing syndrome). Obesity and aging are associated

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with gynecomastia owing to increased aromatase activity in the periphery. Estrogen-secreting tumors (such as Leydig or Sertoli cell tumors or adrenal cortical carcinoma) and HCG-secreting tumors (such as germ cell tumors and hepatic carcinomas) are associated with gynecomastia.

A thorough history should be obtained. The breasts should be examined for glandular enlargement, which typically extends concentrically from under the areolae, and is firm, mobile, and rubbery. The breasts may be tender if the time course is acute. Pseudogynecomastia is subareolar adipose tissue, without glandular proliferation, that is associated with obesity. True gynecomastia typically distorts the normally flat contour of the male nipple, causing it to protrude owing to the mass of glandular tissue beneath it. In pseudogynecomastia, the nipple is typically still flat but soft, and nondescript subcutaneous fat tissue is present in the breast area.

Mild, chronic, asymptomatic gynecomastia does not warrant evaluation. Evaluation of gynecomastia that is asymmetric or concerning for malignancy (bloody nipple discharge, hard and fixed, associated with regional lymphadenopathy), of rapid and recent onset, or larger than 2 cm (>5 cm in obese men owing to the known increase in aromatase activity in obesity), should include measurement of total testosterone, LH, FSH, and TSH levels, as well as assessment of liver and kidney function. If indicated by findings on history and/or physical examination, measurement of prolactin, estradiol, and HCG may also be indicated. If the biochemical evaluation demonstrates abnormalities, further evaluation with testicular ultrasound, adrenal CT, or pituitary MRI may be indicated; consultation with an endocrinologist is recommended before imaging is ordered.

KEY POINTS

- Unilateral gynecomastia in the male patient is concerning for malignancy and warrants immediate evaluation with a mammogram.

HVC

- Mild, chronic, asymptomatic gynecomastia in the male patient does not warrant evaluation.

Calcium and Bone Disorders

Calcium Homeostasis and Bone Physiology

Serum calcium levels are tightly regulated on a moment-to-moment basis by the actions of vitamin D and parathyroid hormone (PTH). The amount of calcium that is albumin bound can be affected by hydration and nutritional status. If albumin levels decrease, total serum calcium levels may appear low (pseudohypocalcemia). Conversely, if albumin levels increase, total calcium levels will appear elevated (pseudohypercalcemia). In both cases, ionized calcium should be measured. It will usually be normal, indicating normal circulating free levels of calcium. There are also instances of artificially increased calcium levels due to high protein states as in multiple myeloma (elevated monoclonal immunoglobulins), hyperalbuminemia, Waldenström macroglobulinemia, and thrombocytosis. In these patients, ionized calcium would be normal with elevated total serum calcium.

Vitamin D is a fat-soluble vitamin, and body sources include de novo production from the skin, through forms found in food, and through supplementation (**Table 30**). There are two forms of vitamin D supplementation: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Although both forms are useful in raising vitamin D levels, vitamin D_3 may be more beneficial because of tighter bonding to vitamin D receptors, longer shelf life, greater potency than vitamin D_2, and being identical to the vitamin D that naturally occurs in humans after ultraviolet light exposure.

Regardless of the method of ingestion, vitamin D_3 and D_2 are both inactive forms that must be hydroxylated twice before becoming active. The first occurs in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms

TABLE 30. Sources of Vitamin D

Sources	Type of Vitamin D	Amount of Vitamin D
Food Sources		
Cod liver oil	Cholecalciferol	400-1000 U/teaspoon
Salmon, wild caught	Cholecalciferol	600-1000 U/4 oz
Salmon, canned	Cholecalciferol	300 U/4 oz
Mackerel, canned	Cholecalciferol	250 U/4 oz
Sundried shitake mushrooms	Ergocalciferol	1600 U/4 oz
Egg yolk	Ergocalciferol	20 U/yolk
Sunlight (one minimal erythermal dose)		20,000 U in bathing suit
Fortified Foods		
Milk	Cholecalciferol	
Orange juice	Cholecalciferol	
Infant formula	Cholecalciferol	
Pharmaceutical Sources		
Vitamin D_2	Ergocalciferol	50,000 U/capsule
Liquid vitamin D_2	Ergocalciferol	8000 U/capsule
Multivitamin	Ergocalciferol and cholecalciferol	400, 500, or 1000 U/capsule
Vitamin D_3	Cholecalciferol	400, 800, 1000, 2000, 5000, 10,000, 50,000 U/capsule

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the physiologically active 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], also known as calcitriol (**Figure 14**).

Because 25-hydroxyvitamin D has a relatively long half-life of several weeks, it is the best indicator of whole body vitamin D status. Active vitamin D acts on three organ systems to achieve and maintain normal serum calcium: bone, intestine, and kidney. With adequate vitamin D, bone resorption is increased, intestinal uptake of dietary calcium is increased, and excretion of calcium through the kidney is decreased. PTH is secreted to increase the calcium in the blood in response to even the slightest degree of hypocalcemia; it acts on the kidney to increase production of active vitamin D and promote calcium reabsorption in the distal convoluted tubule and loop of Henle, and increased resorption in bones, thereby increasing release of calcium into the blood.

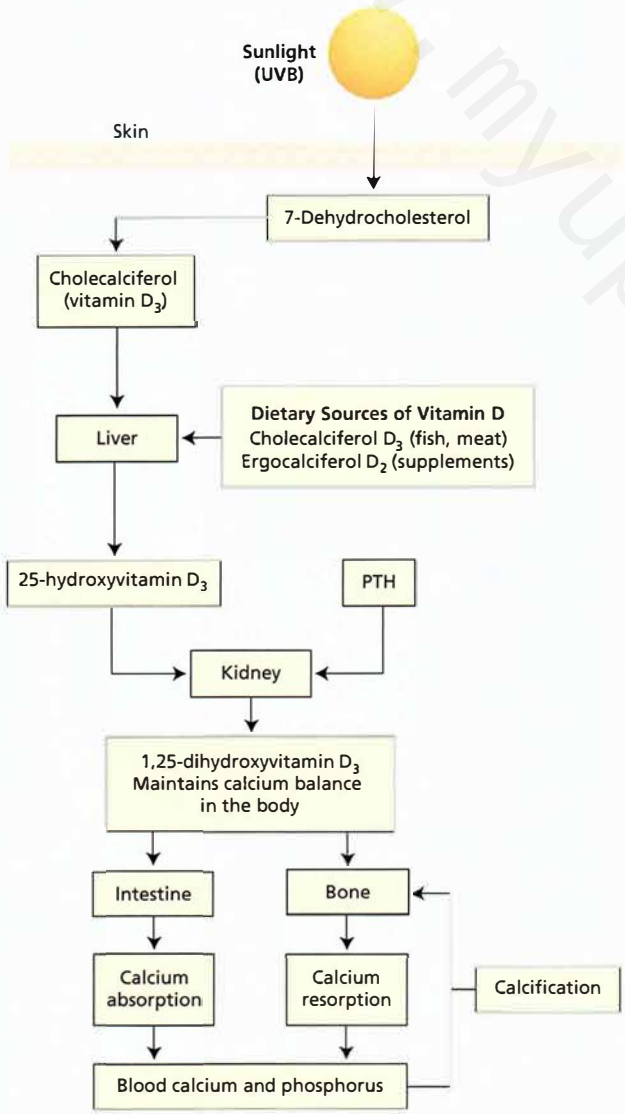

FIGURE 14. Production of vitamin D. PTH = parathyroid hormone; UVB = ultraviolet B.

Hypercalcemia

Clinical Features of Hypercalcemia

Hypercalcemia is marked by serum calcium levels above the normal range, usually greater than 10.5 mg/dL (2.6 mmol/L). Most patients are asymptomatic, and hypercalcemia may be noted incidentally on laboratory tests obtained for other reasons. Symptoms may occur with any degree of hypercalcemia but are more likely when serum calcium levels exceed 12 mg/dL (3 mmol/L). Classic symptoms of polyuria, polydipsia, and nocturia sometimes occur with elevated calcium levels of 11 mg/dL (2.8 mmol/L) or less. Other symptoms such as anorexia, nausea, abdominal pain, constipation, increased creatinine levels, and mild mental status changes are more likely to occur with levels greater than 11 mg/dL (2.8 mmol/L). As serum calcium levels continue to increase beyond 12 mg/dL (3 mmol/L), symptoms become more severe such as profound mental status changes, obtundation, acute kidney injury due to profound dehydration, and increased creatinine concentration.

KEY POINTS

- Classic symptoms of hypercalcemia are polyuria, polydipsia, anorexia, nausea, abdominal pain, constipation, and mental status changes; as serum calcium levels increase and/or the rate of change increases, symptoms become more severe, with profound mental status changes, obtundation, and acute kidney injury.
- 25-Hydroxyvitamin D has a relatively long half-life of several weeks, is the best indicator of whole body vitamin D status, and is the recommended test for vitamin D deficiency. **HVC**

Diagnosis and Causes of Hypercalcemia

When serum calcium elevation is incidentally noted, repeat measurement of serum calcium is indicated, and if a second hypercalcemic level is noted, further evaluation is warranted to determine the cause (**Table 31**). The next step is determining if the hypercalcemia is PTH- or non-PTH-mediated by simultaneous measurement of serum calcium and intact PTH levels (**Figure 15**). Ionized calcium may be used in evaluating hypercalcemia, but it is rarely helpful in diagnosing hypercalcemia in patients with normal albumin levels or no acid-base disturbances.

Parathyroid Hormone–Mediated Hypercalcemia

Primary Hyperparathyroidism

Primary hyperparathyroidism is the most common cause of PTH-mediated hypercalcemia, and is diagnosed with a simultaneously elevated serum calcium level, with an inappropriately normal or elevated intact PTH level. The incidence peaks in the seventh decade and affects mostly women (75%). Before the age of 45 years, rates are similar in men and women. Approximately 80% of patients will have elevated PTH levels with simultaneously elevated calcium levels. Most commonly,

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TABLE 31. Causes of Hypercalcemia
Parathyroid Hormone-Mediated Hypercalcemia
Primary hyperparathyroidism (adenoma, hyperplasia)
Parathyroid cancer
Tertiary hyperparathyroidism
Familial hypocalciuric hypercalcemia
Normocalcemic primary hyperparathyroidism
Non-Parathyroid-Mediated Hypercalcemia
Hypercalcemia of malignancy (humoral and local osteolytic)
Vitamin D toxicity
Vitamin A toxicity
Milk alkali syndrome
Thyrotoxicosis
Prolonged immobilization
Granulomatous diseases (sarcoidosis, tuberculosis)
Lymphomas
Total parenteral nutrition

primary hyperparathyroidism is due to a single parathyroid adenoma; however, rarely it may be attributed to multigland hyperplasia (typical in patients with end-stage kidney disease or multiple endocrine neoplasia syndromes) or parathyroid gland carcinoma (calcium is typically >14 mg/dL [3.5 mmol/L] and intact PTH levels >250 pg/mL [250 ng/L] on presentation; diagnosis is made histopathologically given the overlap with benign primary hyperparathyroidism).

Once diagnosed, measurement of serum phosphorus, 24-hour urine calcium, and serum 25-hydroxyvitamin D levels may facilitate management. Serum phosphorus levels are typically low or low-normal in these patients. In contrast, phosphorus levels will be elevated in patients with vitamin D toxicity. Approximately 50% of patients with primary hyperparathyroidism will have elevated urine calcium levels, and the other 50% will have normal levels. Occasionally, urine calcium can be low in those patients with concomitant primary hyperparathyroidism and vitamin D deficiency. Additionally, patients with vitamin D deficiency convert more 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D so they may have elevated levels of 1,25-dihydroxyvitamin D.

Parathyroidectomy is the treatment for primary hyperparathyroidism. Surgical management is curative in roughly 90% of patients, but evidence that the benefit outweighs the risk of the surgical procedure is present under only certain circumstances. There have been several long-term observational studies that found stability in biochemical markers and bone density in patients who do not meet the surgical intervention criteria listed in **Table 32**. When one or more of these criteria are met, surgery is recommended. Surgery can be considered when surgical criteria are not met, but patients should be cautioned that there are no robust data to support that intervention.

It is critical that an experienced surgeon perform the surgery to avoid increased risk of postoperative hypoparathyroidism and damage to the recurrent laryngeal nerve. Historically, a bilateral neck dissection was done to identify parathyroid glands that appeared to have irregular appearance or increased size. With the increased use of sestamibi scans, high-definition ultrasound, and intraoperative measurement of PTH levels, the minimally invasive technique is now preferred. Minimally invasive surgery allows for a smaller incision and a shortened surgical duration.

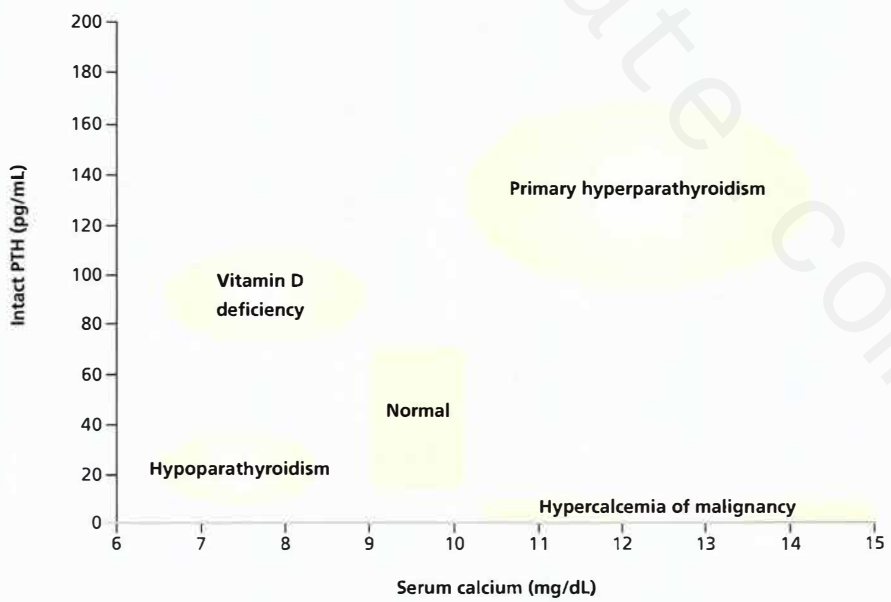

FIGURE 15. Relationship of calcium, PTH, and vitamin D status in normal conditions and in several diseases. PTH = parathyroid hormone.

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TABLE 32. Indications for Surgical Intervention in Patients with Primary Hyperparathyroidism

Increase in serum calcium level ≥1 mg/dL (0.25 mmol/L) above upper limit of normal[a]
Creatinine clearance must be <60 mL/min (0.06 L/min)[a]
T-score (on DEXA scan) of −2.5 or worse at the lumbar spine, total hip, femoral neck, or distal radius[a]
Age 50 years or younger[a]
Surgery also indicated in patients in whom medical surveillance is neither desired nor possible, including those with significant bone, kidney, gastrointestinal, or neuromuscular symptoms typical of primary hyperparathyroidism

DEXA = dual-energy x-ray absorptiometry.

[a]In otherwise asymptomatic patients.

Recommendations from Bilezikian JP, Khan AA, Potts JT Jr. Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Third International Workshop. J Clin Endocrinol Metab. 2009 Feb;94(2):335-9. [PMID: 19193908]

In patients with osteoporosis who are poor surgical candidates or refuse surgery, intravenous bisphosphonate therapy will slow bone resorption and temporarily decrease serum calcium levels. Intravenous bisphosphonate should be redosed when hypercalcemia recurs.

In patients who do not meet the criteria for surgery, surveillance is recommended. Patients should have annual measurement of serum calcium and creatinine levels. A three-site dual-energy x-ray absorptiometry (DEXA) scan should be performed every 1 to 2 years to evaluate bone mineral density of the lumbar spine, hip, and distal radius. The frequency of DEXA scanning should increase to yearly when any treatment has been initiated for bone health or other medications have been added that may affect bone health (antiandrogen, antiestrogen, antiseizure medications, or glucocorticoids).

In patients with asymptomatic primary hyperparathyroidism, other precautions can be taken to prevent disease-related complications. These patients should maintain adequate vitamin D (400-600 U daily) intake to prevent further PTH stimulation. In patients with concomitant vitamin D deficiency, repletion is recommended to replete patients whose levels are below 30 ng/dL (75 nmol/L) with careful attention to urine calcium excretion and serum calcium once values are greater than 30 ng/dL (75 nmol/L). A large study did not show worsening calcium levels when repleting vitamin D in patients with levels less than 30 ng/dL (75 nmol/L). Adequate physical activity to prevent bone resorption and adequate hydration to prevent kidney damage are imperative.

Parathyroid Carcinoma

Parathyroid carcinoma is very rare, accounting for less than 1% of all persons with primary hyperparathyroidism. Mutations in the *HRPT2* gene are thought to be the major genetic link in parathyroid carcinoma, and inactivation of this gene leads to familial hyperparathyroidism as well. When compared with benign primary hyperparathyroidism, parathyroid carcinoma is equally prevalent in both sexes, more commonly presents with kidney and bone involvement and a neck mass, and frequently is associated with a total serum calcium level greater than 14 mg/dL (3.5 mmol/L) and very high parathyroid hormone levels, typically greater than four times the upper limit of normal. Most patients present with single gland involvement. Because parathyroid carcinomas may not appear histologically different from benign adenomas, local spread from the capsule, distant metastasis, or lymph node involvement must be present for carcinoma diagnosis. In these patients, surgical resection is the treatment of choice with calcimimetics used for residual disease or in patients who are poor surgical candidates. Any patient found to have parathyroid carcinoma should be screened for the *HRPT2* gene, and if positive, family members should be screened as well.

Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism is the result of the prolonged PTH stimulation needed to maintain normocalcemia resulting from decreased 1,25-dihydroxyvitamin D levels from kidney impairment. This prolonged stimulation results in increased calcium levels and severe hyperparathyroid hyperplasia and elevated PTH levels that do not respond to phosphate binders and calcitriol therapy. Severe bone loss and other symptoms make surgical resection the treatment of choice.

Normocalcemic Primary Hyperparathyroidism

Normocalcemic primary hyperparathyroidism is defined as increased PTH levels in the absence of elevated calcium levels. This is a diagnosis of exclusion used in patients being evaluated for low bone density in which all secondary causes have been ruled out, including vitamin D deficiency. Approximately 20% of these patients will develop hypercalcemia within 3 years, so they should be monitored closely.

Familial Hypocalciuric Hypercalcemia

The most common form of familial hypercalcemia is familial hypocalciuric hypercalcemia (FHH). It is a rare autosomal dominant condition with a high penetrance that often occurs in childhood. These patients are frequently asymptomatic, but in rare cases the calcium-sensing receptor (*CASR*) gene mutation can increase the risk of pancreatitis. Elevated serum calcium levels are caused by a mutation in the G-coupled protein *CASR* gene. These receptors are in the parathyroid glands and the kidneys. The sensor mutation results in a shift upward in the "normal" range of calcium that the receptor recognizes, resulting in a mildly elevated serum calcium level (usually less than 11.0 mg/dL [2.8 mmol/L]) and high normal or mildly elevated PTH level. An elevated PTH level is more commonly seen in patients with concomitant vitamin D deficiency. The diagnosis is made by measuring 24-hour urine calcium excretion levels. Typically, patients with FHH will have a 24-hour urine calcium level less than 200 mg/24 h (5.0 mmol/24 h). The preferred standard is the calcium-creatinine clearance ratio, using the following formula:

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Ca/Cr clearance ratio = [24-hour urine Ca × serum Cr] ÷ [serum Ca × 24-hour urine Cr]. A ratio less than 0.01 confirms the diagnosis if all other causes of hypocalciuria (thiazides, lithium, vitamin D deficiency) have been excluded. FHH is usually a benign condition that requires no intervention but should be recognized to prevent unnecessary parathyroidectomy.

Other Familial Hypercalcemias

Familial hyperparathyroidism is another rare cause of hypercalcemia. The disease presentation is almost identical to sporadic primary hyperparathyroidism, and a careful family history will suggest the diagnosis. Once a diagnosis of primary hyperparathyroidism is made, screening for familial causes should be done if the patient (1) is younger than 30 years of age at the time of diagnosis, (2) has a family history of hypercalcemia, or (3) has a medical history of other endocrinopathies. These patients should be tested for multiple endocrine neoplasia syndrome types 1 and 2 (MEN1 and MEN2).

MEN1 is characterized by functional pituitary adenoma, functional pancreatic tumors, and primary hyperparathyroidism. MEN2A is characterized by medullary thyroid cancer, pheochromocytoma, and parathyroid gland hyperplasia with the associated *RET* oncogene mutation. Patients with MEN would follow similar guidelines for surgical removal of parathyroid glands.

Medications Causing Hypercalcemia

Thiazide diuretics decrease the reabsorption of calcium in the kidney and result in elevated levels. Primary hyperparathyroidism, however, should also be considered if the patient remains hypercalcemic despite the discontinuation of the thiazide diuretic. In these patients, the thiazide may have been masking the PTH-mediated hypercalcemia.

Lithium decreases the parathyroid glands' sensitivity to calcium and may also reduce urine calcium excretion.

Non–Parathyroid Hormone–Mediated Hypercalcemia

In contrast to PTH-mediated hypercalcemia, non–PTH-mediated hypercalcemia is associated with very low PTH levels, typically less than 10 to 15 pg/dL (10-15 ng/L).

Malignancy-Associated Hypercalcemia

There are two mechanisms of hypercalcemia of malignancy: local osteolytic and humoral. When lytic bone metastases are present, hypercalcemia is the result of increased mobilization of calcium from the bone. Humoral hypercalcemia is less common and occurs when the tumor itself produces parathyroid-related protein (PTHrP) that binds to and activates the parathyroid receptor, raising serum calcium levels. Squamous cell carcinomas, breast cancers, and renal cell carcinomas are the tumors most commonly associated with hypercalcemia of malignancy. In multiple myeloma, the hypercalcemia is caused by the release of factors that stimulate osteoclast activity.

Other Causes

Non–PTH-mediated hypercalcemia can be caused by several other mechanisms. Thyrotoxicosis can lead to mild hypercalcemia through increased bone resorption. Resolution of the thyrotoxicosis should lead to normalization of calcium levels. Prolonged immobilization and increased vitamin A levels can lead to increased bone resorption. Increased levels of calcium absorption from the gut can be from markedly high vitamin D levels or increased intake of calcium carbonate products (milk-alkali syndrome). Granulomatous diseases, such as sarcoidosis and Wegener granulomatosis, and malignant lymphomas cause hypercalcemia through increased 1-α-hydroxylation activity that increases 1,25-dihydroxyvitamin D levels and calcium reabsorption in the gastrointestinal tract.

Treatment of Hypercalcemia

The treatment of hypercalcemia should focus on decreasing the serum calcium level by increasing calcium excretion and decreasing bone resorption or intestinal calcium absorption, as well as volume repletion. Polyuria, due to the decreased concentration ability of the distal tubule, is the main cause of dehydration in these patients. Although many patients do not require hospitalization, those with marked mental status changes, acute kidney injury, or calcium levels greater than 12 mg/dL (3 mmol/L) should be hospitalized for treatment. First-line therapy is aggressive intravenous fluid resuscitation. Once the patient is volume replete, an intravenous loop diuretic should be added if the calcium level has not normalized. Intravenous bisphosphonate therapy is usually given for longer-term control of hypercalcemia. Caution should be exercised with these agents in the setting of kidney dysfunction. Zoledronic acid, while more expensive, is a more effective therapy for patients with malignancy-related hypercalcemia. In patients resistant to or intolerant of bisphosphonate therapy, off-label use of denosumab, which also reduces osteoclast-mediated bone resorption can be used. Attention should be turned as quickly as possible to treatment of the underlying cause of the patient's hypercalcemia to ensure long-term maintenance of normocalcemia. If the underlying cause is increased 1,25-dihydroxyvitamin D hydroxylation, glucocorticoids can be effective therapy but may need to be dosed on a regular basis. For patients who present with serum calcium levels greater than 18 mg/dL (4.5 mmol/L) with neurologic symptoms or compromised kidney function, hemodialysis is an appropriate choice to quickly reduce calcium levels.

KEY POINTS

- Primary hyperparathyroidism is the most common cause of parathyroid hormone-mediated hypercalcemia and is diagnosed with simultaneously elevated serum calcium levels, with an inappropriately normal or elevated intact parathyroid hormone level.
- Parathyroidectomy is curative in approximately 90% of patients with primary hyperparathyroidism, but should be performed by an experienced surgeon using minimally invasive techniques.

(Continued)

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KEY POINTS (continued)

- In contrast to parathyroid hormone-mediated hypercalcemia, nonparathyroid hormone-mediated hypercalcemia is associated with very low parathyroid hormone levels, typically less than 10 to 15 pg/dL (10-15 ng/L).
- The acute treatment of hypercalcemia focuses on decreasing the serum calcium level by increasing calcium excretion with vigorous volume replacement, decreasing bone resorption with bisphosphonates.

Hypocalcemia

Clinical Features of Hypocalcemia

Hypocalcemia, defined by serum calcium levels below the normal range, may be asymptomatic if mild. As calcium levels decrease, particularly below 8.0 mg/dL (2.0 mmol/L), symptoms may develop, including paresthesias (numbness/tingling around the mouth, tingling in fingers and toes), muscle cramping (Trousseau and Chvostek signs), decreased muscle strength, electrocardiogram changes (prolonged Q/T interval), tetany, and seizures.

Diagnosis and Causes of Hypocalcemia

Asymptomatic hypocalcemia may be noted incidentally on routine laboratory tests. When this occurs, the calcium level should be repeated in conjunction with a serum albumin level. If hypocalcemia is confirmed, simultaneous intact PTH and serum calcium must be measured to confirm if PTH is responding appropriately. The appropriate physiologic response to lower calcium levels is an elevation in PTH levels.

Hypoparathyroidism

Hypoparathyroidism, commonly due to trauma during neck surgery (thyroidectomy or parathyroidectomy), is the most common cause of hypocalcemia. During head and neck surgeries, the parathyroid glands can be inadvertently removed or parathyroid hormone production can be transiently decreased due to disruption of blood supply. Only serial measurements of calcium levels will determine whether the damage is transient. Hypoparathyroidism can also be caused by damage from radiation exposure, parathyroid gland infarction, infiltrative diseases (hemochromatosis, Wilson disease, granulomas), or autoimmune hypoparathyroidism.

Other Causes of Hypocalcemia

Other, less common causes of hypocalcemia include poor calcium intake, activating mutations in the *CASR* gene, PTH resistance, increased phosphate binding in vascular space (rhabdomyolysis or tumor lysis syndrome), increased citrate chelation with large volume blood transfusions, sepsis, vitamin D deficiency, and hypomagnesemia. Low levels of magnesium (due to alcohol abuse or malnutrition) activate G-proteins that stimulate calcium-sensing receptors and decrease PTH secretion.

KEY POINT

- The most common cause of hypocalcemia is hypoparathyroidism, which is most often due to trauma during surgery to the neck.

Treatment of Hypocalcemia

Mild, asymptomatic hypocalcemia (serum calcium 8.0-8.5 mg/dL [2.0-2.1 mmol/L]), is a common finding and does not require treatment.

Calcium carbonate and calcium citrate are the most common oral calcium formulations. Calcium carbonate requires an acidic environment to be absorbed; therefore, all patients who are on proton pump inhibitors should be prescribed calcium citrate. Adequate levels of both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D are also essential. In the acute phase of repletion, 1,25-dihydroxyvitamin D is more effective than 25-hydroxyvitamin D. If the patient is symptomatic or if the hypocalcemia is acute, calcium gluconate and calcium citrate are both available in intravenous form. Goal calcium is 7.0 to 7.5 mg/dL (1.8-1.9 mmol/L) with intravenous repletion, and oral forms can be used once that goal is achieved. The overall goal of repletion is the low to low-normal range (serum calcium 8.0-8.5 mg/dL [2.0-2.1 mmol/L]).

If a patient requires chronic replacement, usually due to hypoparathyroidism, care must be taken to avoid hypercalciuria as calcium nephrolithiasis and decreased glomerular filtration rate can occur. Chronic replacement typically includes calcitriol, calcium, and occasionally magnesium. Calcitriol is the vitamin D source of choice because PTH is needed for optimal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Serum calcium, magnesium, creatinine, and urine calcium levels should be measured at each follow-up visit. The goal calcium levels should be low-normal without hypercalciuria. The magnesium level should ideally be greater than 2 mg/dL (0.83 mmol/L) and creatinine levels should remain in the normal range. If the urine calcium level is greater than 300 mg/24 h (hypercalciuria), calcium and/or vitamin D replacement needs to be decreased. Calcium is usually decreased first if the vitamin D levels are within the normal sufficiency range.

KEY POINT

- If hypoparathyroidism is the cause of hypocalcemia, correction of any coexisting hypomagnesemia to serum magnesium 2 mg/dL (0.8 mmol/L) or higher is necessary.

Metabolic Bone Disease

Osteopenia and Osteoporosis

Physiology

Bone mineral density begins to increase with puberty, and peak bone mass is achieved in early adulthood. Sex hormones, estrogen and testosterone, are crucial to increasing bone mineral density in women and men, respectively. Specifically, estrogen has impact on osteoclast and osteoblast activity in both men and

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women. Towards the end of puberty, estrogen halts bone resorption and signals the closure of epiphyseal plates. Bone mass begins to decline in women after menopause, with decreased estrogen levels, and in men over age 50 years. In men, the loss of testosterone typically accelerates bone loss after 70 years of age. Early cessation of sex hormone production in either sex, for any reason, may accelerate the loss of bone mineral density. Bone loss occurs when the removal of old bone (osteoclastic activity) exceeds the replacement with new bone (osteoblastic activity). Accelerated bone loss can often be attributed to hypogonadism or medications that promote bone loss.

Risk Assessment and Screening Guidelines

Declining bone mineral density is associated with future fracture risk and therefore is an important component of fracture risk assessment. Individual peak bone mass is determined by genetic factors, nutrition, changes in hormone (estrogen, testosterone, thyroxine) levels, concomitant health conditions, and physical activity level.

The National Osteoporosis Foundation recommends that all postmenopausal women and men older than 50 years of age be evaluated for osteoporosis. This evaluation includes a thorough history for potential risk factors and physical examination. This preliminary screening will determine if bone mineral density (BMD) or vertebral imaging is necessary. **Table 33** lists several common risk factors for osteoporosis. If a patient is deemed high risk, a study of BMD with DEXA may help further assess fracture risk. The DEXA is designed to measure BMD and establish risk of fracture in postmenopausal women. In young men and premenopausal women, assessment of BMD for fracture risk is not advised or validated. **Table 34** lists the U.S. Preventive Services Task Force recommendations for BMD testing.

Diagnosis

The diagnosis of osteopenia is based on BMD testing. Osteoporosis, however, can be diagnosed by BMD testing or clinically in the patient with history of fragility fracture, hip fracture, or vertebral compression fracture.

DEXA assesses the density of the vertebral and hip bones compared with healthy young-adult sex-matched reference values. The distal one-third of the radius can be used in patients when the hip or vertebral BMD cannot be measured. The score is based on the number of standard deviations above or below the mean reference value and is known as the T-score. Those patients with T-scores at -1.0 and above have normal bone density. A T-score between -1.0 and -2.5 is defined as low bone mass (osteopenia). Osteoporosis is defined as a T-score below -2.5. Severe osteoporosis is defined as a T-score of -2.5 or below with one or more fractures. In women and men younger than 50 years, the International Society for Clinical Densitometry recommends that ethnic- or race-adjusted Z-scores be used. The Z-score compares a patient's BMD with others of their same age and ethnicity, and osteoporosis/osteopenia cannot be diagnosed in these patients. A Z-score of -2.0 or lower should be described as "low bone mineral density for chronologic age" or "below the expected range for age." Patients with Z-scores above -2.0 are "within the expected range for age."

In 2008, the World Health Organization (WHO) created the Fracture Risk Assessment Tool (FRAX) calculator that further defines the 10-year fracture risk for patients with osteopenia, defined as a T-score between -1.0 to -2.5 on DEXA. The FRAX score notes the probability of major osteoporotic fracture and hip fracture in the next 10 years. If the risk of major osteoporotic fracture is greater than or equal to 20% or the risk of hip

TABLE 33. Low Bone Mineral Density Associations

Lifestyle	Comorbid Illness	Hormonal States	Medications	Nonmodifiable Risk Factors
Alcohol use	Vitamin D insufficiency	Premature menopause	Anticonvulsants	Race
BMI <17	Hypercalciuria	Premature ovarian insufficiency	Glucocorticoids (≥5 mg/d of prednisone or equivalent for ≥3 months)	Age
Low calcium intake	Osteogenesis imperfect	Panhypopituitarism	GnRH antagonists and agonists	Gender
Smoking	Homocystinuria	Hyperprolactinemia	SSRIs	First-degree relative with low bone mineral density
Immobilization	Hemochromatosis	Androgen insufficiency	Thiazolidinediones	
Weight loss	Glycogen storage disease	Thyrotoxicosis	Aromatase inibitors	
Malabsorptive bariatric surgery	Cystic fibrosis		Anticoagulants	
Gastric bypass surgery	Celiac disease		Lithium	
Recurrent falls	Cushing syndrome			
	Inflammatory bowel disease			
	Diabetes mellitus (types 1 and 2)			

GnRH = gonadotropin-releasing hormone; SSRI = selective serotonin reuptake inhibitor.

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TABLE 34. U.S. Preventive Services Task Force Recommendations for Measurement of Bone Mineral Density and Vertebral Imaging

Bone Mineral Density Testing[a]
Women age 65 and older and men age 70 and older
Postmenopausal women and men age 50 to 69, based on risk factor profile
Those who have had a fracture, to determine degree of disease severity
Radiographic findings suggestive of osteoporosis or vertebral deformity
Glucocorticoid therapy for more than 3 months
Primary hyperparathyroidism
Treatment for osteoporosis (to monitor therapeutic response)
Vertebral Imaging[b]
Women ≥70 and men ≥80 if T-score at the spine, total hip, or femoral neck is ≤ −1.0
Women aged 65-69 and men aged 75-79 if T-score at the spine, total hip, or femoral neck is ≤1.5
In postmenopausal women age 50-64 and men aged 50-69 with the following risk factors:
Low-trauma fractures
Historic height loss of 1.5 in or more (4 cm)
Height loss of 0.8 inches or more (2 cm)
Recent or ongoing long-term glucocorticoid treatment

[a]BMD testing should be performed at DEXA facilities using accepted quality assurance measures.

[b]Vertebral imaging should be repeated when a new loss of height is noted or new back pain is reported.

fracture is greater than or equal to 3%, the patient's benefit from therapy exceeds the risk, and treatment should be offered.

The FRAX was validated for use in persons 40 to 90 years of age who are not currently or previously treated with pharmacotherapy for osteoporosis. The WHO has a web site that offers an online FRAX calculator at www.shef.ac.uk/FRAX.

In additional to BMD testing, vertebral imaging using radiographs is recommended in high-risk groups since many vertebral fractures are asymptomatic. The presence of a vertebral compression fracture establishes the clinical diagnosis of osteoporosis, regardless of T-score on DEXA, and treatment is recommended. Once a vertebral image is obtained, it only needs to be repeated if there is noted height loss or new back pain.

Evaluation of Secondary Causes of Bone Mineral Density Loss

Most cases of osteoporosis are due to declining levels of sex hormones which are non-modifiable, such as age, sex, menopause, height, and build. Some patients, however, have osteoporosis caused by secondary causes. Measurement of complete blood count (for malignancy), complete metabolic panel (for calcium levels and kidney function), thyroid-stimulating hormone, 25-hydroxyvitamin D, and urine calcium (screening for hypercalciuria) is an appropriate set of laboratory tests to screen for secondary causes of BMD loss. These are modifiable conditions that, if corrected, will result in increased BMD. These patients are typically young with either markedly low BMD for age or a new fracture or patients of any age with multiple fractures.

With all secondary causes of decreased BMD, reversal of the cause should be the first line of therapy and subsequent DEXA should be performed. If the BMD has not improved or the FRAX score suggests increased risk of fracture, treatment should be started. In the event of a fracture, the underlying cause should still be addressed in addition to initiating pharmacologic therapy for osteoporosis.

Pharmacologic Treatment Options

Currently there are six categories of pharmacologic agents that are FDA approved for the treatment of postmenopausal osteoporosis. These medications are bisphosphonates, calcitonin, estrogens, estrogen agonists, parathyroid hormone, and the receptor activator of nuclear factor κB (RANK) ligand inhibitor family. Bisphosphonates are usually first-line therapy unless there is a compelling reason why another therapy should be used. The other modalities are typically used after a bisphosphonate failure or inability to use the medication. Most of these medications can also be used for prevention of osteoporosis. Prevention therapy may be used in patients with osteopenia who do not meet FRAX standards for therapy but have multiple risk factors such as high-risk medications (glucocorticoids or antiestrogen, antiandrogen, or antiseizure medications) in combination with a strong family history of osteoporosis.

Bisphosphonates

Bisphosphonate medications work by inhibiting osteoclastic activity. Before starting any bisphosphonate therapy, vitamin D status and calcium levels should be evaluated, as bisphosphonates can lead to hypocalcemia. For oral bisphosphonates, integrity of the esophageal lining and ability to swallow pills are important. Kidney function should be assessed as bisphosphonates are contraindicated in patients with an estimated glomerular filtration rate less than 35 mL/min/1.73 m^2. Although rare, osteonecrosis of the jaw has been reported with bisphosphonate usage, particularly with high-dose intravenous administration and increased duration of the bisphosphonate. Additionally, atypical femur fractures have been reported with long-term usage. Regular questioning about pain in the thigh or groin area is recommended for patients on bisphosphonates. If patients report discomfort, a radiograph should be obtained. To reduce the risk of these side effects, a drug holiday has been suggested in patients with low-risk osteoporosis (T-score greater than -2.5 or single fractures) who have been on therapy for 3 to 5 years with stable BMD. During bisphosphonate therapy for prevention or treatment, men 50 to 70 years of age should consume 1000 mg/d of calcium and women aged 51 years and older and men aged 71 years and older consume 1200 mg/d of calcium.

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Alendronate has been approved by the FDA for prevention and treatment of osteoporosis. The prevention dose is a 5-mg tablet daily or a 35-mg tablet weekly. The treatment dose is a 10-mg tablet daily or a 70-mg tablet weekly. Alendronate is also approved for treatment of men with osteoporosis as well as treatment of both women and men with glucocorticoid-induced osteoporosis. Alendronate has been shown to reduce the incidence of spine and hip fractures by approximately 50% over 3 years in patients with previous fractures.

Ibandronate is FDA approved for the treatment and prevention of postmenopausal osteoporosis. The dosage is a 150-mg tablet monthly or 3 mg every 3 months by intravenous injection. There is FDA approval for the oral formulation for osteoporosis prevention only. Ibandronate primarily reduces risk of vertebral fractures by 50% in 3 years.

Risedronate is FDA approved for the prevention and treatment of osteoporosis. The treatment dose is a 5-mg tablet daily, a 35-mg tablet weekly, a 75-mg tablet on two consecutive days every month, or a 150-mg tablet monthly. Risedronate is also approved for treatment of osteoporosis in men and women with glucocorticoid-induced osteoporosis. Risedronate reduces the incidence of vertebral fracture by approximately 45% and nonvertebral fractures by one-third over 3 years.

Zoledronic acid has been FDA approved for the prevention and treatment of postmenopausal osteoporosis in women, for improvement of bone mass in men with osteoporosis, and for the prevention and treatment of glucocorticoid-induced osteoporosis in men and women. Recently zoledronic acid has been approved for secondary prevention of fractures in patients who have had recent low-trauma hip fracture. The treatment dose of zoledronic acid is 5 mg intravenously annually or once every 2 years for prevention.

Calcitonin

Calcitonin is FDA approved for the treatment of osteoporosis in women who are 5 or more years postmenopausal. Calcitonin (200 U) is delivered in a single daily intranasal spray. Subcutaneous administration is also available but is used less frequently. Calcitonin should be used with caution with patients who have an allergy to salmon, allergic rhinitis, or epistaxis. Very rarely, patients can also have an anaphylactic response that requires emergency attention and discontinuation of the medication.

Estrogen Agonists and Antagonists

The use of estrogen to maintain bone health in postmenopausal women has fallen out of favor because of data indicating that estrogen increases the risk of cardiovascular disease and breast cancer. Therefore, estrogen use for osteoporosis prevention should be limited to younger women with premature ovarian failure and postmenopausal women who also require its beneficial effects for hot flushes or vaginal dryness.

Raloxifine has been approved for the treatment of postmenopausal osteoporosis. The treatment dose is a 60-mg tablet to be taken with or without food.

Parathyroid Hormone

Teriparatide (recombinant human PTH [1-34]) has been FDA approved for the treatment of osteoporosis in postmenopausal women and men who are at high risk for fracture. "High risk" is defined as patients with a T-score of -3.0 or less or patients who have either had a fracture or decreased BMD while on bisphosphonate therapy. It is also approved for men and women at high risk of fracture due to long-time glucocorticoid use. Teriparatide has bone-building properties in addition to the antiresorptive properties of the other agents. It is the only bone-building treatment option for osteoporosis.

Teriparatide is an anabolic steroid that is administered by a 20-μg daily subcutaneous injection; it is approved for up to 24 months over a patient's lifetime. After the 24-month duration, an antiresorptive agent (such as bisphosphonates or denosumab) can be administered to maintain BMD gains achieved with teriparatide.

Receptor Activator of Nuclear Factor κB (RANK) Ligand Inhibitors

Denosumab is a receptor activator of nuclear factor κB (RANK) ligand inhibitors that is FDA approved for the treatment of osteoporosis in postmenopausal women who are at high risk of fracture. It is an antiresorptive agent, like the bisphosphonates with much the same effect and outcomes. It is also approved for treatment of osteoporosis in men and those undergoing treatment of certain cancers, such as prostate cancer, who are at high risk for fractures. Denosumab is given by subcutaneous injection (60 mg every 6 months).

Annual Reassessment of Patients with Low Bone Mass

Once an initial DEXA scan has been obtained, every effort should be made to have subsequent scans done on the same machine. Once a repeat scan has been done, change in BMD, not T-score, from year to year is the appropriate way to interpret whether there has been a significant change in BMD. Most reports will not show a statistically significant change in the BMD from the previous test. If not noted on the report, a calculated change of about 4% likely represents a statistically significant change. Annually, a complete clinical evaluation of the patient, determination of risk factors for bone loss, and evaluation for development of secondary causes of bone loss should be performed, starting with a history and physical examination.

Vitamin D Deficiency

In promoting absorption from the gut, vitamin D enables proper bone mineralization by maintenance of calcium and phosphorus levels. Vitamin D also modulates the actions of osteoblasts and osteoclasts to ensure proper bone growth and remodeling. Chronically low levels of vitamin D can lead to rickets in children and osteomalacia in adults (see MKSAP 17 Nephrology).

In addition to bone health, vitamin D plays a role in inflammation reduction, growth regulation of various cell types, immune function, and neuromuscular signaling.

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In assessing serum levels of vitamin D, concentrations of 25-hydroxyvitamin D are the best indicator of vitamin D status. It reflects vitamin D produced cutaneously and that obtained from food and supplements and has a circulating half-life of 15 days.

There are three levels of vitamin D status: sufficient (25-hydroxyvitamin D ≥30 ng/mL [75 nmol/L]), insufficient (25-hydroxyvitamin D 21-29 ng/mL [52.4-72.4 nmol/L]), and deficient (25-hydroxyvitamin D ≤20 ng/mL [50 nmol/L]). Because vitamin D levels can be affected by sun exposure, fall through winter months are ideal times to measure vitamin D levels. It is best to measure vitamin D levels at the same time each year unless treatment is being followed. In general, the optimal levels of vitamin D are those that prevent PTH levels from increasing to above normal levels. Increased PTH levels will lead to increased calcium withdrawal from the bones. In an attempt to find the optimal vitamin D level, several studies have looked at vitamin D levels related to cancer incidence, muscle stability and falls, immune status, and mood, in addition to bone health. Among most experts, a level between 30 and 40 ng/mL (75-100 nmol/L) is deemed sufficient for preventive health. Based on these levels, about 30% to 60% of Americans have low vitamin D levels, therefore most expert groups recommend screening all patients at least once. Those with darker skin, decreased sun exposure, or increased demands (pregnancy) often have low levels.

Special populations will have lower levels of vitamin D owing to medical conditions or medication side effects. In addition, obesity has been correlated with lower vitamin D levels possibly related to fat sequestration. Certain antiseizure medications (phenobarbital and phenytoin) may increase the metabolism of vitamin D to inactive forms. Glucocorticoids can decrease vitamin D metabolism. Agents that decrease absorption such as orlistat and cholesterol lowering agents can decrease vitamin D absorption. Similarly, patients with malabsorption disorders, including those with celiac disease and those who had bariatric surgery, can have decreased levels of vitamin D. In these special patient populations, not only does screening for deficiency need to be more frequent, but repletion may be more challenging. It is recommended that these populations be given at least two to three times more vitamin D to maintain adequate levels.

Recommendations

The current National Osteoporosis Foundation and Endocrine Society recommendation for adults 19 to 70 years of age is at least 600 U/d of vitamin D to maximize bone health; however, to raise blood levels consistently above 30 ng/dL (75 nmol/L) may require 1500 to 2000 U/d. In adults older than 70 years of age, 800 U of supplemental vitamin D per day is recommended to maximize bone health; however, 1500 to 2000 U/d may be required to keep levels consistently above 30 ng/dL (75 nmol/L). In treating the deficient patient, 50,000 U of either ergocalciferol or cholecalciferol is recommended, once weekly for 8 weeks. Once sufficiency is attained, maintenance therapy of 1500 to 2000 U/d is recommended.

Vitamin D toxicity is a very rare entity but one to be aware of. The effects of vitamin D levels greater than 90 ng/mL (225 nmol/L) include hypercalcemia. As a fat-soluble vitamin, decreasing vitamin D levels that are once elevated can be a slow process requiring continued monitoring.

KEY POINTS

- The U.S. Preventive Services Task Force recommends screening for osteoporosis in women aged 65 years and older and in younger women whose fracture risk is equal to or greater than that of a 65-year old white women who has no additional risk factors.
- The presence of a vertebral compression fracture makes the clinical diagnosis of osteoporosis, regardless of T-score on dual-energy x-ray absorptiometry (DEXA) scan, and treatment is recommended.
- Fracture Risk Assessment Tool (FRAX) score can help identify which patients are most likely to benefit from osteoporosis treatment; bisphosphonate therapy is first-line therapy for postmenopausal osteoporosis treatment and prevention.
- A 25-hydroxyvitamin D level between 30 and 40 ng/mL (75-100 nmol/L) is deemed sufficient for bone health; most expert groups recommend screening all groups at least once for evidence of deficiency since U.S. incidence is 30% to 60% of the population, however, it should not be a serial, recurring screening test. HVC

Paget Disease of Bone

Paget disease of bone is characterized by rapid and chaotic bone remodeling leading to disorganized bone microarchitecture. This disease more commonly affects persons of European descent during the sixth decade, with a prevalence of 3% to 10% in the elderly. Paramyxovirus infection of osteoclastic precursors is thought to be one possible cause, although about 15% of people with Paget disease have a family member with the disease. Paget disease appears to be inherited in an autosomal dominant manner with incomplete penetrance.

Clinical Presentation

The most common clinical manifestation is asymptomatic elevated serum alkaline phosphatase levels; only 30% of patients have symptoms at diagnosis. In some patients, the dysfunctional bone structure creates expansion in the bone leading to pain, swelling, and warmth. Bones of the axial skeleton are most frequently affected, namely the pelvis (70%), femur (55%), lumbar spine (53%), skull (42%), and tibia (30%). As a result, patients tend to have headache, sensorineural hearing loss, and bowing of the long bones (**Figure 16**). The abnormal bone growth may also lead to nerve impingement causing pain or neurologic deficits. Rarely, patients can develop increased vascular shunting to bones with resultant right-sided heart failure, cellular transformation to osteosarcoma, and hypercalcemia of immobilization.

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FIGURE 16. Radiograph showing Paget disease of bone in the left lateral tibia of a 71-year-old woman. Note the anterior bone, cortical thickening, and bone enlargement as compared with the normal radiograph on the right. The long-standing Paget disease resulted in a left leg that was 2.5 cm (1 in) shorter than the right.

Diagnosis

The diagnosis of Paget disease should be suspected in asymptomatic patients with an isolated elevation of alkaline phosphatase without evidence of liver disease. In these patients the most sensitive test is a nuclear bone scan which will detect areas of increased metabolic activity. Plain films of these areas should be obtained to identify pathognomonic pagetic lesions such as focal osteolysis with coarsening of the trabecular pattern and cortical thickening. In symptomatic patients with bone pain, plain films of painful areas may be the initial imaging test, although many experts recommend a baseline bone scan once the diagnosis is confirmed prior to initiating treatment.

Treatment

The main therapies for Paget disease of bone are the nitrogen-containing bisphosphonate medications (alendronate, pamidronate, risedronate, and zoledronic acid). The main indications for antiresorptive therapy are (1) pain caused by the increased metabolic activity; (2) planned surgery at site of pagetic bone disease, and (3) hypercalcemia due to multiple affected sites. There is no evidence that antiresorptive therapy is beneficial in asymptomatic patients. These medications are ideal because they suppress the rapid bone turnover that is characteristic of Paget disease. Decreases in alkaline phosphatase can be noted within 10 to 14 days after the initiation of therapy with a nadir reached in 3 to 6 months. NSAIDs and antineuropathic medications can also be used for pain control in these patients. For patients with pseudofractures, orthopedic stabilization may be required.

KEY POINTS

- The most common clinical manifestation of Paget disease of bone is asymptomatic elevated alkaline phosphate levels.
- The main therapy for Paget disease of bone is the nitrogen-containing bisphosphonate medications (alendronate, pamidronate, risedronate, and zoledronic acid).

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 23-year-old woman is evaluated because of a 1-week history of palpitations. She also reports some heat intolerance and mild anxiety during the last several weeks, but she otherwise feels well. She is in the first trimester of an otherwise uncomplicated first pregnancy. Her only medication is a prenatal vitamin.

On physical examination, she is afebrile, blood pressure is 110/72 mm Hg, pulse rate is 105/min, and respiration rate is 13/min. BMI is 20. The skin is warm and moist. There is no proptosis or lid lag. Examination of the neck shows a diffusely enlarged thyroid with an audible bruit over both lobes. Cardiopulmonary and abdominal examinations are unremarkable. Neurologic examination reveals a fine resting tremor of the hands and brisk reflexes.

Laboratory studies:

Thyroid-stimulating hormone	<0.008 μU/mL (0.008 mU/L)
Free thyroxine (T_4)	5.5 ng/dL (70.9 pmol/L)
Total triiodothyronine (T_3)	400 ng/dL (6.2 nmol/L)
Thyroid-stimulating immunoglobulin index	4.5 (normal <1.3)

Which of the following is the most appropriate treatment?

(A) Methimazole
(B) Propylthiouracil
(C) Radioactive iodine
(D) Thyroidectomy

Item 2

A 34-year-old man is evaluated for episodic palpitations of 8 months' duration. The palpitations last 5 to 10 minutes and then resolve spontaneously. They are usually associated with sweating and anxiety. Medical history is significant for thyroidectomy for medullary thyroid carcinoma diagnosed at 12 years of age. His father has also undergone thyroidectomy for medullary thyroid cancer. His only medication is levothyroxine.

On physical examination, blood pressure is 164/92 mm Hg, pulse rate is 106/min, and respiration rate is 12/min. Auscultation of the heart reveals a regular tachycardia without murmurs. The remainder of his examination is unremarkable.

Laboratory studies show a 24-hour urine excretion of catecholamines of 310 μg/m²/24 h (1832.1 nmol/m²/24 h) and metanephrines of 3400 μg/24 h (17,238 nmol/24 h).

In addition to the presenting diagnosis, which of the following disorders is this patient most likely to develop?

(A) Insulinoma
(B) Neurofibroma
(C) Primary hyperparathyroidism
(D) Prolactinoma

Item 3

A 31-year-old woman is evaluated following her recent discovery that she is pregnant at approximately 10 weeks' gestation. Medical history is significant for a prolactinoma diagnosed 2 years ago during an evaluation for amenorrhea. At the time of diagnosis, her serum prolactin level was 184 ng/mL (184 μg/L), and a 1.4-cm pituitary adenoma extending above the sella was detected on MRI without evidence of mass effect. She was treated with bromocriptine with return of regular menses. She discontinued the bromocriptine when she found that she was pregnant. She is currently without symptoms. She does not have new or severe headache. Medical history is otherwise unremarkable, and her only current medication is a prenatal multivitamin.

On physical examination, vital signs are normal. Visual fields are full to confrontation, and the remainder of her examination is normal.

Which of the following is the most appropriate next step in management?

(A) Check serum prolactin level
(B) Formal visual field testing
(C) Repeat pituitary MRI
(D) Restart bromocriptine

Item 4

A 48-year-old woman returns for a follow-up visit for management of type 1 diabetes mellitus. She reports doing well since the last visit. Overall, she believes that most of her blood glucose levels are at goal, but is concerned about occasional episodes of hyperglycemia occurring in the morning before breakfast. She eats a bedtime snack every night that is not covered with mealtime insulin. Review of her blood glucose log demonstrates morning fasting blood glucose values from 80 to 190 mg/dL (4.4-10.5 mmol/L). Her other premeal and bedtime values range from 100 to 120 mg/dL (5.5–6.7 mmol/L). She exercises two to three times per week in the evening. Medical history is significant for hypertension and hyperlipidemia.

Medications are insulin glargine, insulin lispro, ramipril, simvastatin, and aspirin.

On physical examination, blood pressure is 130/72 mm Hg and pulse rate is 67/min. BMI is 24. The remainder of the examination is unremarkable.

Results of laboratory studies show a hemoglobin A_{1c} level of 6.9% and serum creatinine level of 1.0 mg/dL (88.4 μmol/L). Serum electrolytes are normal.

Which of the following is the most appropriate management of this patient's occasional fasting hyperglycemia?

(A) Add insulin lispro at bedtime
(B) Add metformin
(C) Increase insulin glargine dose
(D) Measure 3 AM blood glucose level
(E) Continue current regimen

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Item 5

A 70-year-old woman is seen for follow-up evaluation for possible Cushing syndrome. She presented with new-onset diabetes mellitus and a 9.1-kg (20-lb) weight gain over the last 6 months. Medical history is otherwise unremarkable, and she is currently taking no medications and has had no exposure to exogenous glucocorticoids in the past year.

On physical examination, blood pressure is 160/90 mm Hg, pulse rate is 80/min, and respiration rate is 12/min. BMI is 30. Facial plethora, central obesity, and bilateral supraclavicular fat pads are noted. There are violaceous abdominal striae measuring 1 cm wide and multiple ecchymoses on the extremities.

Initial laboratory studies show a serum cortisol level of 9 µg/dL (248.4 nmol/L) following a 1-mg dose of dexamethasone the night before, and a 24-hour urine free cortisol level that is greater than 3 times the upper limit of normal, which is confirmed on a second measurement. A plasma adrenocorticotropic hormone (ACTH) level is undetectable.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT scan of the adrenal glands
(B) Inferior petrosal sinus sampling
(C) Late night salivary cortisol measurement
(D) MRI of the pituitary gland

Item 6

A 44-year-old man is evaluated for management of type 2 diabetes mellitus. He was diagnosed with diabetes 6 months ago after being admitted to the hospital with diabetic ketoacidosis. He was discharged from the hospital on a basal and preprandial insulin regimen. Medications are regular insulin before meals and neutral protamine Hagedorn (NPH) insulin at bedtime. He completed diabetes education and nutrition classes and has been adherent with lifestyle modifications. His insulin doses have been decreased gradually over the last 4 to 5 months. His most recent hemoglobin A_{1c} level is 6.7%. Blood glucose values from his log book average 130 mg/dL (7.2 mmol/L).

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 128/68 mm Hg, and pulse rate is 72/min. BMI is 30. His physical examination is unremarkable.

Laboratory studies at the time of hospital admission:

Glucose, fasting	825 mg/dL (45.8 mmol/L)
Antibody to glutamic acid decarboxylase 65 (GAD-65)	Negative
Antibody to islet antigen 2 (IA-2)	Negative
C-peptide, fasting	0.5 ng/mL (0.16 nmol/L) Normal range: 0.8-3.1 ng/mL (0.26-1.03 nmol/L)

Which of the following is the most appropriate next step in his management?

(A) Discontinue current insulin regimen, initiate sliding-scale insulin
(B) Discontinue insulin, initiate metformin
(C) Repeat measurement of antibodies to glutamic acid decarboxylase 65 and islet antigen 2
(D) Repeat measurement of fasting C-peptide and glucose levels

Item 7

A 43-year-old man is evaluated in the emergency department for the "worst headache of my life." It occurred suddenly without warning. He has had mild headaches that come and go over the past 3 years, but nothing this severe. Soon after the headache began, he lost vision in his left eye, and the vision in his right eye became blurry. He vomited twice in the emergency department. His medical history is significant for progressive erectile dysfunction and loss of libido over the past 3 years.

On physical examination, temperature is 37.4 °C (99.3 °F), blood pressure is 156/92 mm Hg, pulse rate is 104/min, and respiration rate is 16/min. BMI is 28. He has loss of vision in his left eye and in the upper quadrants of his right eye. He also has left eye ptosis. Other cranial nerves are intact. Strength and sensation in all extremities are normal as are his speech and gait.

CT of the head shows acute pituitary hemorrhage. Pituitary MRI shows a 3.1 × 2.5 × 2.2-cm pituitary mass with central hemorrhage. The mass compresses the optic chiasm and the left cavernous sinus.

After administering high-dose glucocorticoids, which of the following is the most appropriate immediate management?

(A) Assess pituitary function
(B) Repeat imaging in 2 weeks
(C) Urgent transsphenoidal pituitary decompression
(D) Whole brain external beam radiation

Item 8

A 42-year-old woman is evaluated during an annual physical examination. She feels well. She has no pertinent personal or family medical history, and she takes no medications.

On physical examination, vital signs are normal. Palpation of the thyroid reveals a possible nodule in the right lobe that is not mobile with swallowing. The remainder of the gland is unremarkable, and there is no palpable cervical lymphadenopathy. Other physical examination findings are normal.

Laboratory studies reveal a serum thyroid-stimulating hormone level of 1.7 µU/mL (1.7 mU/L).

Ultrasound of the neck shows a right 1.5-cm hypoechoic nodule with internal microcalcifications.

Which of the following is the most appropriate next step in management?

(A) CT with contrast of the neck
(B) Fine-needle aspiration of the nodule
(C) Levothyroxine therapy
(D) Measurement of serum thyroglobulin level
(E) Thyroid scan with technetium

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Item 9

An 18-year-old woman is evaluated for primary amenorrhea. Her cognitive function is normal, and she is not sexually active. Her personal and family medical history is unremarkable. She takes no medications.

On physical examination, temperature is 36.1 °C (97.0 °F), blood pressure is 110/70 mm Hg, pulse rate is 72/min, and respiration rate is 16/min; BMI is 20. Her height is 147 cm (58 in). Physical examination and secondary sex characteristics are normal, with Tanner stage IV breast and pubic hair development.

Pregnancy testing is negative. On subsequent laboratory studies estradiol level was undetectable, serum follicle-stimulating hormone level is 72 mU/mL (72 U/L), and serum luteinizing hormone level is 46 mU/mL (46 U/L).

Which of the following is the most appropriate management?

(A) Initiate estrogen and progestin therapy
(B) Measure serum prolactin
(C) Measure thyroid-stimulating hormone
(D) Perform pituitary MRI

Item 10

A 32-year-old man is evaluated for a 1-week history of severe neck pain. He also has heat intolerance, palpitations, and insomnia. Medical history is significant only for a viral upper respiratory tract infection 3 weeks ago. He takes no medications.

On physical examination, he appears anxious and is sweating. There is no proptosis or lid lag. Examination of the thyroid reveals a normal-sized gland that is very tender to palpation. There are no thyroid nodules. The heart rate is regular but tachycardic. The lungs are clear.

Laboratory studies:

Thyroid-stimulating hormone	<0.008 µU/mL (0.008 mU/L)
Free thyroxine (T_4)	3.2 ng/dL (41.3 pmol/L
Total triiodothyronine (T_3)	310 ng/dL (4.8 nmol/L)
Thyroid-stimulating immunoglobulin index	<1.3 (normal, <1.3)
24-Hour radioactive iodine uptake	5% (low)

Which of the following is the most appropriate treatment?

(A) Methimazole
(B) Metoprolol
(C) Propylthiouracil
(D) Radioactive iodine

Item 11

A 30-year-old woman is evaluated for amenorrhea. She and her husband are interested in pregnancy in the next year, and they are concerned that they will not be able to conceive. Her menses became irregular about 2 years ago. In the past 12 months, she has had menses twice. Her last menstrual period was 4 months ago. She also notes low libido and dyspareunia. She has not had weight changes, constipation, hair loss or hirsutism, or skin changes.

Her medical history is significant for primary hypothyroidism and bipolar disorder. Medications are levothyroxine, lithium, and risperidone. She reports that she has been stable on these medications for a few years and feels well. She plans to discuss her medications with her psychiatrist prior to pregnancy.

On physical examination, blood pressure is 118/72 mm Hg and pulse rate is 82/min. BMI is 24. The thyroid is normal. Visual fields are intact.

Laboratory studies:

Follicle-stimulating hormone	1.3 mU/mL (1.3 U/L)
Luteinizing hormone	2.0 mU/mL (2.0 U/L)
Prolactin	102 ng/mL (102 µg/L)
Thyroid-stimulating hormone	1.1 µU/mL (1.1 mU/L)

Which of the following is the most likely cause of her hyperprolactinemia?

(A) Hypothyroidism
(B) Lithium
(C) Pituitary adenoma
(D) Risperidone

Item 12

A 55-year-old woman is evaluated for a new-patient visit. Medical history is significant for an eating disorder. Although she has maintained a normal weight for the past 20 years, she notes that prior to that time her weight would fluctuate in a range correlating with BMIs of 17 to 19. She has otherwise been healthy and currently feels well. She is postmenopausal and a never-smoker. Family history is significant for postmenopausal osteoporosis in her mother. Her medications are over-the-counter calcium and vitamin D supplements.

On physical examination, temperature is 36.3 °C (97.3 °F), blood pressure is 137/81 mm Hg, pulse rate is 76/min, and respiration rate is 11/min. BMI is 21. She has mild thoracic kyphosis but no skeletal tenderness. The remainder of the examination is unremarkable.

Results of laboratory studies are significant for a serum calcium level of 9.1 mg/dL (2.3 mmol/L) and 25-hydroxyvitamin D level of 40 ng/mL (99.8 nmol/L); thyroid function studies are normal.

Dual-energy x-ray absorptiometry (DEXA) scan shows T-scores of -1.8 in the femoral neck and -1.9 in the lumbar spine. Ten-year fracture risk using the Fracture Risk Assessment Tool (FRAX) is 6.9% for major osteoporotic fracture and 0.7% for hip fracture. Plain radiographs of the spine show no evidence of compression fracture.

Which of the following is the most appropriate management of this patient?

(A) Begin raloxifene
(B) Repeat DEXA scan in 2 years
(C) Replace calcium with cholecalciferol
(D) Start bisphosphonate therapy

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Item 13

A 64-year-old man in the ICU is evaluated because of abnormal thyroid function tests. He was admitted 3 days ago for community-acquired pneumonia requiring intubation, mechanical ventilation, intravenous fluids, and dopamine support for his blood pressure.

On physical examination, temperature is 38.8 °C (101.8 °F), blood pressure is 95/60 mm Hg, and pulse rate is 130/min. The skin is warm and dry. There is no proptosis. Examination of the neck shows a normal-sized thyroid without nodules. Cardiovascular examination reveals regular tachycardia. On neurologic examination, reflexes are slightly delayed.

The serum thyroid-stimulating hormone (TSH) level is 0.1 μU/mL (0.1 mU/L), the serum free thyroxine level (T_4) is 0.9 ng/dL (11.6 pmol/L), and the serum total triiodothyronine (T_3) level is 50 ng/dL (0.8 nmol/L).

Which of the following is the most likely cause of this patient's abnormal thyroid function?

(A) Euthyroid sick syndrome
(B) Graves disease
(C) Hashimoto thyroiditis
(D) Subacute thyroiditis

Item 14

A 43-year-old man is evaluated during a follow-up visit for management of type 1 diabetes mellitus. He was diagnosed at 18 years of age and has multiple chronic complications from his diabetes, including end-stage kidney disease requiring hemodialysis, gastroparesis, frequent hypoglycemia with hypoglycemic unawareness, painful peripheral neuropathy, and proliferative retinopathy. The patient uses an insulin pump and a continuous glucose monitoring system to manage his diabetes. He is adherent with his regimen and performs multiple fingerstick blood glucose measurements with values ranging from 65 to 250 mg/dL (3.6-13.9 mmol/L). His most recent hemoglobin A_{1c} level is 7.5%.

Which of the following is the most appropriate next step in the management of this patient?

(A) Alter insulin pump settings to attain a hemoglobin A_{1c} goal of less than 7.0%
(B) Alter insulin pump settings to decrease the insulin doses
(C) Discontinue the insulin pump, start subcutaneous insulin injections
(D) Start gabapentin for treatment of painful peripheral neuropathy

Item 15

A 55-year-old woman is seen in follow-up for low bone mass and vitamin D deficiency. Cortical bone thinning was noted on radiographs of her right ankle following a fall 3 months ago. Subsequent evaluation included a dual-energy x-ray absorptiometry (DEXA) scan showing osteopenia. Her serum 25-hydroxyvitamin D level is 4 ng/mL (10 nmol/L). She was started on 50,000 U of vitamin D_2 (ergocalciferol) weekly, 6 weeks ago. Medical history is significant for vitiligo and chronic fatigue. Medications are vitamin D_2 and calcium carbonate.

On physical examination, temperature is 36.1 °C (96.9 °F), blood pressure is 132/71 mm Hg, pulse rate is 83/min, and respiration rate is 12/min. BMI is 19. The remainder of her examination is unremarkable.

Laboratory studies:

Calcium	9.1 mg/dL (2.3 mmol/L)
Creatinine	0.9 mg/dL (79.6 μmol/L)
Parathyroid hormone	101 pg/mL (101 ng/L)
25-Hydroxyvitamin D, after 6 weeks	7 ng/mL (17.5 nmol/L)
24-Hour urine calcium	150 mg/24 h (3.7 mmol/24 h)

Which of the following is the most appropriate next step in management?

(A) Parathyroid sestamibi scan
(B) Refer for parathyroidectomy
(C) Switch to vitamin D_3 (cholecalciferol)
(D) Tissue transglutaminase antibody testing

Item 16

A 54-year-old woman is evaluated because of fatigue. Although she follows a daily 1400-kcal diet and exercises 3 to 4 nights per week for 30 minutes, she has gained 2.3 kg (5.0 lb) in the last month. She has hypercholesterolemia requiring statin therapy. Her mother was diagnosed with hypothyroidism shortly after the birth of her last child.

On physical examination, blood pressure is 145/90 mm Hg, pulse rate is 80/min, and BMI is 25. The skin is dry. The thyroid is mildly enlarged with a diffusely nodular texture. No discrete thyroid nodules are palpated. Reflexes are normal.

Laboratory studies:

Thyroid-stimulating hormone (TSH)	6.5 μU/mL (6.5 mU/L)
Free thyroxine (T_4)	0.9 ng/dL (11.6 pmol/L)
Thyroid peroxidase antibody	Positive

Similar results for TSH and T_4 were obtained 4 months ago.

Which of the following is the most appropriate next step in management?

(A) Initiate levothyroxine therapy
(B) Measure thyroid-stimulating immunoglobulins
(C) Repeat serum TSH measurement in 12 months
(D) Schedule thyroid radioactive iodine uptake and scan

Item 17

A 74-year-old woman is evaluated for a diagnosis of primary hyperparathyroidism made after an elevated serum calcium level was incidentally discovered on laboratory studies. She has no symptoms associated with hypercalcemia. Medical history is significant for hypertension and chronic kidney disease. Her only medication is amlodipine. She has never smoked.

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On physical examination, temperature is 36.8 °C (98.3 °F), blood pressure is 134/87 mm Hg, pulse rate is 92/min, and respiration rate is 14/min. BMI is 27. The remainder of her examination is unremarkable.

Laboratory studies:

Calcium	11.3 mg/dL (2.8 mmol/L)
Creatinine	1.3 mg/dL (114.9 µmol/L)
Parathyroid hormone	76 pg/mL (76 ng/L)
Estimated glomerular filtration rate	40 mL/min/1.73 m^2

Dual-energy x-ray absorptiometry (DEXA) scan shows a T-score of -1.3 in the right femoral neck. Her Fracture Risk Assessment Tool (FRAX) score indicates a 2.1% 10-year probability of hip fracture and 17% 10-year probability of any fracture.

Which of the following is the most appropriate therapy to recommend to this patient?

(A) Alendronate
(B) Cinacalcet
(C) Parathyroidectomy
(D) Clinical observation

Item 18

A 74-year-old woman is evaluated because of new-onset anxiety and insomnia. For the last 6 weeks, she has been waking up multiple times each night. She does not have heat intolerance, change in bowel habits, palpitations, or dyspnea on exertion. She takes no medications.

On physical examination, blood pressure is 125/68 mm Hg and pulse rate is 89/min. BMI is 18. There is no proptosis or lid lag. Examination of the thyroid reveals a 1.5-cm firm nodule in the left lobe that moves upward with swallowing. A fine resting hand tremor is present bilaterally.

Laboratory studies reveal a serum thyroid-stimulating hormone level of 0.05 µU/mL (0.05 mU/L), a serum free thyroxine (T_4) level of 2.9 ng/dL (37.4 pmol/L), and a serum total triiodothyronine (T_3) level of 250 ng/dL (3.8 nmol/L).

Ultrasound of the neck shows two thyroid nodules, a 1.5-cm nodule in the right lobe and a 2.0-cm nodule in the left lobe.

Which of the following is the most appropriate next step in management?

(A) Fine-needle aspiration of both thyroid nodules
(B) Initiation of methimazole
(C) Radioactive iodine (^{123}I) uptake and scan of the thyroid
(D) Total thyroidectomy

Item 19

A 34-year-old woman is evaluated for amenorrhea, headache, and fatigue. She reports that from the time of menarche until 2.5 years ago, her menses were regular and predictable. Two and a half years ago, her menses became irregular and then stopped completely 6 months ago. She has had a few hot flushes and fatigue. She has noted galactorrhea. She began having headaches 2 years ago. In addition, she notes blurry peripheral vision.

The rest of her medical history is unremarkable. She takes no medications.

On physical examination, blood pressure is 112/72 mm Hg and pulse rate is 68/min. BMI is 21. White milky substance is expressed from her breasts bilaterally. Ocular movements and cranial nerves are intact. There are no stigmata of Cushing disease or acromegaly.

Laboratory studies:

Cortisol 8 AM after 1 mg of dexamethasone the night before	16 µg/dL (441.6 nmol/L)
Estradiol	<32 pg/mL (117.4 pmol/L)
Follicle-stimulating hormone	1.1 mU/mL (1.1 U/L)
Luteinizing hormone	0.8 mU/mL (0.8 U/L)
Prolactin	472 ng/mL (472 µg/L)
Thyroid-stimulating hormone	1.1 µU/mL (1.1 mU/L)

MRI shows a 2.4-cm pituitary tumor that elevates the optic chiasm and surrounds the left carotid artery.

Which of the following is the most appropriate treatment?

(A) Cabergoline
(B) Octreotide
(C) Radiation
(D) Surgery

Item 20

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A 74-year-old woman is evaluated in the emergency department for several hours of altered mental status. She is from out-of-state and is visiting with relatives. One of her young relatives was recently ill with gastrointestinal symptoms. The patient developed anorexia 3 days ago and vomiting 2 days ago. She has been unable to tolerate any liquid or solid foods for the last 24 hours. Medical history is significant for type 2 diabetes mellitus, hypertension, hyperlipidemia, and hypothyroidism. Medications are aspirin, lisinopril, glimepiride, levothyroxine, and atorvastatin. Her last dose of medications was 48 hours ago.

On physical examination, her temperature is 37.5 °C (99.5 °F), blood pressure is 115/65 mm Hg, and pulse rate is 95/min. She is arousable but confused. Mucous membranes are dry. Her neck is supple. Cardiac examination reveals no murmurs. Her chest is clear to auscultation. Bowel sounds are present, and mild tenderness to palpation is noted throughout the abdomen. There is no rebound or guarding. There are no focal neurologic deficits.

Laboratory studies are pending.

Which of the following is the most likely cause of this patient's altered mental status?

(A) Cerebrovascular accident
(B) Hypoglycemia
(C) Hypothyroidism
(D) Statin toxicity

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Item 21

A 38-year-old woman is evaluated because of a 3-week history of palpitations. She notes that her heart "races" at night and after minimal exertion. She also reports heat intolerance but has no change in bowel habits or menses.

On physical examination, the patient is restless and has pressured speech. Temperature is 36.8 °C (98.2 °F), blood pressure is 130/60 mm Hg, pulse rate in 110/min, and respiration rate is 12/min. Her skin is warm and moist, and a bilateral hand tremor is present. There is no proptosis or lid lag. The thyroid is enlarged without nodules or bruits.

Serum thyroid-stimulating hormone level is 0.08 µU/mL (0.08 mU/L), and the serum free thyroxine (T_4) level is 1.7 ng/dL (21.9 pmol/L).

Which of the following is the most appropriate next step in management?

(A) Measure serum triiodothyronine (T_3) level
(B) Measure serum thyroid peroxidase antibody titer
(C) Repeat thyroid function tests in 6 weeks
(D) Schedule ultrasound of the neck

Item 22

A 34-year-old woman is evaluated for a diagnosis of hypercalcemia after presenting to the emergency department 3 days ago for treatment of a kidney stone. She presented with severe right flank pain with nausea and vomiting. A 2-mm kidney stone was identified in the right ureter by ultrasonography that passed spontaneously; multiple additional intrarenal calcifications were noted to be present. Laboratory studies at that time showed normal kidney function and a serum calcium level of 11.5 mg/dL (2.9 mmol/L). Medical history is otherwise significant for hypertension and sarcoidosis. Her only medication is hydrochlorothiazide.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 138/87 mm Hg, pulse rate is 89/min, and respiration rate is 12. BMI is 32. The remainder of the examination is unremarkable.

Laboratory studies are significant for a parathyroid hormone level of 4 pg/mL (4 ng/L).

Which of the following is most likely responsible for causing this patient's hypercalcemia?

(A) Calcium-sensing receptor mutation
(B) Elevated 1,25-dihydroxyvitamin D levels
(C) 25-Hydroxyvitamin D level
(D) Thiazide-induced renal calcium reabsorption

Item 23

A 40-year-old woman is evaluated for amenorrhea of 4 months' duration. She has had weight gain, facial hair, alopecia, and debilitating fatigue. Her medical history is significant for psoriasis. She seems to be gaining weight in her face, abdomen, and neck. She also bruises easily. Her only medication is clobetasol for psoriasis.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 148/90 mm Hg, pulse rate is 88/min, and respiration rate is 12/min. BMI is 38. She is obese with a round face. She has terminal hairs on her chin, upper lip, chest, and back. Mild facial acne, central obesity, and a few wide purple striae on the back of her arms are also noted. She has supraclavicular fat. Her skin has psoriatic plaques. Muscle strength in the upper and lower extremities is 4/5.

Which of the following is the most likely diagnosis?

(A) Adrenocortical carcinoma
(B) Cushing disease
(C) Ectopic adrenocorticotropic hormone production
(D) Iatrogenic Cushing syndrome

Item 24

A 20-year-old woman is evaluated in the emergency department for polyuria, polydipsia, polyphagia, and an unintentional 5.4-kg (11.9-lb) weight loss over the past month. She has had increasing lethargy over the last 24 hours. Her medical history and family history are unremarkable. She takes no medications.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 98/52 mm Hg, pulse rate is 120/min, and respiration rate is 30/min. BMI is 17. She is lethargic with dry mucous membranes, tachypnea, and tachycardia. Chest auscultation is clear. Abdominal examination shows diffuse mild tenderness and normal bowel sounds. There is no rebound tenderness or guarding with palpation.

Laboratory studies:

Hemoglobin	17 g/dL (170 g/L)
Leukocyte count	14,200/µL (14.2×10^9/L)
Blood gases, arterial	
pH	7.25
PCO_2	21 mm Hg (2.8 kPa)
Creatinine	1.3 mg/dL (114.9 µmol/L)
Electrolytes	
Sodium	130 mEq/L (130 mmol/L)
Potassium	3.0 mEq/L (3.0 mmol/L)
Chloride	99 mEq/L (99 mmol/L)
Bicarbonate	9 mEq/L (9 mmol/L)
Glucose	620 mg/dL (34.4 mmol/L)
Lactic acid	8 mg/dL (0.89 mmol/L)

Intravenous 0.9% saline is initiated through a central venous catheter.

An electrocardiogram shows sinus tachycardia 120/min. Chest radiograph is normal.

Which of the following is the most appropriate next step in the management?

(A) Administer intravenous ceftriaxone
(B) Administer intravenous potassium chloride
(C) Administer intravenous sodium bicarbonate
(D) Initiate intravenous insulin therapy

Item 25

A 65-year-old woman is evaluated following a recent diagnosis of osteoporosis discovered on a screening dual-energy x-ray absorptiometry (DEXA) scan that showed T-scores of −2.5 at the femoral neck and −2.7 at the hip. Overall she

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feels well, although she notes a 5-cm (2-in) loss of height over the past 15 years and a 2.3-kg (5-lb) weight loss over the last year. She is postmenopausal. Medical history is unremarkable, and she is a never-smoker. Family history is negative for osteoporosis or nontraumatic fractures. She takes no medications.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 144/68 mm Hg, pulse rate is 92/min, and respiration rate is 14/min. BMI is 22. The remainder of the examination is unremarkable.

Laboratory studies are significant for a normal basic metabolic profile and complete blood count. Serum calcium is 9.5 mg/dL (2.4 mmol/L) and serum phosphorus is 3.8 mg/dL (1.2 mmol/L). Serum 25-hydroxyvitamin D level is 32 ng/dL (79.9 nmol/L).

Which of the following tests is indicated prior to initiation of pharmacologic therapy?

(A) Serum and urine markers of bone turnover
(B) Serum estradiol level
(C) Serum parathyroid hormone level
(D) Serum thyroid-stimulating hormone level

Item 26

A 24-year-old woman is evaluated for excessive menstrual bleeding. She was recently diagnosed with polycystic ovary syndrome during an evaluation for hirsutism. Menarche occurred at age 11 years, and she has always had irregular menses occurring approximately every 60 days. However, her periods over the past year have been associated with heavy bleeding that is increasingly bothersome. Medical history is otherwise unremarkable, and she takes no medications. She currently does not desire fertility.

On physical examination, she is afebrile. Blood pressure is 110/70 mm Hg, pulse rate is 78/min, and respiration rate is 14/min. BMI is 32. Excess terminal hair growth is present on the upper lip, chin, and chest. The physical examination is otherwise normal.

A urine pregnancy test is negative.

Which of the following is the most appropriate therapy for this patient?

(A) Combined oral contraceptive pills
(B) Levonorgestrel intrauterine system
(C) Metformin
(D) Periodic progestin withdrawal

Item 27

A 55-year-old man is evaluated for abdominal fullness and nausea of 2 weeks' duration. He has no vomiting or fever. One month ago, he was diagnosed with type 2 diabetes mellitus. He reports an unintentional weight loss of 5 kg (11 lb) over the past month, generalized weakness, and poor appetite. Metformin is his only medication.

On physical examination, blood pressure is 158/90 mm Hg and pulse rate is 90/min. BMI is 29. His face is round and red. A dorsocervical fat pad is present. His abdomen is distended, but nontender. Violaceous striae measuring 8 to 12 mm wide are noted on his upper arms and abdomen. There is 1+ bilateral lower extremity edema. Multiple ecchymoses and acanthosis nigricans are present.

Laboratory studies:

Adrenocorticotropic hormone	<5 pg/mL (1.1 pmol/L)
24-Hour urine cortisol excretion	
Initial measurement	280 µg/24 h (771.6 nmol/24 h)
Repeat measurement	300 µg/24 h (826.7 nmol/24 h)
Cortisol, serum	46 µg/dL (1269.6 nmol/L)
Urine	
Catecholamines	40 µg/m²/24 h (236.4 nmol/m²/24 h)
Metanephrines	1000 µg/24 h (5070 nmol/24 h)

CT scan of the abdomen with and without contrast reveals a 5.6-cm heterogeneous right adrenal mass with focal areas of calcifications and hemorrhage. The density of the mass is 50 Hounsfield units, and the contrast washout at 10 minutes is 20%.

Which of the following is the most appropriate next step in the management of this patient's adrenal mass?

(A) Chemotherapy
(B) Fine-needle biopsy
(C) Radiation therapy
(D) Surgical excision

Item 28

A 47-year-old man presents to the emergency department with weakness and shakiness. He has a long history of alcohol abuse but significantly decreased his usual daily alcohol intake over the past week because of gastrointestinal upset, nausea, and diarrhea. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, the patient is awake and oriented but tremulous. Mucous membranes are dry. Temperature is 37.3 °C (99.1 °F), blood pressure is 139/76 mm Hg, pulse rate is 101/min, and respiration rate is 15/min. BMI is 19. Cardiopulmonary examination is unremarkable. The abdomen is diffusely tender to palpation. Periodic spontaneous twitching is noted in the major muscle groups.

Laboratory studies are significant for a serum calcium level of 6.5 mg/dL (1.6 mmol/L), serum albumin level of 2.6 g/dL (26 g/L), serum potassium of 3.4 mEq/L (3.4 mmol/L), and normal kidney function studies. Serum parathyroid hormone and 25-hydroxyvitamin D levels are pending.

An electrocardiogram shows prolongation of the QT interval.

Which of the following is the most appropriate next diagnostic test to evaluate this patient's hypocalcemia?

(A) 1,25-Dihydroxyvitamin D level
(B) 24-Hour urine calcium excretion
(C) Ionized calcium level
(D) Magnesium level

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Item 29

A 52-year-old woman presents for follow-up evaluation after being diagnosed with type 2 diabetes mellitus 6 weeks ago. Her initial hemoglobin A_{1c} level was 8.0%. Management at this time is with lifestyle modifications. She has worked closely with a diabetes educator and a nutritionist since her diagnosis. She has lost 3.2 kg (7 lb) by making changes to her diet and activity level. Review of her blood glucose log for the past 2 weeks shows preprandial blood glucose values in the 150 to 160 mg/dL (8.3-8.9 mmol/L) range and several 2-hour postprandial blood glucose values of 190 to 200 mg/dL (10.5-11.1 mmol/L). Her only other medical problem is hypertension for which she takes lisinopril.

On physical examination, blood pressure is 125/70 mm Hg and pulse rate is 74/min. BMI is 28. There is no evidence of diabetic retinopathy. She has normal monofilament and vibratory sensation in her extremities.

Except for her blood glucose parameters, basic laboratory studies obtained at the time of her initial diagnosis were normal.

In addition to continuing lifestyle modifications, which of the following is the most appropriate management for this patient's diabetes?

(A) Initiate dapagliflozin
(B) Initiate glipizide
(C) Initiate metformin
(D) Initiate sitagliptin

Item 30

A 28-year-old man is evaluated for fatigue and erectile dysfunction. His symptoms have been progressive over the past year. He notes decreased libido and reports loss of morning erections. He also feels tired, has difficulty concentrating, and notes diffuse joint aches. He believes he has less strength and has had to decrease his level of exercise.

Medical history is unremarkable. He had normal puberty and normal growth. He takes no medications.

On physical examination, temperature is 37.4 °C (99.3 °F), blood pressure is 108/72 mm Hg, pulse rate is 68/min, and respiration rate is 14/min. BMI is 23. The liver edge is palpable 4 cm below the costal margin. The penis is normal, and the testes are normal volume but soft and freely mobile without masses. Visual fields are intact.

Laboratory studies:

Follicle-stimulating hormone	3.0 mU/mL (3.0 U/L)
Luteinizing hormone	2.2 mU/mL (2.2 U/L)
Prolactin	12 ng/mL (12 µg/L)
Testosterone, total (8 AM)	178 ng/dL (6.2 nmol/L)
Testosterone, total (8 AM), repeated	162 ng/dL (5.6 nmol/L)
Thyroid-stimulating hormone	2.3 µU/mL (2.3 mU/L)

Pituitary MRI is normal.

Which of the following is the most appropriate next step in management?

(A) Begin testosterone replacement therapy
(B) Karyotyping
(C) Serum ferritin level and transferrin saturation
(D) Testicular ultrasound

Item 31

A 59-year-old man is evaluated for hypercalcemia. He was recently diagnosed with multiple myeloma. He does not have anorexia, nausea, constipation, polydipsia, polyuria, or confusion. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, temperature is 36.4 °C (97.5 °F), blood pressure is 134/80 mm Hg, pulse rate is 80/min, and respiration rate is 12/min. BMI is 30. The remainder of his physical examination is normal, and no weakness is noted on neurologic examination.

Serum calcium level is 10.8 mg/dL (2.7 mmol/L).

Which of the following is the most appropriate next laboratory test for evaluating this patient's hypercalcemia?

(A) 1,25-Dihydroxyvitamin D level
(B) Ionized calcium level
(C) Parathyroid hormone level
(D) Parathyroid hormone–related protein level

Item 32

A 37-year-old man is evaluated for a 2-year history of low libido, loss of morning erections, fatigue, and decreasing muscle mass. His medical history is otherwise unremarkable. He takes no medications.

On physical examination, vital signs are normal. BMI is 35. The remainder of the examination, including genital examination, is normal.

Laboratory studies:

Follicle-stimulating hormone	12 mU/mL (12 U/L)
Luteinizing hormone	10 mU/mL (10 U/L)
Prolactin	Normal
Morning testosterone (total)	148 ng/dL (5.1 nmol/L)
Confirmatory morning testosterone (total)	137 ng/dL (4.7 nmol/L))
Thyroid-stimulating hormone	Normal

A pituitary MRI is normal.

Before initiating therapy for this patient, which of the following should be determined?

(A) Bone mineral density
(B) Desire for fertility
(C) Fasting plasma glucose level
(D) Scrotal ultrasound

Item 33

A 55-year-old woman is evaluated in the emergency department because of a 1-week history of palpitations, chest pain, shortness of breath, diarrhea, and weight loss. Medical history is significant for an episode of chest pain 4 weeks ago; the chest pain was evaluated with an exercise stress test, which was positive. A subsequent cardiac catheterization was negative for epicardial coronary artery

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disease. She also has a history of Graves disease treated with daily methimazole; she stopped this medication on the day of her catheterization and has not restarted it since that time.

On physical examination, she is restless and confused. Temperature is 38.9 °C (102.0 °F), blood pressure is 175/94 mm Hg, pulse rate is 135/min and regular, and respiration rate is 20/min. The skin is warm and moist. There is mild proptosis with scleral injection. Examination of the thyroid reveals a diffusely enlarged gland that is nontender to palpation. A thyroid bruit is heard. Abdominal examination is unremarkable. There is edema of the lower extremities to the mid-lower leg. On neurologic examination, she is oriented to place but not to time, as she does not know the correct year.

Laboratory studies:

Leukocyte count	10,500/μL (10.5×10^9/L)
Creatinine	1.3 mg/dL (115 μmol/L)
Thyroid-stimulating hormone	<0.008 μU/mL (0.008 mU/L)
Free thyroxine (T_4)	7.5 ng/dL (96.7 pmol/L)

Which of the following is the most likely diagnosis?

(A) Euthyroid sick syndrome
(B) Pheochromocytoma
(C) Subacute thyroiditis
(D) Thyroid storm

Item 34

A 39-year-old man is seen for a follow-up examination. Three months ago, he underwent an organ-sparing procedure for squamous cell carcinoma of the throat. As part of his surgery, his thyroid and all four parathyroid glands were removed. He was started on 1,25-dihydroxyvitamin D (calcitriol) and supplemental calcium carbonate following surgery. He subsequently completed a course of concurrent cisplatin-based chemotherapy and radiation therapy without significant complications and currently feels well with no new signs or symptoms. Medical history is otherwise unremarkable except for a 25-pack-year smoking history; he discontinued tobacco use at the time of diagnosis. Medications are calcitriol, calcium carbonate, and levothyroxine.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 125/84 mm Hg, pulse rate is 85/min, and respiration rate is 12/min. BMI is 24. Well-healed surgical incisions are noted on the anterior neck. The remainder of the examination is unremarkable.

Laboratory studies:

Calcium	8.5 mg/dL (2.1 mmol/L)
Creatinine	0.8 mg/dL (70.7 μmol/L)
1,25-Dihydroxyvitamin D	Within therapeutic range
24-Hour urine calcium	375 mg/24 h (9.4 mmol/24 h)

Which of the following is the most appropriate management of this patient's postsurgical calcium therapy?

(A) Check 25-hydroxyvitamin D level
(B) Check parathyroid hormone level
(C) Continue current treatment regimen
(D) Decrease calcium supplementation

Item 35

A 40-year-old man with type 1 diabetes mellitus presents to the office. He seeks advice on his diabetes management as he intensifies his exercise routine in preparation for participation in a 10-K race. He reports prolonged hypoglycemia during intense exercise, despite eating a meal prior to the activity. His insulin regimen is insulin glargine and insulin glulisine. His most recent hemoglobin A_{1c} level was 7.0%.

Which of the following is the most appropriate management of this patient's hypoglycemia on the days that he exercises?

(A) Decrease meal-time insulin glulisine dose prior to exercise, continue insulin glargine dose
(B) Discontinue insulin glargine, continue insulin glulisine dose
(C) Increase meal-time protein prior to exercise, continue current insulin doses
(D) Switch insulin glulisine to a sliding-scale regimen, continue insulin glargine dose

Item 36

A 54-year-old man is evaluated because of fatigue. He also notes constipation and cold intolerance. Medical history is significant for tonsillar squamous cell carcinoma treated with radiation 3 years ago. There is no family history of thyroid disorders.

On physical examination, the skin is dry. Mild periorbital edema is present. The thyroid is of normal size and without nodules. Reflexes are delayed.

Laboratory studies show a hemoglobin level of 11 g/dL (110 g/L), a serum sodium level of 129 mEq/L (129 mmol/L), and a serum thyroid-stimulating hormone (TSH) level of 1.4 μU/mL (1.4 mU/L).

Which of the following is the most appropriate next step in management?

(A) Free thyroxine (T_4) measurement
(B) Repeat TSH measurement in 4 weeks
(C) Thyroid scintigraphy
(D) Thyroid ultrasound

Item 37

A 24-year-old woman is evaluated for hypercalcemia incidentally discovered on laboratory studies performed for another indication. She reports no hypercalcemia-related symptoms. Medical history is significant for gastroesophageal reflux disease and menstrual migraine. Family history is notable for a brother who has a "calcium" problem. Medications are omeprazole and sumatriptan as needed.

On physical examination, temperature is 36.2 °C (97.2 °F), blood pressure is 127/68 mm Hg, pulse rate is 73/min, and respiration rate is 12/min. BMI is 25. Chest, heart, and abdominal examinations are normal, as is the remainder of her examination.

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Laboratory studies are significant for a serum calcium level of 11.2 mg/dL (2.8 mmol/L), parathyroid hormone level of 55 pg/mL (55 ng/L), and 25-hydroxyvitamin D level of 35 ng/mL (87.4 nmol/L). Kidney and thyroid function studies are normal.

Which of the following is the most appropriate next step in management?

(A) Bone densitometry
(B) Measurement of urine calcium and creatinine levels
(C) Parathyroid sestamibi scan
(D) Referral for parathyroidectomy

Item 38

A 25-year-old woman with type 1 diabetes mellitus is evaluated for recent-onset glycemic fluctuations without symptomatic hypoglycemia. She was diagnosed with diabetes 7 years ago. Her hemoglobin A_{1c} levels since diagnosis have ranged from 6.4% to 7.3%, with the most recent value at 7.3%. She reports eating a carbohydrate-consistent diet at each meal, with little variation in her selection of meals or snacks. She started a new job several months ago but continues her daily exercise routine and sleep schedule. She has no other medical problems or symptoms. Her diabetes treatment regimen is insulin glargine once daily and insulin lispro three times daily.

Physical examination findings and vital signs are normal.

Estimate glomerular filtration rate, serum creatinine level, and urine albumin-creatinine ratio are normal. Her blood glucose values from the previous week are shown below.

Blood glucose values:

Breakfast (mg/dL [mmol/L])	Lunch (mg/dL [mmol/L])	Dinner (mg/dL [mmol/L])	Bedtime (mg/dL [mmol/L])
124 (6.9)	190 (10.5)	109 (6.1)	210 (11.6)
110 (6.1)	92 (5.1)	112 (6.2)	126 (7.0)
115 (6.4)	118 (6.5)	112 (6.2)	126 (7.0)
117 (6.5)	127 (7.0)	204 (11.3)	110 (6.1)
108 (6.0)	101 (5.6)	122 (6.8)	114 (6.3)
101 (5.6)	111 (6.2)	106 (5.9)	72 (4.0)
126 (7.0)	187 (10.4)	102 (5.7)	196 (10.9)

Which of the following is the most likely cause of the fluctuating glycemic control?

(A) Antibodies to exogenous insulin
(B) Gastroparesis
(C) Inadequate insulin doses
(D) Inappropriate insulin timing

Item 39

A 20-year-old woman is admitted to the hospital for an elective adrenalectomy. Her history is significant for recent onset of hypertension, weight gain, generalized weakness, and easy bruising. Laboratory evaluation demonstrated an elevated urine free cortisol and lack of suppression of serum cortisol following a low-dose overnight dexamethasone suppression test. Subsequent testing revealed a suppressed adrenocorticotropic hormone level.

A contrast-enhanced adrenal CT scan revealed a well-circumscribed 3.7-cm right adrenal mass with a contrast washout of greater than 50% at 10 minutes.

Which of the following is the most appropriate perioperative management?

(A) Postoperative hydrocortisone
(B) Postoperative mitotane
(C) Postoperative norepinephrine
(D) Preoperative phenoxybenzamine

Item 40

A 62-year-old man is evaluated for right leg pain. The pain has developed progressively over the past 6 months and worsens with prolonged activity, such as playing golf. Medical history is unremarkable, and he takes no medications.

On physical examination, temperature is 36.3 °C (97.3 °F), blood pressure is 128/67 mm Hg, pulse rate is 73/min, and respiration rate is 10/min. BMI is 29. There is no pain to palpation over the femoral region, and he has normal range of motion.

Laboratory studies are significant for a serum alkaline phosphatase level of 200 U/L and serum calcium level of 9.0 mg/dL (2.3 mmol/L).

Plain radiograph of the right femur is shown.



Which of the following is the most appropriate next step in management?

(A) Antiresorptive therapy
(B) Bone biopsy
(C) Evaluation for multiple myeloma
(D) Clinical observation

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Item 41

A 29-year-old woman is evaluated during her first prenatal visit. She feels well. Medical history is significant only for hypothyroidism, for which she has taken levothyroxine, 100 µg/d, for the last 3 years. Her only other medication is a prenatal vitamin.

On physical examination, she is afebrile. Blood pressure is 98/72 mm Hg, pulse rate is 88/min, and respiration rate is 12/min. The thyroid is of normal size and without nodules. There is no cervical lymphadenopathy. Cardiovascular and pulmonary examinations are unremarkable. Abdominal examination reveals normal bowel sounds. The uterus is not palpable.

Laboratory studies show a serum thyroid-stimulating hormone level of 3.6 µU/mL (3.6 mU/L) and a serum total thyroxine (T_4) level of 4.5 µg/dL (58 nmol/L).

Which of the following is the most appropriate treatment of this patient's hypothyroidism?

(A) Continue levothyroxine dose
(B) Decrease levothyroxine dose
(C) Discontinue levothyroxine
(D) Increase levothyroxine dose

Item 42

A 62-year-old man is evaluated in the hospital for several hours of nausea, lightheadedness, and back and abdominal pain. He underwent uncomplicated mechanical aortic valve replacement 3 days ago. He had been doing well postoperatively until the development of his current symptoms. Medical history is significant only for hypothyroidism. Medications are therapeutic unfractionated heparin, levothyroxine, and as-needed oxycodone.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 80/50 mm Hg, pulse rate is 110/min, and respiration rate is 18/min. BMI is 26. Examination of the chest shows a clean and dry sternal wound. Cardiac examination reveals regular tachycardia and mechanical S_1. There is no pain with palpation of the abdomen or lower back. His skin pigmentation is normal.

Laboratory studies:

Hemoglobin	7.3 g/dL (73 g/L) 9.0 g/dL (90 g/L) postoperatively
Leukocyte count	11,000/µL (11×10^9/L)
Activated partial thromboplastin time	70 s
Creatinine	1.0 mg/dL (88.4 µmol/L)
Sodium	130 mEq/L (130 mmol/L)
Potassium	6.0 mEq/L (6.0 mmol/L)
Cortisol, random	<2 µg/dL (55.2 nmol/L)

Which of the following is the most likely diagnosis?

(A) Autoimmune adrenalitis
(B) Bilateral adrenal hemorrhage
(C) Opiate-induced adrenal insufficiency
(D) Pituitary apoplexy

Item 43

A 44-year-old woman is evaluated for weight gain, muscle weakness, and metabolic syndrome. She has hirsutism but also notes hair loss on her head. She has been amenorrheic for 2 years.

Medical history is significant for hyperlipidemia, type 2 diabetes mellitus, hypertension, and obesity. Medications are atorvastatin, metformin, and lisinopril.

On physical examination, blood pressure is 156/92 mm Hg and pulse rate is 78/min. BMI is 42. She has a cushingoid appearance, acne, and moderate hirsutism affecting the chin, upper lip, breasts, back, and chest. There are several wide violaceous striae across the abdomen and the back of her arms.

Laboratory studies:

Adrenocorticotropic hormone (ACTH)	52 pg/mL (11.4 pmol/L)
Cortisol 8 AM after 1 mg of dexamethasone the night before	5.2 µg/dL (143.5 nmol/L)
24-Hour urine cortisol excretion	
Initial measurement	124 µg/24 h (341.7 nmol/24 h)
Repeat measurement	98 µg/24 h (270.0 nmol/24 h)

Intrapetrosal sinus sampling identifies a pituitary microadenoma as the source of the high ACTH level.

Which of the following is the most appropriate test to perform next?

(A) 8-mg dexamethasone suppression test
(B) 24-Hour urine free catecholamine and metanephrine measurement
(C) Dual-energy x-ray absorptiometry scan
(D) PET scan

Item 44

A 28-year-old woman is being discharged from the hospital with a diagnosis of autoimmune adrenalitis. Medical history is otherwise unremarkable, and she was on no medications prior to admission.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 120/80 mm Hg, pulse rate is 80/min, and respiration rate is 12/min. BMI is 22. Increased skin pigmentation is noted over the extensor surfaces of the extremities bilaterally. The remainder of her examination is normal.

Which of the following is the most appropriate long-term medication regimen for this patient?

(A) Dexamethasone, 1 mg once daily
(B) Fludrocortisone, 0.05 mg once daily
(C) Hydrocortisone, 10 mg three times daily
(D) Prednisone, 5 mg once daily, and fludrocortisone, 0.05 mg once daily

Item 45

A 78-year-old woman is evaluated for a 2-week history of unintentional weight loss, night sweats, and neck swelling. She has more recently also had difficulty swallowing solid

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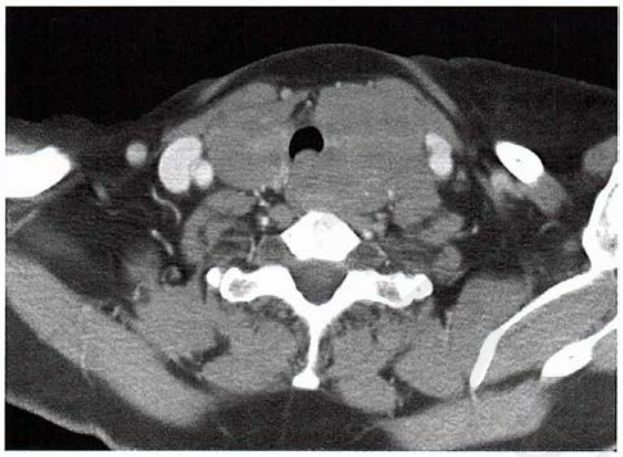
foods and positional shortness of breath. She does not have hoarseness, palpitations, or change in bowel habits. Prior to the development of these symptoms, she had been in her usual state of health with no illnesses. She has hypothyroidism and has been taking levothyroxine for 40 years, with a stable dose for the past 10 years.

On physical examination, temperature is 36.9 °C (98.4 °F), blood pressure is 140/88 mm Hg, pulse rate is 75/min, and respiration rate is 12/min. The thyroid is symmetrically enlarged, firm, and fixed. There is no thyroid bruit.

CT scan of the neck is shown.



Which of the following is the most likely diagnosis?

(A) Graves disease
(B) Papillary thyroid cancer
(C) Primary thyroid lymphoma
(D) Subacute thyroiditis

Item 46

A 67-year-old man is evaluated for a recent diagnosis of primary hyperparathyroidism after an elevated serum calcium level was incidentally detected on laboratory testing. Medical history is significant only for hypertension, and his only medication is ramipril.

On physical examination, temperature is 35.8 °C (96.4 °F), blood pressure is 120/68 mm Hg, pulse rate is 62/min, and respiration rate is 14/min. BMI is 32. The remainder of his examination is unremarkable.

Laboratory studies:

Calcium	10.9 mg/dL (2.7 mmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)
Parathyroid hormone	98 pg/mL (98 ng/L)
25-Hydroxyvitamin D	19 ng/mL (47.4 nmol/L)
Estimated glomerular filtration rate	>60 mL/min/1.73 m^2

A dual-energy x-ray absorptiometry (DEXA) scan shows T-scores of -1.3 in the right femoral neck, -1.0 in the lumbar spine, and -1.4 in the non-dominant forearm. Fracture Risk Assessment Tool (FRAX) score indicates a 13% risk of major osteoporotic fracture and a 1.9% risk of hip fracture over the next 10 years.

Which of the following is the most appropriate management of this patient?

(A) Refer for parathyroidectomy
(B) Start alendronate
(C) Start calcitonin
(D) Start cinacalcet
(E) Start vitamin D_3 (cholecalciferol)

Item 47

A 57-year-old man is admitted to the hospital for evaluation of substernal chest pain. His medical history is significant for type 2 diabetes mellitus, coronary artery disease, hypertension, and hyperlipidemia. He manages his diabetes as an outpatient with diet, exercise, and metformin. His other medications are aspirin, metoprolol, atorvastatin, and sublingual nitroglycerin as needed. His inpatient plasma glucose values are 170 to 210 mg/dL (9.4-11.6 mmol/L). Results of all other laboratory studies are normal.

Which of the following is the most appropriate treatment for this patient's diabetes while hospitalized?

(A) Basal and prandial insulin
(B) Glipizide
(C) Metformin
(D) Sliding-scale insulin

Item 48

A 43-year-old woman is evaluated for progressive weight gain over the past 2 years. Her previous weight was 72.6 kg (160 lb) but has steadily risen to her current weight of 106.6 kg (235 lb). She notes a slight increase in her appetite but minimal change in her lifestyle or activity level. She has tried to lose weight with increased exercise and nutritional counseling but without significant results. More recently she reports having trouble sleeping and decreased exercise tolerance with activites such as walking up steps. Medical history is significant for impaired fasting glucose, hypertension, and hyperlipidemia. Medications are hydrochlorothiazide and atorvastatin. She has not been prescribed glucocorticoids or had glucocorticoid joint injections.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 136/86 mm Hg, pulse rate is 88/min, and respiration rate is 12/min. BMI is 38. She has rounded facies, thin hair, mild hirsutism, and prominent fat deposition in the dorsocervical and supraclavicular areas. Her skin is thin, and she bruises easily, although striae are not present. Her examination is otherwise unremarkable.

Laboratory studies are significant for a fasting plasma glucose level of 120 mg/dL (6.7 mmol/L) and normal thyroid-stimulating hormone level.

Which of the following is the most appropriate next step in evaluation?

(A) Adrenocorticotropic hormone measurement
(B) 1-mg dexamethasone suppression test
(C) 8-mg dexamethasone suppression test
(D) Pituitary MRI
(E) Serum cortisol measurement

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Item 49

A 50-year-old man undergoes follow-up evaluation for type 2 diabetes mellitus. His daily log demonstrates average blood glucose levels of 120 to 150 mg/dL (6.7–8.3 mmol/L), with hypoglycemia in the 50 mg/dL (2.8 mmol/L) range noted once or twice per week without a discernible pattern. He is unable to detect the hypoglycemia.

The patient has a medical history of diabetic retinopathy, chronic kidney disease, peripheral neuropathy, hypertension, hyperlipidemia, obstructive sleep apnea (on bilevel positive airway pressure), gastroesophageal reflux disease, and osteoarthritis in both knees. He reports intolerance to strenuous exercise due to knee pain. He is able to walk 15 minutes daily. He has worked closely with a nutritionist, resulting in a 5.0-kg (11-lb) weight loss over 1 year, which has plateaued recently.

Medications are insulin glargine, insulin aspart, lisinopril, carvedilol, pantoprazole, aspirin, and atorvastatin.

On physical examination, blood pressure is 140/90 mm Hg and pulse rate is 65/min. BMI is 37. Bilateral proliferative retinopathy is present. There are no carotid bruits or cardiac murmurs. Bilateral loss of monofilament and vibratory sensation on the feet and decreased ankle reflexes are noted. The remainder of the examination is normal.

Results of laboratory studies show hemoglobin A_{1c} level of 8.2% and serum creatinine level of 1.7 mg/dL (150.3 µmol/L).

Which of the following is the most appropriate treatment of this patient?

(A) Bariatric surgery
(B) Increase insulin
(C) Initiate metformin
(D) Initiate pramlintide

Item 50

A 47-year-old woman is evaluated for an incidentally discovered right adrenal mass.

On physical examination, blood pressure is 120/80 mm Hg in both arms and pulse rate is 84/min. The abdomen is nontender, and there are no palpable masses. The remainder of the examination is unremarkable.

Noncontrast CT of the abdomen demonstrates a 3.2-cm well-circumscribed, partially cystic right adrenal lesion with a density of 30 Hounsfield units. A low-dose dexamethasone suppression test is negative for evidence of cortisol hypersecretion.

Which of the following is the most appropriate next step in management?

(A) Adrenalectomy
(B) CT-guided transcutaneous biopsy
(C) Plasma aldosterone to plasma renin ratio
(D) Plasma free metanephrines
(E) No additional testing is indicated

Item 51

A 64-year-old man with type 2 diabetes mellitus and stage 4 chronic kidney disease is evaluated for continued glycemic management. He is followed closely by the nephrology service in preparation for impending hemodialysis, with initiation of erythropoietin therapy within the last 3 months. His average fasting and preprandial blood glucose values are in the 145 to 190 mg/dL (8.0-10.5 mmol/L) range. He does not have hypoglycemia. His insulin regimen consists of insulin detemir at bedtime and insulin glulisine before meals. His most recent hemoglobin A_{1c} value has decreased from 7.5% to 6.2%.

Which of the following is the most appropriate management for this patient's diabetes?

(A) Continue current therapy
(B) Decrease insulin detemir dose
(C) Discontinue preprandial insulin glulisine
(D) Measure postprandial glucose level

Item 52

A 34-year-old woman is evaluated for hirsutism and acne that began 4 months ago. She also reports that her voice has become deeper. Her menstrual periods have remained regular, occurring every 28 days.

She has one son 5 years of age. She reports that her pregnancy was uncomplicated and she had no difficulty conceiving. She had a tubal ligation following the birth of her child. She has a sister with polycystic ovary syndrome. She takes no medications.

On physical examination, blood pressure is 140/84 mm Hg, and pulse rate is 62/min. BMI is 21. She has hyperpigmented terminal hairs on the chin, neck, abdomen, and lower back and comedones and pustules on the face and upper back. There is frontotemporal hair loss. The remainder of the examination is unremarkable.

Laboratory studies:

Cortisol, free (urine)	26 µg/24 h (71.6 nmol/24 h)
Dehydroepiandrosterone sulfate	8.2 µg/mL (22.1 µmol/L)
Prolactin	8 ng/mL (8 µg/L)
Testosterone	96 ng/dL (3.3 nmol/L)

Which of the following is the most appropriate diagnostic test to perform next?

(A) Abdominal CT scan
(B) Low-dose dexamethasone suppression test
(C) Pelvic ultrasound
(D) Pituitary MRI

Item 53

A 27-year-old woman is evaluated for management of her type 1 diabetes mellitus. She was diagnosed 10 years ago. She has no known complications from her diabetes. She eats a healthy diet and exercises an average of 60 minutes per day in the evening. She takes insulin glargine and insulin aspart. She is adherent with her insulin regimen and checks her blood

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glucose level three to five times per day. Her average blood glucose value is 125 mg/dL (6.9 mmol/L), with fasting glucose values ranging from 80 to 150 mg/dL (4.4-8.3 mmol/L). She routinely measures her 2-hour postprandial glucose values, and they are consistently less than 150 mg/dL (8.3 mmol/L). She has several overnight blood glucose values ranging from 90 to 140 mg/dL (5.0-7.8 mmol/L). Her hemoglobin A_{1c} values over the last 6 months have been 7.3% to 7.5%. She is discouraged that her hemoglobin A_{1c} values remain above 7.0%.

Laboratory studies, including creatinine and complete blood count, are normal.

Which of the following is the most appropriate management of her elevated hemoglobin A_{1c} level?

(A) Begin continuous glucose monitoring
(B) Increase exercise
(C) Increase insulin aspart
(D) Increase insulin glargine

Item 54

A 25-year-old woman is evaluated after a recent diagnosis of polycystic ovary syndrome. She is concerned about hirsutism and irregular menses. She has no desire to be pregnant at this time. She takes no medications.

On physical examination, she is afebrile. Blood pressure is 110/60 mm Hg, pulse rate is 68/min, and respiration rate is 16/min; BMI is 37. Coarse hair is noted on the chin, jawline, and periumbilical area. The remainder of her physical examination, including pelvic examination, is normal.

Which of the following is the most appropriate treatment?

(A) Combined oral contraceptive pills
(B) Intermittent progestin withdrawal
(C) Levonorgestrel intrauterine system
(D) Spironolactone therapy

Item 55

A 46-year-old man is evaluated following a diagnosis of pheochromocytoma. He has no signs or symptoms at this time. Except for hypertension, his medical history is unremarkable. Medications are lisinopril and hydrochlorothiazide.

On physical examination, blood pressure is 170/90 mm Hg and pulse rate is 90/min. The remainder of the physical examination is unrevealing.

Which of the following is the most appropriate next step in management?

(A) Increase lisinopril dosage
(B) Perform contrast-enhanced adrenal CT scan
(C) Start phenoxybenzamine
(D) Start propranolol

Item 56

A 38-year-old man with panhypopituitarism is evaluated for worsening fatigue and weight gain over the past 3 months. He is sleeping 9 hours each night, but he feels tired during the day and has decreased his usual exercise level. He has morning erections but reports low libido and occasional erectile dysfunction during intercourse. He wakes once during the night to urinate and drink water. He estimates that he urinates 5 to 8 times during the day, which is unchanged.

Medical history is significant for transsphenoidal resection of a craniopharyngioma at age 18 years. He has required anterior pituitary hormone replacement and desmopressin since that time. Medications are desmopressin, hydrocortisone, levothyroxine, somatropin, and testosterone enanthate.

On physical examination, temperature is 37.0°C (98.6°F), blood pressure is 118/64 mm Hg, pulse rate is 74/min, and respiration rate is 14/min. No orthostatic changes are noted. BMI is 24. There are no facial changes suggestive of acromegaly or Cushing syndrome. The thyroid is normal without goiter or nodules. Hair distribution and skin turgor are normal. There is no gynecomastia or striae. Normal penis and testicular volume are noted. Visual fields are intact on neurologic examination.

Laboratory studies:

Sodium	138 mEq/L (138 mmol/L)
Insulin-like growth factor 1	Normal
Prolactin	18 ng/mL (18 µg/L)
Thyroid-stimulating hormone	0.8 µU/mL (0.8 mU/L)
Thyroxine (T_4), free	0.7 ng/dL (9.0 pmol/L)
Testosterone (11 days after injection)	482 ng/dL (16.7 nmol/L)

Follow-up MRIs show no residual tumor.

Which of the following is the most appropriate management?

(A) Increase desmopressin
(B) Increase hydrocortisone
(C) Increase levothyroxine
(D) Increase testosterone enanthate
(E) Stop somatropin

Item 57

A 55-year-old man is evaluated following a screening for type 2 diabetes mellitus. He is asymptomatic. He has a history of hypertension and hyperlipidemia. There is no history of anemia, liver disease, or kidney disease. Medications are lisinopril and rosuvastatin.

On physical examination, blood pressure is 123/76 mm Hg and pulse rate is 72/min. BMI is 28. The remainder of the examination is unremarkable.

Laboratory studies:

Hematocrit	45.6%
Creatinine	1.0 mg/dL (88.4 µmol/L)
Glucose, fasting	128 mg/dL (7.1 mmol/L)
Hemoglobin A_{1c}	5.6%

Which of the following is the most appropriate diagnostic test to perform next?

(A) Fasting plasma glucose
(B) Hemoglobin A_{1c}
(C) Oral glucose tolerance test
(D) Random blood glucose

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Item 58

A 34-year-old man is evaluated for a 2-year history of fatigue, low libido, and infertility. His family history is notable for a brother with infertility. His medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. His height is 195.6 cm (77 in), and his weight is 86.2 kg (190 lb). Genital examination reveals small, firm testes bilaterally.

Laboratory studies reveal a morning serum total testosterone level of 140 ng/dL (4.9 nmol/L) (which was confirmed on repeat testing), a serum follicle-stimulating hormone level of 24 mU/mL (24 U/L), and a serum luteinizing hormone level of 18 mU/mL (18 U/L). Repeated semen analyses reveal azoospermia.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Karyotype
(B) MRI of the pituitary
(C) Scrotal ultrasound
(D) Serum prolactin measurement

Item 59

An 84-year-old man is evaluated for moderate fatigue. He otherwise feels well and does not have constipation, cold intolerance, weight gain or loss, anxiety, tremor, palpitations, or dyspnea. Medical history is significant for hypertension, and his only medication is felodipine.

On physical examination, he is alert and oriented. Blood pressure is 144/83 mm Hg; other vital signs are normal. The thyroid is not palpable. Cardiopulmonary examination is normal. There is no peripheral edema. Neurologic examination is nonfocal, and deep tendon reflexes are normal.

Laboratory studies:

Complete blood count	Normal
Comprehensive metabolic profile	Normal
Thyroid-stimulating hormone (TSH)	6.4 µU/mL (6.4 mU/L)
Free thyroxine (T_4)	1.3 ng/dL (16.8 pmol/L)

Which of the following is the most appropriate management?

(A) Levothyroxine therapy
(B) Measurement of serum total triiodothyronine (T_3) level
(C) Measurement of serum total T_4 level
(D) Repeat TSH and free T_4 measurement in 6 to 12 weeks

Item 60

A 62-year-old woman is evaluated for an incidentally discovered left adrenal mass. Two weeks ago, the patient was evaluated in the emergency department for diffuse abdominal pain and vomiting. A CT scan was obtained that was normal except for the adrenal mass. Three hours after presentation to the emergency department, the pain resolved spontaneously.

Her medical history is significant for diet-controlled type 2 diabetes mellitus diagnosed 1 year ago and osteoporosis diagnosed 4 years ago. Her only medication is alendronate.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 120/80 mm Hg, and pulse rate is 70/min. BMI is 26. The remainder of the physical examination is normal.

Laboratory evaluation reveals a serum sodium level of 139 mEq/L (139 mmol/L) and serum potassium level of 4.1 mEq/L (4.1 mmol/L). The previously obtained CT scan shows a 2.0-cm well-circumscribed, left adrenal lesion with a density of 5 Hounsfield units.

In addition to screening tests for pheochromocytoma, which of the following is the most appropriate diagnostic test to perform next?

(A) Adrenal vein sampling
(B) Low-dose dexamethasone suppression test
(C) Plasma renin activity and aldosterone concentration measurement
(D) No further testing

Item 61

A 68-year-old man is seen in follow-up for a recent diagnosis of acromegaly. He presented with chronic fatigue, joint and back pain, and an increase in his shoe size over the past 2 years. Medical history is significant for hypertension and type 2 diabetes mellitus. Current medications are lisinopril, metformin, and as-needed acetaminophen.

On physical examination, blood pressure is 146/88 mm Hg and pulse rate is 90/min. BMI is 29. He has a prominent brow. Macroglossia is present. Lung and heart examinations are unremarkable. Musculoskeletal examination reveals large hands and knees with bone swelling and crepitus. Skin is thickened, and there is excessive perspiration. On neurologic examination, bitemporal hemianopsia is noted.

Laboratory studies are significant for an elevated serum insulin-like growth factor 1 level of 996 ng/mL (996 µg/L) and serum prolactin level of 42 ng/mL (42 µg/L).

MRI shows a 2.5×1.8-cm pituitary macroadenoma that elevates the optic chiasm and appears to envelop the left carotid artery and invade the left cavernous sinus. The optic chiasm is mildly atrophied.

Which of the following is the most appropriate next step in therapy for this patient?

(A) Dopamine agonist
(B) Growth hormone receptor blockade
(C) Somatostatin analogue
(D) Stereotactic radiation therapy
(E) Transsphenoidal pituitary surgery

Item 62

A 47-year-old man is evaluated postoperatively following thyroidectomy for papillary thyroid cancer. Preoperative evaluation showed no evidence of distant metastatic disease, and he underwent total thyroidectomy with central

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and left lateral neck dissections. The patient's medical history is otherwise unremarkable.

On physical examination, vital signs are normal. The neck surgical sites are clean and dry. The remainder of the examination is unremarkable.

The surgical pathology report reveals a 3.5-cm papillary thyroid cancer in the left lobe of the thyroid and six malignant lymph nodes out of 35 dissected. There is evidence of minor extrathyroidal extension and vascular invasion by the primary tumor.

Which of the following is the most appropriate postoperative treatment?

(A) Doxorubicin chemotherapy
(B) External-beam radiotherapy
(C) Radioactive iodine therapy
(D) No additional therapy

Item 63

A 66-year-old man is evaluated in the office after being treated in the emergency department for an exacerbation of chronic obstructive pulmonary disease. While in the emergency department, he was noted to have a random blood glucose level of 211 mg/dL (11.7 mmol/L). His hemoglobin A_{1c} was 7.8% at the time. A repeat random fingerstick blood glucose level in office is 204 mg/dL (11.3 mmol/L).

The patient reports recent polyuria and polydipsia. He has lost 6 kg (13.2 lb) over the last 3 months. He has chronic epigastric pain associated with loose, oily stools due to chronic pancreatitis.

He has a 20-pack-year history of tobacco use and prior alcohol use, however, he does not currently use alcohol. Current medications are enteric-coated pancreatic enzymes, vitamins, tiotropium inhaler, and an albuterol inhaler as needed.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 130/75 mm Hg, and pulse rate is 90/min. BMI is 22. He has mild epigastric pain on palpation without rebound tenderness or guarding. The rest of his examination is unremarkable.

Which of the following is the most appropriate treatment for his diabetes?

(A) Exenatide
(B) Glipizide
(C) Insulin
(D) Metformin

Item 64

A 34-year-old woman is evaluated because she and her male partner have been trying to conceive for 13 months without success. Her medical history is notable for a 6-year history of irregular menses and a recent diagnosis of polycystic ovary syndrome. Her only medication is a prenatal vitamin.

On physical examination, vital signs are normal. BMI is 36. Terminal hair growth on the chin, upper lip, and sides of the face is noted. No evidence of abdominal or pelvic masses, clitoromegaly, or galactorrhea is detected.

Which of the following is the most appropriate treatment?

(A) Clomiphene citrate
(B) In vitro fertilization
(C) Injectable gonadotropin
(D) Metformin

Item 65

A 64-year-old woman is seen for follow-up evaluation. Two weeks ago, she was in a car accident, and an incidental pituitary adenoma was found on a cervical spine CT scan. She has no residual injuries from the car accident.

She is otherwise healthy and takes no medications. She went through menopause at age 51. She has night sweats two to three times per month and occasional hot flushes. These have improved over the past decade and are not bothersome. She is not sexually active. She has never taken hormone replacement therapy. She has had no change in vision, headaches, or galactorrhea.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 110/63 mm Hg, pulse rate is 82/min, and respiration rate is 14/min. BMI is 26. There is axillary and pubic hair loss. Visual fields are intact. There are no findings suggestive of Cushing syndrome or acromegaly.

Laboratory studies:

Estradiol	<20 pg/mL (73.4 pmol/L)
Follicle-stimulating hormone	6.4 mU/mL (6.4 U/L)
Luteinizing hormone	3.2 mU/mL (3.2 U/L)
Prolactin	53 ng/mL (53 µg/L)
Thyroid-stimulating hormone	3.2 µU/mL (3.2 mU/L)
Thyroxine (T_4), free	1.1 ng/dL (14.2 pmol/L)

Pituitary MRI shows a 7-mm adenoma in the anterior sella. The tumor is not invasive. It does not approximate the optic chiasm. The pituitary stalk is mid-line.

Which of the following is the most appropriate management?

(A) Begin dopamine agonist
(B) Gamma knife stereotactic radiosurgery
(C) Repeat testing in 12 months
(D) Transphenoidal resection

Item 66

A 57-year-old man with a 15-year history of type 2 diabetes mellitus is evaluated for bilateral burning sensation in his feet for the last 6 to 12 months. The sensation worsens at night. His hemoglobin A_{1c} levels have remained less than 7.0% for the last 2 years but were between 8.0% and 9.0% before implementing significant lifestyle changes and transitioning to insulin therapy from metformin therapy 2 years ago.

His medical history includes coronary artery disease, first-degree atrioventricular block, nonproliferative diabetic retinopathy, hypertension, and hyperlipidemia.

Medications are regular insulin, neutral protamine Hagedorn (NPH) insulin, aspirin, metoprolol, atorvastatin, and lisinopril.

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On physical examination, findings are compatible with distal polyneuropathy.

Which of the following is the most appropriate management of this patient's neuropathy?

(A) Amitriptyline
(B) Duloxetine
(C) Nerve conduction study
(D) Vitamin B_{12} measurement

Item 67

A 72-year-old man presents to the emergency department overnight. His wife noted that he was diaphoretic and restless during the night, and his initial blood glucose level measured by emergency medical services was 41 mg/dL (2.3 mmol/L). He was given a single dose of intravenous glucose, which increased his blood glucose level to 85 mg/dL (4.7 mmol/L). His symptoms recurred en route to the hospital, and he responded to a second dose of intravenous glucose. While in the emergency department, he was provided food and his glucose level has remained above 80 mg/dL (4.4 mmol/L) without further treatment. The patient's wife reports several recent episodes of overnight diaphoresis over the last several weeks. His last meal prior to this episode was approximately 7 hours before symptom onset.

His medical history is significant for hypertension and osteoarthritis. Medications are lisinopril and as-needed ibuprofen.

On physical examination, the patient is alert and oriented. Blood pressure is 135/84 mm Hg, and pulse rate is 82/min. BMI is 23. The general physical and neurologic examinations are normal.

Laboratory studies are significant for a normal complete metabolic profile and blood count. An insulin secretagogue screen is obtained, and hypoglycemic studies consisting of measurement of insulin, C-peptide, proinsulin, and β-hydroxybutyrate levels are planned.

Which of the following is the most appropriate diagnostic strategy for this patient?

(A) Hypoglycemic studies now
(B) Mixed-meal testing with hypoglycemic studies at the time of symptomatic hypoglycemia
(C) Oral glucose tolerance testing with hypoglycemic studies at the time of symptomatic hypoglycemia
(D) 72-Hour fast with hypoglycemic studies at the time of symptomatic hypoglycemia

Item 68

A 24-year-old woman is evaluated for a 3-month history of amenorrhea accompanied by cyclic pelvic pain. Preceding the onset of amenorrhea, she had a recent dilatation and curettage to remove retained products of conception after a first-trimester spontaneous abortion. Her personal and family medical history is unremarkable. She takes no medications.

On physical examination, she is afebrile. Blood pressure is 110/60 mm Hg, pulse rate is 68/min, and respiration rate is 16/min. BMI is 24. Pelvic examination reveals a nontender, mobile uterus.

Laboratory studies:

Estradiol	<80 pg/mL (293.6 pmol/L)
Follicle-stimulating hormone	6.2 mU/mL (6.2 U/L)
Luteinizing hormone	4.1 mU/mL (4.1 U/L)
Prolactin	Normal
Thyroid-stimulating hormone	Normal
Urine human chorionic gonadotropin	Negative

Which of the following is the most appropriate diagnostic test to perform next?

(A) MRI of the pituitary
(B) Peripheral karyotype
(C) Progestin withdrawal test
(D) Transvaginal ultrasound

Item 69

A 29-year-old woman comes to the office for a follow-up evaluation. She was diagnosed with type 2 diabetes mellitus 2 years ago. Her fasting and premeal blood glucose values range from 120 to 150 mg/dL (6.7-8.3 mmol/L). She has had no hypoglycemic events. She has been adherent with her insulin regimen along with diet and exercise modifications. Her hemoglobin A_{1c} level has decreased from 9.0% to 7.5% over the last 12 months. She expresses frustration over the need for multiple medications to treat her diabetes. Medical history is otherwise unremarkable.

Medications are insulin glargine, insulin aspart, and metformin.

On physical examination, blood pressure is 120/72 mm Hg and pulse rate 80/min. BMI is 27. The remainder of the examination is normal.

Hemoglobin A_{1c} level is currently 7.4%. Results of all other laboratory studies are normal.

Which of the following is the most appropriate management of this patient's diabetes?

(A) Increase insulin glargine dose
(B) Measure 3 AM blood glucose level
(C) Measure postprandial blood glucose levels
(D) Switch metformin to sitagliptin

Item 70

A 32-year-old woman is evaluated for a 2-week history of foreign body sensation in her eyes. Despite flushing the eyes numerous times with saline, the sensation remains. She also feels pressure behind her eyes. She is not pregnant. Medical history is unremarkable.

On physical examination, scleral injection and periorbital edema are present bilaterally, right worse than left. Diplopia is noted on lateral gaze. There is no lid lag or proptosis. The thyroid is diffusely enlarged, and a bruit is noted. Neurologic examination discloses brisk reflexes and a bilateral hand tremor.

Laboratory studies reveal a serum thyroid-stimulating hormone level of less than 0.008 μU/mL (0.008 mU/L), a

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serum free thyroxine (T_4) level of 4.5 ng/dL (58.0 pmol/L), and a serum total triiodothyronine (T_3) level of 365 ng/dL (5.6 nmol/L).

Which of the following is the most appropriate next step in treatment?

(A) External-beam radiotherapy to the orbits
(B) Methimazole
(C) Radioactive iodine
(D) Total thyroidectomy

Item 71

A 42-year-old man is evaluated for resistant hypertension. He was diagnosed with hypertension at age 35 years and reports that his blood pressure has never been well controlled. He is taking his medications as prescribed. He does not have headaches, chest pain, palpitations, shortness of breath, or symptoms of panic attack. He has no history of cardiovascular disease, does not smoke, and does not drink alcohol. Medications are lisinopril, amlodipine, hydrochlorothiazide, metoprolol, and potassium chloride supplementation. He is not taking any over-the-counter medications.

On physical examination, blood pressure is 150/86 mm Hg and pulse rate is 65/min. BMI is 24. Examination of the heart is significant for an S_4 but no murmurs. The remainder of his examination is unremarkable.

Laboratory studies are significant for a serum creatinine level of 1.0 mg/dL (88.4 µmol/L), fasting plasma glucose level of 82 mg/dL (4.5 mmol/L), and serum potassium level of 3.2 mEq/L (3.2 mmol/L).

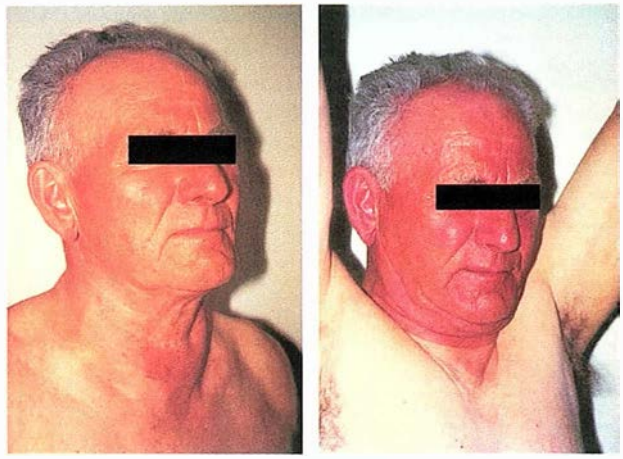
Which of the following is the most appropriate next diagnostic step?

(A) Dexamethasone suppression test
(B) Plasma aldosterone-plasma renin activity ratio
(C) Plasma metanephrines and catecholamines
(D) Renal artery Doppler flow study

Item 72

A 65-year-old man is evaluated because of painless neck swelling and difficulty swallowing that has progressively worsened over the last year. He does not have hoarseness, but he feels as though his voice is not as strong as it was in the past. Medical history is significant for multiple thyroid nodules. Fine-needle aspiration of three of the largest nodules 5 years ago showed that all nodules were benign on cytologic examination. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. The thyroid is diffusely enlarged and mobile with swallowing. He has facial flushing when raising his hands above his head as shown (see top of next column).



No cervical lymphadenopathy is noted. Cardiovascular and pulmonary examinations are normal. Reflexes are normal, and there is no visible tremor.

Laboratory studies show a serum thyroid-stimulating hormone (TSH) level of 4.0 µU/mL (4.0 mU/L).

Thyroid ultrasound shows innumerable coalescent nodules with no suspicious sonographic features. There is diffuse enlargement of the thyroid, and the inferior edge of the gland cannot be visualized. CT scan shows substernal extension of the goiter in the left lobe with mild tracheal narrowing and tracheal deviation to the right.

Which of the following is the most appropriate treatment?

(A) External-beam radiotherapy
(B) Levothyroxine
(C) Radioactive iodine
(D) Thyroidectomy

Item 73

A 26-year-old woman is evaluated because she and her husband have been trying to conceive for 14 months without success. Her husband fathered a child in a previous marriage. Her medical history is notable for pelvic inflammatory disease, which was diagnosed and successfully treated at age 18 years. Her only medication is a prenatal vitamin.

Physical examination findings are unremarkable.

Which of the following studies is most likely to be diagnostic?

(A) Diagnostic laparoscopy
(B) Hysterosalpingogram
(C) Peripheral karyotype of the patient
(D) Semen analysis of the patient's husband
(E) Transvaginal ultrasound assessment of follicle count

Item 74

A 46-year-old man is evaluated for a right lateral neck mass. He first noted the mass while shaving 2 weeks ago. He does not have hoarseness or difficulty swallowing. Medical history is significant only for hypertension. His only medication is hydrochlorothiazide.

On physical examination, blood pressure is 165/95 mm Hg, pulse rate is 88/min, and respiration rate is 12/min. There is a firm 2-cm mass in the right lateral neck and a mobile 1-cm right thyroid node.

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Laboratory studies:

Calcium	10.5 mg/dL (2.6 mmol/L)
Creatinine	1.8 mg/dL (159.1 µmol/L)
Thyroid-stimulating hormone	4.8 µU/mL (4.8 mU/L)

Ultrasound of the neck reveals a hypoechoic thyroid nodule with microcalcifications measuring 1.6 cm. There is a 2.2-cm mass with internal calcifications in the area of the palpable abnormality.

Fine-needle aspiration of the thyroid nodule and the lateral neck mass reveals medullary thyroid cancer. *RET* testing is positive for a mutation in codon 634.

Which of the following is the most appropriate next step in management?

(A) 18-Fluoro-deoxyglucose positron emission tomography scan
(B) Plasma fractionated metanephrine levels
(C) Serum parathyroid hormone level
(D) Total thyroidectomy and lateral neck dissection

Item 75

A 55-year-old woman is evaluated in the emergency department for altered mental status that has developed over the past week. Her family notes that she has become increasingly confused, and her oral intake has decreased significantly. Her medical history includes breast cancer that was diagnosed 5 years ago. Additional medical history is significant for hypertension. Her only medication is chlorthalidone.

On physical examination, the patient is minimally responsive. Mucous membranes are dry. Temperature is 36.2 °C (97.2 °F), blood pressure is 100/59 mm Hg, pulse rate is 110/min, and respiration rate is 12/min. BMI is 22. There is mild, diffuse abdominal tenderness to palpation. The remainder of the examination is unremarkable.

Laboratory studies are significant for a serum sodium level of 148 mEq/L (148 mmol/L), creatinine level of 4.0 mg/dL (353.6 µmol/L), baseline creatinine level is 1.6 mg/dl. (141.4 µmol/L), and calcium level of 18.2 mg/dL (4.6 mmol/L).

Chlorthalidone is discontinued, and intravenous normal saline is started.

Which of the following is the most appropriate immediate next step in management?

(A) Calcitonin
(B) Cinacalcet
(C) Hemodialysis
(D) Zoledronic acid

Item 76

A 60-year-old man is evaluated during a routine follow-up examination. He has type 2 diabetes mellitus. Review of his blood glucose log demonstrates fasting blood glucose values ranging from 120 to 160 mg/dL (6.7-8.9 mmol/L) and variable 2-hour postprandial blood glucose values ranging from 50 to 190 mg/dL (2.8-10.5 mmol/L). His overnight blood glucose values range from 120 to 140 mg/dL (6.7-7.8 mmol/L). He is unable to detect hypoglycemia. The patient is concerned about hyperglycemia, and he desires to reach a hemoglobin A_{1c} level of less than 7%.

Medical history is significant for diabetic retinopathy, peripheral neuropathy, hypertension, and hyperlipidemia. Medications are neutral protamine Hagedorn (NPH) insulin, regular insulin, losartan, chlorthalidone, metformin, rosuvastatin, and aspirin.

On physical examination, blood pressure is 125/82 mm Hg and pulse rate is 80/min. BMI is 24. Retinal examination demonstrates nonproliferative retinopathy. His lower extremities have diminished sensation to a 10-g monofilament and vibration with a 128-Hz tuning fork.

Hemoglobin A_{1c} level is 7.2%, and the results of all other laboratory studies are normal.

Which of the following is the most appropriate treatment of this patient's diabetes?

(A) Continue current insulin and metformin doses
(B) Continue current insulin, increase metformin dose
(C) Decrease meal-time insulin, add pramlintide
(D) Decrease meal-time insulin, continue metformin

Item 77

A 28-year-old woman is evaluated for a 6-month history of infertility. In order to predict her fertile period, the patient has been using a home urinary luteinizing hormone (LH) kit. The kit can identify an LH surge and therefore predict ovulation and the optimal time for intercourse. Her urinary LH kit result has been consistently positive but her pregnancy test result consistently negative. She has been exercising recently in an attempt to lose weight. Her medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. BMI is 38. Coarse terminal hairs are noted on the chin, neck, and anterior chest. Pelvic examination is normal.

Pelvic ultrasound reveals a thickened endometrium and polycystic-appearing ovaries bilaterally.

Which of the following is the most likely diagnosis?

(A) Hypothyroidism
(B) Late-onset congenital adrenal hyperplasia
(C) Polycystic ovary syndrome
(D) Prolactinoma

Item 78

A 72-year-old woman is evaluated in follow-up for osteoporosis. Medical history is significant for a hip fracture 5 years ago sustained after a mild fall. Evaluation at that time included a dual-energy x-ray absorptiometry (DEXA) scan showing a left hip T-score of -2.8 and vertebral T-score of -2.7. She has been maintained on alendronate therapy since that time. Medical history is also significant for hypertension. Medications are alendronate, hydrochlorothiazide, calcium, and vitamin D. Family history

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is significant for osteoporosis in her mother, sister, and maternal aunt. She has a 35-pack-year tobacco use history and continues to smoke.

On physical examination, temperature is 36.9 °C (98.4 °F), blood pressure is 138/87 mm Hg, pulse rate is 89/min, and respiration rate is 12/min. BMI is 28. She has marked thoracic kyphosis and increased central adiposity.

Laboratory studies show a serum calcium level of 8.6 mg/dL (2.2 mmol/L) and 25-hydroxyvitamin D level of 44 ng/mL (109.8 nmol/L); kidney function studies are normal.

Repeat DEXA shows a stable bone mineral density.

Which of the following is the most appropriate treatment of this patient's osteoporosis?

(A) Change to denosumab
(B) Change to teriparatide
(C) Continue alendronate therapy
(D) Initiate a drug holiday

Item 79

A 55-year-old man presents for follow-up of a recent diagnosis of hyperaldosteronism. Medical and family history are unremarkable. Medications are losartan, metoprolol, amlodipine, and chlorthalidone.

On physical examination, blood pressure is 150/90 mm Hg and pulse rate is 70/min. The rest of the examination is unremarkable.

Additional studies include a noncontrast CT scan of the abdomen that shows a 1.2-cm homogeneous left adrenal lesion with a density of -5 Hounsfield units. Adrenal vein sampling indicates similar ratios of aldosterone to cortisol bilaterally.

Which of the following is the most appropriate therapy for this patient?

(A) Bilateral adrenalectomy
(B) Dexamethasone
(C) Left adrenalectomy
(D) Spironolactone

Item 80

A 24-year-old woman is evaluated for 3 months of galactorrhea, worsening fatigue, and malaise. She was well 6 months ago and without explanation began feeling tired and lethargic. She has noted milk leaking spontaneously from her breasts. Her menses have been unpredictable. She had a normal cycle 3 months ago and 4 months ago, but then her next cycle was delayed. Her last menstrual period was 6 weeks ago, and she had excessive bleeding. She has stopped exercising and has gained 3.6 kg (8 lb). She also reports headaches that occur about 2 to 3 times per week. She has noted constipation and breast tenderness. She has no libido, which is a significant change. She took a home pregnancy test, which was negative. She has a history of depression. There is no family history of pituitary disease. Her only medication is sertraline for depression.

On physical examination, her temperature is 37.2 °C (99.0 °F), blood pressure is 118/68 mm Hg, pulse rate is 72/min, and respiration rate is 10/min. BMI is 28. Otherwise, her physical examination is unremarkable.

Laboratory studies:

Human chorionic gonadotropin	Negative
Prolactin	68 ng/mL (68 µg/L)
Thyroid-stimulating hormone	15 µU/mL (15 mU/L)
Thyroxine (T_4), free	0.82 ng/dL (10.6 pmol/L)

Which of the following is the most appropriate management?

(A) Begin cabergoline
(B) Begin levothyroxine
(C) Hold sertraline and retest
(D) Order pituitary MRI

Item 81

A 33-year-old man is evaluated for infertility. As part of this evaluation, azoospermia is identified on two sequential semen analyses. His medical history is otherwise notable for chronic sinusitis. He takes no medications.

On physical examination, vital signs are normal. BMI is 24. There is no evidence of inguinal hernia. A small left-sided varicocele is present that empties when the patient is recumbent. Testicles are of normal size. Absence of the vas deferens is noted bilaterally.

Which of the following is most likely responsible for this patient's infertility?

(A) Anabolic steroid abuse
(B) Cystic fibrosis
(C) Klinefelter syndrome
(D) Varicocele
(E) Y chromosome microdeletions

Item 82

A 22-year-old woman is evaluated for fatigue and weight loss over the last 2 months. She describes a lack of energy, decreased appetite, and an unintentional 3.6-kg (8-lb) weight loss. Over the last week she has experienced nausea and occasional vomiting. She notes no other focal symptoms. She has no significant medical history. Family history is remarkable for hypothyroidism in her mother and type 1 diabetes mellitus in her brother. She takes no medications.

On physical examination, temperature is normal, blood pressure is 100/68 mm Hg, pulse rate is 90/min, and respiration rate is 12/min. BMI is 19. Hyperpigmentation is pronounced over the knuckles of the hands and elbows bilaterally. The remainder of the physical examination is unremarkable.

Laboratory evaluation demonstrates an 8 AM serum cortisol level of 2 µg/dL (55.2 nmol/L), a serum sodium level of 133 mEq/L (133 mmol/L), and a serum potassium level of 5.8 mEq/L (5.8 mmol/L).

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Which of the following is the most appropriate next step in management?

(A) Cosyntropin stimulation test
(B) Hydrocortisone and fludrocortisone
(C) Plasma adrenocorticotropic hormone (ACTH) measurement
(D) Prednisone

Item 83

A 21-year-old woman is evaluated for management of type 1 diabetes. She was diagnosed 3 months ago after presenting to the emergency department with diabetic ketoacidosis. Her hemoglobin A_{1c} level at the time of diagnosis was 15.2%. She was discharged from the hospital on a basal and prandial insulin regimen with minor adjustments required as an outpatient. Her blood glucose log demonstrates a recent change manifesting as frequent symptomatic episodes of both fasting and postprandial hypoglycemia with blood glucose levels ranging from 50 to 65 mg/dL (2.8-3.6 mmol/L). Medications are insulin glargine and insulin aspart.

On physical examination, blood pressure is 110/70 mm Hg and pulse rate is 70/min. BMI is 19. The remainder of the examination is unremarkable.

Hemoglobin A_{1c} level is 6.2%.

Which of the following is the most appropriate management for this patient's hypoglycemia?

(A) Decrease insulin glargine, decrease insulin aspart
(B) Decrease insulin glargine, decrease insulin aspart, add pramlintide
(C) Discontinue insulin glargine, change insulin aspart to a sliding-scale regimen
(D) Discontinue insulin glargine, discontinue insulin aspart

Item 84

A 34-year-old man is evaluated for a 1-year history of decreased libido and severe erectile dysfunction, including absence of morning erections. He and his female partner would like to conceive. His medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. BMI is 27. Atrophic testes are noted bilaterally.

Laboratory studies:

Follicle-stimulating hormone	1.2 mU/mL (1.2 U/L)
Luteinizing hormone	0.8 mU/mL (0.8 U/L)
Prolactin	110 ng/mL (110 µg/L)
Morning testosterone (total)	120 ng/dL (4.2 nmol/L)
Thyroid-stimulating hormone	Normal

MRI of the pituitary reveals a 0.8-cm anterior pituitary mass consistent with an adenoma.

Which of the following is the most appropriate treatment?

(A) Cabergoline
(B) Clomiphene citrate
(C) Sildenafil
(D) Testosterone replacement therapy

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Answers and Critiques

Item 1 Answer: B

Educational Objective: Treat hyperthyroidism during pregnancy.

This patient has hyperthyroidism occurring during pregnancy and should be treated with propylthiouracil (PTU). Based on this patient's age and sex, the most likely cause of her hyperthyroidism is Graves disease. Clinical findings supporting this diagnosis are the diffuse thyromegaly, thyroid bruit, and elevated thyroid-stimulating immunoglobulin index. Treatment of hyperthyroidism during pregnancy is typically with medical management, and PTU, rather than methimazole, is the drug of choice during the first trimester. Although rare, methimazole has been associated with development of aplasia cutis (absence of a portion of skin on the scalp in a localized or widespread area) and choanal atresia (blockage of the posterior nasal passage due to failed recanalization of the nasal fossae during fetal development) when used in the first trimester. Once organogenesis is complete, methimazole can be substituted for PTU. Methimazole is typically the preferred agent in patients with hyperthyroidism because it has a longer intrathyroidal half-life than PTU and usually can be administered once daily.

Radioactive iodine is contraindicated during pregnancy because it can cause destruction of the fetal thyroid.

Thyroidectomy is generally avoided during pregnancy unless the hyperthyroidism cannot be controlled or the patient cannot tolerate either PTU or methimazole. When needed, surgery is typically performed during the second trimester, if possible.

KEY POINT

- In pregnant patients with hyperthyroidism, propylthiouracil, rather than methimazole, should be used in the first trimester because of the teratogenic effects of methimazole during this time.

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Item 2 Answer: C

Educational Objective: Diagnose the multiple endocrine neoplasia type 2 (MEN2) syndrome.

This patient is most likely to develop primary hyperparathyroidism. He has symptoms related to catecholamine excess from a pheochromocytoma and has a personal and family history of medullary thyroid cancer. This is typical of multiple endocrine neoplasia type 2A (MEN2A) resulting from a mutation in the *RET* proto-oncogene. Primary hyperparathyroidism due to multiple gland hyperplasia frequently occurs in patients with MEN2A. Patients with primary hyperparathyroidism may present with symptoms related to hypercalcemia (polydipsia, polyuria, and constipation), or the hyperparathyroidism may be found during an evaluation for osteoporosis or nephrolithiasis. Pheochromocytomas in MEN2A are usually benign and intra-adrenal in location, but can be multiple or bilateral.

Insulinoma and prolactinoma occur in multiple endocrine neoplasia type 1 (MEN1). In MEN1, one mutated allele of the *MEN1* gene is usually inherited, and a somatic mutation in the other allele is later acquired and results in the formation of neoplasia. The most common endocrine disorder in MEN1 is primary hyperparathyroidism resulting from one or more parathyroid adenomas.

Neurofibroma is not a clinical feature of MEN2A. Neurofibromas, café-au-lait spots, and pheochromocytoma are among the clinical features of the autosomal dominant disorder neurofibromatosis type 1.

KEY POINT

- Medullary thyroid cancer, pheochromocytoma, and primary hyperparathyroidism occur in patients with multiple endocrine neoplasia type 2A (MEN2A).

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Item 3 Answer: B

Educational Objective: Treat prolactinoma during pregnancy.

The patient should undergo formal visual field testing. During pregnancy, there is concern that prolactinomas can grow due to estrogenic stimulation. The risk of significant growth depends on the size of the prolactinoma prior to pregnancy. With microadenomas (<10 mm), the risk is considered to be low, whereas the risk is higher with macroprolactinomas (≥10 mm). Significant expansion may cause vision loss by compressing the optic chiasm. It is therefore appropriate to obtain visual field testing during pregnancy in women with macroadenomas even without symptoms to diagnose vision field loss (such as bitemporal hemianopsia) that may be due to an enlarging prolactinoma. Testing in these women is recommended every trimester of pregnancy. Because this patient is in her first trimester and has a history of a macroadenoma, visual field testing now is indicated.

It is not helpful to check the serum prolactin level. Prolactin is normally elevated in pregnancy and can be greater

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than 200 ng/mL (200 μg/L). Additionally, this patient has a known prolactinoma, so her prolactin will likely be elevated for both reasons. Elevated prolactin itself is not necessarily harmful. Prolactinomas cause concern when they cause hypogonadism or mass effect. In this patient, an elevated prolactin level will not change the treatment plan because it is expected to be elevated and does not help clarify whether the prolactinoma is causing harm.

Routine monitoring of women with prolactinomas with MRI during pregnancy is not indicated because the absolute risk of significant enlargement of pituitary adenomas is low. However, MRI is indicated in women with a pituitary macroadenoma and abnormalities on visual field testing or change in headache possibly attributable to expansion of the adenoma.

Bromocriptine is avoided in pregnancy when possible because its safety during gestation has not been established, although when a patient has symptoms of mass effect during pregnancy, bromocriptine may need to be restarted. However, it would not be appropriate to restart dopamine agonist therapy in this patient without a clear indication for treatment such as an enlarging pituitary adenoma.

KEY POINT

- Because prolactinomas may increase in size in pregnant women and lead to loss of vision, close clinical monitoring and formal visual field testing should be performed during each trimester.

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Item 4 Answer: D

Educational Objective: Manage overnight hypoglycemia.

This patient should measure her blood glucose level at 3 AM. The etiology of fluctuating fasting glucose values in diabetes can be multifactorial, including overnight hypoglycemia, dawn phenomenon, or inadequate insulin doses. To maintain normal blood glucose levels upon rising, an early morning physiologic release of catecholamines, cortisol, and growth hormone occurs to stimulate endogenous glucose production from the liver. Overnight hypoglycemia caused by overtreatment of diabetes or prolonged effects of recent physical exertion can lead to low-normal fasting glucose values and amplify the release of catecholamines, cortisol, growth hormone, and glucagon to increase endogenous glucose production, which can lead to hyperglycemia (Somogyi effect). With the dawn phenomenon, fasting hyperglycemia occurs in the setting of inadequate basal insulin coverage to maintain the endogenous glucose value within a normal range. Food intake in the evening can also contribute to fasting hyperglycemia if it is inadequately covered with insulin. Overnight hypoglycemia and the dawn phenomenon can be distinguished by measuring the glucose level at 3 AM. Medications that affect the overnight glucose level need to be decreased if the 3 AM glucose level is low. Medications that affect the overnight glucose should be increased or added if the 3 AM glucose level is elevated.

Fast-acting insulin such as insulin lispro at bedtime increases the risk of hypoglycemia.

Metformin will decrease gluconeogenesis from the liver and improve fasting hyperglycemia. However, for similar reasons, overnight hypoglycemia must be excluded before this treatment could be safely initiated.

Increasing the insulin glargine dose could also worsen overnight hypoglycemia if that is the cause of the fasting hyperglycemia.

Despite the hemoglobin A_{1c} level of less than 7%, the etiology of the patient's fasting hyperglycemia should be investigated. Detection of overnight hypoglycemia would necessitate immediate changes in her insulin regimen or food intake regardless of her hemoglobin A_{1c} value.

KEY POINT

- Overnight blood glucose monitoring can help detect hypoglycemia or dawn phenomenon.

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Item 5 Answer: A

Educational Objective: Evaluate the cause of Cushing syndrome.

The most appropriate diagnostic test to perform next is a CT scan of the adrenal glands. This patient was suspected to have Cushing syndrome (CS) based on pathognomonic clinical findings and is not taking exogenous glucocorticoids. Two screening tests for CS are abnormal, which is adequate to establish the diagnosis. The next step in evaluation is measurement of the plasma adrenocorticotropic hormone (ACTH) level to differentiate between ACTH-dependent and ACTH-independent CS. With ACTH-dependent causes, the plasma ACTH is usually greater than 20 pg/mL (4.4 pmol/L). However, the low plasma ACTH reported in this patient is consistent with ACTH-independent CS. A CT scan of the abdomen to evaluate the adrenal glands is therefore indicated because the most common causes of ACTH-independent CS are adenomas and carcinomas of the adrenal cortex.

Inferior petrosal sinus sampling and MRI of the pituitary gland are used to confirm the presence of a corticotroph adenoma of the pituitary gland in ACTH-dependent CS, which is the most common cause of CS overall. However, neither is indicated in this patient because biochemical testing has not revealed ACTH-dependent CS.

The diagnosis of CS requires that at least two first-line screening tests be abnormal, including the low-dose

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dexamethasone suppression test (LDST) (both standard and overnight), 24-hour urine free cortisol (UFC), or late-night salivary cortisol. This patient failed to suppress cortisol levels following an overnight LDST and had an elevated 24-hour UFC level confirmed by a repeat collection. Therefore, measurement of late night salivary cortisol is unnecessary because the diagnosis of CS has already been established.

KEY POINT

- CT of the adrenal glands should be performed in patients with ACTH-independent Cushing syndrome because adenomas and carcinomas of the adrenal cortex are common causes.

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Item 6 Answer: D

Educational Objective: Manage ketosis-prone type 2 diabetes mellitus.

This patient should have a repeat measurement of fasting C-peptide and glucose levels. He has ketosis-prone type 2 diabetes mellitus. Patients with ketosis-prone type 2 diabetes do not fulfill the classic phenotype associated with autoimmune type 1 diabetes. These patients are often older, overweight or obese, and of black or Latino ethnicity. Patients with new-onset ketosis-prone diabetes require insulin therapy initially but might be able to be managed with oral agents in the future. Prior to switching from insulin to oral therapy, his pancreatic beta-cell function should be assessed with fasting C-peptide and glucose measurements. Ketosis-prone type 2 diabetes is heterogeneous condition in that the presence of autoantibodies is variable across the population, as is the degree of pancreatic beta cell function. His initial C-peptide level in the setting of hyperglycemia and diabetic ketoacidosis is not an accurate indication of his pancreatic function. Due to the toxic effects of prolonged hyperglycemia on the pancreatic beta cells, the fasting C-peptide and glucose or a glucagon-stimulated C-peptide should be measured 7 to 14 days after the correction of the acidosis in order to better assess function. If his repeat fasting C-peptide value is greater than or equal to 1.0 ng/mL (0.33 nmol/L) or his glucagon-stimulated C-peptide value is greater than or equal to 1.5 ng/mL (0.5 nmol/L), his beta cell function is preserved.

A sliding-scale insulin regimen that does not include basal insulin and does not begin insulin administration unless the blood glucose level is at or above a threshold level will cause wide swings from hyperglycemia to hypoglycemia, and this is inappropriate treatment.

Discontinuation of his insulin and switching to an oral agent such as metformin could be attempted with evidence of beta cell function preservation. Close follow-up would be necessary to monitor for worsening hyperglycemia or development of ketoacidosis, which would require restarting insulin therapy.

Determining autoimmunity, in conjunction with beta cell function, is helpful in assessing whether a patient has the potential to become insulin-independent in the future. His autoantibodies were negative at the time of his presentation, and it is unlikely that these would now be positive. It is not necessary to retest antibodies in this setting.

KEY POINT

- Prior to switching from insulin to oral therapy in patients with ketosis-prone diabetes, fasting C-peptide and glucose levels should be checked.

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Item 7 Answer: C

Educational Objective: Treat pituitary apoplexy.

The patient has acute apoplexy caused by pituitary hemorrhage and requires urgent transsphenoidal decompression of the hemorrhage to preserve vision. Given his history of previous headache, loss of libido, and erectile dysfunction, he likely had a preexisting prolactinoma that acutely bled. Prolactinomas are almost always treated with dopamine agonists, but this patient requires urgent surgery to decrease pressure on the optic chiasm to save his vision. Transsphenoidal resection is the preferred method of pituitary surgery. He also requires urgent stress-dose glucocorticoids because of risk of secondary cortisol deficiency, which would be life-threatening.

The patient has appropriately received glucocorticoids for possible adrenocorticotropic hormone deficiency. There is no indication to assess other pituitary function. In the next 2 to 4 weeks, thyroid function will need to be assessed, but thyroxine (T_4) has a long half-life and does not need to be emergently measured or replaced. Treatment of hypogonadism or growth hormone deficiency is not urgent; surgical decompression is.

Waiting 2 weeks to repeat imaging could lead to permanent vision loss. He needs immediate intervention to preserve his vision. Similarly, whole brain external beam radiation is not appropriate for this patient who needs rapid surgical decompression.

KEY POINT

- Patients with pituitary apoplexy and vision loss should receive immediate stress-dose glucocorticoids in addition to undergoing urgent transsphenoidal pituitary decompression.

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Item 8 Answer: B

Educational Objective: Manage a solitary thyroid nodule.

Fine-needle aspiration (FNA) is the most appropriate next step in the evaluation to determine whether this patient's thyroid nodule is malignant or benign. She has already had an ultrasound examination. Ultrasonography is a sensitive means of identifying nodules and providing further characterization of the nodules, which is more predictive of malignancy than size alone. The ultrasonographic features that are considered more suspicious for malignancy include hypoechogenicity, microcalcifications, irregular margins, and increased intranodular Doppler flow. According to American Thyroid Association guidelines, this patient with a hypoechoic nodule that is 1.5 cm should have an FNA to rule out malignancy.

Nodular features are not readily identified on CT, and this study has a lower sensitivity than ultrasonography for identifying the presence of nodules. CT of the neck would therefore not provide any additional information about this patient, who has already had an ultrasound examination. In addition, CT would expose this patient to unnecessary radiation. If a patient has a substernal goiter, CT is beneficial for determining the extent of the goiter. However, this patient has no extension of the thyroid into the mediastinum.

Levothyroxine therapy to suppress growth of benign nodules is no longer recommended. Randomized clinical trials have failed to show a significant effect on nodule volume. Additionally, the required dose can induce thyrotoxicosis, which is associated with significant risk for cardiovascular complications.

Measurement of the serum thyroglobulin level is reserved for patients who have had a total thyroidectomy and is useful as a tumor marker for detection of residual or recurrent thyroid cancer. In a patient with an intact thyroid, serum thyroglobulin measurement is an insensitive and nonspecific means of testing for malignancy.

Thyroid scanning with technetium is unlikely to be helpful in this patient. Thyroid scanning is used to determine the functional status of the nodule. Isotope scanning is most useful in the setting of a nodule accompanied by a low serum thyroid-stimulating hormone level because toxic (or hyperfunctioning) nodules typically do not require FNA as the vast majority are benign. This patient has a normal serum thyroid-stimulating hormone level and is likely to have an indeterminate result ("cold" or "warm") on thyroid scanning.

KEY POINT

- Fine-needle aspiration is the most appropriate next step in the management of a patient with a solid thyroid nodule measuring greater than 1 cm on ultrasonography.

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Item 9 Answer: A

Educational Objective: Manage primary amenorrhea.

The most appropriate management is to initiate estrogen and progestin therapy in this patient with primary amenorrhea. Primary amenorrhea is defined as the lack of menses by age 16 years accompanied by a normal body hair pattern and normal breast development. Pregnancy must be ruled out in all patients with primary amenorrhea. Approximately 50% of patients with primary amenorrhea have a chromosomal abnormality. Primary ovarian insufficiency due to Turner syndrome, a syndrome characterized by short stature and the loss of a portion or all of one X chromosome, is one of the most common causes of primary amenorrhea. The diagnosis of Turner syndrome can be made on the basis of a karyotype, and this should be the next diagnostic test for this patient. Such a patient may also have fragile X premutation; however, no cognitive impairment is typically seen in this patient population. Diagnosing Turner syndrome is critical because affected patients have a higher incidence of cardiovascular disease, metabolic syndrome, and thyroid dysfunction. Patients with Turner syndrome may have either primary or secondary amenorrhea and commonly have normal secondary sexual characteristics. The mechanism involved appears to be early follicular depletion, such that ovaries are devoid of follicles and oocytes. Serum evaluations in these patients will reveal low estradiol levels (typically below the detectable level in the assay) and markedly elevated gonadotropin levels. This constellation of findings is consistent with hypergonadotropic hypogonadism. Such patients should receive hormone replacement therapy with estrogen and cyclic progestin to prevent endometrial hyperplasia, osteoporosis, and other sequelae of hypoestrogenism.

A pituitary prolactinoma causes secondary amenorrhea through direct inhibition of gonadotropin-releasing hormone secretion by prolactin. Because this patient has elevated levels of gonadotropins, neither a pituitary MRI nor a prolactin measurement is necessary.

Both hypothyroidism and hyperthyroidism also cause secondary amenorrhea. Hypothyroidism results in increased levels of thyrotropin-releasing hormone through negative feedback, and this hormone, in turn, stimulates prolactin secretion and suppresses gonadotropin secretion. Hyperthyroidism can cause rapid weight loss, which is known to cause functional hypothalamic amenorrhea. Since this patient has elevated gonadotropin levels and no signs of hyperthyroidism, thyroid-stimulating hormone measurement is not needed.

KEY POINT

- Patients with primary amenorrhea associated with hypergonadotropic hypogonadism should receive hormone therapy with estrogen to prevent endometrial hyperplasia and osteoporosis and cyclic progestin to prevent endometrial hyperplasia.

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Item 10 Answer: B

Educational Objective: Treat subacute thyroiditis.

A β-blocker, such as metoprolol, is the most appropriate treatment for this patient with thyrotoxicosis who has subacute granulomatous (de Quervain) thyroiditis based on the low radioactive iodine uptake (RAIU) and the painful thyroid on examination. An antecedent event, in this case a viral illness, destroys the thyroid follicles and triggers the release of preformed thyroid hormones into the bloodstream, creating the thyrotoxic phase. During this phase, further release of thyroid hormones ceases, resulting in a low RAIU as seen in this patient. β-Blockers are beneficial in the thyrotoxic phase to block the adrenergic effects of the high circulating thyroid hormone levels. Treatment of subacute thyroiditis is otherwise typically supportive, with NSAIDs for pain as needed. In patients with severe pain, glucocorticoids may occasionally be used.

Blocking further release of thyroid hormones with a thionamide (either methimazole or propylthiouracil) is ineffective because the thyroid has already released preformed thyroid hormone into the bloodstream and is currently not producing or secreting additional thyroxine.

Administration of radioactive iodine for treatment of the hyperthyroidism is also ineffective because this patient's thyroid is not currently taking in iodine, as evidenced by the low uptake on his thyroid scan. More importantly, radioactive iodine will not treat this patient's underlying problem of damaged thyroid follicles and release of preformed thyroid hormone into the bloodstream.

KEY POINT

- Treatment of subacute granulomatous (de Quervain) thyroiditis typically is supportive, with NSAIDs and occasionally glucocorticoids for severe pain; β-blockers are beneficial in the thyrotoxic phase to block the adrenergic effects of the high circulating thyroid hormone levels.

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Item 11 Answer: D

Educational Objective: Diagnose hyperprolactinemia caused by an antipsychotic agent.

Hyperprolactinemia is a known side effect of antipsychotic agents, and this patient's hyperprolactinemia is likely due to risperidone. Antipsychotics block dopamine and decrease inhibition of prolactin release at the pituitary, causing hyperprolactinemia. Stopping the medication can reverse the hyperprolactinemia but should only be done under the supervision of a psychiatrist. The patient's risperidone should not be discontinued unless her psychiatrist is consulted.

Hypothyroidism can cause hyperprolactinemia when uncontrolled, but her hypothyroidism is well treated. She has no symptoms of hypothyroidism, and her thyroid function tests are normal, so uncontrolled hypothyroidism is not the cause of her hyperprolactinemia.

Antipsychotic agents cause hyperprolactinemia by blocking dopamine, but lithium does not cause hyperprolactinemia.

Although the patient has a likely explanation for her hyperprolactinemia, a prolactinoma is still possible. Risperidone can cause prolactin levels above 200 ng/mL (200 µg/L), so her level of 102 ng/mL (102 µg/L) is not unreasonable. Remeasuring the prolactin level following discontinuation of the drug is recommended before further evaluation for a pituitary adenoma; the patient's psychiatrist should be consulted before withholding the risperidone for testing. A patient with hyperprolactinemia without a clear secondary or drug-induced cause should be assessed by an imaging study (preferably, MRI of the pituitary gland) to a exclude pituitary lesion.

KEY POINT

- Antipsychotic agents block dopamine and decrease inhibition of prolactin release at the pituitary, causing hyperprolactinemia.

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Item 12 Answer: B

Educational Objective: Manage low bone mass.

A repeat dual-energy x-ray absorptiometry (DEXA) scan should be repeated in 2 years in this patient with low bone mass and relatively low 10-year fracture risk. The Fracture Risk Assessment Tool (FRAX) calculator defines the 10-year fracture risk for patients with T-scores in the -1.0 to -2.5 ranges. The FRAX calculator (www.shef.ac.uk/FRAX) incorporates multiple risk factors including sex, fracture history, femoral neck bone mineral density, glucocorticoid use, smoking, BMI, age, and alcohol intake to determine projected fracture risk. If the risk of major osteoporotic fracture is greater than or equal to 20% or the risk of hip fracture is greater than or equal to 3%, then the patient's benefit from therapy exceeds the risk, and she should be offered treatment. Because of her history of low body weight and limited nutritional intake during the time of development of peak bone mass, she is at increased risk for low bone mass or osteoporosis and is therefore an appropriate candidate for early screening. Her DEXA scan shows low bone mass. Spine film shows no evidence of fracture. Additionally, her calcium and vitamin D levels are normal. Continuing lifestyle activities (such as maximizing

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weight-bearing exercise and avoidance of tobacco or excessive alcohol) in addition to calcium and vitamin D supplementation is appropriate management of this patient.

Raloxifene is a selective estrogen receptor modulator (SERM) that is a treatment option for women with osteoporosis because it has been shown to increase bone mineral density and reduce the risk of vertebral (but not nonvertebral) fractures. However, raloxifene is also associated with an increased risk of thromboembolic events and vasomotor symptoms. There is limited data supporting use of raloxifene or other SERMs for treating patients with low bone mass, although some guidelines recommend considering treatment in patients with low bone mass and 10-year fracture risk determined by the FRAX calculator of greater than or equal to 20% for a major osteoporotic fracture or greater than or equal to 3% for hip fracture. Raloxifene would therefore not be appropriate therapy for this patient.

Cholecalciferol (D_3), a metabolite of vitamin D, is commonly used to supplement low serum vitamin D levels in patients with vitamin D deficiency. This patient has normal serum vitamin D levels; therefore, there is no indication for treatment with vitamin D metabolites.

Bisphosphonates are considered first-line therapy for osteoporosis, although they are not used routinely in women with low bone mass. Similar to the use of SERM therapy, guidelines recommend consideration of treatment with a bisphosphonate for low bone mass only if there is 10-year fracture risk determined by the FRAX calculator of greater than or equal to 20% for a major osteoporotic fracture or greater than or equal to 3% for hip fracture.

KEY POINT

- Treatment for low bone mass in postmenopausal women involves lifestyle modification (maximizing weight-bearing exercise and avoidance of tobacco or excessive alcohol) and vitamin D and calcium supplementation; the need for pharmacologic therapy is based on the 10-year estimated fracture risk (≥20% for a major osteoporotic fracture or ≥3% for hip fracture).

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Item 13 Answer: A

Educational Objective: Diagnose euthyroid sick syndrome.

This patient's clinical picture is consistent with euthyroid sick syndrome (also called nonthyroidal illness syndrome). Unless there is a strong suspicion of an underlying thyroid disorder that may be contributing to a patient's clinical findings, thyroid function tests should not be performed during critical illness. In hospitalized patients, especially ones as ill as the patient described here, thyroid function test results are highly likely to be abnormal. The first deviation that may occur during an acute illness is lowering of the serum total triiodothyronine (T_3) level. The serum thyroid-stimulating hormone (TSH) and serum free thyroxine (T_4) levels may also decline as the illness increases in severity. The pattern of these test results is often indistinguishable from that seen with central hypothyroidism. In fact, some controversy exists about whether the clinical picture of a low serum TSH level and low serum T_4 and T_3 levels is an adaptive response to the critical illness in order to alter the body's metabolism and thereby aid in recovery from the acute illness.

This patient does not have any definite findings of underlying Graves disease. The tachycardia and fever are likely the result of his severe infection. If he was also experiencing thyroid storm, high serum T_4 and T_3 levels would most likely be associated with the low serum TSH concentration.

The most common cause of hypothyroidism is Hashimoto thyroiditis. Physical examination findings can include a reduced basal temperature, diastolic hypertension, an enlarged thyroid gland, bradycardia, pallor, dry and cold skin, brittle hair, hoarseness, and a delayed recovery phase of deep tendon reflexes. Patients with Hashimoto thyroiditis have low T_4 and T_3 levels and elevated TSH. This patient's low TSH level is not compatible with Hashimoto thyroiditis.

This patient is unlikely to have subacute thyroiditis based on the timing of the illness. Although the infection could have triggered destruction of the thyroid, the subsequent release of preformed thyroid hormones into the serum should result in an elevation of serum T_4 and T_3 levels in the early phase of the disease, which is not consistent with the findings in this case.

KEY POINT

- Unless there is a strong suspicion of an underlying thyroid disorder that may be contributing to a patient's clinical findings, thyroid function tests should not be performed during critical illness because test results are highly likely to be abnormal.

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Item 14 Answer: B

Educational Objective: Liberalize glycemic targets in a patient with multiple diabetic complications and advanced microvascular disease.

The most appropriate next step in management of this patient is to decrease the risk of hypoglycemia by decreasing the insulin doses delivered by the pump. This patient has had type 1 diabetes for 25 years with subsequent development of advanced microvascular disease. His frequent hypoglycemic events and hypoglycemic unawareness increase the risk of morbidity and mortality from recurrent hypoglycemia that may occur with stringent glycemic goals. Glycemic goals should be individualized to account

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for patient-specific factors, such as age and comorbidities. The American Diabetes Association suggests a hemoglobin A_{1c} goal of less than 8.0% in patients with a decreased life expectancy, history of severe hypoglycemia, multiple comorbidities, or advanced microvascular or macrovascular disease. The less stringent hemoglobin A_{1c} goal should be implemented to avoid recurrent hypoglycemia; however, the goal may need to be increased above 8.0% if it cannot be achieved safely.

Altering the pump settings to deliver more insulin to attain a hemoglobin A_{1c} goal of less than 7.0% will increase his risk of hypoglycemia. His hemoglobin A_{1c} goal should be liberalized to avoid hypoglycemia.

The risk of hypoglycemia can be reduced with lower insulin doses delivered by either an insulin pump or subcutaneous injections. Since the patient is already using an insulin pump, alteration of his insulin pump settings to deliver less insulin should occur next.

Gabapentin for treatment of his painful peripheral neuropathy is appropriate, but avoidance of recurrent hypoglycemia is the most serious issue that needs to be addressed next due to the associated increased risk of morbidity and mortality.

KEY POINT

- A less stringent hemoglobin A_{1c} goal is appropriate for persons with diabetes mellitus with a decreased life expectancy, history of severe hypoglycemia, multiple comorbidities, or advanced microvascular or macrovascular disease.

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Item 15 Answer: D

Educational Objective: Determine causes of vitamin D deficiency.

This patient with refractory vitamin D deficiency, despite aggressive attempts at repletion, should be screened for celiac disease. The fact that supplementation with a therapeutic dose of vitamin D has failed to replete her body stores should raise concern for a malabsorption disorder. Based on her history of another autoimmune disorder (vitiligo), lower range BMI, and nonspecific signs and symptoms such as fatigue, subclinical celiac disease would be a reasonable cause of her malabsorption. Celiac disease may present with classic symptoms of diarrhea, overt malabsorption, and weight loss, but may also exist in a very mild form and may go largely undetected since patients have only nonspecific symptoms and subclinical malabsorption. If this patient tests positive for celiac disease, removing gluten from her diet will improve her intestinal lining and improve absorption of vitamin D. Even with therapy, patients with malabsorption will likely require increased doses of vitamin D supplementation.

Parathyroid imaging with a sestamibi scan is not indicated because the patient does not have primary hyperparathyroidism. Her parathyroid hormone level is elevated as an appropriate physiologic response to her markedly low vitamin D levels. Once her vitamin D levels are sufficient (>30 ng/dL [75 nmol/L]), her parathyroid hormone level should be remeasured to ensure that it has returned to the normal range. The parathyroid hormone level should be remeasured in approximately 4 weeks.

Referral for parathyroidectomy would also not be indicated in this patient without an established diagnosis of primary hyperparathyroidism.

A person her age with normal diet and minimal sun exposure should require about 1000 U daily of vitamin D to maintain adequate vitamin D stores. The choice to use cholecalciferol versus ergocalciferol is often based on the level of vitamin D deficit. Since the ergocalciferol is more readily available in the 50,000 U form and has a shorter half-life, it is recommended when a patient's vitamin D level is less than 10 ng/mL (25 nmol/L). Cholecalciferol is often used when the level is between 20 and 30 ng/mL (50-75 nmol/L) or for maintenance and therefore would not be ideal to replete this patient. Clinical discretion can be used for levels between 10 and 20 ng/mL (25-50 nmol/L).

Although vitamin D_3 (cholecalciferol) is a reasonable option for treatment of vitamin D deficiency, as mentioned above, cholecalciferol is best used for maintenance of vitamin D levels or repletion when the 25-hydroxyvitamin D level is between 20 ng/mL (50 nmol/L) and 30 ng/mL (75 nmol/L). Neither form of repletion, however, will be effective in the presence of significant malabsorption.

KEY POINT

- When vitamin D repletion efforts fail, secondary causes, such as malabsorption, should be considered.

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Item 16 Answer: A

Educational Objective: Treat subclinical hypothyroidism.

The most appropriate next step in management is to initiate levothyroxine therapy. This patient has subclinical hypothyroidism with a mild elevation of the serum thyroid-stimulating hormone (TSH) level and normal serum free thyroxine (T_4) level. Her family history of hypothyroidism and her thyroid peroxidase antibody positivity increase the likelihood of progression to overt thyroid failure. In patients with a mild serum TSH elevation (between the upper limit of normal and 10 μU/mL [10 mU/L]), beginning levothyroxine therapy is reasonable if symptoms suggestive of hypothyroidism are present.

Thyroid-stimulating immunoglobulins (TSIs) are highly associated with Graves disease. When the diagnosis of

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Graves disease cannot be made clinically in a patient with hyperthyroidism, measurement of the serum level of these antibodies is recommended, especially if radioactive iodine uptake studies are not available or if radioactive iodine exposure is contraindicated, as in pregnancy and breastfeeding. This patient does not have hyperthyroidism, and these tests are therefore not indicated.

Repeating a serum TSH measurement in this patient was reasonable, since up to 30% of patients with an initially abnormal serum TSH level will have a normalization of this value upon retesting. Since this patient has persistent elevation of TSH and symptoms that may be attributable to hypothyroidism, waiting 12 months before initiating therapy is not appropriate.

A radioactive iodine uptake (RAIU) scan is reserved for patients with hyperthyroidism. Patients with Graves disease typically have an elevated RAIU. Conversely, in patients with thyroiditis or exposure to exogenous thyroid hormone, the RAIU will be low (<5%) despite biochemical hyperthyroidism. Obtaining a thyroid RAIU in this patient is not indicated.

KEY POINT

- Levothyroxine therapy is reasonable in a patient with subclinical hypothyroidism and symptoms suggestive of hypothyroidism.

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Item 17 Answer: C

Educational Objective: Define surgical indications for primary hyperparathyroidism.

The most appropriate treatment recommendation for this patient is parathyroidectomy. She has primary hyperparathyroidism as shown by her elevated serum calcium and parathyroid hormone levels. She also has evidence of kidney compromise with an elevated creatinine level and decreased estimated glomerular filtration rate (eGFR). Impaired kidney function (defined as eGFR <60 mL/min/1.73 m^2, 24-h urine calcium >400 mg/24 h [10 mmol/24 h], or the presence of nephrolithiasis or nephrocalcinosis by radiograph, ultrasound, or CT) is an indication for surgical treatment of hyperparathyroidism in otherwise asymptomatic patients. Other indications for surgery in asymptomatic patients include age younger than 50 years; a serum calcium level greater than or equal to 1 mg/dL (0.25 mmol/L) above upper limit of normal; a T-score of -2.5 or worse at the lumbar spine, total hip, femoral neck, or distal radius; or in those in whom medical surveillance is neither desired nor possible. Patients with these indications are considered to have the highest potential benefit from surgery.

A bisphosphonate, such as alendronate, would not be the treatment of choice for this patient as she does not have osteoporosis nor does she meet Fracture Risk Assessment Tool (FRAX) criteria for therapy. The FRAX calculator defines the 10-year fracture risk for patients with T-scores in the -1.0 to -2.5 range. The FRAX calculator (www.shef.ac.uk/FRAX) incorporates multiple risk factors including gender, fracture history, femoral neck bone mineral density, glucocorticoid usage, smoking, BMI, age, and alcohol intake to determine projected fracture risk. If the risk of major osteoporotic fracture is greater than or equal to 20% or the risk of hip fracture is greater than or equal to 3%, the patient's benefit from therapy exceeds the risk, and she should be offered treatment. Additionally, bisphosphonates should be used with caution in patients with compromised kidney function.

If the patient declines surgical intervention, a calcimimetic agent such as cinacalcet would be an appropriate therapy. Cinacalcet has recently been FDA approved as an alternative for patients unable or unwilling to undergo parathyroidectomy. Cinacalcet lowers calcium levels by stimulating the calcium-sensing receptors of the parathyroid glands and inhibiting parathyroid hormone secretion. However, it is expensive and has multiple drug interactions, which make it less desirable in this patient.

Because this patient is considered to be at increased risk of complications due to untreated hypercalcemia, clinical observation alone would not be appropriate.

KEY POINT

- Decreased estimated glomerular filtration rate (<60 mL/min/1.73 m^2) is an indication for surgical treatment of primary hyperparathyroidism in otherwise asymptomatic persons.

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Item 18 Answer: C

Educational Objective: Evaluate a toxic thyroid nodule.

Performing a radioactive iodine (^{123}I) uptake and scan is the most appropriate management for this patient, who most likely has a toxic nodule or nodules as the cause for her mild hyperthyroidism. Since multiple nodules were identified on ultrasound, it is important to ascertain which of the nodules are autonomous, as the likelihood of malignancy in such lesions is very low. Performing a thyroid scan will help identify whether one or more of the nodules is responsible for her thyroid function abnormalities.

A thyroid scan will also determine if fine-needle aspiration is indicated elsewhere in the gland. Nodules identified as autonomously functioning (or "hot") do not require fine-needle aspiration, whereas nodules that are either "cold"

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or "warm" (of similar uptake to the surrounding non-nodular thyroid tissue) may require cytologic evaluation.

This patient may ultimately benefit from methimazole therapy, but since her hyperthyroidism is mild, it is safe to wait to initiate medical therapy until after the thyroid scan is performed. In patients with a greater degree of thyrotoxicosis, beginning methimazole to lower the thyroid hormone levels prior to performing additional testing is reasonable. Once the hormone levels are nearing the normal range, the thionamide should be withheld for 5 days prior to the thyroid scan.

If the patient is found to have a toxic nodule or multiple toxic nodules, surgical removal is a reasonable treatment approach, particularly if there are compressive symptoms from the goiter. Since this is considered an elective procedure, administering low-dose methimazole to normalize of her thyroid hormone levels would be advisable prior to surgery.

KEY POINT

- Performing a radioactive iodine (^{123}I) thyroid uptake and scan is the most appropriate initial management for a patient who has mild hyperthyroidism most likely caused by a toxic nodule or nodules.

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Jameson JL. Minimizing unnecessary surgery for thyroid nodules. N Engl J Med. 2012 Aug 23;367(8):765-7. [PMID: 22731671]

Item 19 Answer: A

Educational Objective: Treat a macroprolactinoma.

The patient has a macroprolactinoma, which is best treated with a dopamine agonist such as cabergoline. The most common cause of hyperprolactinemia is a prolactinoma, which is a benign adenoma. Microprolactinomas are less than 10 mm in diameter, and macroprolactinomas are 10 mm or greater in diameter. Prolactinomas are the most common type of secretory pituitary adenoma. The patient's tumor is causing significant mass effect, including compression of the optic chiasm, invasion into the cavernous sinus, secondary hypothyroidism, and likely growth hormone deficiency; however, even with these complications, the macroprolactinoma is best treated with medication instead of surgery. A dopamine agonist can cause a rapid decrease in the serum prolactin level and shrinkage of the prolactinoma. More specifically, in as many as 90% of patients, it can normalize prolactin levels, reverse hypogonadism, and shrink tumors by at least 50%. Because of these rapid decreases in tumor size, dopamine agonists can be used as first-line therapy, even in patients with mild visual field defects, as long as visual acuity is not threatened by rapid progression of the tumor or recent tumor hemorrhage.

Octreotide is used to treat acromegaly but has no role in the first-line treatment of prolactinoma.

Medical therapy is preferred over surgery and radiation for the treatment of prolactinomas. Stereotactic surgery (a specific kind of radiation therapy) would be considered in a patient with a tumor that is refractory to medical therapy and incompletely resectable.

Because this patient has a prolactinoma, the treatment of choice is a dopamine agonist, not surgery. There is an excellent chance that the prolactinoma will respond to cabergoline, and the patient can avoid surgery.

KEY POINT

- Dopamine agonists, such as cabergoline, are first-line therapy for symptomatic patients with prolactinomas.

Bibliography

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Item 20 Answer: B

Educational Objective: Diagnose hypoglycemia in a patient with diabetes mellitus taking a sulfonylurea.

Hypoglycemia is the most likely cause of this patient's altered mental status. In patients taking a sulfonylurea for diabetes who develop dehydration, such as this patient with decreased oral intake in conjunction with nausea and vomiting, impaired kidney perfusion may lead to altered pharmacokinetics and an increased risk of hypoglycemia related to ongoing effects of the medication and minimal carbohydrate intake. Although sulfonylureas are very effective antihyperglycemic medications, most agents have relatively long half-lives, allowing convenient daily dosing. However, this slower clearance predisposes to hypoglycemia compared with other antiglycemic medications, particularly when kidney function is impaired. Glyburide, in particular, has a longer half-life than other sulfonylureas and its use is recommended against in older patients by the Beers Criteria, a list of medications that should be avoided or used with caution in older patients. Although she last took glimepiride more than 24 hours before her presentation with altered mental status, she was dehydrated, thus prolonging the glucose-lowering effects of this insulin secretagogue for several days.

Although patients with diabetes are at increased risk for atherosclerotic cardiovascular disease, this patient does not have focal abnormalities suggesting a cerebrovascular accident, and stroke itself is not a common cause of isolated altered mental status.

Levothyroxine also has a relatively long half-life allowing once daily dosing in most patients. Missing one or several doses of levothyroxine would therefore not likely lead to a degree of hypothyroidism causing acute mental status changes.

Statin toxicity is unusual, and the most common toxicity associated with statin use is musculoskeletal symptoms. Increased statin levels are not typically associated with mental status changes and would likely not be the cause of this patient's mental status changes.

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KEY POINT

- Sulfonylureas with long half-lives, such as glimepiride, may lead to acute kidney injury and hypoglycemia in older persons with diabetes mellitus.

Bibliography

American Diabetes Association. (7) Approaches to glycemic treatment. In: Standards of Medical Care in Diabetes-2015. Diabetes Care. 2015 Jan;38 Suppl 1:S41-8. [PMID: 25537707]

Item 21 Answer: A

Educational Objective: Evaluate triiodothyronine (T_3) hyperthyroidism.

The serum triiodothyronine (T_3) level should be measured next. This patient exhibits signs and symptoms of hyperthyroidism. Even though the available laboratory data are consistent with subclinical hyperthyroidism, the diagnostic evaluation is not complete until the T_3 level is checked. Although rare, an elevated T_3 level and a normal serum free thyroxine (T_4) level may be present in patients with hyperthyroidism. Measurement of the T_3 concentration should therefore be obtained in all patients suspected of having thyrotoxicosis. Measurement of the T_3 level is not indicated in patients with hypothyroidism because the T_3 concentration is conserved and may remain within the normal range, even in patients with significant hypothyroidism.

Measuring the thyroid peroxidase (TPO) antibody titer will not provide additional information about this patient. Determining TPO antibody status is helpful in patients with a mildly elevated serum thyroid-stimulating hormone (TSH) level and is associated with Hashimoto thyroiditis and future risk of developing permanent hypothyroidism. However, this patient demonstrates signs and symptoms consistent with hyperthyroidism.

Repeating the thyroid function tests (TFTs) in 6 weeks may be appropriate if the total or free T_3 level is found to be normal. If the T_3 is normal, the patient has subclinical hyperthyroidism, and repeating the TFTs may be indicated to determine if the abnormality is transient or permanent.

Ultrasound of the neck is appropriate for the evaluation of this patient if a nodule is suspected. However, this patient's diffusely enlarged thyroid gland is not suggestive of nodular disease. In addition, even if the physical examination were suggestive of nodular disease, the first step would be evaluation of the functional thyroid status.

KEY POINT

- Most patients with thyrotoxicosis will have elevations of both free thyroxine (T_4) and triiodothyronine (T_3), but isolated T_3 elevation is rare.

Bibliography

Vaidya B, Pearce SH. Diagnosis and management of thyrotoxicosis. BMJ. 2014 Aug 21;349:g5128. [PMID: 25146390]

Item 22 Answer: B

Educational Objective: Diagnose hypercalcemia in a patient with sarcoidosis.

This patient most likely has hypercalcemia due to increased 1,25-dihydroxyvitamin D levels. She has an elevated calcium level with a low parathyroid hormone level, indicating non-parathyroid hormone (PTH)–mediated hypercalcemia. The differential diagnosis of non–PTH-mediated hypercalcemia includes cancer-related hypercalcemia caused by osteolytic lesions of bone, humorally mediated by tumor-secreted parathyroid hormone-related protein (PTHrP), or granulomatous diseases, such as sarcoidosis. In granulomatous diseases, the hydroxylase in disease-associated macrophages actively converts 25-hydroxyvitamin D to the highly active 1,25-dihydroxyvitamin D metabolite. The increased levels of active vitamin D lead to increased absorption of calcium in the gut, promotion of increased bone resorption of calcium, and decreased calcium and phosphate excretion by the kidney.

Elevated serum calcium can be due to a mutation in the G-coupled protein calcium–sensing receptor (*CASR*) gene. These receptors are in the parathyroid glands and the kidneys. The sensor mutation results in a shift upward in the "normal" range of calcium that the receptor recognizes, resulting in a mildly elevated serum calcium level (usually <11.0 mg/dL [2.7 mmol/L]) and high normal or mildly elevated PTH level, unlike this patient whose PTH level was low.

25-Hydroxyvitamin D is the major circulating form of vitamin D and is minimally metabolically active relative to 1,25-dihydroxyvitamin D. Levels in this patient are likely to be low due to excessive conversion to the 1,25-dihydroxyvitamin D form, and would not identify the likely mechanism of hypercalcemia in this patient.

Hydrochlorothiazide, a thiazide diuretic, reduces blood volume by acting on the kidneys to reduce sodium (Na^+) reabsorption in the distal convoluted tubule. Thiazides increase the reabsorption of calcium in the distal convoluted tubule by their action on a Na^+-Cl^- calcium co-transporter. However, any increase in calcium caused by thiazides is mild and rarely reduces the PTH level below the lower range of normal.

KEY POINT

- Granulomatous diseases, such as sarcoidosis, cause hypercalcemia through increased 1-α-hydroxylation activity that increases 1,25-dihydroxyvitamin D levels and calcium reabsorption.

Bibliography

Sharma OP. Hypercalcemia in granulomatous disorders: a clinical review. Curr Opin Pulm Med. 2000 Sep;6(5):442-7. [PMID: 10958237]

Item 23 Answer: D

Educational Objective: Diagnose Cushing syndrome from exogenous glucocorticoids.

The patient has iatrogenic Cushing syndrome caused by use of topical glucocorticoids in the treatment of

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psoriasis. Cushing syndrome presents similarly whether it is due to a pituitary adenoma (Cushing disease), adrenal tumor cortisol production, ectopic adrenocorticotropic hormone production, or excessive use of glucocorticoids. Her presentation would be consistent with any of these diagnoses; however, she is on high-potency topical glucocorticoids, so this alone explains her symptoms and presentation. Exogenous glucocorticoid use as a cause of Cushing syndrome is common, whereas the other causes are rare.

KEY POINT

- The most common cause of Cushing syndrome is an elevated level of cortisol resulting from both endogenous and exogenous exposure to glucocorticoids.

Bibliography

Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008 May;93(5):1526-40. [PMID: 18334580]

Item 24 Answer: B

Educational Objective: Treat a patient with diabetic ketoacidosis.

This patient has diabetic ketoacidosis (DKA) and a low serum potassium level, so potassium chloride should be administered. The patient should be making adequate urine before administration of potassium replacement. Low potassium stores in the body will need correction prior to initiation of insulin therapy to avoid cardiac arrhythmias. Potassium chloride should be added to each liter of intravenous fluids to maintain the serum potassium level in the 4.0 to 5.0 mEq/L (4.0-5.0 mmol/L) range with the continued use of intravenous insulin therapy.

Antibiotic therapy is not warranted at this time. The mild leukocytosis upon presentation is most likely related to stress from DKA rather than an infectious process. In addition, the chest radiograph is normal.

Sodium bicarbonate provides no added benefit when the arterial blood pH is greater than 6.9 and may be associated with harm. A 2011 systematic review found that bicarbonate administration worsened ketonemia. Several studies found higher potassium requirements in patients receiving bicarbonate. Studies in children found a possible association between bicarbonate therapy and cerebral edema.

During the treatment of DKA, initiation of insulin therapy and correction of acidosis will shift the extracellular potassium back into the intracellular space. Significant worsening of the hypokalemia noted at presentation could occur if this is not corrected to a serum potassium level higher than 3.3 mEq/L (3.3 mmol/L) prior to initiation of insulin therapy, which could lead to the development of arrhythmias. Insulin therapy can be safely initiated once the serum potassium level is greater than 3.3 mEq/L (3.3 mmol/L).

KEY POINT

- During the initial management of diabetic ketoacidosis, hypokalemia should be corrected before initiation of intravenous insulin therapy to avoid significant worsening of the serum potassium levels that could cause cardiac arrhythmias.

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Wilson JF. In the clinic. Diabetic ketoacidosis. Ann Intern Med. 2010 Jan 5;152(1):ITC1-15. [PMID: 20048266]

Item 25 Answer: D

Educational Objective: Identify secondary causes of bone loss prior to initiating bisphosphonate therapy.

Checking this patient's serum thyroid-stimulating hormone (TSH) level would be the most appropriate test to obtain prior to initiation of pharmacologic therapy. Although osteoporosis in postmenopausal women is most commonly associated with nonmodifiable risk factors such as age, sex, menopausal status, height, and build, it is always important to assess for possible secondary causes of bone loss that might be amenable to treatment, particularly if there is clinical suspicion in a specific patient. Appropriate laboratory testing for most patients with newly diagnosed osteoporosis includes complete blood count (for malignancy), complete metabolic profile (for calcium levels and kidney function), TSH, 25-hydroxyvitamin D, and urine calcium (screening for hypercalciuria), most of which were normal in this patient. However, this patient's history of unintentional weight loss over the past year may be her only symptom of hyperthyroidism, which could be contributing to her osteoporosis and would be important to treat in addition to therapy directed toward her osteoporosis. Therefore, measuring this patient's TSH level would be appropriate prior to starting therapy for osteoporosis.

Both serum and urine markers of bone turnover measure collagen breakdown products and other chemicals released from osteoclasts and osteoblasts as part of bone metabolism. However, they are not commonly used in most patients with osteoporosis primarily because there is significant variability in the different measures in an individual patient or between different patients, making standardization of results difficult. Therefore, their use is typically limited to research settings or in management of specific patients who have failed to respond to usual therapy for osteoporosis.

There is evidence that estrogen is effective for prevention and possibly treatment for osteoporosis, although the significant nonskeletal risks associated with this therapy have led to its not being used in favor of bisphosphonates. As this patient is postmenopausal and has no clinical suggestion of excess estradiol secretion, and bisphosphonate therapy would be considered preferable to estrogen despite serum levels, testing for estradiol would not be indicated in this patient.

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Hyperparathyroidism should always be considered as a possible secondary cause of bone loss. However, since this patient had normal calcium and 25-hydroxyvitamin D levels, hyperparathyroidism would be highly unlikely, and checking a parathyroid hormone level would not be indicated.

KEY POINT

- Testing for secondary causes of bone loss is appropriate before beginning pharmacologic therapy for newly diagnosed osteoporosis.

Bibliography

Hudec SM, Camacho PM. Secondary causes of osteoporosis. Endocr Pract. 2013;19:120-8. [PMID: 23186949]

Item 26 Answer: A

Educational Objective: Manage heavy menstrual bleeding caused by polycystic ovary syndrome.

This patient with polycystic ovary syndrome (PCOS) with heavy menstrual bleeding and hirsutism should be treated with combined estrogen-progestin oral contraceptive pills. Patients with PCOS remain in a stagnant follicular stage resulting in unopposed estradiol secretion from small ovarian follicles, causing proliferation of the endometrium in the absence of progesterone secretion from a corpus luteum. This predisposes patients to endometrial hyperplasia and heavy menstrual bleeding as a result of anovulatory bleeding. Intraovarian androgen production is also increased in PCOS, resulting in the hyperandrogenism and hirsutism associated with the disorder. Estrogen-progestin oral contraceptive pills are first-line therapy for the menstrual irregularities and hirsutism associated with PCOS. This therapy prevents unopposed estrogen-induced proliferation of the endometrium and suppresses the excess androgen production associated with PCOS. This would be appropriate therapy to treat both issues in this patient, who does not currently desire fertility.

Progestin therapy alone, either through periodic progestin withdrawal or use of a progesterone-eluting intrauterine device, will provide endometrial protection and treat this patient's menstrual irregularity. However, progestin therapy alone does not suppress androgen production and would not treat this patient's hirsutism.

Metformin has several favorable metabolic effects in patients with PCOS, including increased insulin sensitivity and reduced serum free testosterone. However, it has been shown to be less effective than oral contraceptives for improving the menstrual pattern and reducing serum androgens. It also does not provide endometrial protection and is considered a second-line therapy for patients with PCOS with significant menstrual irregularities and hirsutism who are unable to tolerate oral contraceptive pills.

KEY POINT

- In women with polycystic ovary syndrome, heavy menstrual bleeding, and hirsutism who do not desire fertility, estrogen-progestin oral contraceptive pills are first-line therapy to provide endometrial protection and suppress androgen production.

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Legro RS, Arslanian SA, Ehrmann DA, et al; Endocrine Society. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013 Dec;98(12):4565-92. [PMID: 24151290]

Item 27 Answer: D

Educational Objective: Treat adrenocortical carcinoma.

Adrenocortical carcinoma (ACC) is the most likely cause of this patient's Cushing syndrome, and surgical excision is the most appropriate management. The patient has classic clinical manifestations of Cushing syndrome (CS), and the 24-hour urine cortisol is markedly elevated on repeated measurements. Plasma adrenocorticotropic hormone (ACTH) is suppressed consistent with an ACTH-independent cause. The imaging characteristics of ACC include a large mass with irregular borders or shape, calcification, high attenuation (high Hounsfield units) on CT, and delay in contrast medium washout (less than 50% at 10 minutes), findings all present in this patient.

The treatment of ACC depends on the extent of disease at presentation. Surgical removal after appropriate biochemical assessment remains the best option, especially in patients with early disease. Even after apparent complete resection, adjuvant therapy with mitotane, a known adrenal cytotoxic drug, may be beneficial. Treatment with mitotane is recommended for patients with persistent disease and others with known metastases and is associated with objective remissions in approximately 25% of patients. The main factors limiting the use of mitotane include nausea, vomiting, lethargy, and neurologic side effects. Experience with other cytotoxic chemotherapy is limited, but has usually been ineffective. A poorer prognosis is associated with advanced stages of the disease, the presence of metastasis at diagnosis, an older age, and cortisol hypersecretion by the tumor. In patients without clinically evident disease after initial surgery, the median survival rate is 60% at 5 years.

Fine-needle biopsy cannot distinguish a benign adenoma from a carcinoma and is not used in the evaluation of ACC. It is sometimes used to distinguish ACC from metastatic disease. Its use in this patient is both unnecessary and inappropriate.

Radiation therapy is not used as the principal initial treatment in ACC; however, it may be used as adjuvant therapy after surgery to prevent tumor recurrence. Radiation therapy can also be used to treat areas of metastasis, such as to the bones or brain.

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KEY POINT

- Surgical removal after appropriate biochemical assessment is the most appropriate treatment for adrenocortical carcinoma, especially in patients with early disease.

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Item 28 Answer: D

Educational Objective: Diagnose hypomagnesemia as a cause of hypocalcemia.

This patient's magnesium level should be checked. He has a very low calcium level that is likely contributing to his clinical findings of tremulousness, muscle irritability, and electrocardiogram changes. He struggles with alcohol abuse, and his low albumin level suggests malnutrition, likely due to his chronic alcohol intake as a primary source of calories. Magnesium deficiency is common in persons who abuse alcohol. Furthermore, he has had diarrhea for several days, which will also deplete his magnesium stores. This patient's low calcium level should promote parathyroid hormone (PTH) secretion to help correct the hypocalcemia. However, decreased levels of magnesium impair release of PTH; levels in patients with significant magnesium deficiency are either low or inappropriately in the normal range. Low magnesium levels are also associated with resistance to PTH activity at the level of bone, further contributing to hypocalcemia. Therefore, in patients with hypocalcemia and hypomagnesemia, it is crucial to correct the magnesium level (to at least 2 mg/dL [0.83 mmol/L]), as it is difficult to increase calcium levels until this is done.

1,25-Dihydroxyvitamin D has a short half-life, and its measurement only reflects the active levels of vitamin D. Since active levels tend to vacillate frequently based on immediate need, this level would not be diagnostically helpful. 25-Hydroxyvitamin D levels have a longer half-life and, therefore, more accurately reflect the total body stores of vitamin D.

Measuring 24-hour urine calcium excretion in this patient would not be diagnostically helpful as significant urinary loss of calcium is uncommon, and the urine calcium level in this patient would be expected to be low due to compensatory kidney retention of calcium.

Checking the ionized calcium level is indicated in settings where abnormal serum protein binding of calcium is possible. This test is not needed in this symptomatic patient who has no suggestion of excessive protein binding of calcium.

KEY POINT

- Low serum magnesium levels impair parathyroid hormone secretion and require repletion before serum calcium levels may be corrected.

Bibliography

Shoback, D. Hypoparathyroidism. N Engl J Med. 2008 Jul 24;359(4):391-403. [PMID: 18650515]

Item 29 Answer: C

Educational Objective: Manage early type 2 diabetes mellitus.

The most appropriate management for this patient is to initiate metformin. The patient is early in her diabetes disease course without evidence of microvascular disease. For otherwise healthy adults meeting these criteria, the American Diabetes Association recommends a hemoglobin A_{1c} level of less than 7.0%, preprandial glucose values of 70 to 130 mg/dL (3.9-7.2 mmol/L), and 1- to 2-hour postprandial glucose values of less than 180 mg/dL (10 mmol/L). Because the patient has not met these goals, a pharmacologic agent should be added at this time. Lifestyle recommendations consisting of increased physical activity, dietary modifications, and weight loss (if BMI is elevated) are the initial first step in treating diabetes. When lifestyle modifications fail to meet glycemic goals within 6 weeks, metformin is the recommended first-line therapy to be started in conjunction with continued lifestyle modifications. If glycemic goals are not met after 3 months of lifestyle modifications and metformin use, additional agents should be added to the regimen every 3 months until glucose goals are met.

Dapagliflozin, a sodium-glucose transporter-2 (SGLT-2) inhibitor, increases excretion of glucose through the kidney. It is a second-line agent that should be used after lifestyle modifications and metformin fail to reach glycemic goals.

The sulfonylurea glipizide stimulates insulin secretion from the pancreatic beta cells. This agent could improve the patient's postprandial hyperglycemia, but it may also induce weight gain in a patient actively working on weight loss. Glipizide is a second-line agent that should be used after lifestyle modifications and metformin fail to reach glycemic goals.

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, improves glycemic control by slowing gastric emptying and suppressing glucagon secretion. It is also considered a second-line agent that might be considered if lifestyle modifications and metformin fail to reach glycemic goals.

KEY POINT

- For most patients with type 2 diabetes mellitus, lifestyle modifications and metformin therapy are the most appropriate initial treatments.

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Item 30 Answer: C

Educational Objective: Identify hemochromatosis as a cause of hypogonadotropic hypogonadism.

The patient has a clinical history suspicious for hemochromatosis and should be further evaluated by measuring serum transferrin saturation and ferritin levels. The patient has hypogonadism based on his clinical symptoms of decreased libido and erectile dysfunction, associated with a low morning serum testosterone level. A hypogonadotropic etiology is indicated by his low luteinizing and follicle-stimulating hormone levels. Causes of hypogonadotropic hypogonadism include infiltrative diseases such as hemochromatosis, sarcoidosis, cancer metastatic to the pituitary, and lymphoma. Pituitary tumors that impair gonadotropin function may also be a cause. This patient has several clinical findings suggestive of possible hemochromatosis, including a report of arthralgia and hepatomegaly on physical examination. Therefore, the next step in evaluation of this patient's hypogonadotropic hypogonadism is measurement of serum ferritin level and transferrin saturation to evaluate for possible hemochromatosis.

The cause of hypogonadism must be evaluated prior to the initiation of testosterone replacement. If testosterone therapy is started without testing for hemochromatosis, the diagnosis may be missed.

Although genetic disorders such as Klinefelter syndrome (47,XXY) may cause hypogonadism, patients with this syndrome have hypergonadotropic hypogonadism with elevated luteinizing and follicle-stimulating hormone values, unlike this patient. Therefore, karyotyping is not indicated.

A testicular ultrasound is used to evaluate the cause of primary testicular failure and is not indicated in the evaluation of hypogonadotropic hypogonadism. This patient's low gonadotropin levels indicate either a hypothalamic or pituitary disorder, instead of testicular disease. Although hemochromatosis may also directly affect testicular function in addition to its central hypogonadal effect, testicular ultrasound is not helpful in establishing the diagnosis of hemochromatosis as a cause of hypogonadism.

KEY POINT

- Patients with symptoms of hypogonadotropic hypogonadism should have serum transferrin saturation and ferritin concentration levels measured to identify hemochromatosis prior to initiating any therapy.

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Item 31 Answer: B

Educational Objective: Diagnose pseudohypercalcemia.

This patient's ionized calcium level should be checked. His total calcium level is elevated, but he is without clear symptoms associated with hypercalcemia. Approximately 40% to 45% of the calcium in serum is bound to protein, principally albumin, although the physiologically active form of calcium is in an ionized (or free) state. In most patients with relatively normal serum albumin levels, the total calcium usually accurately reflects the ionized calcium fraction. However, in clinical settings where increased protein binding of calcium may occur, the serum total calcium level may be elevated without a rise in the actual serum ionized calcium concentration. This may occur in patients with hyperalbuminuria (as may occur in those who are severely dehydrated), and in patients with a paraprotein capable of binding calcium (such as occasionally occurs in some patients with multiple myeloma). This phenomenon is sometimes termed pseudohypercalcemia (or factitious hypercalcemia). If present, a normal ionized calcium level may indicate that the elevated total calcium levels are due to excessive protein binding and potentially eliminate the need for further evaluation for hypercalcemia.

Measuring the 1,25-dihydroxyvitamin D level is useful in further assessing patients with non-parathyroid hormone (PTH)-mediated hypercalcemia to assess for excess vitamin D production. PTH testing is indicated in patients with hypercalcemia to differentiate between PTH-mediated and non-PTH-mediated hypercalcemia.

The hypercalcemia associated with multiple myeloma is caused primarily by tumor-induced, osteoclast-mediated bone resorption due to cytokines released by myeloma cells and is not PTH-mediated or due to excessive vitamin D levels. Measurement of PTH level and 1,25-dihydroxyvitamin levels may be indicated as part of this patient's evaluation only after true hypercalcemia has been established.

Parathyroid hormone-related protein (PTHrP) level measurement is useful in evaluating patients with non-PTH-mediated hypercalcemia but would not be indicated as a next study in this patient in whom pseudohypercalcemia has not been excluded.

KEY POINT

- In patients with conditions in which increased protein binding of calcium may occur, such as hyperalbuminemia or paraproteinemia, an artificially elevated total serum calcium level must be excluded.

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Item 32 Answer: B

Educational Objective: Manage androgen therapy in the setting of hypogonadism.

Before initiating therapy for this patient with hypogonadism, his desire for fertility should be explored. Testosterone replacement therapy can be associated with decreased spermatogenesis and infertility. Exogenous testosterone

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suppresses both hypothalamic gonadotropin-releasing hormone and pituitary follicle-stimulating hormone and luteinizing hormone (LH) production, resulting in depletion of intratesticular testosterone. The effect is suppression of spermatogenesis so pronounced that testosterone replacement therapy has been studied as a male hormonal contraceptive. Based on Endocrine Society guidelines, men with hypogonadism should be treated with exogenous testosterone when they have consistent signs and symptoms of hypogonadism and low serum testosterone levels. Symptomatic men may report reduced libido, erectile dysfunction, mood changes, irritability, fatigue, or memory loss. Although this patient's symptoms would likely be improved with exogenous administration of androgen, replacement therapy may also result in infertility due to oligospermia. Patients with hypogonadism who desire fertility may require treatment with human chorionic gonadotropin (HCG). HCG has LH-like activity and stimulates the production of intratesticular testosterone, resulting in the high concentrations required for induction and maintenance of spermatogenesis.

Asymptomatic men with low serum testosterone levels may experience decreased bone mineral density and osteoporosis. Hormone replacement therapy will decrease the risk of osteoporosis. A bone mineral density measurement prior to the initiation of hormone replacement therapy is not needed.

Male hypogonadism is associated with increased visceral fat and insulin resistance, and hormone replacement therapy improves these metabolic parameters. There is no recommendation that hypogonadal patients initiating hormone replacement therapy be screened for diabetes mellitus with fasting plasma glucose measurement or other testing.

A 2010 systematic review of hypogonadal men receiving testosterone therapy found no evidence of increased risk of prostate cancer when compared with the placebo/nonintervention group. The Endocrine Society guideline on testosterone replacement therapy recommends a digital rectal examination and prostate-specific antigen (PSA) level determination at 3 and 6 months following the initiation of replacement therapy. Continued regular screening is recommended for men older than 40 years of age with a baseline PSA level greater than 6 ng/mL (6 µg/L). Scrotal ultrasound is unnecessary prior to initiation of testosterone therapy; a clinical testicular examination to rule out abnormalities or a testicular mass is sufficient.

KEY POINT

- Prior to initiation of testosterone therapy for hypogonadism, the desire for fertility should be ascertained because exogenous testosterone replacement therapy may result in oligospermia and infertility.

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Item 33 Answer: D

Educational Objective: Diagnose thyroid storm.

This patient has thyroid storm, most likely precipitated by the iodine contained in the dye load from the cardiac catheterization in the context of undertreated Graves disease following her discontinuation of methimazole. Graves disease is the most common underlying condition associated with thyroid storm, and onset may be triggered by a number of factors in addition to iodine, including infection, surgery, myocardial infarction, trauma, or parturition. This patient has typical features of thyroid storm: fever, tachycardia, heart failure, gastrointestinal dysfunction, and mental status changes. Scoring systems exist that can be used to provide a more objective measurement of the severity of the thyrotoxicosis. Treatment of thyroid storm is directed toward supportive care, reduction of thyroid hormone production, decreasing peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3), addressing adrenergic symptoms and thermoregulatory changes, and treating any identified precipitating factors. Thionamides and β-blockers are the mainstay of treatment to reduce thyroid hormone production and control adrenergic symptoms.

This patient's clinical presentation is not consistent with euthyroid sick syndrome. Although this patient's low level of serum thyroid stimulating hormone (TSH) is consistent with euthyroid sick syndrome, her elevated serum thyroid hormone level is not. In euthyroid sick syndrome, serum thyroid hormone levels are typically low, creating a clinical picture similar to that seen in central hypothyroidism.

Pheochromocytoma typically presents with hypertension and tachycardia but thyromegaly is not a clinical feature of this disorder. Additionally, confusion and altered mental status are not presenting signs of the disease.

Subacute thyroiditis is typically precipitated by a recent viral illness. An iodine load, such as this patient had, is an unlikely cause. Although patients with subacute thyroiditis may present with significant thyrotoxicosis, the thyroid is typically painful to palpation, a clinical finding that was not present in this patient.

KEY POINT

- In patients with underlying Graves disease, thyroid storm may be precipitated by the iodine content found in contrast media.

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Item 34 Answer: D

Educational Objective: Manage postsurgical hypoparathyroidism.

This patient without parathyroid function should be advised to decrease his calcium supplementation intake. In patients without parathyroid function, stimulation of the kidney to convert 25-hydroxyvitamin D (from the liver) into the active

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form, 1.25- dihydroxyvitamin D (calcitriol), is lost, as is the signal to increase reabsorption of calcium in the kidney in the distal convoluted tubule and loop of Henle. As a result, both calcitriol and calcium supplementation must be provided, as was done in this patient. However, without reabsorption of calcium by the kidney, oral calcium will be absorbed and passed through the kidney, resulting in higher levels of urine calcium than in patients with normal parathyroid hormone levels. In monitoring calcium status in hypoparathyroid patients, the recommended goal should be a 24-hour urine calcium level of less than 300 mg/24 hours (7.5 mmol/24 h) with a concomitant serum calcium level in the low normal range (8.0-8.5 mg/dL [2.0-2.1 mmol/L]). If the urine calcium levels are surpassed, it is appropriate to decrease the calcium intake first; in patients with serum calcium levels greater than 8.5 mg/dL (2.1 mmol/L) and urine calcium greater than 300 mg/24 hours (7.5 mmol/24 h), concurrent decreases in both calcium supplementation and calcitriol are indicated.

Although 25-hydroxyvitamin D levels are the best indicator of total body vitamin D stores in patients with normal parathyroid function, it would not be helpful for therapeutic decision-making in this patient as the lack of PTH requires treatment with activated (1,25-dihydroxy) vitamin D. In this patient, 1,25-dihydroxyvitamin D levels measured concurrently with the serum and urine calcium levels are the most appropriate indicators of therapeutic effect.

Removal of the parathyroid glands does not allow the PTH level to be used to monitor appropriateness of therapy. It would be expected to be low or undetectable in this patient who has had resection of his parathyroid glands and chemotherapy and radiation.

It would be inappropriate to continue the current regimen given the elevated 24-hour urine calcium levels. Persistently elevated levels could lead to nephrolithiasis or nephrocalcinosis.

KEY POINT

- The urine and serum calcium goals are different in patients with hypoparathyroidism; the urine calcium goal is less than 300 mg/24 hours (7.5 mmol/24 h) and serum calcium goal is between 8.0 and 8.5 mg/dL (2-2.1 mmol/L) in these patients.

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Item 35 Answer: A

Educational Objective: Manage exercise-induced hypoglycemia.

This patient should decrease his meal-time insulin glulisine dose prior to exercise and continue his insulin glargine. Exercise can increase glucose utilization by the muscles, which can induce hypoglycemia in the setting of exogenous insulin. This patient consumes a meal and administers insulin glulisine, a rapid-acting insulin, before intensive exercise. Since the duration of action of insulin glulisine can extend up to 4 hours, covering the meal consumption prior to exercise with a smaller dose of insulin glulisine can reduce the risk of hypoglycemia in the setting of intense or prolonged exercise.

Discontinuation of insulin glargine in a patient with type 1 diabetes will lead to hyperglycemia if the rapid-acting insulin isn't adjusted to provide basal insulin coverage. The hyperglycemia and insulin deficiency that develop in the absence of basal insulin coupled with the stress associated with exercise will lead to an increase in the release of counterregulatory hormones. In this scenario, there may not be sufficient insulin to decrease lipolysis and subsequent oxidation of free fatty acids. This could lead to diabetic ketoacidosis.

The meal-time insulin prior to exercise should be decreased; however, modification of the diet with increase in carbohydrates, rather than protein, can also help avoid exercise-induced hypoglycemia. Consumption of 15 to 30 grams of carbohydrates prior to exercise and/or a snack with complex carbohydrates after prolonged exercise can help mitigate the risk of hypoglycemia. Carbohydrates, especially simple ones, can rapidly provide glucose to the bloodstream and maximize glycogen stores in the liver that can be utilized for fuel during exercise. The digestion time for protein is prolonged compared with carbohydrates, thus providing a slower source of energy during exercise

A sliding-scale regimen of insulin glulisine is a reactive management plan for glucose control. In this scenario, it is possible that the patient could have an increased risk of hyperglycemia or hypoglycemia prior to, during, or after exercise secondary to insufficient or excessive doses of insulin from the sliding-scale regimen.

KEY POINT

- Because exercise can increase glucose utilization by the muscles, reducing the doses of mealtime insulin in a patient with diabetes mellitus will decrease the risk of hypoglycemia with intense or prolonged exercise.

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Item 36 Answer: A

Educational Objective: Diagnose central hypothyroidism.

Measurement of the serum free thyroxine (T_4) level is the most appropriate next step in management for this patient who has clinical evidence of hypothyroidism (fatigue, constipation, cold intolerance, dry skin, delayed reflexes, anemia, and mild hyponatremia) but has had radiation to the base of the skull, including the pituitary gland. Although measurement of thyroid-stimulating hormone (TSH) is the

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most accurate reflection of thyroid status in patients with an intact hypothalamic-pituitary-thyroid axis, it is not a reliable measure of thyroid function in patients in whom there is loss of hypothalamic-pituitary function, such as seen in this patient. His low-normal TSH in the context of clinical hypothyroidism suggests possible central hypothyroidism, and measurement of the circulating level of thyroid hormone, the free serum T_4, would therefore be a more accurate indication of his thyroid status.

Repeating the TSH measurement would not be appropriate in this patient with signs and symptoms of hypothyroidism, as untreated hypothyroidism leads to increased cardiovascular morbidity and mortality. In addition, because of likely central hypothyroidism, the TSH level would remain an inaccurate indicator of thyroid function.

Thyroid scintigraphy is unlikely to distinguish the source of the hypothyroidism, as patients with primary or secondary hypothyroidism have decreased radioactive uptake. Thyroid scanning is most helpful in elucidating the cause of hyperthyroidism.

Ultrasound of the neck is normal in patients with central hyperthyroidism and would be unlikely to provide any additional information about this patient's thyroid status.

KEY POINT

- When central hypothyroidism is suspected, measurement of the serum free thyroxine (T_4) level is essential.

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Persani L. Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. J Clin Endocrinol Metab. 2012 Sep;97(9):3068-78. [PMID: 22851492]

Item 37 Answer: B

Educational Objective: Diagnose familial hypocalciuric hypercalcemia.

This patient's urine calcium and creatinine levels should be measured. Her laboratory values are consistent with hypercalcemia, and her parathyroid hormone level is toward the upper end of the normal range. In her age group and with a family member with a suspicious history, it is important to distinguish between primary hyperparathyroidism and familial hypocalciuric hypercalcemia (FHH). The distinction between primary hyperparathyroidism and FHH can be made by a 24-hour urine collection for calcium and creatinine, which will establish the amount of kidney calcium excretion and will allow evaluation of the calcium-creatinine ratio. Total urine calcium of less than 200 mg/24 h (5 mmol/24 h) and a calcium-creatinine ratio less than 0.01 are highly suggestive of familial hypocalciuric hypercalcemia. FHH results from a mutation in a specific calcium-sensing receptor in the parathyroids and kidneys, and results in an upward shift in the range of calcium and PTH leading to these clinical findings. Although a rare entity, making this diagnosis is crucial because it may prevent unnecessary parathyroidectomy for the patient. The course of FHH is rarely associated with hypercalcemia and therefore does not require therapy to lower serum calcium levels. Screening other family members for the disorder is indicated.

Bone densitometry is not indicated in this age group in the absence of fragility fractures or other risk factors such as long-term high-dose glucocorticoid use or primary hyperparathyroidism.

A parathyroid sestamibi scan is a very useful nuclear imaging study for localization of adenomas in patients with primary hyperparathyroidism or parathyroid cancer. However, primary hyperparathyroidism has not been confirmed in this patient with suspicion for FHH, making this study premature.

The need for surgical treatment in this patient has also not been established. Therefore, surgical referral for parathyroidectomy would not be appropriate.

KEY POINT

- Measurement of 24-hour urine calcium and creatinine levels will distinguish between primary hyperparathyroidism and familial hypocalciuric hypercalcemia.

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Item 38 Answer: D

Educational Objective: Evaluate timing of prandial insulin in a patient with diabetes mellitus.

The mismatch of timing of insulin administration to food intake with meals, possibly related to the time demands of her new job, is the most likely explanation for the erratic glycemic fluctuations noted on this patient's blood glucose log. The adequacy of her nocturnal long-acting insulin is reflected in her near-goal pre-breakfast blood glucose levels. However, the major fluctuations occurring around mealtimes are best explained by inconsistent use of her immediate-acting insulin relative to food intake. Meal coverage with insulin should mimic the physiologic pattern seen with endogenous insulin secreted from pancreatic beta cells. Administration of immediate-acting insulins should therefore ideally occur just prior to or at the time of the meal consumption. Because of the rapid onset of action with these agents, shifting the timing of administration away from this physiologic pattern may result in the blood glucose fluctuations seen in this patient. An important aspect of diabetes education is helping patients understand the actions of their prescribed insulin regimen and the importance of timing issues when using them.

Antibodies can develop in response to exposure to exogenous insulin; however, these antibodies are rarely clinically significant and would not adequately explain the blood glucose pattern seen in this patient.

Gastroparesis can cause erratic blood glucose values due to either rapid transit or delayed emptying of food within the

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digestive system. However, the lack of gastrointestinal symptoms, absence of clinical evidence of other diabetes-related complications, and her hemoglobin A_{1c} history suggesting good diabetic control make gastroparesis a less likely cause of her erratic blood glucose readings.

Inadequate insulin dosing can cause fluctuations in glycemic control. However, this patient reports little variability in her daily diet. She also has several days with evidence of adequate glycemic control on her current insulin regimen doses. Therefore, inadequate dosing is less likely to be the cause of her glycemic variability.

KEY POINT

- Because meal coverage with insulin should mimic the physiologic pattern seen with endogenous insulin secreted from the pancreatic beta cells as closely as possible, insulin administration in patients with diabetes mellitus should ideally occur prior to or at the time of the meal consumption.

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Item 39 Answer: A

Educational Objective: Manage a patient with Cushing syndrome following adrenalectomy.

The most appropriate management of this patient undergoing right adrenalectomy for Cushing syndrome (CS) is postoperative hydrocortisone. The patient has adrenocorticotropic hormone (ACTH)-independent CS, and a contrast-enhanced adrenal CT scan demonstrated a right adrenal mass with imaging characteristics consistent with a benign adenoma. Adrenocortical adenomas typically have low attenuation on unenhanced CT scan (density less than 10 Hounsfield units) and exhibit rapid washout of intravenous iodine contrast media (>50% at 10 minutes). Following adrenalectomy, patients with adrenal CS may develop acute adrenal failure because of hypothalamic-pituitary-adrenal (HPA) axis suppression and contralateral adrenal atrophy. All patients should be treated with stress-dose glucocorticoids and tapered to physiologic replacement until HPA axis recovery is confirmed. Most patients have adrenal insufficiency lasting as long as 12 months.

Postoperative administration of mitotane, an adrenolytic drug, is recommended as adjuvant therapy for patients with locally persistent or metastatic adrenocortical carcinoma (ACC). In these patients, mitotane is associated with objective remissions in approximately 25% of patients. This patient's CT scan findings are not consistent with ACC. Adrenal cancers are typically large (>4-6 cm) with irregular margins and areas of necrosis or calcification. Unenhanced CT will demonstrate high attenuation (density >10 Hounsfield units), and washout of intravenous iodine contrast media is less than 50% at 10 minutes.

Postoperative norepinephrine is not indicated. If the patient were to experience hypotension or shock postoperatively, treatment with vasopressors in addition to glucocorticoid replacement would be considered; however, this would not replace the administration of glucocorticoids in this population at risk for acute hypocortisolism.

Preoperative phenoxybenzamine is indicated in the management of patients with pheochromocytoma, not CS. The purpose of preoperative α-blockade is to provide blood pressure control and decrease the risk of cardiovascular complications related to excessive catecholamine release during intraoperative manipulation of the tumor.

KEY POINT

- Following adrenalectomy, patients with adrenal Cushing syndrome should be treated with stress-dose glucocorticoids during the postoperative period to avoid the risk of acute hypocortisolism.

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Item 40 Answer: A

Educational Objective: Manage Paget disease of bone.

Initiating antiresorptive therapy in this patient with symptomatic Paget disease of bone is the most appropriate next step in management. Paget disease of bone is characterized by focal areas of accelerated bone remodeling that ultimately causes overgrowth of bone at one or more sites that may impair the integrity of affected bone. Areas commonly affected include the skull, spine, pelvis, and long bones of the lower extremities, such as in this patient who has thickened cortical bone and coarsening of the trabecular bone of the femur. The main indications for antiresorptive therapy in most patients include pain caused by increased bone metabolic activity (as in this patient) and hypercalcemia due to multiple affected sites. The most commonly used treatment agents are nitrogen-containing bisphosphonates (alendronate, pamidronate, risedronate, and zoledronic acid); these are the newer bisphosphonates and have been the most extensively studied for treatment of Paget disease of bone. Bisphosphonates stabilize bone turnover by suppressing bone resorption and new bone formation with a resulting reduction in serum alkaline phosphatase levels. There is no evidence that antiresorptive therapy is beneficial in asymptomatic patients.

Bone biopsy is rarely needed to establish the diagnosis of Paget disease of bone when there are characteristic radiographic findings of bone turnover (concurrent osteolytic and osteoblastic changes) and consistent laboratory studies (such as elevated serum alkaline phosphatase levels). Bone biopsy may be useful in certain situations in which bone lesions are primarily osteoblastic (suggesting possible metastatic disease) or osteolytic (possibly indicating multiple myeloma), neither of which are present in this patient.

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The bone lesions of multiple myeloma are primarily osteolytic, in which case further evaluation for that diagnosis with a serum and urine protein electrophoresis would be appropriate. However, this patient's radiographic findings are not consistent with a diagnosis of multiple myeloma, and further evaluation for this disorder would therefore not be indicated.

Most patients with Paget disease of bone are asymptomatic and are identified only by elevated serum alkaline phosphatase levels detected on laboratory studies obtained for other reasons. In many patients with mild disease, clinical observation without initiation of therapy is appropriate. However, in this patient with symptomatic disease in a critical weight-bearing skeletal area, clinical observation without treatment would not be appropriate.

KEY POINT

- Treatment of Paget disease of bone with antiresorptive agents is indicated in symptomatic patients, those with elevated calcium levels, or patients with involvement of skeletal areas at high risk of complications, including fractures.

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Item 41 Answer: D

Educational Objective: Treat hypothyroidism in pregnancy.

This pregnant patient's levothyroxine dose should be increased to lower the serum thyroid-stimulating hormone. Maternal thyroid hormone production typically increases by 30% to 50% during pregnancy; therefore, in pregnant patients requiring levothyroxine supplementation, the replacement dose usually needs to be increased to provide adequate thyroxine (T_4) for the neurologic development of the fetus. The combination of this patient's elevated thyroid-stimulating hormone (TSH) level and low total T_4 level suggest that her levothyroxine dose should be increased. During pregnancy, the physiologic changes in thyroid hormone levels include a reduction in the serum TSH level and an increase in the serum total T_4 level. This change in the serum TSH level is partly due to the rise in the serum human chorionic gonadotropin (HCG) level; both hormones share sequence homology in their α subunit. As the serum HCG level rises with progression of pregnancy, the hormone can bind to the TSH receptors, resulting in a reduction in serum TSH levels. Consequently, the normal reference range for serum TSH during pregnancy shifts to a lower value, from 0.5 to 5.0 μU/mL (0.5-5.0 mU/L) pre-pregnancy to 0.03 to 2.5 μU/mL (0.03-2.5 mU/L) during the first trimester. Additionally, the serum total T_4 level rises 1.5-fold above the normal nonpregnant reference range. Part of this increase is due to the higher levels of estrogen associated with pregnancy, which cause an increase in serum total protein levels, including serum thyroid hormone–binding proteins. The increased thyroid hormone requirements of the fetus also contribute to this change in serum T_4 levels.

In this patient, with a serum TSH value above 2.5 μU/mL (2.5 mU/L) during the first trimester, the dose of levothyroxine needs to be increased rather than decreased or discontinued. The serum TSH level should be rechecked in 4 weeks to ensure that the dose adjustment continues to be adequate. Likewise, thyroid function tests should be repeated at least once during each trimester to ensure that additional adjustments in the levothyroxine dose are not needed.

KEY POINT

- On confirmation of pregnancy in a patient taking levothyroxine, serum thyroid-stimulating hormone should be checked to determine the need for levothyroxine dose adjustment.

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Item 42 Answer: B

Educational Objective: Diagnose the cause of adrenal failure.

This patient most likely has primary adrenal failure due to bilateral adrenal hemorrhage. He has acute onset nausea, lightheadedness, back and abdominal pain, and hypotension. While nonspecific, these findings are consistent with adrenal failure. Additionally, laboratory studies show hyponatremia, hyperkalemia, and hypocortisolemia, which are also consistent with the diagnosis. A sudden drop in the hemoglobin and hematocrit, as seen in this patient, may be present without evidence of bleeding elsewhere. Risk factors for adrenal hemorrhage include anticoagulant therapy (and may occur with treatment levels within the therapeutic range), the postoperative state, abnormalities of hemostasis (such as heparin induced thrombocytopenia or antiphospholipid antibody syndrome), and sepsis. Because adrenal hemorrhage is uncommon and the associated findings may be relatively nonspecific, an increased level of suspicion is required for the diagnosis in at-risk patients; failure to identify acute adrenal failure in a timely manner may lead to cardiovascular collapse. Adrenal hemorrhage can often be visualized on abdominal CT imaging. Treatment of acute adrenal failure is with stress-dose glucocorticoids (hydrocortisone, 50-100 mg intravenously every 6-8 hours) and supportive care with intravenous fluids and vasopressors as needed for hemodynamic compromise.

Although autoimmune adrenalitis may cause primary adrenal failure and is associated with the presence of other autoimmune diseases (such as hypothyroidism in this patient), the onset of symptoms related to hypocortisolism are usually more gradual, and skin hyperpigmentation is often seen on examination.

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Chronic administration of long-acting opiate medications is a known cause of hypogonadotropic hypogonadism and a potential etiology of secondary adrenal insufficiency. The administration of relatively short-acting opiates (oxycodone) on an as-needed basis for postoperative pain is unlikely to cause clinically significant hypothalamic-pituitary-adrenal axis disturbance. Hypogonadotropic hypogonadism would also not present with hyperkalemia because mineralocorticoid secretion is preserved.

Pituitary apoplexy results from acute hemorrhage into the pituitary and may result in adrenal insufficiency. Although this patient might be at increased risk due to anticoagulation, he does not have headache or visual disturbances, which are common in pituitary apoplexy. Because pituitary apoplexy causes secondary adrenal insufficiency, it would not result in hyperkalemia.

KEY POINT

- Patients with bilateral adrenal hemorrhage typically present with clinical features of acute cortisol and aldosterone deficiency, including gastrointestinal disturbance, lethargy, weakness, hypotension, shock, hypoglycemia, and electrolyte imbalances, such as hyponatremia and hyperkalemia.

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Item 43 Answer: C

Educational Objective: Evaluate a patient with a new diagnosis of hypercortisolism for osteoporosis.

This patient with newly diagnosed hypercortisolism is at high risk for osteoporosis and fracture, and a screening dual-energy x-ray absorptiometry (DEXA) scan is indicated. The mechanism of osteoporosis in patients with Cushing syndrome is related to decreased intestinal calcium absorption, decreased bone formation, increased bone resorption, and decreased renal calcium reabsorption. Patients with low bone density should be considered for bisphosphonate treatment to reduce the risk of fracture.

An 8-mg dexamethasone suppression test can be used to help localize the source of adrenocorticotropic hormone (ACTH) in a patient with Cushing syndrome. Patients with pituitary Cushing disease respond to 8 mg of dexamethasone with a suppressed cortisol level. In comparison, patients with ectopic ACTH production do not respond to 8 mg of dexamethasone, and their cortisol levels remain elevated. However, this test is associated with a number of false-positive results. The 8-mg dexamethasone suppression test is not indicated for this patient because she has already had a more definitive test. Intrapetrosal sinus sampling has better sensitivity and specificity when completed by a skilled interventional radiologist.

Measuring 24-hour urine free catecholamine and metanephrine levels would be used to screen for pheochromocytoma. If this patient had an adrenal adenoma, she would certainly need to be screened for pheochromocytoma prior to surgery, but she does not have a known adrenal lesion. Her symptoms and comorbidities are explained by her diagnosis of Cushing disease, and she has no specific signs or symptoms that require an evaluation for pheochromocytoma.

A PET scan is not necessary or indicated in the evaluation of Cushing syndrome. Cushing disease is caused by a pituitary adenoma and is not malignant. Cushing syndrome due to ectopic ACTH production is often caused by a cancer. PET scan may be indicated to try to localize the source of ectopic ACTH, but the source of the excessive ACTH is already known to be from a pituitary adenoma.

KEY POINT

- Patients with hypercortisolism should have a screening dual-energy x-ray absorptiometry scan because they are at a high risk of osteoporosis and fracture.

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Item 44 Answer: D

Educational Objective: Manage primary adrenal failure.

The most appropriate regimen for the long-term treatment of this patient's primary adrenal failure would be prednisone, 5 mg once daily, and fludrocortisone, 0.05 mg once daily. In primary adrenal failure, there is a failure in the production of all the hormones of the adrenal cortex. Patients therefore require both glucocorticoid and mineralocorticoid replacement. Because she is no longer ill, physiologic replacement doses are appropriate. Prednisone primarily has glucocorticoid activity, with 5 mg being considered a physiologic replacement dose. It is also long-acting so may be administered once daily in combination with fludrocortisone, which has almost pure mineralocorticoid properties. Physiologic replacement doses of fludrocortisone are 0.05 to 2 mg per day.

Dexamethasone is primarily a glucocorticoid and could be used as the glucocorticoid portion of combination replacement therapy with a mineralocorticoid such as fludrocortisone. However, dexamethasone alone would not be appropriate therapy for primary adrenal failure due to its intrinsic lack of mineralocorticoid activity.

Fludrocortisone alone is also inappropriate because it would not provide glucocorticoid replacement.

Hydrocortisone has both glucocorticoid and mineralocorticoid properties, with primarily glucocorticoid activity at physiologic replacement doses of 12.5 to 25 mg in two to three divided doses daily. At total daily doses above 50 mg, hydrocortisone has adequate mineralocorticoid activity to allow for its use as monotherapy. However, treatment with hydrocortisone, 10 mg three times daily, does not provide

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adequate mineralocorticoid replacement, while it supplies a supraphysiologic amount of glucocorticoid that could lead to iatrogenic Cushing syndrome if administered on a long-term basis.

Patients with primary adrenal failure require additional glucocorticoid at times of physiologic stress. Treatment for minor stress (upper respiratory infection, fever, minor surgery under local anesthesia) is typically two to three times the basal dose of hydrocortisone (or equivalent), for moderate stress (minor or moderate surgery with general anesthesia) usually 45 to 75 mg/day, and major stress (major surgery, trauma, critical illness, or childbirth) up to 150 to 200 mg/day with a gradual taper following resolution of the stress.

KEY POINT

- Patients with primary adrenal failure require both glucocorticoid and mineralocorticoid replacement in physiologic doses.

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Item 45 Answer: C

Educational Objective: Diagnose primary thyroid lymphoma.

The patient has primary thyroid lymphoma, which most often occurs in elderly women with a long-standing history of Hashimoto thyroiditis. The clinical presentation is typically one of rapid onset (weeks) of an enlarging goiter with weight loss and night sweats. The diagnosis is made by biopsy of the thyroid with flow cytometry. Treatment typically involves chemotherapy and/or radiation therapy. Thyroidectomy is usually not needed.

CT scan of the neck, rather than ultrasound, was ordered in this patient because of the compressive symptoms and positional breathing issues. CT scan allows visualization of the enlarged thyroid gland and assessment of the patency of the trachea. In this image, the "doughnut" sign can be seen, whereby the enlarged thyroid extends behind and completely encircles the trachea.

New-onset Graves disease is unlikely to occur in a patient of this age, particularly with her long-standing history of hypothyroidism. Furthermore, there is no bruit or other clinical sign of Graves disease, and the thyromegaly associated with Graves disease is not acute in onset.

This patient is unlikely to have papillary thyroid cancer, as these tumors typically grow very slowly, in contrast to the acute onset of her findings. Additionally, the thyroid is not typically diffusely enlarged, as seen on this CT scan. Rather, a distinct nodule and potentially concomitant cervical lymphadenopathy would be expected.

Subacute (de Quervain) thyroiditis is associated with acute onset of anterior neck pain. It is typically seen following a viral illness in the preceding months. The changes on CT are typically a patchy infiltrate with minimal lymphadenopathy. This patient's image reveals marked diffuse enlargement of the thyroid, and she did not have a history of prior illness.

KEY POINT

- Primary thyroid lymphoma most often occurs in elderly women with underlying hypothyroidism; the typical presentation includes rapidly enlarging goiter, weight loss, and night sweats, and imaging reveals a diffusely enlarged thyroid.

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Item 46 Answer: E

Educational Objective: Treat primary hyperparathyroidism and concomitant vitamin D deficiency.

The most appropriate treatment of this patient is to replete his vitamin D deficiency with a supplement such as vitamin D_3 (cholecalciferol). He has primary hyperparathyroidism as shown by his elevated serum calcium and parathyroid hormone levels. However, there is a high prevalence of concurrent vitamin D deficiency and insufficiency in patients with primary hyperparathyroidism, and low levels of 25-hydroxyvitamin D can stimulate parathyroid hormone secretion in non-adenomatous glands. Because of this, measurement of vitamin D levels should be ordered as part of the evaluation of primary hyperparathyroidism, and repletion should be provided if identified. In these patients, it is important to replace their vitamin D to a level of at least 30 ng/dL (75 nmol/L). After this level is reached, the patient should be placed on a vitamin D dosage to maintain that value. The choice to use cholecalciferol versus ergocalciferol is often based on the level of vitamin D deficiency. Since ergocalciferol is more readily available in the 50,000 U form and has a shorter half-life, it is recommended when a patient's vitamin D level is less than 10 ng/mL (25 nmol/L). Cholecalciferol is often used when the level is between 20 and 30 ng/mL (50-75 nmol/L) or for maintenance. Since this patient already has hypercalcemia and low-dose repletion is desired, the lower doses (400 U daily) of vitamin D_3 (over-the-counter cholecalciferol) should be used. This patient's serum calcium should be monitored at least monthly.

This patient does not meet the threshold for surgery. His serum total calcium level is less than 1 standard deviation from upper limit of normal, his bone density score is not in the osteoporotic or treatment range, he is older than 50 years of age, and his glomerular filtration rate is preserved.

Alendronate would be an excellent option for calcium reduction and simultaneous treatment of osteoporosis if his T-scores were lower or Fracture Risk Assessment Tool (FRAX) scores were higher. The FRAX calculator defines the 10-year fracture risk for patients with T-scores in the -1.0 to -2.5 range. The FRAX calculator (www.shef.ac.uk/FRAX)

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incorporates multiple risk factors including sex, fracture history, femoral neck bone mineral density, steroid usage, smoking, BMI, age, and alcohol intake to determine projected fracture risk. If the risk of major osteoporotic fracture is greater than or equal to 20% or the risk of hip fracture is greater than or equal to 3%, the patient's benefit from therapy exceeds the risk and treatment should be offered.

Calcitonin is an option for reducing his calcium levels, but he is currently asymptomatic and does not warrant calcium lowering.

Cinacalcet, a calcimimetic agent, is another option for lowering calcium for symptomatic patients with kidney involvement. This patient has preserved kidney function and no symptoms. Due to the cost and potential side effects of cinacalcet, it would not be indicated at this time.

KEY POINT

- In patients with primary hyperparathyroidism and concomitant vitamin D deficiency, 25-hydroxyvitamin D levels should be repleted to at least 30 ng/dL (75 nmol/L) to prevent further parathyroid hormone stimulation.

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Item 47 Answer: A

Educational Objective: Manage diabetes mellitus in a hospitalized patient.

The most appropriate treatment for this patient's diabetes mellitus while hospitalized is a weight-based treatment plan that includes basal and prandial insulin. Hyperglycemia in the hospital is associated with poor outcomes. According to the American Diabetes Association and American Association of Clinical Endocrinologists, glucose goals in hospitalized patients in a non-ICU setting are premeal values less than 140 mg/dL (7.8 mmol/L) and random values less than 180 mg/dL (10 mmol/L). The American College of Physicians recommends avoiding values less than 140 mg/dL (7.8 mmol/L) to decrease the risk of hypoglycemic complications. The patient's plasma glucose values exceed the recommended guidelines and require treatment.

Oral agents do not have safety or efficacy data for use in the hospital. Glipizide is an insulin secretagogue that can potentially induce hypoglycemia in the hospital setting, particularly with unpredictable changes in oral intake.

With metformin use, hospitalized patients can develop poor organ perfusion, which can increase the risk of lactic acidosis. Intravenous contrast dye can also impair kidney function in the setting of metformin use in the hospital. Reinitiation of the patient's home regimen of metformin at or near the time of discharge is most appropriate after all procedures have been completed and organ function is stable and glucose levels have returned to baseline values.

Sliding-scale insulin is nonphysiologic and can result in large fluctuations in blood glucose levels. Sliding-scale insulin is not recommended as the sole insulin therapy in the hospital setting.

KEY POINT

- For non-critically ill hospitalized patients with diabetes mellitus and hyperglycemia, a weight-based treatment plan that includes basal and prandial insulin is recommended.

Bibliography

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Item 48 Answer: B

Educational Objective: Diagnose Cushing syndrome.

The most appropriate next diagnostic test for this patient is the 1-mg dexamethasone suppression test. She has the typical clinical features and findings of cortisol excess, or Cushing syndrome. The most common cause of Cushing syndrome is exogeneous glucocorticoid use; however, she has not received glucocorticoids. To evaluate for Cushing syndrome, biochemical evidence of hypercortisolism must be confirmed by use of several screening tests. Three screening tests are used for Cushing syndrome: the 1-mg dexamethasone suppression test (given late at night with assessment of cortisol suppression the next morning), 24-hour urine free cortisol excretion (to quantify total daily cortisol secretion), and measurement of evening salivary cortisol (which normally reaches a nadir at that time but remains elevated in patients with Cushing syndrome). At least two abnormal first-line screening tests are required for diagnosis. Only after establishing biochemical hypercortisolism should the source of excess cortisol production be sought.

Measurement of adrenocorticotropic hormone (ACTH) is not a screening test for Cushing syndrome. After documentation of excess cortisol production, ACTH levels may be useful in determining if hypercortisolism is ACTH-dependent or -independent; however, it is not an appropriate initial screening test.

An 8-mg dexamethasone suppression test is helpful in differentiating between Cushing disease (pituitary tumor–secreting ACTH) and ectopic ACTH production. However, it is not a screening test for Cushing syndrome and would be appropriate only in specific situations after Cushing syndrome is diagnosed.

A pituitary MRI should be ordered only after hypercortisolism and Cushing syndrome are diagnosed and a pituitary adenoma is suspected as a cause.

Measurement of serum cortisol levels lacks sensitivity and specificity for diagnosing Cushing syndrome, primarily

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due to the pulsatile nature of cortisol secretion, and is not used as a screening test.

KEY POINT

- To screen for Cushing syndrome, biochemical evidence of hypercortisolism must be confirmed by a 1-mg dexamethasone suppression test, 24-hour urine free cortisol testing, and/or measurement of evening salivary cortisol levels.

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Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing's syndrome: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008 May;93(5):1526-40. [PMID: 18334580]

Item 49 Answer: A

Educational Objective: Treat an obese patient with type 2 diabetes mellitus with bariatric surgery.

Patients with a BMI between 35 and 40 with one or more complications associated with obesity should be considered for bariatric surgery, with the goal of significant weight loss and improvement in metabolic abnormalities. This obese patient has type 2 diabetes mellitus with advanced microvascular disease along with other complications associated with obesity including hypertension, hyperlipidemia, obstructive sleep apnea, gastroesophageal acid reflux disease, and osteoarthritis. His attempts at lifestyle management with diet and exercise did not result in weight loss that substantially improved his metabolic abnormalities or obesity.

Increasing the insulin doses could potentially exacerbate the weekly hypoglycemic events occurring in a patient with hypoglycemic unawareness. This could also lead to more weight gain due to frequent treatments of hypoglycemia.

Metformin is contraindicated in men with a serum creatinine level above 1.5 mg/dL (132.6 µmol/L) due to the possibility of lactic acidosis and will not address the underlying problem of obesity.

Pramlintide slows gastric emptying, which can decrease appetite. The weight loss associated with the use of pramlintide is modest, and it may not be sufficient to improve the metabolic abnormalities and obesity-related complications in this patient. In addition, the patient's hypoglycemia may be exacerbated by pramlintide.

KEY POINT

- Obese persons (BMI between 35 and 40) with type 2 diabetes mellitus and associated complications should be considered for bariatric surgery.

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Item 50 Answer: D

Educational Objective: Diagnose an incidentally noted adrenal mass.

The most appropriate next step in management is to evaluate for pheochromocytoma, preferably by measurement of plasma free metanephrines in this patient. Approximately 10% to 15% of incidentally discovered adrenal masses are functional, although most have no overt clinical manifestations. Therefore, all patients with an incidentally noted adrenal mass should be evaluated for the autonomous secretion of cortisol and catecholamines, and those with hypertension should also undergo testing for primary hyperaldosteronism. The low-dose dexamethasone suppression test should be performed to evaluate for subclinical Cushing syndrome given its superior sensitivity compared with other screening tests (24-hour urine free cortisol and late-night salivary cortisol); this test was negative in this patient. Measurement of 24-hour urine metanephrines and catecholamines is the usual first test in most asymptomatic patients to evaluate for catecholamine hypersecretion, although in those with imaging suggestive of pheochromocytoma, measurement of plasma free metanephrines is the preferred study because of its very high sensitivity and high negative predictive value for a normal study. Imaging in this patient reveals a well-circumscribed partially cystic lesion with high attenuation on noncontrast CT scan, which is in keeping with a pheochromocytoma and is not typical of an adrenocortical adenoma, which characteristically has low attenuation on CT scan (density <10 Hounsfield units) due to relatively high lipid content.

Management of an adrenal incidentaloma depends on its size, imaging characteristics (phenotype), and hormonal functioning. Almost all adrenal tumors that are overtly functional are larger than 6 cm in size or have unfavorable imaging characteristics should be considered for surgical removal. However, biopsy or surgical resection of any adrenal mass prior to ruling out a pheochromocytoma is not recommended, as any manipulation of a catecholamine-secreting tumor without appropriate preoperative management can precipitate a hypertensive crisis.

Measurement of the plasma aldosterone to plasma renin ratio is indicated as part of the evaluation of an incidentally discovered adrenal mass in a patient with hypertension, but not in this individual who has normal blood pressure.

Not performing additional testing may miss a subclinical pheochromocytoma and would therefore not be an appropriate next step in management.

KEY POINT

- A patient with an incidentally noted adrenal mass should undergo biochemical testing for subclinical Cushing syndrome and pheochromocytoma, and those with hypertension should also be evaluated for primary hyperaldosteronism.

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Item 51 Answer: D

Educational Objective: Manage the limitations of hemoglobin A_{1c} measurements in a patient with diabetes mellitus and chronic kidney disease.

This patient should measure his postprandial glucose level. The hemoglobin A_{1c} measurement is not always reliable in the setting of chronic kidney disease; thus fingerstick blood glucose measurements should be closely evaluated to help guide therapy. This patient's slightly elevated fasting and premeal blood glucose values may be indicative of postprandial hyperglycemia that could be detected with postprandial glucose measurements and used to guide therapy. For patients trying to achieve hemoglobin A_{1c} levels less than 7.0%, fasting and premeal glucose targets usually are set at approximately 80 to 130 mg/dL (4.4-7.2 mmol/L). This patient's slightly out of range fasting and premeal glucose measurements seem at odds with the recent drop in his hemoglobin A_{1c} level to 6.2%. Specific scenarios unique to end-stage kidney disease can affect the accuracy of the hemoglobin A_{1c} measurement. Hemoglobin A_{1c} can be falsely elevated in the setting of chronic kidney disease due to carbamylated hemoglobin secondary to uremia interfering with some of the assays. Hemoglobin A_{1c} can be falsely decreased in the setting of a reduced erythrocyte lifespan, iron deficiency, blood transfusions, and increased erythropoiesis with erythropoietin use. In this patient, the fingerstick blood glucose measurements do not correlate with the most recent hemoglobin A_{1c} after initiation of erythropoietin. The hemoglobin A_{1c} value is falsely decreased after erythropoietin therapy as a result of a change in the proportion of young and old erythrocytes and a change in the rate of glycation.

The patient's fingerstick blood glucose values are elevated, which further increases risk for microvascular and macrovascular damage. The current regimen should be adjusted to decrease hyperglycemia.

Decreasing the insulin detemir dose would increase hyperglycemia based on daily blood glucose data provided by the patient.

Discontinuation of the preprandial insulin glulisine based on the falsely decreased hemoglobin A_{1c} level would increase the hyperglycemia noted in the fingerstick blood glucose values.

KEY POINT

- End-stage kidney disease in patients with diabetes mellitus can affect the accuracy of the hemoglobin A_{1c} measurement, which should not be used to guide therapy.

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Ng JM, Cooke M, Bhandari S, et al. The effect of iron and erythropoietin treatment on the A1c of patients with diabetes and chronic kidney disease. Diabetes Care. 2010 Nov;33(11):2310-3. [PMID: 20798337]

Item 52 Answer: A

Educational Objective: Diagnose an androgen-producing adrenal tumor.

The most appropriate diagnostic test to perform next is an abdominal CT scan to confirm the diagnosis of an androgen-producing adrenal tumor. Approximately 50% of androgen-producing adrenal tumors are benign adenomas, while the other half are malignant. Symptoms are usually minimal or absent in adult men. Women typically present with rapidly progressive signs and symptoms of androgen excess, including acne, hirsutism, and virilization (deepening of the voice, clitoromegaly, and male-pattern hair loss), and may also have irregular menses. In patients with clinical evidence of hyperandrogenism, biochemical testing is performed prior to imaging and should include measurement of serum testosterone and dehydroepiandrosterone sulfate (DHEAS), an adrenal androgen. This patient's biochemical evaluation has revealed marked elevation of DHEAS and mild elevation of testosterone, making an androgen-producing adrenal tumor the most likely diagnosis. DHEAS levels above 8 µg/mL (21.6 µmol/L) are diagnostic of an androgen-producing adrenal tumor. The elevated serum testosterone level seen in this patient is likely a consequence of the peripheral metabolism of adrenal androgens to testosterone. The serum testosterone level would be more than 150 to 200 ng/dL (5.2-6.9 nmol/L) in the setting of an androgen-producing ovarian tumor.

Performing a low-dose dexamethasone suppression test or pituitary MRI is not indicated because Cushing syndrome is unlikely with a normal 24-hour urine free cortisol level and in the absence of specific features of hypercortisolism (facial plethora, violaceous striae, and supraclavicular or dorsocervical fat pads).

Pelvic ultrasound is not an appropriate initial imaging test because the marked elevation of DHEAS makes an androgen-producing adrenal tumor much more likely than an ovarian neoplasm. Although the patient has a family history of polycystic ovary syndrome (PCOS), the tempo and severity of her clinical presentation are not in keeping with this disorder. Although adrenal androgen excess occurs in 30% to 40% of women with PCOS, only a mild elevation of DHEAS (3 µg/mL [8.1 µmol/L]) is expected.

KEY POINT

- In female patients, signs of androgen excess such as progressive hirsutism and virilization over a short period of time suggest the diagnosis of an androgen-producing adrenal or ovarian tumor.

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Cavlan D, Bharwani N, Grossman A. Androgen- and estrogen-secreting adrenal cancers. Semin Oncol. 2010 Dec;37(6):638-48. [PMID: 21167382]

Item 53 Answer: A

Educational Objective: Manage diabetes mellitus with continuous glucose monitoring.

There is a discrepancy between this patient's fingerstick blood glucose values and her hemoglobin A_{1c} values that can be quickly reconciled with a 72-hour continuous blood glucose monitoring system. Continuous blood glucose monitoring systems use an electrochemical enzymatic sensor to measure the glucose content of interstitial fluid via insertion of

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a subcutaneous needle. In some systems data recording can be made available in real time to the patient, whereas other models store the data for later access and analysis. Since she does not have kidney disease or anemia that could affect the accuracy of hemoglobin A_{1c} measurements, she likely has episodes of hyperglycemia not detected by her current monitoring efforts. Fingerstick blood glucose values only provide a small snapshot of the glucose variability that occurs throughout the day. Undetected hyperglycemia or hypoglycemia can lead to significant differences between the fingerstick blood glucose values and the expected hemoglobin A_{1c} level. Her wide range of fasting blood glucose values could be indicative of undetected overnight hypoglycemia. Intermittent continuous glucose monitoring is recommended when postprandial hyperglycemia, dawn phenomenon, or overnight hypoglycemia is suspected.

Lifestyle modifications are recommended for glycemic management; however, because this patient exercises in the evening, overnight hypoglycemia should be considered and evaluated with continuous glucose monitoring. Additional exercise may exacerbate the hypoglycemia.

This patient does not have evidence of postprandial hyperglycemia on her fingerstick blood glucose measurements, although it could be missed since she only measures after her meals periodically. Given the discrepancy in her blood glucose values and A_{1c} level, hypoglycemia should be ruled out first before increasing her insulin doses that may increase the risk of hypoglycemia.

KEY POINT

- Continuous glucose monitoring may be useful in persons with postprandial hyperglycemia, dawn phenomenon, or overnight hypoglycemia.

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Item 54 Answer: A

Educational Objective: Treat irregular menses and hirsutism in a patient with polycystic ovary syndrome.

The most appropriate treatment is combined oral contraceptive pills. Hirsutism is present in approximately 70% of women with polycystic ovary syndrome (PCOS). The combined oral contraceptive pill is the optimal treatment to address both this patient's concerns of menstrual irregularity and hirsutism. The estrogen component increases hepatic production of sex hormone–binding globulin, decreasing the patient's circulating free testosterone level. For women in whom hirsutism is a major concern, treatment is focused on reducing androgen production, decreasing the fraction of circulating free testosterone, and limiting androgen bioactivity to hair follicles. Coarse, thick hairs that are already noted on examination will need to be removed with a depilatory method; however, terminal hair growth will be slowed with combined oral contraceptive use. Oral contraceptives that contain 30 to 35 μg of ethinyl estradiol appear to be more effective in managing hirsutism than formulations containing less ethinyl estradiol. Six months of treatment is considered the minimal interval in which to determine the level of response. Adherence to an oral contraceptive regimen will provide this patient with predictable menses as well as contraceptive benefit. In addition, the risk of endometrial hyperplasia is diminished.

Intermittent progesterone withdrawal, although effective for decreasing the risk of endometrial hyperplasia, would have no effect on this patient's concern regarding hirsutism.

The levonorgestrel intrauterine system is a long-acting, reversible contraceptive device that diminishes long-term risk of endometrial hyperplasia in patients with PCOS; however, it provides no benefit for hirsutism and has no effect on androgen production.

Spironolactone is a potent antiandrogen and is very effective against male-pattern hirsutism in patients with PCOS. However, it offers no benefit for control of the menstrual cycle. When spironolactone is prescribed, patients should be counseled regarding the potential teratogenicity in male fetuses, and a concurrent reliable contraceptive method should be established to prevent fetal exposure. Pregnancy can still occur in patients with oligo-ovulatory PCOS, and reliance on menstrual irregularity is not a substitute for a more proven contraceptive plan.

KEY POINT

- The combined oral contraceptive pill is the optimal treatment to address both irregular menses and hirsutism in patients with polycystic ovary syndrome.

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Item 55 Answer: C

Educational Objective: Manage a patient with pheochromocytoma.

The most appropriate next step in management is to begin treatment with an α-adrenoceptor antagonist, such as phenoxybenzamine. The purpose of preoperative α-blockade is to provide blood pressure control and decrease the risk of cardiovascular complications related to excessive catecholamine release during intraoperative manipulation of the tumor. Most patients are treated for 1 to 2 weeks before surgery with phenoxybenzamine with upward titration based on blood pressure. The target blood pressure is below 130/80 mm Hg seated and greater than 90 mm Hg (systolic) standing. Because of phenoxybenzamine's side effects including orthostasis, nasal stuffiness, fatigue, and retrograde ejaculation, some clinicians use short-acting specific α-antagonists, such as prazosin, doxazosin, or terazosin. In patients with tachycardia, β-blockers

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can be added after α-blockade is achieved. Labetalol, a combined α- and β-blocking agent, also can be used, especially in patients with tachyarrhythmias. A heart rate of 60 to 70/min seated and 70 to 80/min standing can be targeted in most patients. Patients with pheochromocytoma who are normotensive also should be treated with α-blockers because they often become hypertensive during surgical resection.

Increasing the dosage of lisinopril does not address the need for preoperative pharmacologic management of the patient's pheochromocytoma with α-blockade.

Although indicated for tumor localization following the biochemical diagnosis of pheochromocytoma, a contrast-enhanced adrenal CT scan should not be performed until after an α-adrenoceptor antagonist has been initiated. Administering iodine contrast media to a patient who has not received α-blockade could incite a hypertensive crisis.

Similarly, the β-adrenoceptor antagonist propranolol should not be given prior to α-blockade because unopposed α-adrenoceptor stimulation could also precipitate a hypertensive crisis.

KEY POINT

- In patients with a confirmed diagnosis of pheochromocytoma, α-blockade should be instituted before surgery to reduce the risk of cardiovascular complications and to control blood pressure.

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Item 56 Answer: C

Educational Objective: Manage hormone replacement therapy in a patient with panhypopituitarism.

The patient's hypothyroidism is inadequately treated, causing symptoms of fatigue and weight gain and a low free thyroxine (T_4) level. Therefore, his levothyroxine dose should be increased. Patients with secondary hypothyroidism from pituitary dysfunction have low or low-normal thyroid-stimulating hormone (TSH) values which cannot be used to assess the adequacy of thyroid hormone replacement. Because of this, the levothyroxine dose is adjusted based on free T_4 levels instead of TSH values. His free T_4 is low, suggesting inadequate treatment as the likely cause of his symptoms.

The patient's desmopressin dosing is adequate to treat his diabetes insipidus. His symptoms are well controlled without evidence of excessive urination, and his serum sodium level is normal. In addition, increasing the dose would risk potentially causing water retention and hyponatremia.

He is on a physiologic dose of hydrocortisone. Hydrocortisone dose is not adjusted based on laboratory test results because his endogenous adrenocorticotropic hormone (ACTH) and cortisol levels will remain low on adequate therapy and are therefore not used to alter therapy. Instead, hydrocortisone is adjusted based on symptoms, such as orthostasis, weight loss, nausea, vomiting, and lightheadedness. He does not have these symptoms, so his cortisol deficiency is adequately treated. Increasing his hydrocortisone to higher than necessary doses increases the risk of iatrogenic Cushing syndrome and glucocorticoid-induced osteoporosis.

His testosterone value is normal, and he has normal morning erections. These are two signs that his hypogonadism is adequately treated. Possibly, his erectile dysfunction is a result of fatigue from hypothyroidism or is functional instead of physiologic.

There is no reason to stop somatropin. He has no evidence of residual tumor. Growth hormone (GH) replacement can improve lean mass distribution and quality of life in a patient with true GH deficiency, so it is reasonable to continue. Discontinuing GH will likely worsen his fatigue.

KEY POINT

- Patients with secondary hypothyroidism from pituitary dysfunction have low or low-normal thyroid-stimulating hormone values, so levothyroxine dose should be adjusted based on free thyroxine (T_4) level.

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Schneider HJ, Aimaretti G, Kreitschmann-Andermahr, et al. Hypopituitarism. Lancet. 2007 Apr 28;369(9571):1461-70. [PMID: 17467517]

Item 57 Answer: A

Educational Objective: Diagnose type 2 diabetes mellitus.

A fasting plasma glucose measurement is the most appropriate diagnostic test for this patient. Diabetes mellitus can be diagnosed with an abnormal result of one screening test performed on two separate occasions. Although the hemoglobin A_{1c} is normal in this patient, the fasting plasma glucose is abnormally elevated within the diagnostic range for diabetes mellitus. When discrepant results occur among different screening tests for diabetes, the American Diabetes Association recommends repeating the abnormal screening test. If the repeat fasting plasma glucose measurement is abnormal, the diagnosis of diabetes is confirmed. Screening for type 2 diabetes should begin in all asymptomatic patients at age 45 years. In adult patients with a BMI greater than or equal to 25, screening should occur at any age if one or more additional risk factors for diabetes is present.

Use of the hemoglobin A_{1c} as an initial screening test in this patient is appropriate as there is no evidence for anemia or kidney or liver disease that could decrease the reliability of the test. The value was normal and does not warrant a repeat measurement as the next diagnostic test to perform in this scenario.

A 2-hour 75-g oral glucose tolerance test can be used as a screening tool for diagnosing diabetes. Since this test was not initially used for screening in this patient, it is most

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appropriate to repeat the abnormal screening test (fasting plasma glucose) that was already used for comparison.

A random blood glucose measurement would be useful in this patient if he presented with classic hyperglycemic symptoms in the setting of a blood glucose level of 200 mg/dL (11.1 mmol/L) or above, as that would be diagnostic of diabetes. This patient is not symptomatic.

KEY POINT

- When discrepant results occur among different screening tests for diabetes mellitus, the American Diabetes Association recommends repeating the abnormal screening test.

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Item 58 Answer: A

Educational Objective: Diagnose Klinefelter syndrome.

The most appropriate diagnostic test to perform next is a karyotype. This patient has evidence of hypergonadotropic hypogonadism based on elevated gonadotropin levels and low testosterone level. Klinefelter syndrome is a common cause of hypergonadotropic hypogonadism and azoospermia, resulting in infertility. A 47,XXY karyotype is diagnostic of Klinefelter syndrome. Mosaic variants of this condition exist but typically present with oligoasthenospermia, testicular failure, or hypogonadism. Concomitant symptoms often include sexual dysfunction and generalized fatigue. Tall stature is a common finding. Patients with Klinefelter syndrome may fail to achieve puberty or may present after sexual maturation with azoospermia. Fertility may be achieved from ejaculated sperm, if present, or extracted testicular sperm; however, advanced reproductive techniques such as in vitro fertilization and intracytoplasmic sperm injection are necessary to achieve pregnancy. Some couples may opt to include genetic testing by preimplantation genetic diagnosis and embryo biopsy to avoid transmission of the disorder to subsequent generations. Typically, gonadotropin levels are high in patients with Klinefelter syndrome, representing testicular hypofunction. After plans for conception are completed, supplementation with exogenous androgens may be considered to prevent osteoporosis. Conception with donor sperm is an alternative fertility treatment option.

MRI of the pituitary would be needed only to rule out a pituitary mass in the setting of hypogonadotropic hypogonadism. Because this patient's gonadotropin levels are high, a pituitary mass is unlikely.

Scrotal ultrasound would identify small testicles in a patient with suspected Klinefelter syndrome, but it would not identify the cause of this patient's elevated gonadotropin levels.

Serum prolactin level would likely be normal, as Klinefelter syndrome is characterized by primary hypogonadism with normal prolactin levels. Therefore, measurement of serum prolactin is not the most useful test for this patient.

KEY POINT

- Klinefelter syndrome is a common cause of hypergonadotropic hypogonadism and azoospermia.

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Item 59 Answer: D

Educational Objective: Interpret thyroid function test results in an elderly patient.

Clinical follow-up with repeat measurement of thyroid-stimulating hormone (TSH) and free thyroxine (T_4) is the most appropriate management for this patient. In persons over 80 years of age, the serum TSH level may be mildly elevated above the typical reference range for younger adults. The upper limit of the normal range in this elderly population without thyroid dysfunction may be as high as 8.0 μU/mL (8.0 mU/L). Since this patient's TSH level is 6.4 μU/mL (6.4 mU/L), his clinical symptoms are nonspecific, and his physical examination is normal, additional evaluation or treatment is not indicated at this time. However, his clinical symptoms should be monitored, and his serum TSH and free T_4 levels should be measured repeatedly several times over a period of months to ensure that the TSH value is not part of a trend to the development of overt thyroid dysfunction.

Because this patient's serum free T_4 level is normal and a diagnosis of hypothyroidism has not been established, he does not require levothyroxine therapy.

Measurement of the serum total triiodothyronine (T_3) level is not typically helpful in diagnosing hypothyroidism because total T_3 levels may remain within the normal range well into the evolution of hypothyroidism. However, total T_3 levels are useful in evaluating patients with possible hyperthyroidism because the value may be elevated out of proportion to the T_4 level, and failure to recognize an elevated T_3 value may underestimate the degree of hyperthyroidism present.

Total T_4 measures both the bound and unbound thyroid hormone fractions, whereas the free T_4 reflects the unbound portion of hormone, and may more accurately reflect available hormone levels in patients who may have an abnormality in protein metabolism (such as liver or kidney disease). However, measurement of total T_4 in addition to free T_4 would not provide additional diagnostic information in this patient.

KEY POINT

- In patients over 80 years of age, the serum thyroid-stimulating hormone level may be mildly elevated above the typical reference range.

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Item 60 Answer: B

Educational Objective: Evaluate an incidentally noted adrenal mass.

The most appropriate diagnostic test to perform next is the low-dose dexamethasone suppression test to screen for the autonomous secretion of cortisol. The increasing use of imaging studies for various medical indications has revealed otherwise unrecognized adrenal masses in less than 1% of the population younger than 30 years and up to 7% of those older than 70 years. Ten to 15% of adrenal incidentalomas are functional, although most have no overt clinical manifestations. Therefore, testing is usually necessary to identify functional tumors secreting catecholamines, cortisol, or aldosterone. Of the functional adenomas, most secrete excessive amounts of cortisol. In subclinical Cushing syndrome (CS), classic signs or symptoms of cortisol excess are not observed; however, complications of long-standing hypercortisolism may result. The patient has two disorders that can be seen in association with subclinical CS: type 2 diabetes mellitus and osteoporosis. Obesity and hypertension are also common. The low-dose overnight dexamethasone suppression test is recommended as the initial screening test for this condition due to its high sensitivity. Screening for pheochromocytoma, such as by measuring 24-hour urine fractionated metanephrines and catecholamines, is also indicated in all patients with an incidentally noted adrenal mass.

Adrenal vein sampling (AVS) is not needed. AVS is most often performed to evaluate for a bilateral versus unilateral adrenal cause of primary hyperaldosteronism.

Measurement of plasma renin activity and aldosterone concentration is not indicated in patients without hypertension.

No further testing is also inappropriate. Although the imaging characteristics of the mass are in keeping with a benign adrenal adenoma, further diagnostic evaluation is needed. This includes testing for autonomous hormonal secretion and subsequent radiographic surveillance (first at 3-6 months and then annually for 1-2 years).

KEY POINT

- Ten to 15% of adrenal incidentalomas are functional; biochemical testing is needed to identify functional tumors secreting catecholamines, cortisol, or aldosterone.

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Item 61 Answer: E

Educational Objective: Treat acromegaly with transsphenoidal pituitary surgery.

Transsphenoidal resection of the pituitary adenoma is the initial treatment of choice in patients with acromegaly. It is also the only treatment that is potentially curative. Because this patient's tumor is invading the left cavernous sinus and compressing the optic chiasm, complete resection will likely not be possible; however, surgery can effectively debulk the tumor and preserve vision in addition to significantly decreasing growth hormone (GH) secretion as measured by insulin-like growth factor 1 (IGF-1) levels. In patients in whom complete resection is not possible, such as this patient, additional therapy may be required such as stereotactic radiation therapy or medical therapy to inhibit GH secretion or block its effect on the tissues. However, surgical resection remains an essential first step in the treatment of acromegaly.

A small number of GH-secreting pituitary adenomas co-secrete prolactin. Although dopamine agonist therapy with agents such as bromocriptine would treat the associated prolactin elevation, it is minimally effective in acromegaly and would not adequately treat GH secretion or address the mass effect of a GH-secreting adenoma.

A GH receptor blocker, pegvisomant, is available. Pegvisomant works in the peripheral tissues as an antagonist to GH but does not decrease its production by the tumor. This patient needs intervention to treat mass effect at this time because the tumor is damaging the optic chiasm and the patient's vision, and this treatment would not be expected to decrease the tumor size.

Somatostatin analogues, such as octreotide and lanreotide, inhibit GH secretion and are helpful in treating some patients with acromegaly. They are used primarily in patients with unresectable tumors without significant mass effect or those with a contraindication to surgery. They may also be used in patients with continued GH secretion following incomplete transsphenoidal resection. However, they would not be an appropriate treatment in this patient with a large, invasive, vision-threatening pituitary tumor.

Radiation therapy may be added to surgical or medical therapy to help increase the chance for remission or cure. Radiation to the pituitary carries a high risk of causing pituitary insufficiency and damage to surrounding tissues (particularly the optic nerves); therefore, it is not usually an initial treatment for acromegaly in most patients. In those in whom it is used, stereotactic surgery (gamma knife) is the preferred approach to minimize potential complications.

KEY POINT

- The primary therapy for acromegaly is transsphenoidal surgery to remove the causative growth hormone–secreting pituitary adenoma.

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Item 62 Answer: C

Educational Objective: Treat high-risk thyroid cancer postoperatively.

Radioactive iodine (RAI) therapy is the most appropriate postoperative treatment in this patient who is at high risk of

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cancer recurrence based on his age, the size of the primary tumor, the presence of vascular invasion and extrathyroidal extension, and the number of involved lymph nodes. He therefore may benefit from adjuvant RAI therapy, which may decrease the likelihood of recurrent disease in patients with nodal metastases. This is given in conjunction with levothyroxine suppression therapy, which is indicated in all patients who have had a total thyroidectomy. Because of his high-risk disease, it would be appropriate to lower the thyroid-stimulating hormone level to less than 0.1 μU/mL (0.1 mU/L) in the absence of contraindications such as pre-existing cardiovascular disease or age greater than 65 years.

Traditional chemotherapeutic agents, such as doxorubicin, are generally ineffective in the management of differentiated thyroid cancer and would not be indicated for this patient. In patients with anaplastic carcinoma of the thyroid, however, some studies have demonstrated a possible benefit with concomitant use of paclitaxel-based chemotherapy and external-beam radiotherapy. This patient has classic papillary thyroid cancer histology and would not benefit from such treatment.

External-beam radiotherapy is rarely used in patients with differentiated thyroid cancer. An exception would be the management of patients with inoperable disease that threatens to cause local extension into vital structures in the neck such as the trachea, esophagus, or major blood vessels.

Because of the extent of disease found at surgery and this patient's high risk of recurrence, providing no additional therapy would not be an appropriate next step in management.

KEY POINT

- A patient who has undergone total thyroidectomy for thyroid cancer and is at high risk for disease recurrence should receive adjuvant radioactive iodine therapy.

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Item 63 Answer: C

Educational Objective: Manage acquired type 1 diabetes mellitus.

This patient has an acquired form of type 1 diabetes mellitus caused by chronic pancreatitis (pancreoprivic diabetes), which necessitates the use of insulin for treatment of the hyperglycemia. Chronic pancreatitis results in permanent destruction of the pancreas and may impair both the endocrine and exocrine functions of the pancreas. The pancreatic exocrine abnormalities arise from loss of the pancreatic enzymes required for digestion and absorption of food. The pancreatic endocrine abnormalities can present in a similar manner as type 1 diabetes with hyperglycemia from insulin deficiency secondary to destruction of beta cells. Therefore insulin is the recommended treatment. Unlike autoimmune type 1 diabetes, chronic pancreatitis also destroys the pancreatic alpha cells causing a glucagon deficiency that increases the risk of spontaneous hypoglycemia. Glucagon acts on the liver to increase glucose production through glycogenolysis and gluconeogenesis. The recovery from hypoglycemia is also impaired with alpha cell destruction. Early recognition of hypoglycemic symptoms and strategic hypoglycemic treatment plans should be emphasized with patients with pancreoprivic diabetes.

Exenatide, a glucagon-like protein-1 (GLP-1) mimetic, suppresses glucagon and promotes insulin secretion. The pancreatic beta cell and alpha cell destruction associated with chronic pancreatitis precludes this treatment option. Postmarketing reports of pancreatitis are also cause for concern for the use of this class of medication in patients with a history of pancreatitis.

The sulfonylurea glipizide increases insulin secretion. The effect would likely be minimal to nonexistent in this patient with hyperglycemia resulting from substantial beta cell destruction from chronic pancreatitis.

Metformin decreases hepatic glucose output by inhibiting gluconeogenesis and increases insulin-mediated glucose utilization in peripheral tissues. Metformin is a first-line agent for initial treatment of type 2 diabetes; however, this patient has an insulin deficiency from pancreatic beta cell destruction and should be treated as a patient with type 1 diabetes.

KEY POINT

- Hyperglycemia caused by chronic pancreatitis is an acquired form of type 1 diabetes mellitus and should be treated with insulin.

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Item 64 Answer: A

Educational Objective: Treat infertility related to polycystic ovary syndrome.

The most appropriate treatment is a selective estrogen receptor modulator (SERM) such as clomiphene citrate. SERMs are the established first-line treatment for ovulation induction in anovulatory patients with infertility from polycystic ovary syndrome (PCOS). Typically, therapy is started after menses and is given orally for 5 days. Common side effects include vasomotor symptoms and mood changes. Escalating doses of clomiphene are typically prescribed if a patient does not ovulate on lower doses. More recently, evidence suggests the effectiveness and possible superiority of aromatase inhibitor therapy (such as with letrozole) in women with PCOS for ovulation induction. However, this therapy is not currently FDA approved for this indication.

A small subset of patients with PCOS may require in vitro fertilization, but this therapy is typically explored only

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after several failed cycles of ovulation induction with clomiphene citrate.

In patients with clomiphene resistance, gonadotropin therapy would be an appropriate next step; however, caution is warranted because higher-order multiple gestation may result.

A 2012 Cochrane review of the effect of insulin-sensitizing drugs in women with infertility and PCOS included 44 trials, the majority of which involved metformin. Rates of pregnancy were improved with metformin compared with placebo and metformin plus clomiphene compared with clomiphene alone, but metformin did not change rates of live births compared with placebo or with clomiphene compared to clomiphene alone.

KEY POINT

- Selective estrogen receptor modulators such as clomiphene citrate are the established first-line treatment for ovulation induction in anovulatory patients with infertility from polycystic ovary syndrome.

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Item 65 Answer: C

Educational Objective: Treat a microprolactinoma in a postmenopausal woman.

No therapy is necessary at this time, and the patient should be retested in 12 months. The patient has a microprolactinoma, but she is postmenopausal. Luteinizing hormone and follicle-stimulating hormone levels are normally high in postmenopausal women because of ovarian failure; however, her levels are lower than expected, likely because the elevated prolactin is providing negative feedback. This causes hypogonadism but is not clinically relevant because she is already hypogonadal from normal menopause. She has minimal symptoms from menopause and is tolerating it well.

The prolactinoma was found incidentally. On MRI, it has no concerning features, and her other pituitary hormone levels are normal. Although no treatment is necessary for this asymptomatic patient, it is advisable to retest in 6 to 12 months to make sure that the tumor does not grow.

Dopamine agonists, such as cabergoline, are used to treat symptomatic prolactinomas, but it is not necessary in this asymptomatic patient.

Radiosurgery is not necessary. It is an option to treat pituitary tumors that are not amenable to standard surgery or cannot be fully resected, but it is not indicated for this asymptomatic patient.

Transsphenoidal resection of the pituitary tumor is overly invasive and unnecessary because she is doing well. In addition, first-line therapy for symptomatic prolactinomas are dopamine agonists, not surgery.

KEY POINT

- Microprolactinomas in asymptomatic patients do not require treatment; however, surveillance is recommended.

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Item 66 Answer: B

Educational Objective: Manage diabetic neuropathy.

Duloxetine is a reasonable initial option for this patient's painful peripheral neuropathy. The typical presentation for distal symmetric polyneuropathy is a bilateral "stocking-glove" distribution. Damage to the small nerve fibers can result in pain, numbness, burning, and tingling. It can also impair light touch and temperature sensation. Damage to the large nerve fibers leads to abnormal vibration sensation and proprioception. Diminished or loss of ankle reflexes is commonly seen early with diabetic polyneuropathy. Motor weakness can occur as the polyneuropathy progresses. Several classes of drugs are frequently used for symptomatic pain relief, including the tricyclic antidepressants (amitriptyline), other classes of antidepressants (duloxetine, venlafaxine), anticonvulsants (pregabalin, gabapentin, valproate), and capsaicin cream. There are few head-to-head comparison trials for these classes of drugs for distal symmetric polyneuropathy, thus selection must take into consideration the potential risks and benefits associated with each drug for an individual patient. Duloxetine has fewer risks than amitriptyline for this patient given his cardiac history.

Tricyclic antidepressants, such as amitriptyline, should be used cautiously in patients with known cardiac disease due to an association between this class of drugs and arrhythmias, heart block, and sudden death. The patient's history of cardiac disease and a first-degree atrioventricular block may increase his risk of side effects from amitriptyline.

A nerve conduction study is not routinely required for diagnosis or management in patients with diabetes with a typical presentation of symmetric distal polyneuropathy. Atypical clinical features should prompt additional work-up, including electrophysiologic testing.

Vitamin B_{12} deficiency has been associated with long-term use of metformin and can present with peripheral neuropathy. It is also commonly seen in the setting of megaloblastic anemia. It is unlikely that vitamin B_{12} deficiency is the cause of this patient's peripheral neuropathy as he has a classic presentation for symmetric distal polyneuropathy, discontinued metformin 2 years ago, and has a normal complete blood count.

KEY POINT

- Treatment options for diabetic polyneuropathy include the tricyclic antidepressants, other classes of antidepressants (duloxetine, venlafaxine), anticonvulsants (pregabalin, gabapentin, valproate), and capsaicin cream.

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Item 67 Answer: D

Educational Objective: Evaluate hypoglycemia in a patient without diabetes mellitus.

This patient should undergo a 72-hour fast with hypoglycemic testing at the time of symptomatic hypoglycemia. He had symptomatic hypoglycemia with prolonged fasting (>5 hours) overnight that resolved with glucose administration. Since he is not currently hypoglycemic or symptomatic, fasting is necessary in an attempt to recreate the metabolic scenario that induced the hypoglycemia to allow definitive diagnosis. Glucose and hypoglycemic studies, including measurement of insulin, C-peptide, proinsulin, and β-hydroxybutyrate levels, should be obtained at the beginning of the fast and then repeated every 6 hours until the blood glucose level falls below 60 mg/dL (3.3 mmol/L), at which time they should be repeated every 1 to 2 hours until (1) symptomatic hypoglycemia (≤45 mg/dL [2.5 mmol/L]) occurs, (2) asymptomatic hypoglycemia (≤55 mg/dL [3.0 mmol/L]) occurs with previously documented Whipple triad, or (3) the 72-hour fast concludes. Whipple triad consists of three components: neuroglycopenia, concurrent hypoglycemia, and resolution of symptoms with correction of hypoglycemia.

Hypoglycemic studies are not adequately informative when the patient is not experiencing symptomatic hypoglycemia; therefore, testing now would not be appropriate.

Mixed-meal testing involves ingestion of a meal containing a mixture of protein, fat, and carbohydrates intended to raise the plasma blood glucose to assess the metabolic response to increased glucose. This test is appropriate when symptomatic hypoglycemia occurs within 5 hours after meal consumption (postprandial hypoglycemia). However, this patient's symptomatic hypoglycemia occurred 7 hours after his last meal; therefore, evaluation for postprandial hypoglycemia with a mixed-meal test would not be appropriate.

Oral glucose tolerance testing was previously used to evaluate postprandial hypoglycemia. However, it has not demonstrated effectiveness for this purpose and also would not be an appropriate study for evaluating fasting hypoglycemia.

KEY POINT

- Symptomatic fasting hypoglycemia is best evaluated with glucose and hypoglycemic studies preceding and during a 72-hour fast.

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Item 68 Answer: D

Educational Objective: Diagnose Asherman syndrome with transvaginal ultrasound.

The most appropriate diagnostic test to perform next is a transvaginal ultrasound. This patient has likely developed Asherman syndrome (AS). Because the hormonal evaluation in this patient supports an intact hypothalamic-pituitary-ovarian axis, a structural abnormality such as AS should be suspected. AS is an uncommon complication of dilatation and curettage, intrauterine device placement, or surgical procedures such as hysteroscopic myomectomy; it is caused by lack of basal endometrium proliferation and formation of adhesions (synechiae). Diagnosis should be considered in any woman with amenorrhea and previous exposure to uterine instrumentation. The typical presentation is with secondary amenorrhea, at times associated with cyclic pelvic pain, created by distention of the uterine cavity where pockets of functional endometrium persist but efflux of menstrual flow is blocked or slowed by adhesion formation. Although some patients with AS may be completely amenorrheic, others may demonstrate hypomenorrhea and report scant menses compared with the volume of their menstrual flow before the procedure. AS most commonly occurs in an inflammatory setting such as endometritis or septic abortion. AS may also occur as a result of an overly aggressive curettage. In a patient with AS, transvaginal ultrasound will show a thin endometrial stripe and may reveal small pockets of fluid where menstrual flow has been trapped by neighboring adhesions. A functional uterine examination, such as hysterosalpingogram or saline sonohysterogram, confirms the diagnosis. Treatment consists of hysteroscopic resection of lesions.

Given this patient's normal gonadotropin levels, a pituitary cause for her secondary amenorrhea is unlikely; therefore, imaging of the pituitary is not warranted at this time.

Premature ovarian insufficiency is not the most likely diagnosis given this patient's normal estradiol and gonadotropin levels; therefore, a peripheral karyotype would be expected to be normal and should not be performed.

Results of a progestin withdrawal test are used to delineate between an estrogen-deficient state (no bleeding) and an estrogen-sufficient state (withdrawal bleeding). If the patient is producing estrogen, she will have withdrawal bleeding within 1 week of completing a course of progesterone. If no withdrawal bleeding occurs after the progesterone challenge, then the patient has either a low-estrogen state and hypothalamic amenorrhea is the diagnosis, or there is uterine outflow blockage. This patient's history of a previous uterine procedure prior to the onset of amenorrhea and the possibility of denuded endometrium where synechiae are present will make a negative test (no withdrawal bleeding) uninterpretable.

KEY POINT

- The diagnosis of Asherman syndrome should be considered in any woman with amenorrhea and previous exposure to uterine instrumentation; the classic presentation is with secondary amenorrhea and sometimes cyclic pelvic pain.

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Item 69 Answer: C

Educational Objective: Identify postprandial hyperglycemia as a cause of elevated hemoglobin A_{1c} levels.

This patient should measure her postprandial blood glucose level. Given the patient's young age and lack of other major comorbidities, her hemoglobin A_{1c} goal is less than 6.5% to 7.0%. Postprandial hyperglycemia often remains undetected but still contributes to elevated hemoglobin A_{1c} values. The effect is more profound when the hemoglobin A_{1c} is close to 7.0%. Adequate meal-time coverage with insulin can be determined by measuring postprandial blood glucose levels. If her 1- to 2-hour postprandial blood glucose values are elevated above 180 mg/dL (10.0 mmol/L), her meal-time insulin should be increased or the composition of her meals should be altered to decrease her blood glucose. Changing her diet if it is causing postprandial hyperglycemia could eventually lead to lower insulin requirements.

Checking her postprandial blood glucose values first will help identify where the hyperglycemic issue arises that keeps her hemoglobin A_{1c} above goal.

Increasing her glargine dose will not adequately affect postprandial hyperglycemia and may lead to overnight or fasting hypoglycemia.

Overnight glucose abnormalities can be identified with the measurement of a 3 AM blood glucose level. Large fluctuations in fasting blood glucose values or consistent fasting hyperglycemia can be clues to overnight hypoglycemia with subsequent rebound hyperglycemia (Somogyi effect) or hyperglycemia as a result of rising catecholamines (dawn phenomenon). The patient reports stable fasting and preprandial glucose values throughout the day. The most likely timing for glucose abnormalities that would affect her hemoglobin A_{1c} value is in the postprandial state.

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that slows gastric emptying and suppresses glucagon secretion. Although it has a modest effect on hemoglobin A_{1c} lowering, metformin remains first-line therapy for type 2 diabetes and should be continued as part of her regimen.

KEY POINT

- Monitoring postprandial blood glucose levels can be useful to assess prandial insulin coverage in patients who have type 2 diabetes mellitus with at-goal preprandial readings but with hemoglobin A_{1c} values not at goal.

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Item 70 Answer: B

Educational Objective: Treat Graves ophthalmopathy.

Methimazole is most appropriate for this patient with Graves ophthalmopathy (GO). GO may be manifested by lateral gaze palsy, scleral injection, periorbital edema, and pressure sensation behind the eyes. Additional manifestations include proptosis, lid lag, and, if severe, decreased visual acuity. Excess deposition of glycosaminoglycans in the retro-orbital space results in increased pressure; the ensuing compression of the muscles and cranial nerves causes the ocular palsy. Most patients with GO have mild, nonprogressive symptoms that do not require specific treatment. The decision to treat depends upon the severity and activity of the disease. For patients who need treatment, initial therapy should target controlling the hyperthyroidism. Methimazole will rapidly lower circulating thyroid hormone levels, may reduce serum thyroid autoantibody titers, and may assist in controlling GO symptoms. Additional therapy to control symptoms includes use of ocular lubricants and taping of the eyelids at night (if the lids are unable to completely cover the eye). Because cigarette smoking increases the activity of GO and impairs the response to therapy, smoking cessation is of paramount importance.

External-beam radiotherapy is reserved for treatment of severe GO but typically is employed if symptoms persist or worsen in spite of return to the euthyroid state.

Because radioactive iodine (RAI) treatment has been associated with (at least transient) worsening of GO due to an initial increase in circulating antibody levels, its use is not recommended in patients with moderate to severe GO. When RAI is used, pretreatment with a glucocorticoid to mitigate the rise in antibody levels is recommended prior to RAI therapy.

Total thyroidectomy is typically recommended for long-term control of Graves disease in patients with active GO when medical therapy fails to induce a remission. However, returning the patient to a state of euthyroidism is advisable before surgery. Surgical decompression is also an option to control active GO, particularly if there is compression of the optic nerve.

KEY POINT

- Initial treatment of Graves ophthalmopathy is normalization of thyroid function.

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Item 71 Answer: B

Educational Objective: Diagnose primary hyperaldosteronism as a cause of secondary hypertension.

The most appropriate diagnostic test to perform next is to measure the plasma aldosterone-plasma renin activity ratio. This patient has resistant hypertension, defined as blood pressure

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that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which is a diuretic. Resistant hypertension may occur in as many as 10% of patients with hypertension. Although this patient is being treated with a diuretic, he has significant hypokalemia in the presence of treatment with an ACE inhibitor and potassium supplementation. This raises the possibility of primary hyperaldosteronism as a cause or contributing factor of his resistant hypertension. Appropriate initial evaluation for this diagnosis is measurement of the plasma aldosterone-plasma renin activity ratio. If positive, confirmatory testing is usually accomplished with intravenous salt loading, fludrocortisone suppression testing, or captopril testing. If confirmed, adrenal imaging is indicated to determine if hyperaldosteronism is due to a bilateral or unilateral cause. Mineralocorticoid receptor antagonists (such as spironolactone) are indicated for patients with a bilateral cause of primary hyperaldosteronism and those with a unilateral cause who refuse or are not candidates for surgery.

Dexamethasone suppression testing is used to evaluate for glucocorticoid excess. However, this patient is not taking exogenous glucocorticoids and has no physical examination findings (fat redistribution, striae) or laboratory studies (glucose metabolism abnormalities) suggesting Cushing syndrome. Therefore, testing for this possibility is not an appropriate next step in diagnosis.

Measurement of plasma metanephrines and catecholamines is used to evaluate for the possibility of pheochromocytoma, which classically presents with the triad of diaphoresis, headache, and tachycardia, none of which are present in this patient. In addition, pheochromocytoma would not explain the patient's hypokalemia.

Renal artery Doppler flow studies may be helpful in evaluating for renovascular hypertension. However, most cases of renovascular hypertension occur in patients over 50 years of age and are associated with atherosclerotic cardiovascular disease or evidence of functional impairment of the kidney, neither of which are apparent in this patient.

KEY POINT

- Patients with suspected primary hyperaldosteronism as a cause of resistant hypertension should be screened with a plasma aldosterone-plasma renin activity ratio.

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Item 72 Answer: D

Educational Objective: Treat substernal goiter with compressive symptoms.

This patient should undergo thyroidectomy to treat his obstructive substernal goiter and prevent further airway compromise, which may be rapid and fatal. The thyroid nodule biopsy findings obtained 5 years ago most likely represent adenomatous hyperplasia, and the sonographic features of the gland and slow progression of the compressive symptoms support a diagnosis of a benign lesion. He has evidence of compressive symptoms on physical examination, with facial flushing when raising his arms (Pemberton sign). The flushing indicates venous outflow obstruction by the goiter as the vessels course through the thoracic inlet. Additionally, his symptoms of dysphagia and change in voice quality may suggest a compressive effect on the esophagus and recurrent laryngeal nerves, respectively. Surgical removal of the thyroid offers the best option for immediate relief of symptoms and identification of a possible underlying malignancy.

External-beam radiotherapy can result in eventual shrinkage of the thyroid but will not provide immediate relief of his obstructive symptoms, is unlikely to be curative, potentially increases the risk of secondary malignancy, and is associated with significant morbidity.

Levothyroxine therapy has been shown to reduce thyroid volume by up to 20%, but the clinical significance of this small change in volume with such a large goiter is unlikely to improve symptoms. Additionally, levothyroxine therapy may take many months to years to reduce the thyroid volume, and this patient needs immediate relief of his obstructive symptoms.

Radioactive iodine has been used to shrink multinodular goiters; the volume change is also gradual and optimal reduction averages 40%. However, radioactive iodine therapy may be risky in this patient because acute swelling of the thyroid after iodine uptake can lead to compromise of the vascular structures at the level of the thoracic inlet and further compression of the trachea.

KEY POINT

- In patients with multinodular goiter with compressive features, thyroidectomy is most likely to provide immediate relief of symptoms, decrease the risk of fatal airway compromise, and possibly identify underlying malignancy.

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Item 73 Answer: B

Educational Objective: Evaluate primary infertility with a hysterosalpingogram.

The test most likely to be diagnostic is a hysterosalpingogram (HSG) to evaluate tubal patency. Primary infertility due to a tubal abnormality is common and is best evaluated with dynamic testing of the female reproductive tract under fluoroscopy with an HSG. This patient, owing to her history of pelvic inflammatory disease, is likely to have a distal tubal occlusion and resultant hydrosalpinx. Many women with hydrosalpinx have no symptoms; however, symptoms may include pelvic pain (both unilaterally and bilaterally) and chronic vaginal discharge. Confirmatory evaluation should

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include diagnostic laparoscopy, but this is not typically performed as first-line evaluation given the need for general anesthesia, intubation, and recovery. Repair of the fallopian tubes may be possible with microsurgical techniques; however, reocclusion is possible and the risk of subsequent ectopic pregnancy is high. Many women elect to proceed with in vitro fertilization in lieu of tubal surgery.

Ovarian reserve assessment and semen analysis are essential when evaluating a couple with infertility. Ovarian reserve assessment can be accomplished with early follicular phase testing of follicle-stimulating hormone (FSH) or anti-müllerian hormone (AMH). Transvaginal ultrasound in the early follicular phase allows for counting of antral follicles in each ovary, which if present at greater than eight bilaterally support normal ovarian reserve. However, given this patient's history of pelvic inflammatory disease and her husband's history of fathering a child in a previous marriage, HSG is the diagnostic test that is most likely to reveal an abnormality.

Semen analysis can be performed after a short window of abstinence on an ejaculated sperm specimen. However, it is unlikely to be helpful in this patient's husband.

Karyotyping is usually not indicated as part of the initial evaluation of unexplained female infertility because of the low incidence of discovered abnormalities.

Specialized laboratories with andrology services evaluate sperm concentration, sperm motility, and sperm morphology. Ovarian reserve may be evaluated by serum testing (day 3 follicle-stimulating hormone level, AMH level) or by transvaginal ultrasound assessment of antral follicle count.

KEY POINT

- Primary infertility due to a tubal abnormality is common, particularly in women with a history of pelvic inflammatory disease, and is best evaluated with a hysterosalpingogram.

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Item 74 Answer: B

Educational Objective: Evaluate newly diagnosed medullary thyroid cancer.

The next most appropriate step in the management of this patient with medullary thyroid cancer (MTC) and multiple endocrine neoplasia type 2A (MEN2A) is to evaluate for the presence of a pheochromocytoma by measurement of fractionated plasma metanephrines. All patients with a cytologic diagnosis of MTC should undergo testing of the tumor for genetic abnormalities as the initial step in their evaluation as 25% of patients with MTC will have the inherited form. Identification of a *RET* mutation in this patient means that the he has MEN2A, an inherited syndrome associated with hyperparathyroidism and pheochromocytoma. Failure to identify and treat a pheochromocytoma prior to surgery can result in an intraoperative hypertensive crisis and, potentially, death.

While it is important to assess the risk of metastatic disease in this high-risk patient, 18-fluoro-deoxyglucose positron emission tomography scanning is not the ideal imaging modality in patients with MTC, as there is a high false-negative rate. CT of the lungs and liver is a more effective means of identification of distant metastases.

While evaluation for hyperparathyroidism by measuring the serum parathyroid hormone level is indicated in this patient with MEN2A, it is not the most appropriate next step in management. Testing for hyperparathyroidism is recommended prior to surgery because the parathyroid disease can be managed simultaneously with the thyroid cancer, but would not be an appropriate step before evaluating a patient with MEN2A for the presence of pheochromocytoma.

Total thyroidectomy and lateral neck dissection should not be performed until it is confirmed that this patient does not have a coexisting endocrine neoplasm owing to the high intraoperative risk associated with untreated pheochromocytoma. If identified, pheochromocytomas should be surgically removed prior to thyroidectomy.

Genetic counseling is a very important component of the treatment plan for all patients with newly diagnosed MEN2A as first-degree relatives are at high risk for also having the *RET* mutation. With a nearly 100% penetrance for development of MTC in carriers of *RET* mutations, referral to a team with experience in the management of these disorders is critical for timely diagnosis and treatment.

KEY POINT

- All patients with multiple endocrine neoplasia type 2A should undergo testing to exclude pheochromocytoma prior to thyroidectomy; an elevated level of plasma fractionated metanephrines should prompt treatment for pheochromocytoma before addressing the thyroid malignancy.

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American Thyroid Association Guidelines Task Force.2015 Thyroid. [PMID: 25810047]

Item 75 Answer: C

Educational Objective: Treat severe hypercalcemia.

This patient has severe, malignancy-related (non–parathyroid hormone [PTH]–mediated) hypercalcemia with associated mental status changes and acute kidney injury. Hemodialysis is generally reserved for patients with extremely high serum calcium levels (>18 mg/dL [4.5 mmol/L]) associated with acute kidney injury that precludes other acute treatments because it is able to rapidly lower serum calcium and provide careful management of volume status and electrolytes. Both hemodialysis and peritoneal dialysis are options, although hemodialysis more rapidly lowers calcium levels.

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CONT.

Calcitonin is a rapidly acting agent that interferes with osteoclast function and promotes kidney excretion of calcium. However, its calcium-lowering effect is relatively weak, and it is only able to lower serum calcium levels by 1 to 2 mg/dL (0.25-0.50 mmol/L) over 4 to 6 hours, which would not be optimal lowering of this patient's very high calcium level. Calcitonin will bring her calcium levels down, but not enough to alleviate her symptoms.

Cinacalcet, a calcimimetic agent, is an option for lowering calcium for symptomatic patients, but it is not indicated to acutely reduce life-threatening hypercalcemia.

Intravenous bisphosphonates are used for treatment of malignancy-induced hypercalcemia, with zoledronic acid or pamidronate the most common agents. However, onset of action is not rapid, and bisphosphonates are contraindicated in severe kidney injury. Therefore, zoledronic acid would not be an appropriate next step in treatment.

Once the serum calcium has been lowered by dialysis, calcitonin or an intravenous bisphosphonate may be used to keep the calcium levels at a manageable level. The use of dialysis in the patient is strictly for resolution of the acute mental status changes from the elevated calcium level, and longer-term management of hypercalcemia is required.

KEY POINT

- For patients with serum calcium levels greater than 18 mg/dL (4.5 mmol/L) with neurologic symptoms or acute kidney injury, hemodialysis is an appropriate choice to quickly reduce calcium levels.

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Item 76 Answer: D

Educational Objective: Treat hypoglycemic unawareness.

This patient should decrease his meal-time insulin and continue metformin. He has hypoglycemic unawareness secondary to a diminished counterregulatory response that has developed in the setting of repeated episodes of hypoglycemia. His hypoglycemia occurs in the postprandial state, thus the meal-time insulin should be decreased to allow permissive hyperglycemia for 2 to 3 weeks. Permissive hyperglycemia is defined as allowing an increase in blood glucose values to the level at which no further episodes of hypoglycemia occur. Using less stringent glycemic goals during this period will provide the body an opportunity to reset the counterregulatory response to hypoglycemia to a more appropriate blood glucose range, if possible. Although developing mutual hemoglobin A_{1c} goals with the patient is important, hypoglycemia in this scenario precludes reaching his goal safely. Once he no longer has hypoglycemia, changes to the meal-time insulin doses or to meal content and volume can be evaluated to fine-tune his regimen while avoiding hypoglycemia.

Continuing the current regimen places the patient at increased risk for continued hypoglycemia in the setting of hypoglycemic unawareness.

Increasing the metformin dose may improve insulin sensitivity and decrease hepatic gluconeogenesis, which could improve the hyperglycemia and/or worsen the hypoglycemia. An increased metformin dose does not address the serious complication of hypoglycemic unawareness, which must be corrected first.

Pramlintide could decrease the hemoglobin A_{1c} to the patient's goal; however, hypoglycemia is a side effect of pramlintide in conjunction with insulin use. This may further increase the risk of hypoglycemia in this scenario. Pramlintide is an amylin mimetic that decreases glucagon secretion and increases satiety by decreasing gastric emptying. Pramlintide should be considered when the intended reduction in hemoglobin A_{1c} is modest and the desired effects are a reduction in both weight and postprandial hyperglycemia.

KEY POINT

- Treatment for hypoglycemic unawareness is to reduce the insulin dose and allow permissive hyperglycemia at all times for several weeks to provide the body an opportunity to reset the counterregulatory response to hypoglycemia to a more appropriate blood glucose range.

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Item 77 Answer: C

Educational Objective: Diagnose elevation of luteinizing hormone related to polycystic ovary syndrome.

The most likely cause of this patient's false-positive results using the urinary luteinizing hormone (LH) kit is polycystic ovary syndrome (PCOS). Women with PCOS typically have elevated resting LH levels, which may be mistaken on home urinary LH kits for ovulation. The primary clinical manifestations of PCOS are menstrual irregularity (oligomenorrhea or amenorrhea), ovulatory dysfunction with resultant infertility, insulin resistance, and hyperandrogenism. Oligo-ovulation or anovulation can result in endometrial hyperplasia and/or infertility. Hyperandrogenism presents as hirsutism, acne, or androgenic alopecia. Most patients with PCOS also have insulin resistance, and studies have shown an increased incidence of metabolic syndrome, obesity, impaired glucose tolerance, and frank type 2 diabetes mellitus. PCOS remains a diagnosis of exclusion that is made both clinically and with ancillary testing. A patient with PCOS with a positive urinary LH measurement result may interpret this as a true LH surge and expect ovulation to be imminent. Attempts at conception with intercourse or insemination may be focused on this reading and may therefore be ineffective. A more accurate

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assessment of LH surge and anticipated ovulation in patients with PCOS would be through transvaginal identification of ovarian folliculogenesis and confirmatory serum assessment of reproductive hormones.

Late-onset (nonclassic) congenital adrenal hyperplasia, although a common cause of hirsutism and oligo-ovulation, is typically associated with normal or low LH levels owing to the negative feedback of elevated androgens of adrenal origin on the anterior pituitary.

Functional hypothalamic amenorrhea affects 3% of women between the ages of 18 and 40 years and is a diagnosis of exclusion. Risk factors for this condition include a low body weight and fat percentage, rapid and substantial weight loss, eating disorders, excessive exercise, severe emotional stress, severe nutritional deficiencies, and chronic or acute illness. FSH and LH levels are inappropriately low or normal and cannot account for a positive urinary LH test.

Hypothyroidism and elevated serum prolactin levels suppress rather than elevate serum LH levels and would not account for this patient's increased urinary LH measurement.

KEY POINT

- Women with polycystic ovary syndrome typically have elevated resting luteinizing hormone (LH) levels, which may be mistaken on home urinary LH kits for ovulation.

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Item 78 Answer: C

Educational Objective: Treat a high-risk patient with osteoporosis.

After counseling about smoking cessation, this patient should continue her current alendronate therapy. She has documented osteoporosis and is at high risk for subsequent fractures due to multiple risk factors, including current smoking and a previous fracture. Her bone mineral density (BMD) has been well maintained on an oral bisphosphonate for the last several years. The best way to evaluate a dual-energy x-ray absorptiometry (DEXA) scan from measurement to measurement is to compare the bone mineral density readings from year to year, not the T-score. A change in BMD that is less than about 4% (or the percentage noted by the DEXA machine manufacturer) is not considered a statistically significant change. This regimen should be considered successful therapy since the goal of bisphosphonates is not to build bone mass but to stabilize bone loss. Since this patient has had stable BMD while on alendronate, there is no indication to convert to a more invasive, expensive option at this time. It will be important, however, to continue to follow her for atypical fractures of the long bone due to her prolonged bisphosphonate treatment. If leg pain or an atypical fracture is noted, bisphosphonate therapy should be discontinued.

Denosumab is a receptor activator of nuclear factor κB (RANK) ligand inhibitor FDA approved for the treatment of osteoporosis in postmenopausal women who are at high risk of fracture. Since this patient has not failed bisphosphonate therapy (shown a significant decrease in BMD while on bisphosphonate therapy) nor is she intolerant of the current therapy, there is no reason to change her therapy.

Teriparatide is appropriate as first-line therapy for patients at high risk for fracture (T-score < -3.0) or who have experienced progressive osteoporotic disease while on bisphosphonate therapy. This change would be unnecessary since the patient's BMD has been maintained for the past 5 years.

A drug holiday is indicated for patients who have been on bisphosphonate therapy for 3 to 5 years, have had no progression of the disease, and have minimal risk factors for additional fractures. This patient has multiple risk factors for fractures; therefore, a drug holiday would not be appropriate.

KEY POINT

- In patients at high risk for osteoporosis, it is appropriate to continue bisphosphonate therapy alone if adequate bone stability has been achieved.

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National Osteoporosis Foundation (www.my.nof.org/bone-source). Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2014.

Item 79 Answer: D

Educational Objective: Manage primary hyperaldosteronism.

The most appropriate treatment for this patient is spironolactone. He has primary hyperaldosteronism (PA) due to a bilateral adrenal source as evidenced by the lack of lateralization on adrenal vein sampling (AVS). Bilateral adrenal hyperplasia is the most common etiology of PA, accounting for approximately 60% of cases, and spironolactone is the treatment of choice. Spironolactone is a mineralocorticoid receptor (MR) antagonist that can improve blood pressure, normalize serum potassium concentration, and reduce excess cardiovascular risk related to hyperaldosteronism. Eplerenone is an alternative MR antagonist that is less likely to cause gynecomastia in men because of greater MR selectivity; however, use of eplerenone for this indication is off-label. Antagonists of the aldosterone-sensitive sodium channel (amiloride) can be used as second-line therapy.

Bilateral adrenalectomy is not appropriate for the routine management of PA, as this would risk primary adrenal failure, thus necessitating life-long glucocorticoid and mineralocorticoid therapy.

Dexamethasone, a long-acting synthetic glucocorticoid, has a role in treating only a small percentage of patients who have glucocorticoid-remedial hypertension, a very rare autosomal dominant condition resulting from ectopic expression of aldosterone synthase in the cortisol-producing zona

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fasciculata. Administration of dexamethasone will suppress pituitary adrenocorticotropic hormone (ACTH) secretion in these patients and therefore mineralocorticoid production. However, hyperaldosteronism in most patients is independent of ACTH secretion, and suppression with exogenous glucocorticoid is not an effective therapy.

Left adrenalectomy should not be performed because the patient has a bilateral cause of PA. The left adrenal adenoma detected by CT scan is an incidental finding and is likely not the cause of this patient's hyperaldosteronism. Because nonsecreting adrenal adenomas are common, AVS is needed in most patients with hyperaldosteronism to determine the source of aldosterone secretion when imaging studies show an adrenal adenoma to assess its contribution to excess mineralocorticoid production. AVS should be done at a high-volume referral center due to a high risk of complications when significant procedural experience is lacking.

KEY POINT

- For patients with primary hyperaldosteronism due to bilateral adrenal hyperplasia, medical therapy with a mineralocorticoid antagonist such as spironolactone is the treatment of choice because of its proven efficacy to lower blood pressure, normalize serum potassium concentration, and reduce cardiovascular risk.

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Item 80 Answer: B

Educational Objective: Manage hyperprolactinemia caused by hypothyroidism.

The most appropriate treatment for this patient is to begin levothyroxine. She has primary hypothyroidism with an elevated thyroid-stimulating hormone level and a low free thyroxine (T_4) level. Her symptoms are consistent with hypothyroidism. Hypothyroidism is a cause of hyperprolactinemia. When patients present with hyperprolactinemia and hypothyroidism, the hypothyroidism should be treated and then the patient should be reevaluated to ensure that the hyperprolactinemia resolves. The patient's pituitary gland is normal. There is no tumor.

The hypothyroidism should be treated first, and then the patient's prolactin level should be retested. There is no indication for cabergoline, a dopamine agonist, at this point. Cabergoline is an appropriate therapy for a patient with hyperprolactinemia caused by a prolactinoma. This patient's hyperprolactinemia is explained by hypothyroidism.

Sertraline does not cause hyperprolactinemia or hypothyroidism. Antipsychotic agents are a common cause of hyperprolactinemia, but selective serotonin reuptake inhibitors such as sertraline are not.

There is no indication for pituitary MRI at this time because her hyperprolactinemia is explained by hypothyroidism. It is necessary to make sure that her hyperprolactinemia normalizes after treatment with levothyroxine.

KEY POINT

- In patients with hyperprolactinemia and hypothyroidism, the hypothyroidism should be treated first, then the patient should be reevaluated to ensure that the hyperprolactinemia resolves.

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Item 81 Answer: B

Educational Objective: Diagnose cystic fibrosis as a cause of congenital bilateral absence of the vas deferens and azoospermia.

Congenital bilateral absence of the vas deferens is a common cause of obstructive azoospermia and is frequently associated with cystic fibrosis (CF). It may also present with unilateral absence of the vas deferens. Many patients are unaware that they have CF because they may have a mild form that causes only nonspecific symptoms such as chronic sinusitis. Partner testing for CF-carrier status should be encouraged to assess the likelihood of transmission to a subsequent generation. Sperm production is often normal in these patients; however, the absence of the vas deferens limits any observable sperm in the ejaculate. Therefore, testicular biopsy is necessary to retrieve sperm for use in advanced reproductive techniques (ART) such as in vitro fertilization and intracytoplasmic sperm injection. Utilization of donor sperm is an alternative for couples not interested in ART.

Androgen abuse is common among elite and professional athletes and in young men. Physical examination findings may include excessive muscular bulk, acne, gynecomastia, and decreased testicular volume. Low sperm counts also may be present with exogenous androgen use. Androgen abuse can result in hypogonadism and infertility, which occasionally are irreversible. This patient's normal physical examination, normal testicular volume, and absence of the vas deferens argue against this diagnosis.

Primary hypogonadism is due to testicular failure and is defined as a low testosterone level with elevated luteinizing hormone and follicle-stimulating hormone levels. Primary hypogonadism can have congenital or acquired causes. The most common congenital cause is Klinefelter syndrome (47,XXY karyotype). The extra sex chromosome results in malformation of the seminiferous tubules and typically of the Leydig cells. Physical examination is likely to reveal small, firm testes and decreased virilization. Additional manifestations include oligospermia and infertility. Klinefelter syndrome does not result in obstructive azoospermia due to absence of the vas deferens.

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A clinically palpable varicocele typically affects fertility by lowering sperm motility through a local heat effect. A scrotal bulge may be noted by the clinician, and the patient may note pain that is worse with the Valsalva maneuver. Azoospermia would not be caused by varicocele alone.

Y chromosome microdeletions can be associated with oligospermia or azoospermia and small testicular volume. This chromosomal abnormality is not associated with absence of the vas deferens and is therefore not a likely cause of this patient's findings.

KEY POINT

- Congenital bilateral absence of the vas deferens is a common cause of obstructive azoospermia and is frequently associated with cystic fibrosis.

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Item 82 Answer: B

Educational Objective: Manage primary adrenal failure.

Initiation of cortisol replacement therapy with a glucocorticoid (such as hydrocortisone) and mineralocorticoid (such as fludrocortisone) is the most appropriate next step in management. This patient has symptoms consistent with adrenal insufficiency (fatigue, unintentional weight loss, nausea, and vomiting); her family history of autoimmune disorders, hyperpigmentation noted on physical examination, and hyperkalemia on laboratory testing suggest primary adrenal failure. Patients with primary adrenal failure frequently have increased pigmentation over the extensor surfaces and buccal mucosa due to the excessive secretion of melanocyte-stimulating hormone, which shares a common precursor with adrenocorticotropic hormone (ACTH). Hyperkalemia occurs due to deficiency of aldosterone. The diagnosis of adrenal insufficiency is made by documenting an inappropriately low serum cortisol level. An early morning serum cortisol level that is less than 3 µg/dL (82.8 nmol/L) in the setting of signs and symptoms of cortisol deficiency is diagnostic of this disorder. Treatment should not be withheld while awaiting further diagnostic testing since adrenal insufficiency is a potentially life-threatening condition that may result in hemodynamic instability. Treatment of primary adrenal failure requires both glucocorticoid and mineralocorticoid replacement. Hydrocortisone or another long-acting agent with primarily glucocorticoid activity should be given along with a mineralocorticoid agent such as fludrocortisone.

The synthetic ACTH (cosyntropin) stimulation test is extremely sensitive for detecting either primary or secondary adrenal insufficiency. In patients with nondiagnostic basal cortisol values (4-12 µg/dL [110.4-331.2 nmol/L]), stimulation testing with synthetic ACTH is indicated. A normal response is a peak serum cortisol greater than 20 µg/dL (552 nmol/L). ACTH stimulation testing is not needed if the early morning serum cortisol level is unequivocally low, as in this patient.

Measurement of the plasma ACTH level is used to differentiate primary adrenal failure from other causes of low cortisol. In primary adrenal failure, the plasma ACTH level is typically significantly elevated (200 pg/mL [44 pmol/L]) and would confirm the diagnosis. However, withholding therapy while awaiting diagnostic confirmation would not be appropriate because of the potential life-threatening nature of primary adrenal failure.

Although prednisone is an acceptable agent for glucocorticoid replacement, it has almost pure glucocorticoid activity and would not be an appropriate single agent for treatment of primary adrenal failure in which replacement of both glucocorticoid and mineralocorticoid is required.

KEY POINT

- Cortisol replacement therapy should be initiated immediately in persons with confirmed adrenal insufficiency, which is diagnosed by an early morning serum cortisol level below 3 µg/dL (82.8 nmol/L) in the setting of signs and symptoms of cortisol deficiency.

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Item 83 Answer: A

Educational Objective: Manage the "honeymoon" phase of type 1 diabetes mellitus.

The most appropriate management for this patient's hypoglycemia is to decrease insulin glargine and insulin aspart. The glucose toxicity present at the time of diabetic ketoacidosis has diminished with an intensive insulin regimen. Her remaining functional pancreatic beta cells have regained the ability to produce some insulin in the "honeymoon" phase, which explains the hypoglycemia on previously well-tolerated doses of insulin. The decreased need for insulin will not be long term as pancreatic beta cells continue to be destroyed over the course of type 1 diabetes. Continuing insulin, even at low doses, is recommended during the "honeymoon" phase in order to preserve beta cell function as long as possible by reducing the metabolic stress on these cells. The low-dose insulin regimen can consist of a basal and prandial insulin combination or a basal insulin regimen. She is experiencing symptomatic postprandial and fasting hypoglycemia. Decreasing the insulin aspart and insulin glargine doses would address the prandial and fasting hypoglycemia, while also still providing low-dose insulin to protect the functioning beta cells. She will require close monitoring of her blood glucose levels to determine when insulin doses should be increased as she nears the end of the "honeymoon" phase. The "honeymoon" period may persist for several weeks to months.

Meal-time insulin doses are generally reduced by 50% when pramlintide is initiated due to the risk of hypoglycemia.

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The addition of pramlintide would likely exacerbate the current issue of hypoglycemia even with reduction of meal-time insulin.

The use of sliding-scale insulin without basal insulin is discouraged. When sliding-scale insulin is used without basal insulin, the likelihood of wide swings from hyperglycemia to hypoglycemia increases. Without a basal insulin regimen, she may not consistently receive daily insulin to decrease the metabolic stress on her functioning pancreatic beta cells.

Discontinuation of both insulin glargine and insulin aspart increases metabolic stress on the pancreatic beta cells and accelerates the loss of functional cells producing insulin. As pancreatic beta cell function declines toward the end of the "honeymoon" phase, the risk of diabetic ketoacidosis increases without any exogenous insulin.

KEY POINT

- Continuing insulin, even at low doses, is recommended during the "honeymoon phase" of type 1 diabetes mellitus to reduce metabolic stress on functioning beta cells and preserve any residual function for as long as possible.

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DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA. 2003 May 7;289(17):2254-64. [PMID: 12734137]

Item 84 Answer: A

Educational Objective: Treat hypogonadism secondary to hyperprolactinemia in a male patient.

The most appropriate treatment is a dopamine agonist such as cabergoline. Hyperprolactinemia as a result of a prolactinoma is a possible cause of erectile dysfunction and decreased libido and may be successfully treated with a dopamine agonist. In addition to the sexual dysfunction associated with hyperprolactinemia, semen parameters are often abnormal; patients commonly demonstrate oligoasthenospermia (reduced sperm motility) and at times complete azoospermia. Three months of treatment are typically needed prior to return of improved semen parameters. Prolactin is secreted by the pituitary lactotroph cells under tonic inhibition by dopamine. Dopamine agonist therapy can normalize prolactin levels, reverse hypogonadism, and shrink tumors by at least 50% in almost 90% of patients. Evaluation of the infertile male with abnormal findings on semen analysis should always include investigation of the hypothalamic-pituitary-testicular (HPT) axis. Disturbances in this axis may result in failure of gonadotropin release from the anterior pituitary and insufficient testosterone production as well as absent or diminished spermatogenesis.

Clomiphene citrate is effective only when the HPT axis is intact, which does not apply for this patient. Although the indication for clomiphene citrate in the infertile male population remains controversial, some clinicians use it to increase endogenous follicle-stimulating hormone and luteinizing hormone output from the anterior pituitary to support testosterone production by Leydig cells.

Sildenafil may improve erectile dysfunction in this patient, but it will not increase endogenous testosterone levels and will not improve his hyperprolactinemic state.

Testosterone replacement therapy would be helpful to alleviate the sexual side effects of this patient's hyperprolactinemic state; however, no restoration of spermatogenesis would occur, and therefore infertility would persist. Neither testosterone replacement nor sildenafil therapy will reduce the size of the patient's prolactinoma.

KEY POINT

- Secondary hypogonadism in a male patient caused by hyperprolactinemia as a result of a prolactinoma is a possible cause of erectile dysfunction and should be treated with a dopamine agonist such as cabergoline.

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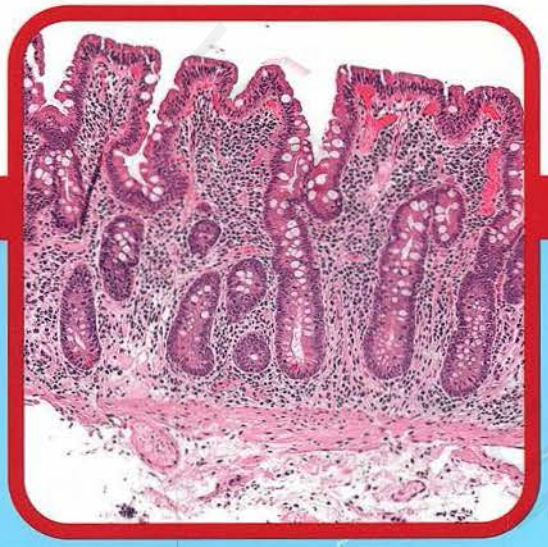

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In these pages, you will find updated information on gastroesophageal reflux disease, Barrett esophagus, *Helicobacter pylori* infection, gastrointestinal complications of NSAIDs, celiac disease, inflammatory bowel disease, liver disease, gallbladder disease, and other clinical challenges. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of gastroenterology and hepatology.

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The core content of MKSAP has been developed as in previous editions—newly generated, essential information in 11 topic areas of internal medicine created by dozens of leading generalists and subspecialists and guided by certification and recertification requirements, emerging knowledge in the field, and user feedback. MKSAP 17 also contains 1200 all-new, psychometrically validated, and peer-reviewed multiple-choice questions (MCQs) for self-assessment and study, including 96 in Gastroenterology and Hepatology. MKSAP 17 continues to include *High Value Care* (HVC) recommendations, based on the concept of balancing clinical benefit with costs and harms, with links to MCQs that illustrate these principles. In addition, HVC Key Points are highlighted in the text. Also highlighted, with blue text, are *Hospitalist*-focused content and MCQs that directly address the learning needs of internists who work in the hospital setting.

MKSAP 17 Digital provides access to additional tools allowing you to customize your learning experience, including regular text updates with practice-changing, new information and 200 new self-assessment questions; a board-style pretest to help direct your learning; and enhanced custom-quiz options. And, with MKSAP Complete, learners can access 1200 electronic flashcards for quick review of important concepts or review the updated and enhanced version of Virtual Dx, an image-based self-assessment tool.

As before, MKSAP 17 is optimized for use on your mobile devices, with iOS- and Android-based apps allowing you to sync your work between your apps and online account and submit for CME credits and MOC points online.

Please visit us at the MKSAP Resource Site (mksap.acponline.org) to find out how we can help you study, earn CME credit and MOC points, and stay up to date.

Whether you prefer to use the traditional print version or take advantage of the features available through the digital version, we hope you enjoy MKSAP 17 and that it meets and exceeds your personal learning needs.

On behalf of the many internists who have offered their time and expertise to create the content for MKSAP 17 and the editorial staff who work to bring this material to you in the best possible way, we are honored that you have chosen to use MKSAP 17 and appreciate any feedback about the program you may have. Please feel free to send us any comments to mksap_editors@acponline.org.

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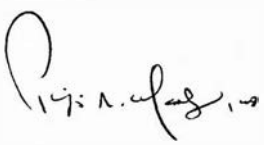

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The learning objectives of MKSAP 17 are to:

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- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

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- General internists and primary care physicians
- Subspecialists who need to remain up-to-date in internal medicine and in areas outside of their own subspecialty area
- Residents preparing for the certification examination in internal medicine
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High Value Care Key Points

Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon (**HVC**).

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Errata for MKSAP 17 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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Gastroenterology and Hepatology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 17 in several important ways. MKSAP 17 now includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Gastroenterology and Hepatology section of MKSAP 17.

- In a patient without alarm features (dysphagia, unintentional weight loss, hematemesis, or melena), symptom relief with an empiric trial of a proton pump inhibitor (PPI) confirms the diagnosis of gastroesophageal reflux disease (see Item 81); upper endoscopy should be reserved for patients whose symptoms are unresponsive to PPIs or have alarm features.
- Patients with gastroesophageal reflux disease with no alarm symptoms who have a partial response to once-daily proton pump inhibitor therapy should have their dose increased to twice daily (see Item 73).
- Gastroesophageal reflux disease is not a clinical indication for *Helicobacter pylori* testing.
- Endoscopic therapies for gastroesophageal reflux disease have not been shown to be effective in the long term.
- Current evidence does not support routine screening for Barrett esophagus based on gastroesophageal reflux disease symptoms.
- In patients with Barrett esophagus and no dysplasia, surveillance with upper endoscopy is recommended in 3 to 5 years (see Item 33).
- For patients younger than age 50 to 55 years who present with dyspepsia without alarm features, testing and treating for *Helicobacter pylori* infection or a trial of proton pump inhibitor therapy should be pursued before any further testing is done.
- Duodenal ulcers and low-risk gastric ulcers (for example, a young patient on NSAIDs) do not typically require endoscopic follow-up.
- Low-risk gastric ulcers are clean-based or have a nonprotuberant pigmented spot; they should be treated with oral proton pump inhibitor therapy, initiation of refeeding within 24 hours, and early hospital discharge (see Item 60).
- Peptic ulcers at low risk for bleeding (clean-based or with a nonprotuberant pigmented spot) can be managed with oral proton pump inhibitor therapy and early hospital discharge (see Item 93).
- Routine second-look endoscopy is not required after upper gastrointestinal bleeding unless rebleeding occurs or the initial examination was incomplete.
- Sporadic fundic gland polyps have been associated with proton pump inhibitor use and do not require excision or surveillance (see Item 41).
- Solitary juvenile polyps are one of the most commonly found polyps; they confer no future health risk once the polyp is removed and do not require surveillance endoscopy (see Item 89).
- Noninvasive testing to confirm eradication of *Helicobacter pylori* (with the urea breath test or fecal antigen test) should be performed given the high rate of treatment failure (roughly 25% in the United States); antibody testing is not appropriate for confirming eradication because antibodies can remain in the serum long after H. pylori has been eradicated.
- Endoscopic removal of type I gastric neuroendocrine tumors is curative when tumors are small (<1 cm) and few lesions are present (<5); further treatment or staging is not necessary (see Item 85).
- Contrast-enhanced CT is not usually required to diagnose acute pancreatitis; it is less sensitive than ultrasound for gallstones, exposes patients to the risk of contrast-medium–induced nephropathy (particularly in underresuscitated patients), and is expensive.
- Poor prognostic indicators for acute pancreatitis are elevated serum blood urea nitrogen level greater than

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20 mg/dL (7.1 mmol/L), a hematocrit greater than 44%, or an elevated serum creatinine level.
- Enteral feeding has been shown to reduce infectious complications, multiple organ failure, operative interventions, and mortality compared with feeding by total parenteral nutrition in patients with severe acute pancreatitis (see Item 36).
- In patients with uncomplicated gallstone pancreatitis, a cholecystectomy should be performed prior to discharge.
- Because most cases of community-acquired diarrhea are self-limited, stool cultures or evaluation for ova and parasites are not required in most patients; studies may be indicated for symptoms lasting longer than 72 hours, particularly in patients with associated fever, tenesmus, or bloody stools (see Item 88).
- Artificial sweeteners have little or no absorption in the small intestine and, when taken in excess, can cause symptoms of carbohydrate malabsorption; patients with malabsorption should be screened for artificial sweetener use and, if positive, a trial of elimination should be done prior to proceeding with a malabsorption evaluation (see Item 2).
- Assessment for intentional or unintentional gluten ingestion is the first step in evaluating recurrent symptoms in a patient with celiac disease (see Item 77).
- Routine complete blood count, serum chemistry studies, thyroid function studies, stool studies for ova and parasites, and abdominal imaging are unnecessary in establishing the diagnosis of irritable bowel syndrome (see Item 14).
- Irritable bowel syndrome was previously considered a diagnosis of exclusion after eliminating organic causes; however, an accurate diagnosis can now be made with fulfillment of the diagnostic criteria without further testing in the absence of alarm features (anemia; weight loss; and family history of colorectal cancer, inflammatory bowel disease, or celiac disease).
- In a healthy, immunocompetent patient with diverticulitis and mild symptoms, outpatient therapy is appropriate and should consist of a liquid diet, oral antimicrobial agents that cover colonic organisms and include anaerobic coverage (such as ciprofloxacin and metronidazole), and as-needed analgesia (see Item 23).
- If clinical features are highly suggestive of diverticulitis, imaging studies are unnecessary.
- Despite a decrease in colorectal cancer mortality that is largely attributable to the use of screening, 35% of eligible Americans have not been screened for colorectal cancer with fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy.
- Patients who are postpolypectomy with large (>2 cm) adenomas or adenomas with invasive cancer and favorable prognostic features may be managed with surveillance colonoscopy every 3 to 6 months and do not need surgical resection or radiation therapy (see Item 57).
- Because *MYH*-associated polyposis is an autosomal recessive disorder, a cost-effective approach to testing includes testing both parents for the *MYH* mutation before testing their children (see Item 63).
- Management of esophageal variceal bleeding includes placement of two large-bore intravenous lines, fluid resuscitation, and erythrocyte transfusion to a goal hemoglobin level of 7 g/dL (70 g/L); more liberal blood transfusion thresholds lead to increased portal pressures and risk of further bleeding.
- A presumptive diagnosis of nonalcoholic steatohepatitis can be made without liver biopsy in a patient with mild abnormalities of aminotransferase levels, risk factors for nonalcoholic fatty liver disease (such as diabetes mellitus, obesity, and hyperlipidemia), and imaging features consistent with hepatic steatosis (see Item 21).
- The finding of predominantly unconjugated hyperbilirubinemia indicates non–liver-disease states such as hemolysis or Gilbert syndrome, which is characterized by benign defects in bilirubin conjugation (see Item 79).
- Patients in the inactive carrier phase of hepatitis B virus (HBV) infection, characterized by a normal serum alanine aminotransferase level and a low HBV DNA level, do not require treatment (see Item 46).
- Acute hepatitis B infection will resolve in 90% of adult patients; thus, serial monitoring of liver enzymes is recommended in place of antiviral therapy for patients without evidence of marked liver dysfunction (see Item 71).
- The preferred method for screening patients with chronic hepatitis B infection for hepatocellular carcinoma is ultrasonography every 6 months, as this is the most widely available, safest, and least expensive imaging modality (see Item 92).
- Patients with a positive antibody to hepatitis C virus (HCV) but negative HCV RNA do not have HCV infection, and no further testing is required (see Item 62).
- There is no utility in monitoring serial ammonia values in patients with hepatic encephalopathy; head CT is warranted only in patients with unwitnessed falls or head trauma, or in cases of diagnostic uncertainty.
- Ultrasound is the most cost-effective diagnostic test for ascites.
- The vast majority of hepatocellular carcinoma can be diagnosed by radiology and does not require a biopsy.
- Observation (not cholecystectomy) is recommended for adult patients with asymptomatic gallstones (see Item 25).
- Patients with lower gastrointestinal bleeding do not require hospitalization when they meet four criteria (based on the 2008 Scottish Intercollegiate Guidelines Network): age less than 60 years, no hemodynamic instability, no evidence of gross rectal bleeding, and identification of an obvious anorectal source of bleeding on rectal examination or sigmoidoscopy (see Item 37).

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Gastroenterology and Hepatology

Disorders of the Esophagus

Symptoms of Esophageal Disorders

Dysphagia

Dysphagia is the awareness of food not passing during the swallowing process. The swallowing mechanism is made up of two distinct components:

1. The oropharyngeal process is the passage of the food bolus from the mouth into the hypopharynx and upper esophagus.
2. The esophageal process is the passage of the food bolus through the upper esophagus into the stomach.

Patients typically describe a feeling of food "getting stuck" or being blocked while eating. Identifying which component of the swallowing process (oropharyngeal or esophageal) is abnormal is key for formulating the differential diagnosis and devising a diagnostic and management plan. There are many causes of dysphagia, which are described in **Table 1**.

Oropharyngeal Dysphagia

Patients with oropharyngeal dysphagia (also known as transfer dysphagia) are unable to initiate the swallowing process despite several attempts to swallow. Patients typically describe coughing, choking, and nasal regurgitation. Choking occurs owing to failure to clear food from the epiglottis and may lead to aspiration. Oropharyngeal dysphagia often occurs within 1 second of starting the swallowing process. Recurrent episodes of pulmonary infections (including pneumonia) can be a result of chronic aspiration. Symptoms of underlying systemic neurologic disease include hoarseness (laryngeal nerve dysfunction) and dysarthria (weakness of the soft palate or pharyngeal constrictors). Regurgitation of undigested food hours after eating or reports of a gurgling noise in the neck are symptoms of Zenker diverticulum. The initial test of choice for evaluation of oropharyngeal dysphagia is a modified barium swallow, also known as videofluoroscopy. The test begins with a liquid phase, which is followed by a solid phase if the liquid phase is not diagnostic. If results of the modified barium swallow are normal, oropharyngeal dysphagia is excluded and further evaluation should focus on the possibility of esophageal dysphagia. Oropharyngeal forms of dysphagia are often managed with dietary adjustment and incorporation of swallowing exercises with the assistance of a speech pathologist.

KEY POINT

- The initial test of choice for evaluation of oropharyngeal dysphagia is a modified barium swallow, also known as videofluoroscopy.

Esophageal Dysphagia

Patients with esophageal dysphagia often localize discomfort to the lower sternum and do not report problems initiating the swallowing process. Dysphagia to solid foods suggests mechanical obstruction; dysphagia to liquids or both solids and liquids suggests a motility disorder. Patients with achalasia describe regurgitation of nonacidic undigested food in combination with dysphagia to solids and liquids. Esophageal spasm is associated with chest pain that may be triggered by consuming liquids of extreme hot or cold temperatures. Systemic symptoms such as Raynaud phenomenon in the setting of heartburn suggest systemic sclerosis, a cause of both mechanical obstruction and motility disorders. Luminal causes of obstruction may include benign strictures, malignancy, esophageal webs, or a Schatzki ring (**Figure 1**). Upper endoscopy is the most appropriate test for esophageal dysphagia; it allows for both diagnostic intervention (biopsies and inspection) and therapeutic intervention (dilation). Treatment is guided by the underlying pathology causing the dysphagia, as discussed in later sections.

KEY POINTS

- Esophageal dysphagia to solid foods suggests mechanical obstruction; dysphagia to liquids or both solids and liquids suggests a motility disorder.
- Upper endoscopy is the most appropriate test for esophageal dysphagia; it allows for both diagnostic intervention (biopsies and inspection) and therapeutic intervention (dilation).

Reflux and Chest Pain

Reflux is the regurgitation of acidic contents from the stomach into the esophagus or back of the throat. Untreated reflux can lead to development of a peptic stricture, causing solid-food dysphagia. Pyrosis, also known as heartburn, is the most common digestive complaint in Western populations. Heartburn often occurs approximately 1 hour after eating and is temporarily relieved with antacids. Factors that can trigger or exacerbate reflux symptoms are listed in **Table 2**.

Patients may have esophageal chest pain symptoms that are identical to those of cardiac chest pain. Esophageal chest

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TABLE 1. Causes of Dysphagia

Condition	Diagnostic Clues
Oropharyngeal Dysphagia	
Structural disorders	
Cervical osteophytes	High dysphagia, degenerative joint disease
Cricoid webs	High dysphagia, iron deficiency
Pharyngoesophageal (Zenker) diverticulum	Aspiration, neck mass, and regurgitation of foul-smelling food
Thyromegaly	Neck mass
Neurologic/myogenic disorders	
Amyotrophic lateral sclerosis	Upper and lower motoneuron signs, fasciculations
Central nervous system tumor	Headache, vision changes, nausea, seizures, balance problem
Stroke	Focal neurologic deficits
Muscular dystrophy	Slow progression of muscular weakness over years
Myasthenia gravis	Weakness with repetitive activity
Multiple sclerosis	Optic neuritis
Parkinson disease	Bradykinesia, rigidity, tremor
Dementia	Altered cognition
Sjögren syndrome	Dry mouth, dry eyes
Esophageal Dysphagia	
Structural disorders	
Dysphagia lusoria (vascular dysphagia)	Vascular extrinsic compression on the esophagus on imaging
Epiphrenic/traction diverticulum	Outpouching of the esophagus at any level on imaging
Esophageal strictures	Intermittent dysphagia, especially for solid food; history of reflux
Eosinophilic esophagitis	Food impactions, atopic history, rings or strictures on endoscopy
Esophageal webs or rings	Usually incidental finding, may be associated with iron deficiency anemia
Neoplasms	Rapidly progressive dysphagia for solids, then liquids; anorexia; weight loss
Motility disorders	
Achalasia	Concomitant liquid and solid dysphagia
Diffuse esophageal spasm	Chest pain
Systemic sclerosis	Tight skin, telangiectasias, sclerodactyly, GERD, Raynaud phenomenon

GERD = gastroesophageal reflux disease.

CONT.

pain may be induced by physical activity, similarly to cardiac chest pain. The most common cause of noncardiac chest pain is untreated gastroesophageal reflux disease (GERD), followed by motility disorders. Cardiac causes must be ruled out before chest pain is attributed to an esophageal cause.

A trial of an acid-reducing agent such as a proton pump inhibitor (PPI) may alleviate symptoms, confirming the diagnosis of GERD. If symptoms are unresponsive to a PPI trial, additional evaluation with upper endoscopy, ambulatory pH testing, and/or esophageal manometry may be warranted. For diagnosis and management of reflux, see Gastroesophageal Reflux Disease. H

KEY POINT

- Cardiac causes must be ruled out before chest pain is attributed to an esophageal cause.

Odynophagia

Odynophagia is defined as pain with swallowing and is an indication of inflammation in the esophagus. Odynophagia is a sign of mucosal injury of the esophagus leading to ulceration. The most common causes of odynophagia are caustic ingestion, pill-induced damage, and infection with *Candida*, herpesvirus, or cytomegalovirus. Rarely, it has been associated with severe GERD or esophageal cancer. Upper endoscopy is the diagnostic test of choice for visual inspection and obtaining tissue biopsies.

Globus Sensation

Globus is the sensation of tightness or a lump in the throat. Globus occurs between swallows and is not related to meals. Stress, psychiatric disorders (anxiety, panic disorders,

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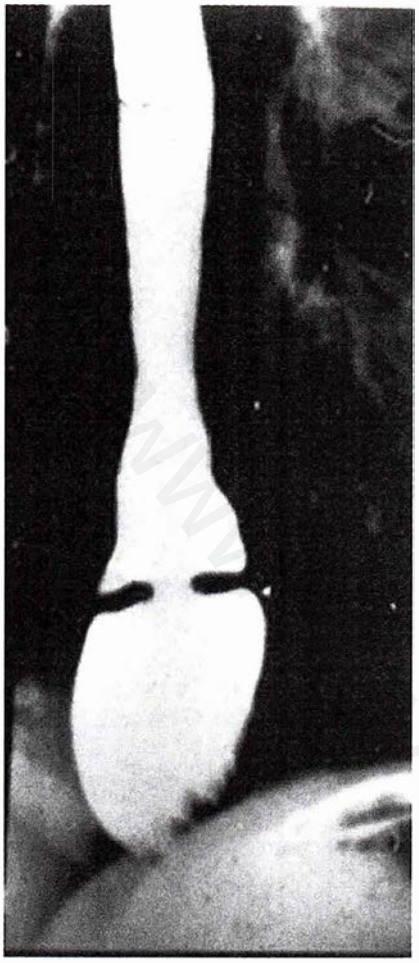

FIGURE 1. Barium esophagography showing a Schatzki ring.

TABLE 2. Factors Associated with Reflux

Category	Factor
Lifestyle	Cigarette smoking
	Obesity
Eating habits	Eating large meals
	Eating late at night
	Lying supine shortly after eating
Foods and beverages	Alcohol
	Chocolate
	Citrus fruits and juices
	Coffee
	Fatty and fried foods
	Onions
	Peppermint
Medications	Anticholinergic agents
	Aspirin and NSAIDs
	Calcium channel blockers
	Nitrates
	Progesterone
	Opioids (due to delayed gastric emptying)
Body position	Bending over, exercising (both result in increased intra-abdominal pressure)
Other	Pregnancy
	Tight-fitting clothing
	Hiatal hernia

somatization), and frequent dry swallowing have been associated with globus. Globus should not be diagnosed in the setting of dysphagia or odynophagia. The management of globus should include ruling out an underlying pharyngeal lesion by nasal endoscopy or barium swallow. If these studies are negative, treatment with acid suppression (PPI) or cognitive behavioral therapy should be considered. Globus has been associated with GERD.

Nonmalignant Disorders of the Esophagus

Esophageal Motility Disorders

The esophagus is the conduit between the hypopharynx and stomach. The tubular esophagus is composed of both skeletal muscle (upper third) and smooth muscle (lower two thirds). Nerve innervations for the striated component are axons of lower motoneurons. The smooth muscle portion of the esophagus is innervated by the vagus nerve. Primary peristalsis begins with swallowing and runs the entire length of the tubular esophagus. The upper and lower esophageal sphincters relax during swallowing (**Figure 2**). Secondary peristaltic activity occurs when the esophagus is distended with air or fluid; peristalsis begins at the point of distention. High-resolution esophageal manometry is a valuable tool in evaluating esophageal physiology.

Hypertonic Motility Disorders

Achalasia and Pseudoachalasia

Achalasia is a motility disorder of the esophagus that results in aperistalsis and inadequate relaxation of the lower esophageal sphincter (LES). The cause of achalasia is unknown, but the pathophysiologic process involves ganglion cell and myenteric plexus degeneration in the esophageal body and LES. This nerve imbalance leads to uncontested action by cholinergic nerves and incomplete LES relaxation. It affects men and women equally, with an annual incidence of 1 in 100,000 individuals. It tends to occur between the ages of 30 and 60 years.

The clinical presentation of achalasia consists of dysphagia to both solids and liquids along with regurgitation of undigested bland food and saliva. Patients may also experience weight loss, chest pain, and even heartburn, resulting in a misdiagnosis of GERD. Symptoms of true achalasia do not respond to an empiric trial of acid reducers such as PPIs.

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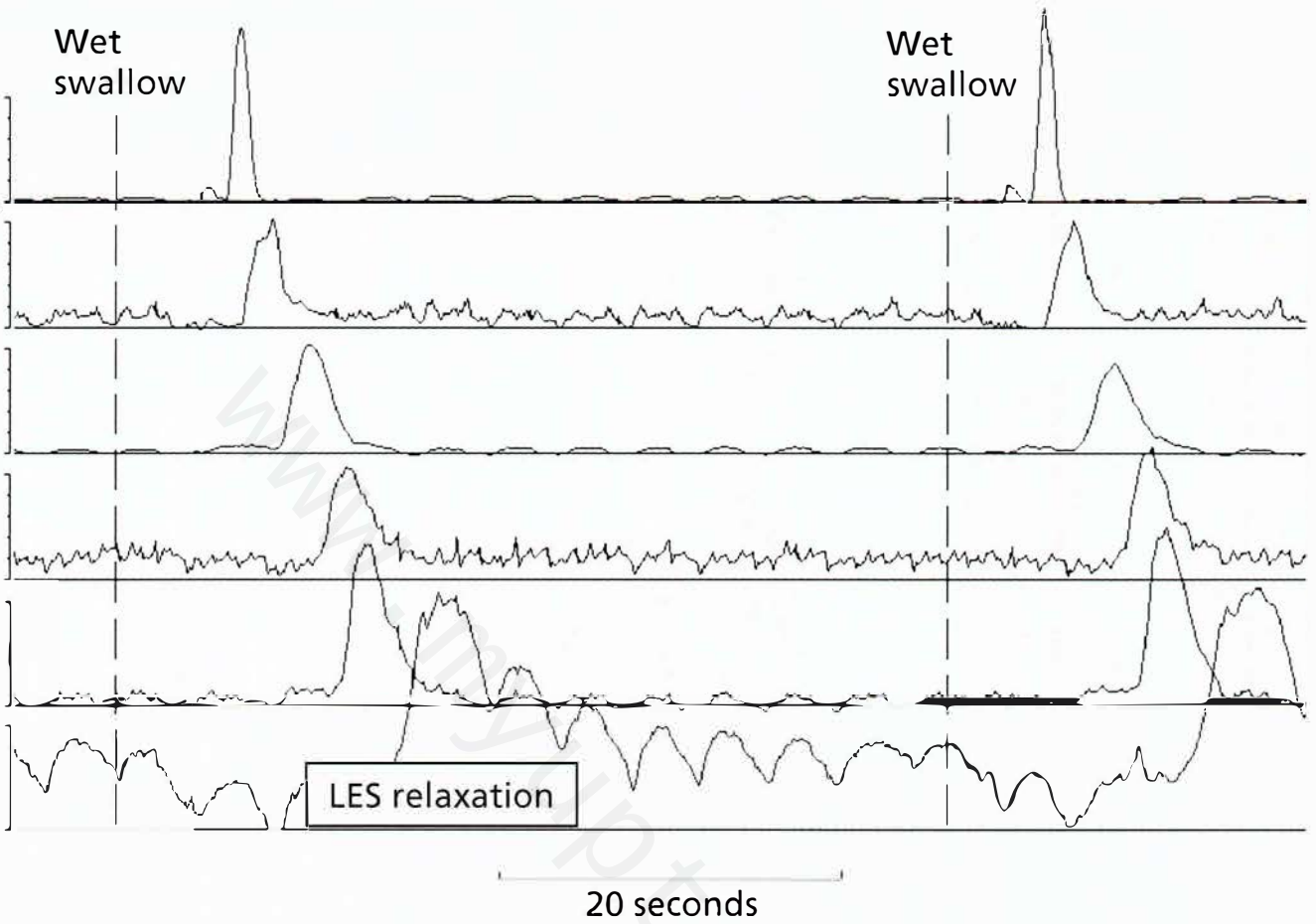

FIGURE 2. Normal esophageal manometric tracing, in which the lower esophageal sphincter (LES) pressure relaxes to baseline during the wet swallow, and peristaltic waves are seen (the scale for the esophageal leads is 100 mm Hg).

The initial test for achalasia is a barium esophagogram, which demonstrates dilation of the esophagus and narrowing at the gastroesophageal junction, described as a "bird's beak" (**Figure 3**). Manometry should be performed to confirm the diagnosis; it is the most sensitive test to demonstrate incomplete LES relaxation and aperistalsis (**Figure 4**). Upper endoscopy shows retained food and saliva, as well as no signs of mechanical obstruction or mass. Upper endoscopy is often performed to exclude mechanical obstruction, particularly if symptoms are concerning for underlying malignancy (shorter duration of symptoms, rapid weight loss).

Other conditions can mimic achalasia; for example, tumors at the gastroesophageal junction may lead to myenteric plexus infiltration, causing esophageal motor abnormalities that are known as pseudoachalasia. Patients with pseudoachalasia often have sudden weight loss and are in their sixth decade of life or older. Secondary achalasia is caused by extrinsic compression after fundoplication or gastric band weight loss surgery.

Achalasia is a chronic disease, and treatment is directed at lowering LES pressure and alleviating symptoms. Endoscopic

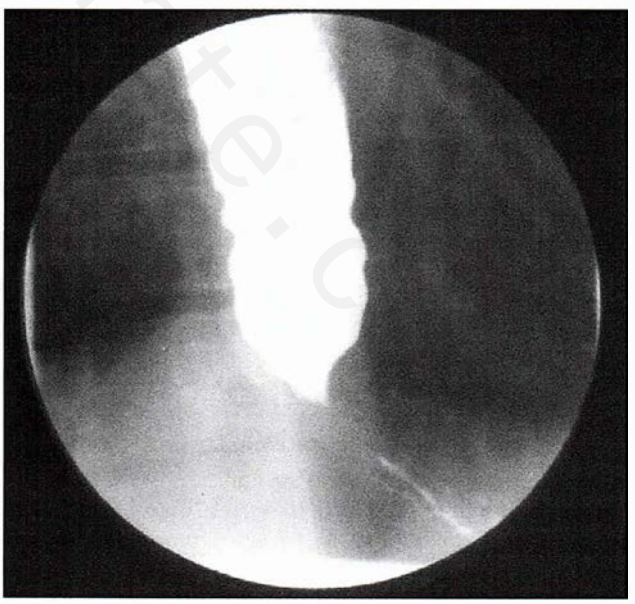

FIGURE 3. Barium esophagogram with the typical "bird's beak" appearance of the distal esophagus in a patient with achalasia.

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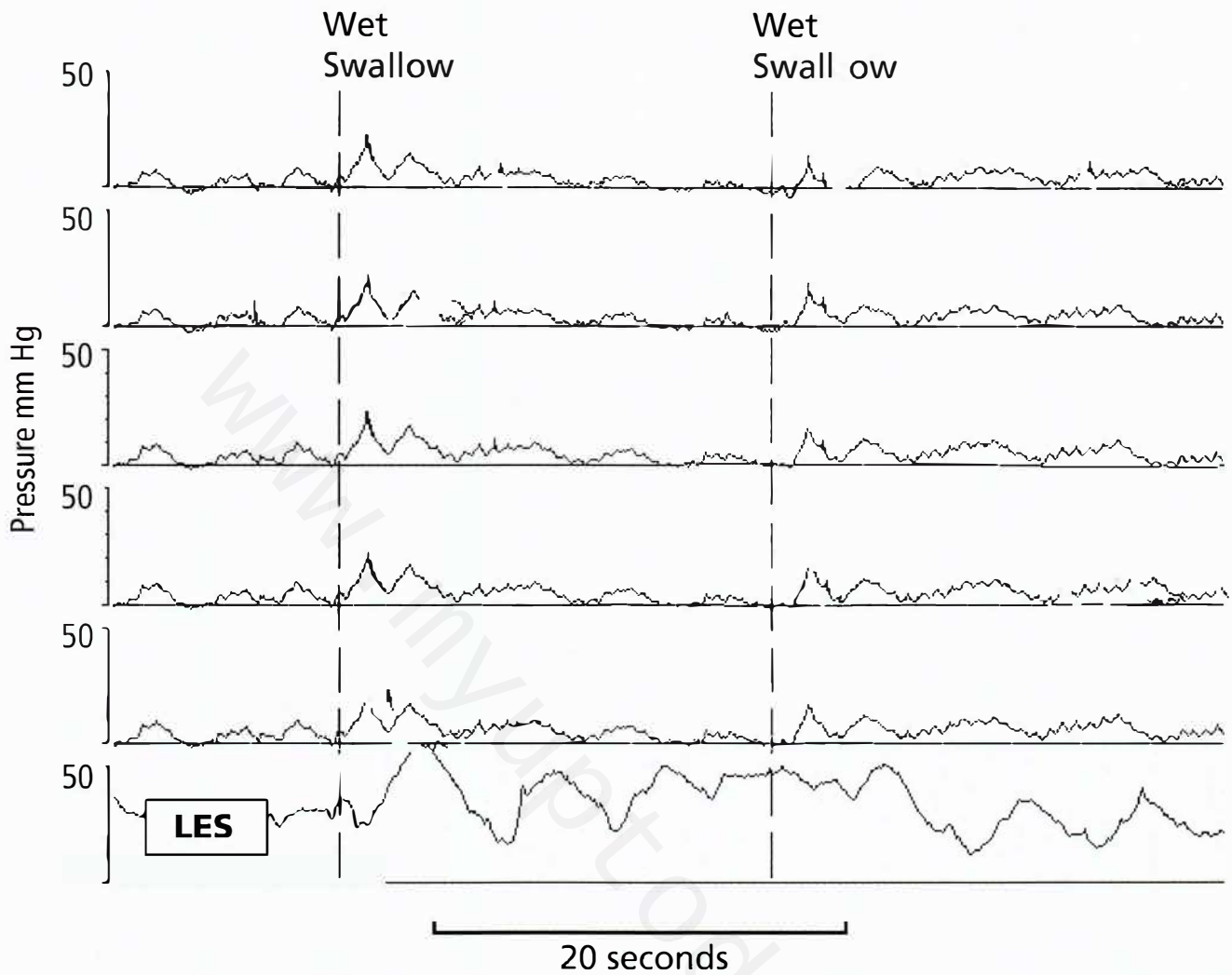

FIGURE 4. Esophageal manometric tracing in a patient with achalasia, in which the elevated lower esophageal sphincter (LES) pressure does not relax during the wet swallow. In addition, there is no esophageal body peristalsis (the waves seen are superimposable). The vertical scale is set in increments of 10 mm Hg (to a maximum of 50 mm Hg).

pneumatic dilation is an effective nonsurgical treatment for achalasia; the main complication is perforation, which occurs in 1.9% of patients. Laparoscopic surgical myotomy leading to disruption of circular muscle fibers is the surgical treatment of choice. Fundoplication is recommended after myotomy to prevent reflux, but PPI therapy may still be needed if heartburn symptoms are present. The choice between pneumatic dilation and surgical myotomy depends on local expertise, as both have comparable success rates. However, pneumatic dilation has been shown to be more cost-effective compared with surgical myotomy. If surgery and pneumatic dilation are not acceptable owing to surgical risk or patient preference, endoscopic injection of botulinum toxin may help relieve symptoms. Endoscopic injection of botulinum toxin inhibits acetylcholine release, resulting in LES relaxation. This treatment has a 50% relapse rate, requiring retreatment in about 6 months. Pharmacologic therapy is third-line therapy reserved for patients who are not candidates for endoscopic intervention or surgery. These therapies include calcium channel blockers (nifedipine) or long-acting nitrates, which cause an inconsistent reduction in LES pressure.

There is an associated risk of squamous cell esophageal cancer in patients who have had achalasia for more than 10 years. Given the very low incidence of malignancy, endoscopic surveillance has not been widely recommended in these patients.

KEY POINTS

- The clinical presentation of achalasia consists of dysphagia to both solids and liquids along with regurgitation of undigested bland food and saliva; weight loss, chest pain, and heartburn may be present.
- The initial test for achalasia is a barium esophagogram, which demonstrates dilation of the esophagus and narrowing at the gastroesophageal junction, described as a "bird's beak."

(Continued)

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KEY POINTS *(continued)*

- Endoscopic pneumatic dilation and laparoscopic surgical myotomy are the primary treatments for achalasia; the choice of therapy depends on local expertise, as both have comparable success rates.

Diffuse Esophageal Spasm and Nutcracker Esophagus

Hypertonic motility disorders of the esophagus often present with dysphagia and/or chest pain. These disorders are differentiated based on manometry findings.

Diffuse esophageal spasm is a rare motility disorder that presents with chest pain or dysphagia. Clinical manifestations are similar to those of angina pectoris. Although the cause of diffuse esophageal spasm is unknown, it may be associated with reflux. On esophageal manometry, simultaneous high-amplitude (>30 mm Hg) esophageal contractions are seen with intermittent aperistaltic contractions. The barium esophagogram finding of a "corkscrew" esophagus (**Figure 5**) is typical of diffuse esophageal spasm. It may progress to achalasia in some patients.

Nutcracker esophagus is characterized by high-amplitude peristaltic contractions of greater than 220 mm Hg.

Management of hypertonic disorders of the esophagus is aimed at symptom relief. The ideal therapy is not clear, but pharmacologic therapy has included calcium channel blockers, hydralazine, botulinum toxin injections, and anxiolytics.

Hypotonic Motility Disorders

Hypotensive disorders of the esophagus can involve a hypotense LES, aperistaltic contractions, or both. A weakened LES can lead to GERD, and poor peristaltic activity can result in dysphagia. In most cases, the cause of the hypotensive esophageal disorder is unknown. However, secondary causes include smooth-muscle relaxants, anticholinergic agents, estrogen, progesterone, connective tissue disorders (such as systemic sclerosis), and pregnancy. Manometry demonstrates hypotensive or nonperistaltic contractions in the distal esophagus. Management consists of therapy for GERD to prevent complications such as erosive esophagitis and stricture formation.

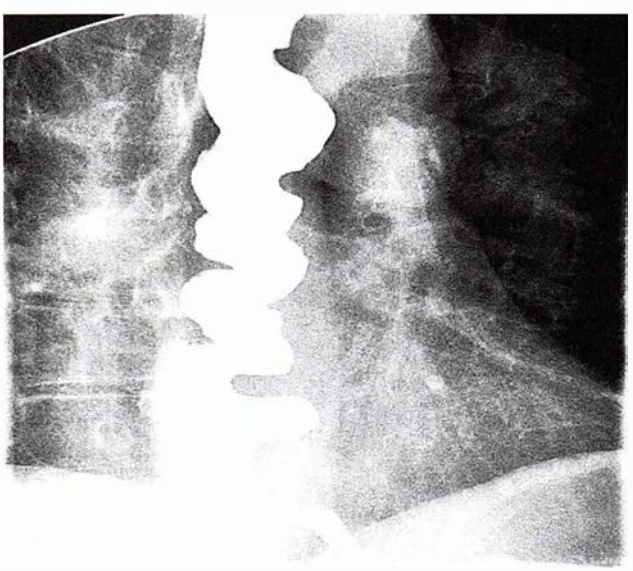

FIGURE 5. Findings of a "corkscrew esophagus" (caused by multiple simultaneous contractions) on esophagogram are typical of diffuse esophageal spasm.

Infectious, Pill-Induced, and Eosinophilic Esophagitis

Infectious Esophagitis

Infectious esophagitis can be caused by bacterial (uncommon), fungal, viral, and parasitic pathogens. Patients may be asymptomatic, but common symptoms are odynophagia or dysphagia. *Candida* infection can occur in both immunocompetent and immunocompromised patients. Upper endoscopy reveals small, white, raised plaques (**Figure 6**), and esophageal brushings confirm the diagnosis. The most common species is *Candida albicans*, which is treated with oral fluconazole. Cytomegalovirus (CMV) is seen in immunocompromised patients and rarely occurs in patients with an intact immune system. Although herpes simplex virus (HSV) can be seen in both immunocompetent and immunocompromised patients, it is much more likely to be found in an immunocompromised individual. Upper endoscopy is needed to confirm the diagnosis, and biopsies of the ulcer base (to detect CMV) and ulcer edge (to detect HSV) should be performed. HSV is treated with acyclovir, and CMV responds to ganciclovir and valganciclovir.

KEY POINT

- The most common cause of infectious esophagitis is *Candida albicans*, which is treated with oral fluconazole.

Pill-Induced Esophagitis

Many medications have been associated with esophageal mucosal injury. Risk factors associated with pill-induced



FIGURE 6. Upper endoscopy showing white adherent plaques suggestive of *Candida* esophagitis.

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esophagitis include decreased salivary output, esophageal dysmotility, ingestion of large pills, medications that alter LES tone (such as opioid analgesics), and ingestion of medications in the supine position. Pill-induced esophagitis is characterized by chest pain, dysphagia, and odynophagia. Symptoms occur several hours to days after taking the medication. Pill-induced esophagitis has been observed with alendronate, quinidine, tetracycline, doxycycline, potassium chloride, ferrous sulfate, and mexiletine. Medications associated with stricture formation include alendronate, ferrous sulfate, NSAIDs, and potassium chloride. Preventive strategies to decrease pill-induced esophagitis are to drink plenty of water with the medication and avoid lying down for 30 minutes after ingestion.

KEY POINT

- Preventive strategies to decrease pill-induced esophagitis are to drink plenty of water with the medication and avoid lying down for 30 minutes after ingestion.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is defined as esophageal squamous mucosal inflammation caused by eosinophilic infiltration. The classic presentation of EoE is an atopic man in the third decade of life with solid-food dysphagia and food impactions requiring removal by endoscopy. EoE has been associated with food allergies, asthma, and eczema. Children may have a nonspecific presentation characterized by feeding issues, vomiting, and pain. The reported prevalence is as high as 54 per 100,000 persons in the United States. Upper endoscopy findings include rings, longitudinal furrows, luminal narrowing, and white exudates and plaques (**Figure 7**). Esophageal biopsies show greater than 15 eosinophils per high-power field. GERD has been associated with esophageal eosinophilia and can mimic EoE.



FIGURE 7. The macroscopic findings of eosinophilic esophagitis on upper endoscopy are nonspecific, but mucosal furrowing (appearing as stacked esophageal rings), white specks, and mucosal friability have been consistently described.

Patients with esophageal eosinophilia should undergo an 8-week trial of a PPI; clinical response to the PPI trial indicates GERD-associated eosinophilia rather than EoE. Repeat upper endoscopy with biopsies should be considered; if esophageal eosinophilia is still present, this confirms a diagnosis of EoE. Treatment endpoints include resolution of clinical symptoms and reduction of eosinophil infiltration in esophageal mucosa. Dietary treatments (elemental diet or targeted elimination diet) can be tried in adults and children. Medical therapy for EoE consists of swallowed aerosolized topical glucocorticoids (fluticasone or budesonide); if symptoms are not responsive, oral prednisone should be used. Esophageal dilation should be considered in patients with a persistent esophageal stricture despite medical therapy. Patients should be advised that EoE is a chronic disease that often recurs after treatment is stopped; therefore, repeat or maintenance therapy may be needed.

KEY POINT

- The classic presentation of eosinophilic esophagitis is an atopic man in the third decade of life with symptoms of solid-food dysphagia and food impactions requiring removal by endoscopy.

Gastroesophageal Reflux Disease

GERD is a common clinical problem that occurs when acid and food from the stomach reflux into the esophagus and throat. GERD-related symptoms occur in 10% to 20% of individuals in the Western world, but prevalence is lower in Asia. In the United States, about 40% of adults have monthly and 20% have weekly GERD symptoms. GERD affects patients' quality of life, causing poor sleep, low productivity, and missed days at work. Symptoms include heartburn, regurgitation, and chest pain. GERD-related chest pain must be differentiated from cardiac chest pain before treatment can begin. Dysphagia can occur with GERD, but additional evaluation is required to rule out an underlying ring, web, malignancy, or motility disorder. Nonacid reflux may occur in patients who are already on maximal acid suppression or in those with achlorhydria; patients note symptoms of regurgitation of liquids similar to those with acid-related reflux.

The major physiologic mechanisms to protect against esophageal acid injury include clearing mechanisms (peristalsis), a competent LES, and intact gastric emptying. A breakdown in these protective mechanisms can lead to symptomatic GERD.

GERD is common in pregnancy and can happen during any trimester, but severity can increase throughout the pregnancy. GERD related to pregnancy is a clinical diagnosis and testing is not required; heartburn symptoms typically resolve after delivery. There is a strong relationship between GERD and obesity. Complications of GERD include erosive esophagitis, stricture, Barrett esophagus, and esophageal cancer.

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KEY POINT

- Complications of gastroesophageal reflux disease include erosive esophagitis, stricture, Barrett esophagus, and esophageal cancer.

Diagnosis

The diagnosis of GERD can be established by clinical history, response to medical therapy, and testing. Symptoms of heartburn and regurgitation are strong predictors for the clinical diagnosis of GERD. In a patient without alarm features (dysphagia, unintentional weight loss, hematemesis, or melena), symptom relief with an empiric trial of a PPI confirms the diagnosis of GERD.

Upper endoscopy is the primary tool to evaluate the esophagus and identify damage in the form of erosive esophagitis, stricture, or Barrett esophagus. Upper endoscopy should be performed in patients whose symptoms are not responsive to an empiric PPI trial, and it should be the first step in evaluation of patients with alarm symptoms. Most patients with symptoms of heartburn and regurgitation have normal upper endoscopy findings.

Ambulatory pH testing or impedance-pH testing is valuable to identify acid exposure within the esophagus. Impedance-pH testing can identify both acid and nonacid reflux. Testing can be done with a 48-hour wireless capsule or 24-hour transnasal catheter to detect active acid reflux. The wireless capsule has been shown to have better patient tolerability.

Esophageal manometry has limited value as a tool to identify GERD; however, manometry should be done before antireflux surgery to rule out a motility disorder such as achalasia or a hypomotility disorder (systemic sclerosis).

Barium radiographs for the diagnosis of GERD have low sensitivity and should not be performed.

KEY POINT

- In a patient without alarm features (dysphagia, unintentional weight loss, hematemesis, or melena), symptom relief with an empiric trial of a proton pump inhibitor (PPI) confirms the diagnosis of gastroesophageal reflux disease; upper endoscopy should be reserved for patients whose symptoms are unresponsive to PPIs or have alarm features. HVC

Treatment

An algorithm describing the management of GERD is shown in **Figure 8**.

Lifestyle Changes

Diet and lifestyle changes are often recommended as part of GERD therapy. Weight reduction is suggested for patients with recent weight gain or for those who are overweight. Interventions such as raising the head of the bed and eliminating meals within 2 to 3 hours of bedtime are helpful for nocturnal GERD. Global elimination of proposed trigger foods (caffeine, chocolate, spicy foods, acidic foods such as oranges, and fatty foods) is not recommended; however, targeted elimination of foods associated with symptoms is a reasonable approach. Cessation of alcohol and tobacco use is universally supported.

Medical Therapy

Pharmacologic therapy for GERD consists of antacids, H_2 blockers, or PPI therapy. PPI therapy once daily for 8 weeks is the therapy of choice for symptom relief. PPI therapy is superior to

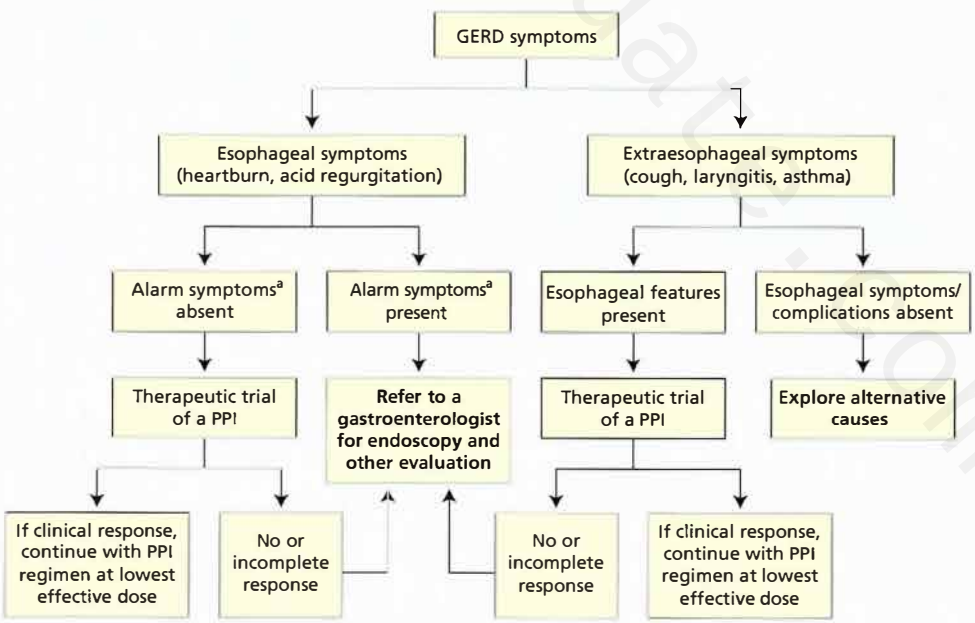

FIGURE 8. Management of gastroesophageal reflux disease. GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor.

[a]Alarm symptoms = dysphagia, unintentional weight loss, hematemesis, or melena.

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H_2 blockers for treatment of GERD. It has been shown to offer faster healing rates for erosive esophagitis and decreased relapse compared with other agents, and it also has been shown to offer faster and more complete relief of symptoms. A PPI should be taken once daily 30 to 60 minutes before the first meal of the day. Patients with a partial response to PPI therapy should have their dose increased to twice daily. Patients who require long-term maintenance therapy should receive the lowest effective PPI dose, including on-demand or intermittent usage.

Common adverse reactions to PPIs are headache and diarrhea; dyspepsia may occur with sudden discontinuation of PPI therapy. Switching to a different PPI may be helpful if the patient has an adverse reaction or if there is no clinical response; however, outcomes may remain the same with a different PPI. Other possible adverse reactions include vitamin (B_{12}) and mineral (calcium and magnesium) malabsorption as well as increased risk of community-acquired pneumonia, *Clostridium difficile* infection, hip fractures, osteoporosis, and cardiovascular events. Hip fracture risk may not be increased unless other risk factors are present. Short-term PPI use has been linked to community-acquired pneumonia, but long-term use has not been similarly associated. Despite earlier concerns that concurrent PPI therapy decreased the activation of clopidogrel, two randomized clinical studies have since failed to show an increased risk of adverse outcomes in patients treated with clopidogrel and PPIs. PPIs are safe in pregnant patients.

Sucralfate has no role in the treatment of GERD. Prokinetic agents (metoclopramide) should not be used in the treatment of GERD unless gastroparesis is present.

Antireflux Surgery

Surgical treatments for GERD consist of laparoscopic fundoplication or bariatric surgery (the latter for obese patients). Indications for surgery include patient preference to stop taking medication, medication side effects, large hiatal hernia, and refractory symptoms despite maximal medical therapy (although patients with medically refractory symptoms may be less likely to benefit from surgery). Patients should undergo objective testing (such as pH-impedance monitoring to demonstrate true reflux with symptom correlation and manometry to rule out a motility disorder) prior to surgery. Surgery is most effective in patients with typical symptoms of heartburn and regurgitation that are responsive to therapy. However, approximately one third of patients will require resumption of PPI therapy 5 to 10 years after surgery. Postoperative complications include dysphagia, diarrhea, and inability to belch because of a tight fundoplication. Carbonated beverages should be avoided.

Endoscopic Therapy

Endoscopic therapies for GERD have not been shown to be effective in the long term. Therapies have included thermal radiofrequency to augment the LES, silicone injection to the LES, and suturing of the LES. Early improvement of reflux symptoms has been seen, but long-term benefits have not been shown. Normalized esophageal pH levels have not been demonstrated after endoscopic therapies. Transoral incisionless fundoplication is a newer therapy that uses a full-thickness suture to create an endoscopic fundoplication; however, there are no long-term data that demonstrate efficacy.

KEY POINTS

- Proton pump inhibitor therapy is superior to H_2 blockers for treatment of gastroesophageal reflux disease.
- In patients with gastroesophageal reflux disease, indications for antireflux surgery include patient preference to stop taking medication, medication side effects, large hiatal hernia, and refractory symptoms despite maximal medical therapy.
- Endoscopic therapies for gastroesophageal reflux disease have not been shown to be effective in the long term.

HVC

Extraesophageal Manifestations

GERD has been associated with asthma, chronic cough, and laryngitis **(Figure 9)**. It is important to eliminate other non-GERD causes when these symptoms are present. Laryngoscopy often demonstrates edema and erythema as signs of reflux-induced laryngitis; however, over 80% of healthy persons also have these findings. Laryngoscopy should not be used to diagnose GERD-related laryngitis. A PPI trial is recommended in patients who have typical GERD symptoms and extraesophageal symptoms.

Refractory Gastroesophageal Reflux Disease

The first step in treating refractory GERD is to optimize PPI therapy by verifying correct administration (30-60 minutes before meals), increasing to twice-daily dosing, or switching to another PPI. If symptoms remain unresponsive, alternative causes should be considered. In patients with typical symptoms, upper endoscopy should be performed to rule out eosinophilic esophagitis or erosive esophagitis. If the endoscopy does not reveal eosinophilic esophagitis or reflux-related changes, pH-impedance testing should be performed. A negative pH-impedance test likely indicates that PPI therapy should be discontinued and that the patient does not have GERD. For those with prominent extraesophageal manifestations, referral to an otolaryngologist, pulmonologist, or allergist should be considered.

Metaplastic and Neoplastic Disorders of the Esophagus

Barrett Esophagus

Epidemiology and Screening

Barrett esophagus (BE) is present when columnar epithelium replaces the normal squamous epithelium in the distal esophagus. Risk factors associated with BE are older age, male

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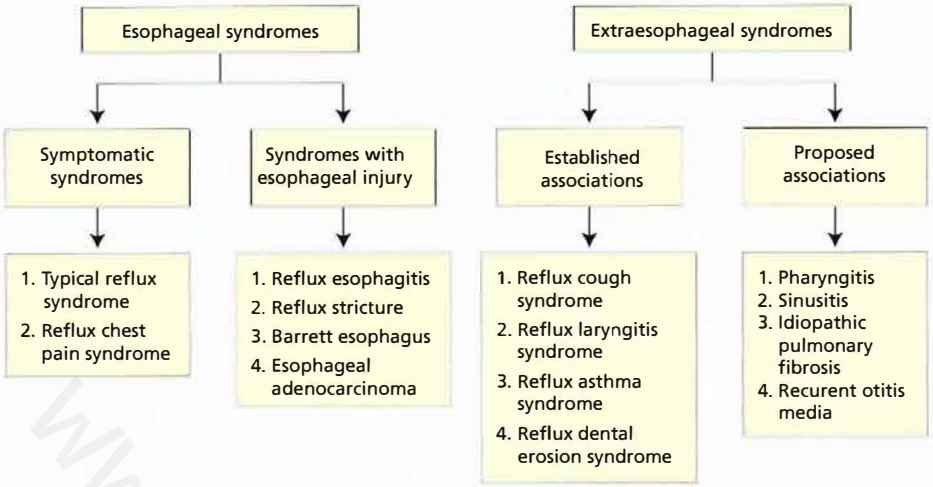

FIGURE 9. Classification of gastroesophageal reflux disease and its subsets.

Reprinted by permission from Macmillan Publishers Ltd: American Journal of Gastroenterology (Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. 101(8):1900-20. [PMID: 16928254]), copyright 2006.

gender, white ethnicity, GERD, hiatal hernia, high BMI, smoking, and an abdominal distribution of fat. Protective factors are moderate wine consumption and a diet rich in fruits and vegetables. BE is a consequence of GERD whether or not patients experience clinical symptoms.

BE is classified as a premalignant condition that could progress to esophageal cancer. The annual incidence of progression to high-grade dysplasia and adenocarcinoma is variable. The cancer risk associated with BE is believed to be 0.5% per year, but a recent study from Denmark reports an estimate of 0.12% per year. Approximately 10% of patients with GERD are found to have BE on upper endoscopy, although 40% of patients diagnosed with adenocarcinoma of the esophagus report no symptoms of GERD. Current evidence does not support routine screening for BE based on GERD symptoms. However, the American College of Physicians suggests that screening for BE may be appropriate in men older than 50 years with chronic GERD (symptoms for more than 5 years) and additional risk factors, including nocturnal reflux symptoms, hiatal hernia, elevated BMI, tobacco use, and intra-abdominal fat distribution. If screening is performed and is negative for BE, no additional endoscopic screening is indicated, even for patients continuing treatment for GERD, unless other symptoms or clinical findings develop.

KEY POINTS

- Barrett esophagus is classified as a premalignant condition that could progress to esophageal cancer.
- HVC Current evidence does not support routine screening for Barrett esophagus based on gastroesophageal reflux disease symptoms.

Diagnosis and Management

The diagnosis of BE is based on the endoscopic finding of columnar epithelium above the normally located gastroesophageal junction (**Figure 10**), followed by histologic confirmation

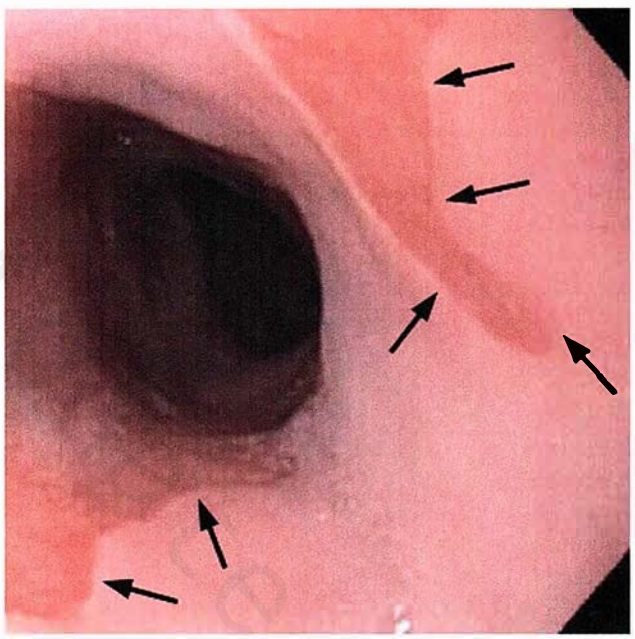

FIGURE 10. Upper endoscopic view of Barrett mucosa, with salmon-colored mucosa (*arrows*) representing Barrett mucosa compared with the normal pearl-colored squamous mucosa.

demonstrating specialized intestinal metaplasia with acid-mucin–containing goblet cells. Upper endoscopy measurements have categorized BE into short segment (less than 3 cm) or long segment (greater than 3 cm) (**Figure 11**). The pathway of progression of BE is from intestinal metaplasia to low-grade dysplasia to high-grade dysplasia to invasive adenocarcinoma.

Recommended surveillance intervals are based on the grade of BE and the presence of dysplasia (**Table 3**); however, the potential risks and benefits of surveillance should be weighed in patients with significant comorbidities or limited life expectancy. Although most patients with BE are treated

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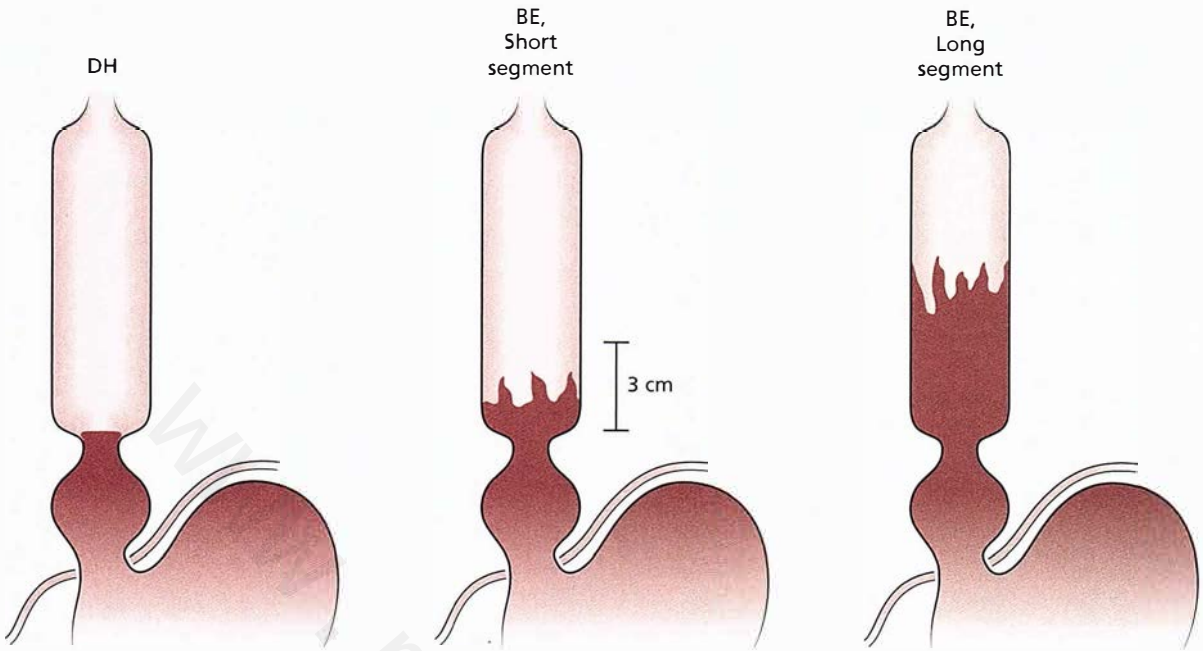

FIGURE 11. Diagram of the esophageal and gastric junction showing replacement of normal esophageal squamous epithelium by specialized intestinal epithelium (shown in red) in Barrett esophagus. BE = Barrett esophagus; DH = diaphragmatic (hiatal) hernia.

Courtesy of Dr. Alan Cameron.

TABLE 3. Practice Guidelines for Endoscopic Surveillance of Barrett Esophagus

Dysplasia Grade	Recommendation
None	If no dysplasia is present, repeat upper endoscopy every 3 to 5 years
Low-grade	Confirmation by expert pathologist
	Repeat upper endoscopy 6 to 12 months after diagnosis to detect prevalent dysplasia
High-grade	Confirmation by expert pathologist
	Endoscopic evaluation for any focal lesion (may indicate more advanced neoplasia); if present, focal lesion(s) should be removed by endoscopic mucosal resection for diagnosis and staging
	Options for further management: esophagectomy, endoscopic ablation, surveillance every 3 months

Data from: American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011 Mar;140(3):1084-91. [PMID: 21376940]

with PPI therapy for GERD symptom control or to heal erosive esophagitis (if present), the use of acid suppression primarily to prevent progression of BE to dysplasia or adenocarcinoma has not been established. Therefore, long-term PPI use in patients with BE should be individualized. There are some data from case-control studies suggesting that aspirin and other NSAIDs may reduce the risk for esophageal adenocarcinoma in patients with BE, but guidelines do not recommend treatment as chemoprevention. Additionally, there is no strong evidence that antireflux surgery can prevent the progression of BE to adenocarcinoma. Treatment to remove BE is recommended for patients with confirmed high-grade dysplasia and can be done with endoscopic therapies that include radiofrequency ablation, photodynamic therapy, or endoscopic mucosal resection. Endoscopic therapies have had similar outcomes to surgery (esophagectomy), but local expertise and patient preference should determine the best course of therapy.

KEY POINTS

- Chemoprevention with a proton pump inhibitor, aspirin or NSAID therapy, or antireflux surgery has not been definitively shown to decrease the risk of progression of dysplasia or development of adenocarcinoma in patients with Barrett esophagus.
- Treatment to remove Barrett esophagus is recommended for patients with confirmed high-grade dysplasia and can be done with endoscopic therapies that include radiofrequency ablation, photodynamic therapy, or endoscopic mucosal resection.

Esophageal Carcinoma

Epidemiology

Esophageal cancer is the sixth leading cause of cancer-related mortality worldwide. The most common types are squamous cell carcinoma (SCC) and adenocarcinoma; the latter is more common in the United States. Esophageal cancer has a male

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CONT. predominance and often occurs in the fifth to sixth decades of life. SCC is more common in black men. In the United States, about 16,000 new cases of esophageal cancer are reported annually, with 14,000 deaths occurring within the same year. The overall 5-year survival rate is between 15% and 25% depending on the stage at time of initial diagnosis. H

KEY POINT

- The overall 5-year survival rate of patients with esophageal carcinoma is between 15% and 25% depending on the stage at time of initial diagnosis.

Risk Factors

The risk factors associated with SCC are tobacco and alcohol use, caustic injury, achalasia, past thoracic radiation, nutritional deficiencies (zinc, selenium), poor socioeconomic status, poor oral hygiene, nonepidermolytic palmoplantar keratoderma (tylosis), human papillomavirus infection, and nitrosamine exposure. Adenocarcinoma risk factors include GERD, BE, obesity, tobacco use, past thoracic radiation, diet low in fruits and vegetables, increased age, male sex, and possibly medications that relax the LES.

Diagnosis and Staging

The most common clinical manifestation of esophageal cancer is solid-food dysphagia; however, esophageal cancer has been diagnosed in asymptomatic individuals during surveillance upper endoscopy. Other symptoms include weight loss, anorexia, and anemia (secondary to gastrointestinal bleeding). Upper endoscopy with biopsy is the preferred initial diagnostic test. SCC is located in the proximal esophagus, whereas adenocarcinoma is usually found in the distal esophagus.

TNM staging is often done with CT scan (to evaluate for metastatic disease), endoscopic ultrasound (to assess locoregional disease), and PET imaging (to follow up on indeterminate lesions). For treatment of esophageal carcinoma, see MKSAP 17 Hematology and Oncology. H

KEY POINTS

- The most common clinical manifestation of esophageal cancer is solid-food dysphagia.
- Upper endoscopy with biopsy is the preferred initial diagnostic test for esophageal carcinoma.

Disorders of the Stomach and Duodenum

Peptic Ulcer Disease

Clinical Features, Diagnosis, and Complications

Peptic ulcer disease (PUD) can present as an uncomplicated gastric and/or duodenal ulcer or as a complicated ulcer. Although the widespread use of potent acid suppressants and the dramatic reduction in *Helicobacter pylori* prevalence have lowered the overall incidence of PUD, the incidence of complicated PUD remains largely unchanged. This phenomenon is largely due to the increased use of aspirin and NSAIDs (see Gastrointestinal Complications of NSAIDs, Aspirin, and Anticoagulants), as well as to the aging population.

The cardinal symptom in uncomplicated PUD is epigastric pain or discomfort. Accompanying symptoms may include nocturnal pain, relief of pain with eating, early satiety, nausea, bloating, or abdominal fullness.

Peptic ulcers are diagnosed not by symptoms but instead by the presence of a mucosal break 5 mm or larger in the stomach or duodenum. Upper endoscopy is considered the gold standard in the diagnosis of PUD.

Complicated PUD can present in a variety of ways depending on the specific complication that has developed. The four major complications of PUD are bleeding, perforation, penetration, and obstruction. The most common presentation of complicated PUD is acute or chronic upper gastrointestinal bleeding (see Gastrointestinal Bleeding). Symptoms of acute gastrointestinal bleeding can include epigastric pain, hematemesis, melena, and/or orthostatic symptoms. Chronic PUD bleeding commonly presents as an iron deficiency anemia. Perforation is likely to present with severe, sudden abdominal pain with peritoneal signs on abdominal examination (tenderness, guarding, rigidity), or possibly with septic shock. Penetration occurs when an ulcer crater erodes through and into adjacent organs including the small bowel, pancreas, liver, and/or biliary tree. It typically presents with a gradual increase in the severity and frequency of abdominal pain, with pancreatitis as a common presentation. Obstruction can be acute or insidious in onset, with symptoms of nausea, vomiting, anorexia, and weight loss accompanying abdominal pain. PUD in the elderly may present atypically, with complications in the absence of abdominal pain. H

When uncomplicated PUD is suspected, definitive diagnosis is made by upper endoscopy (or upper gastrointestinal barium radiography when endoscopy is contraindicated or unavailable). The differential diagnosis for the symptoms of uncomplicated PUD is broad; for further discussion, see Dyspepsia. For patients with complicated PUD or other alarm features (age >55 years with unexplained new-onset epigastric pain, or patients with abdominal pain and unexplained weight loss, gastrointestinal bleeding, microcytic anemia, or recurrent vomiting), a prompt structural evaluation with upper endoscopy, abdominal cross-sectional imaging, or upper gastrointestinal imaging using water-soluble contrast is essential, depending on the complication suspected.

KEY POINTS

- Peptic ulcers are diagnosed not by symptoms but instead by the presence of a mucosal break 5 mm or larger in the stomach or duodenum.
- Upper endoscopy is the gold standard for diagnosis of peptic ulcer disease.

(Continued)

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KEY POINTS *(continued)*

- The four major complications of peptic ulcer disease are bleeding, perforation, penetration, and obstruction.

Management

The primary goals of uncomplicated PUD management are to identify the cause and correct modifiable risk factors for ulcer complications and ulcer recurrence (**Table 4**). There are no guideline recommendations that support follow-up endoscopy in all patients with gastric ulcers given the decreasing incidence of gastric cancer in the United States. If a gastric ulcer is found in a patient who is at low risk for gastric cancer (for example, a young patient on NSAIDs), follow-up endoscopy to assess healing may not be required. However, when a gastric ulcer has an endoscopic appearance that is concerning for malignancy despite initial biopsies being negative, then endoscopy should be repeated after 8 to 12 weeks of antisecretory therapy to assess for healing. Additional biopsies should be obtained if healing has not occurred. Duodenal ulcers do not typically require endoscopic follow-up. An assessment for *H. pylori* infection should be performed in all patients with PUD (see *Helicobacter pylori* Infection).

KEY POINTS

- The primary goals of uncomplicated peptic ulcer disease management are to identify the cause and correct modifiable risk factors for ulcer complications and ulcer recurrence. *(Continued)*

KEY POINTS *(continued)*

- Duodenal ulcers and low-risk gastric ulcers (for example, a young patient on NSAIDs) do not typically require endoscopic follow-up.

HVC

Dyspepsia

Clinical Features

Dyspepsia encompasses a heterogeneous symptom complex that may include epigastric pain or burning, abdominal fullness, nausea, vomiting, bloating, belching, and/or weight loss. After identifiable causes (**Table 5**) have been evaluated and excluded, the term functional dyspepsia (FD) can be used. Approximately two thirds of dyspepsia cases are attributed to FD. Although the cause of FD remains unknown, proposed pathophysiologic mechanisms include abnormal upper gastrointestinal motor and reflex functions, visceral hypersensitivity, altered brain-gut interactions, disrupted gut-immune interactions, psychological factors, and genetic factors. Lacking a definable biomarker, FD is defined by fulfillment of diagnostic criteria developed by the Rome III consensus group, an international panel of experts in the field of functional bowel disorders. FD diagnostic criteria consist of one or more of the following: (1) bothersome postprandial fullness, (2) early satiety, (3) epigastric pain, and/or (4) epigastric burning. These criteria should be met for the past 3 months, with symptom onset at least 6 months prior to diagnosis and with no evidence of structural disease to explain the symptoms.

TABLE 4. Risk Factors for and Interventions to Prevent Peptic Ulcer Disease Recurrence and Complications

Risk Factor	Intervention to Prevent PUD Recurrence
Advanced age (>65 years)	Indefinite use of antisecretory therapy[a]
Aspirin use (high or low dose)	Co-therapy with antisecretory therapy if chronic aspirin use is indicated
Helicobacter pylori infection	Treat and confirm eradication
	If other risk factors for PUD recurrence are present, continue antisecretory therapy indefinitely
NSAID use	Co-therapy with antisecretory therapy if no alternative therapy is available
Tobacco use	Smoking cessation
	Indefinite use of antisecretory therapy
Alcohol use	Reduce or eliminate alcohol use
	Indefinite use of antisecretory therapy
Comorbidities (COPD; chronic kidney disease; coronary artery disease; diabetes mellitus; obesity; chronic anticoagulation, immunosuppression, or glucocorticoid use)	Indefinite use of antisecretory therapy
	Optimization of chronic disease
Other nonmodifiable risk factors (male gender, black ethnicity, complicated PUD)	Indefinite use of antisecretory therapy

PUD = peptic ulcer disease.

[a]Antisecretory therapy: proton pump inhibitor, H_2 blocker.

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TABLE 5. Identifiable Causes of Dyspepsia
Erosive gastroesophageal reflux disease
Nonerosive gastroesophageal reflux disease
Esophageal malignancy
Peptic ulcer disease
Helicobacter pylori infection
Gastric malignancy
Gastroparesis
Celiac disease
Carbohydrate maldigestion (lactose, fructose, small intestinal bacterial overgrowth)
Biliary tract disease
Pancreatitis or pancreatic malignancy
Infiltrative and inflammatory diseases involving the upper gastrointestinal tract
Ischemic bowel disease
Abdominal wall pain (muscle strain, nerve entrapment, myositis)
Medications (most commonly aspirin and NSAIDs)
Alcohol
Systemic and metabolic disorders (diabetes mellitus, thyroid dysfunction, ischemic heart disease)
Pregnancy

KEY POINT

- Diagnostic criteria for functional dyspepsia consist of one or more of the following: (1) bothersome postprandial fullness, (2) early satiety, (3) epigastric pain, and/or (4) epigastric burning; these criteria should be met for the past 3 months, with symptom onset at least 6 months prior to diagnosis and with no evidence of structural disease to explain the symptoms.

Management

Management of dyspepsia is described in **Figure 12**. For patients younger than 50 to 55 years who present with dyspepsia without alarm features (melena, rectal bleeding, unintentional weight loss, anorexia, early satiety, persistent or recurrent vomiting, dysphagia, odynophagia, family history of upper gastrointestinal malignancy, personal history of PUD or malignancy, prior gastric surgery, abdominal mass, or anemia), testing and treating for *H. pylori* infection or a trial of proton pump inhibitor (PPI) therapy should be pursued before any further testing is done. Further structural testing should be performed in patients older than 50 to 55 years, those with alarm features at any age, or those with persistent dyspeptic symptoms despite eradication of *H. pylori* and/or a trial of PPI therapy. Upper endoscopy is considered the gold standard for the exclusion of upper gastrointestinal structural causes of dyspepsia. No other biochemical, structural, or physiologic studies should be performed routinely for evaluation of dyspepsia. Such additional testing may be considered on a case-by-case basis given the patient's age, presence of alarm features, accompanying symptoms, comorbid illnesses, and results of prior testing.

The treatment of FD is largely empiric and consists of dietary and lifestyle modification, over-the-counter and prescription medications, psychological treatments, and complementary and alternative medicine therapies. Dietary and lifestyle strategies may include a food diary to identify behaviors or specific foods that trigger symptoms. Other suggestions include the ingestion of low-fat, smaller, more frequent meals and the avoidance of late-evening meals. Both PPIs and H_2 blockers have demonstrated efficacy in a select subgroup of patients with FD, typically those with a predominant symptom of epigastric pain. There does not appear to be a dose effect with either agent alone. There is no clear synergistic effect when both agents are used concomitantly. Antidepressants, such as tricyclics and selective serotonin reuptake inhibitors, should be reserved for more severe or refractory FD. Psychological therapies such as psychodrama, cognitive-behavioral therapy, relaxation therapy, guided imagery, and hypnotherapy may be beneficial in patients with symptoms related to anxiety or stress, a history of abuse, or comorbid psychological conditions. The best-studied herbal remedies in FD include STW 5 (a liquid formulation of nine herbal extracts), peppermint, and caraway, and limited data exist on artichoke leaf extract and capsaicin. Referral to a gastroenterologist should be considered for patients whose symptoms do not respond to a test-and-treat approach for *H. pylori*, a trial of antisecretory therapy, and dietary modifications.

KEY POINTS

- For patients younger than age 50 to 55 years who present with dyspepsia without alarm features, testing and treating for *Helicobacter pylori* infection or a trial of proton pump inhibitor therapy should be pursued before any further testing is done. HVC
- The treatment of functional dyspepsia is largely empiric and consists of dietary and lifestyle modification, over-the-counter and prescription medications, psychological treatments, and complementary and alternative medicine therapies.

Helicobacter pylori Infection

Indications for *Helicobacter pylori* Testing

Despite the decreasing prevalence of *H. pylori* infection in developed countries such as the United States, it remains linked to a number of important clinical conditions and is deemed a human carcinogen by the World Health

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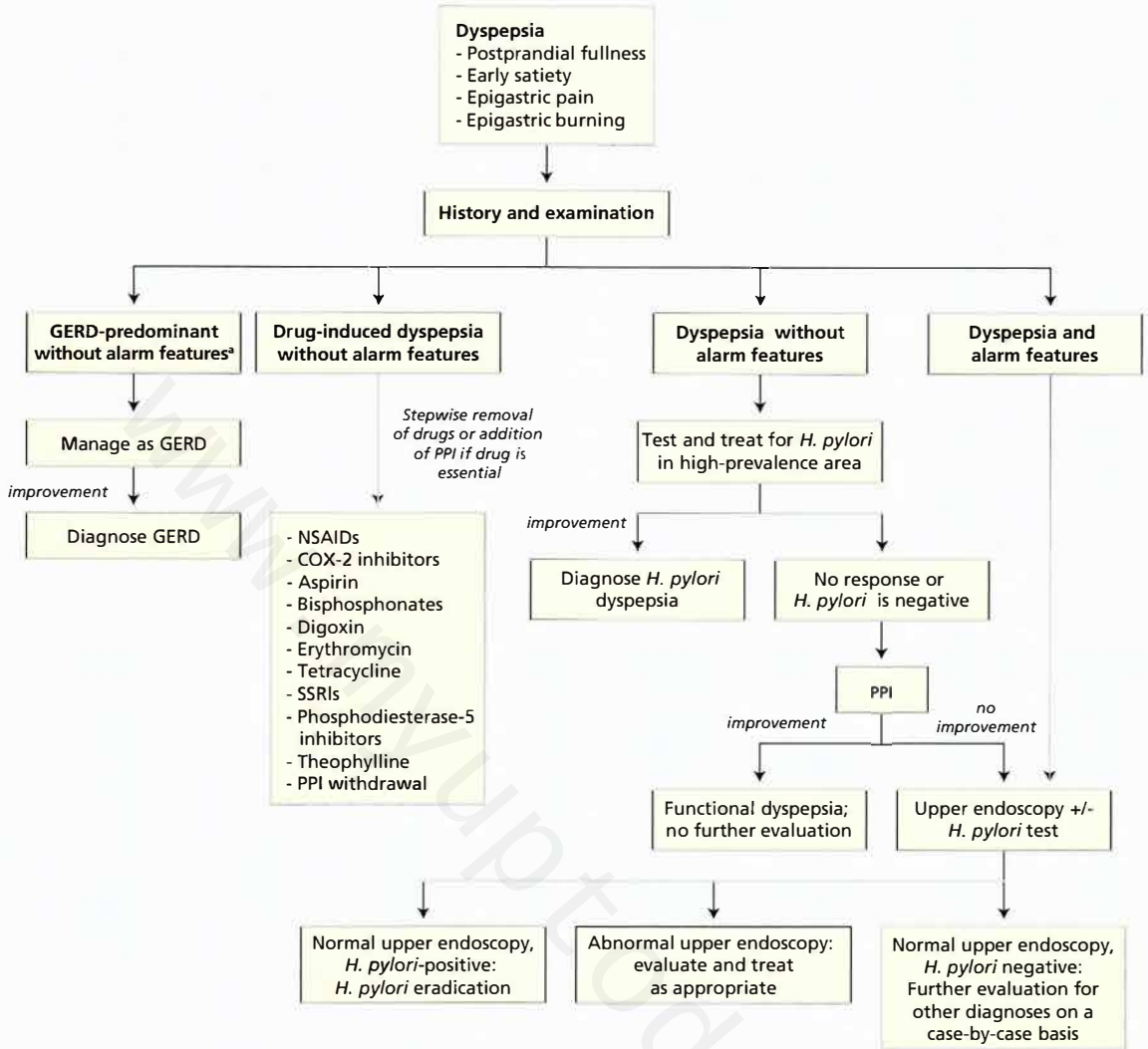

FIGURE 12. Evaluation and management of dyspepsia. COX-2 = cyclooxygenase-2; GERD = gastroesophageal reflux disease; *H. pylori* = *Helicobacter pylori*; PPI = proton pump inhibitor; SSRI = selective serotonin reuptake inhibitor.

[a]Alarm features = melena, rectal bleeding, unintentional weight loss, anorexia, early satiety, persistent or recurrent vomiting, dysphagia, odynophagia, family history of upper gastrointestinal malignancy, personal history of peptic ulcer disease or malignancy, prior gastric surgery, abdominal mass, or anemia.

Organization. Clearly established indications for *H. pylori* testing are active PUD (gastric and/or duodenal ulcer), a confirmed history of PUD, gastric mucosa–associated lymphoid tissue (MALT) lymphoma, uninvestigated dyspepsia, and following endoscopic resection of early gastric cancer. Less-established indications for *H. pylori* testing include unexplained iron deficiency anemia and primary immune thrombocytopenia (previously termed idiopathic thrombocytopenic purpura). Controversial indications for *H. pylori* testing include chronic NSAID and/or aspirin use and a first-degree family member with gastric cancer. Gastroesophageal reflux disease is not a clinical indication for *H. pylori* testing; however, the coexistence of gastroesophageal reflux disease with one of the above-stated indications should not preclude testing for *H. pylori*.

KEY POINTS

- Clearly established indications for *Helicobacter pylori* testing are active peptic ulcer disease (gastric and/or duodenal ulcer), a confirmed history of peptic ulcer disease, gastric mucosa–associated lymphoid tissue lymphoma, uninvestigated dyspepsia, and following endoscopic resection of early gastric cancer.
- Gastroesophageal reflux disease is not a clinical indication for *Helicobacter pylori* testing. HVC

Diagnosis

Noninvasive tests that identify active infection include the urea breath test and fecal antigen test. To improve the diagnostic accuracy of the urea breath test and fecal antigen test, antimicrobial

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agents and bismuth should be avoided for 28 days prior to testing. PPIs should be avoided for 7 to 14 days prior to testing, and H_2 blockers should be avoided for 1 to 2 days prior to testing.

Serum testing for IgG antibodies to *H. pylori* does not identify active infection in populations with low prevalence of disease; however, it remains popular given its ease of administration, rapidity of results, and low cost. Given its marginal sensitivity (85%) and specificity (79%), antibody testing should not be used when there is a low background prevalence of *H. pylori* (prevalence <20%).

Invasive (endoscopic) tests for *H. pylori* include the rapid urease test, histology, and culture; all invasive testing modalities identify active infection.

Owing to the increased risk of false-negative endoscopic and fecal antigen test results in patients with bleeding PUD, serologic antibody testing should also be performed as a second test in this clinical setting, and treatment should be pursued if either test modality is positive.

Table 6 provides a summary of *H. pylori* testing in clinical practice.

Treatment

Treatment regimens should consist of a minimum of three agents, including two antimicrobial agents and one antisecretory agent. Treatment duration should be 10 to 14 days. Second-line therapy following treatment failure should consist of an alternative drug regimen. Recommended treatment regimens are shown in **Table 7**. Reasons for treatment failure include antimicrobial resistance (clarithromycin, metronidazole), patient noncompliance, and tobacco smoking and alcohol ingestion during treatment. Patients in whom two courses of eradication therapy are unsuccessful should be referred to a gastroenterologist for endoscopy. During upper endoscopy, tissue should be obtained for culture of *H. pylori* and determination of antibiotic sensitivities.

TABLE 6. Diagnostic Testing for *Helicobacter pylori* Infection

Test Modality	Advantages	Disadvantages	Use in Clinical Practice
Serum IgG antibody test	Low cost Widely available Allows for office-based testing Rapid results Good negative predictive value (a negative result is helpful)	Does not identify active infection Poor positive predictive value (a positive test is not helpful when pretest probability is low)	Most useful when there is high pretest probability (in individuals from urban areas or communities with large immigrant populations, and in patients with a peptic ulcer) Do not use to confirm *H. pylori* eradication following therapy or to assess for reinfection
Urea breath test	Identifies active *H. pylori* infection (through urease activity) Accurate (sensitivity and specificity >95%)	Limited by need for specialized equipment and personnel Radiation risk if radioactive ^{14}C isotope used (nonradioactive ^{13}C is available) Accuracy decreased by bismuth, antibiotic, and PPI use Costly	Use to confirm a positive antibody test when pretest probability is low (population with low background prevalence of *H. pylori*) Use to confirm eradication after therapy (at least 4 weeks after therapy) Use to assess for reinfection
Fecal antigen test	Identifies active *H. pylori* infection (identifies bacterial antigen by EIA) Costs less than urea breath testing	Requires collection of stool specimen Polyclonal test not as accurate as monoclonal after eradication therapy Accuracy decreased by bismuth, antibiotic, and PPI use	Use to confirm a positive antibody test when pretest probability is low (population with low background prevalence of *H. pylori*) Can use to confirm eradication after therapy (at least 4 weeks after therapy; monoclonal test preferred) Use to assess for reinfection
Endoscopic-based testing (rapid urease test, histology, and culture)	Allows for visualization of stomach Excellent sensitivity and specificity of histology Allows for determination of antibiotic sensitivities	Requires endoscopy Expensive Accuracy decreased by bismuth, antibiotic, and PPI use Limited availability for culture	Use if endoscopy is indicated for other reasons Use to obtain tissue for culture of *H. pylori* and determination of antibiotic sensitivities (after failure of two or more courses of eradication therapy)

EIA = enzyme immunoassay; PPI = proton pump inhibitor.

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TABLE 7. First- and Second-Line Treatment Regimens for *Helicobacter pylori* Infection

First-Line Treatment Options	Caveats
Standard-dose PPI[a] twice daily or esomeprazole daily; clarithromycin, 500 mg twice daily; amoxicillin, 1000 mg twice daily	Avoid where clarithromycin resistance rates are >15%-20%
Standard-dose PPI[a] twice daily or esomeprazole daily; clarithromycin, 500 mg twice daily; metronidazole, 500 mg twice daily	Use metronidazole only when penicillin allergy exists
Ranitidine, 150 mg twice daily, or standard-dose PPI[a] twice daily; bismuth subsalicylate, 525 mg four times daily; metronidazole, 250 mg four times daily; tetracycline, 500 mg four times daily	Doxycycline, 100 mg twice daily, can be used in place of tetracycline if unavailable
Second-Line Treatment Options	
Consider first-line options listed above not used as initial therapy	
Standard-dose PPI[a] twice daily; levofloxacin, 500 mg/d; amoxicillin, 1000 mg twice daily	

PPI = proton pump inhibitor.

[a]Standard-dose PPI: omeprazole, 20 mg; lansoprazole, 30 mg; pantoprazole, 40 mg; rabeprazole, 20 mg

Data from: Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. Am J Gastroenterol. 2007 Aug;102(8):1808-25. [PMID: 17608775]

KEY POINT

- Treatment regimens for *Helicobacter pylori* should consist of a minimum of three agents, including two antimicrobial agents and one antisecretory agent; treatment duration should be 10 to 14 days.

Eradication Testing

Testing to confirm eradication of *H. pylori* should ideally be pursued in all cases given the high rate of treatment failure (roughly 25% in the United States). Eradication testing should definitively be pursued in patients with an *H. pylori*–associated peptic ulcer, *H. pylori*–associated MALT lymphoma, gastric cancer resection, or persistent dyspepsia. Eradication testing should be performed no sooner than 4 weeks after completing antimicrobial therapy. PPI therapy should be stopped at least 2 weeks prior to testing. Antibody testing is not appropriate for confirming eradication because antibodies can remain in the serum long after *H. pylori* has been eradicated. Unless upper endoscopy is indicated for other reasons, noninvasive testing modalities appropriate for confirmation of eradication or assessment for reinfection include the urea breath test or the fecal antigen test. Both testing modalities are equivalent with regard to accuracy; therefore, the specific test chosen should be based on patient preference and/or test availability.

KEY POINT

HVC

- Noninvasive testing to confirm eradication of *Helicobacter pylori* (with the urea breath test or fecal antigen test) should be performed given the high rate of treatment failure (roughly 25% in the United States); antibody testing is not appropriate for confirming eradication because antibodies can remain in the serum long after *H. pylori* has been eradicated.

Miscellaneous Gastropathy

Mucosal gastropathic conditions such as intestinal metaplasia, autoimmune atrophic gastritis, lymphocytic gastritis, and eosinophilic gastritis may be identified at the time of upper endoscopy based on the histopathologic findings of gastric biopsies. Although these relatively uncommon conditions are largely managed by the gastroenterologist, important clinical aspects are relevant to the internist, who often has requested the upper endoscopy.

Atrophic Gastritis

The two forms of atrophic gastritis are *H. pylori*–associated and autoimmune. *H. pylori*–associated atrophic gastritis typically resolves with *H. pylori* eradication. Autoimmune atrophic gastritis, however, has no cure. Important clinical manifestations include pernicious anemia, iron deficiency anemia, and hypergastrinemia, which result from the long-term effects of the associated parietal cell loss and subsequent development of achlorhydria. Pernicious anemia and iron deficiency anemia are likely to require lifelong vitamin B_{12} and/or iron replacement, respectively. Hypergastrinemia is associated with an increased risk for the development of gastric carcinoid and adenocarcinoma; however, the risk is low enough that no endoscopic surveillance program is endorsed in the United States. There is a surveillance program in Europe.

Intestinal Metaplasia

Intestinal metaplasia is a relatively common precancerous lesion of the gastric mucosa. There can be an association with *H. pylori*; however, the infection may be patchy and may be missed on biopsies. Therefore, a second testing modality such as the urea breath test or fecal antigen test should be considered to further evaluate for active *H. pylori* infection. Although

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there is an increased risk for gastric adenocarcinoma, the risk is low enough that endoscopic surveillance is not performed unless the patient has additional risk factors, such as emigration from a geographic location with a high gastric cancer risk (Eastern Asia, Eastern Europe, and South America) or a family history of gastric cancer. However, given the association of gastric adenocarcinoma with *H. pylori*, this infection should be treated if identified.

Eosinophilic Gastritis

Eosinophilic gastritis is a rare, heterogeneous inflammatory condition that can involve the mucosal, muscular, or serosal layers of the stomach and/or duodenum. Eosinophilic gastritis is not considered a premalignant condition, and there are no specific nutritional deficiencies that are known to develop. Symptoms associated with eosinophilic gastritis can be quite variable and may include epigastric pain, nausea, vomiting, other dyspeptic symptoms, gastric outlet obstruction, and in rare cases ascites. Dietary treatment or glucocorticoid therapy may have a role in severe cases.

Lymphocytic Gastritis

Lymphocytic gastritis is a rare, benign chronic inflammatory condition of the gastric mucosa. Clinical manifestations may include dyspepsia, iron deficiency anemia, and diarrhea. Protein-losing gastroenteropathy has also been reported. Lymphocytic gastritis has been associated with celiac disease and *H. pylori* gastritis. Other less common associations include varioliform gastritis (a rare form of chronic gastritis characterized by endoscopic findings of nodules, thickened rugal folds, and erosions), Crohn disease, HIV infection, lymphocytic gastroenterocolitis (when the lymphocytic inflammation involves more than the stomach and is found on small-bowel and colon biopsies), and gastric lymphomas. Treatment is directed at the underlying condition, which in most cases is celiac disease or *H. pylori* infection. Lymphocytic gastritis is not considered a premalignant condition. Endoscopic surveillance is not required; however, small-bowel and colon biopsies should be obtained to determine the extent of the inflammation and to identify underlying conditions.

Gastrointestinal Complications of NSAIDs, Aspirin, and Anticoagulants

Epidemiology and Risk Factors

Low-dose aspirin used for cardioprophylaxis is associated with a two- to fourfold increase in upper gastrointestinal complications. Nearly 25% of chronic NSAID users will develop PUD, and 2% to 4% will develop complications of bleeding or perforation. Risk factors for NSAID-related gastrointestinal complications include a history of PUD or other gastrointestinal bleeding event; *H. pylori* infection; age 65 years or older; concomitant use of aspirin (of any dose), anticoagulants, other NSAIDs, or glucocorticoids; high-dose NSAID use; and chronic comorbid illness.

KEY POINT

- Risk factors for NSAID-related gastrointestinal complications include a history of peptic ulcer disease or other gastrointestinal bleeding event; *Helicobacter pylori* infection; age 65 years or older; concomitant use of aspirin (of any dose), anticoagulants, other NSAIDs, or glucocorticoids; high-dose NSAID use; and chronic comorbid illness.

Prevention of NSAID-Induced Injury

PPIs are the preferred agent for treatment and prophylaxis of NSAID- and aspirin-related gastrointestinal injury. Misoprostol at full dose (800 μg/d) is effective in preventing PUD and ulcer complications with NSAID use; however, its use is limited by side effects (diarrhea, abortifacient). In patients with a history of PUD, testing and treating for *H. pylori* infection should be performed before starting chronic antiplatelet therapy. Prevention recommendations based on risk stratification of NSAID-induced gastrointestinal injury are summarized in **Figure 13**.

Selective cyclooxygenase-2 (COX-2) inhibitors preferentially inhibit the COX-2 isoenzyme, which primarily modulates pain and inflammation, and minimally inhibit the COX-1 isoenzyme, which promotes generation of the gastric mucosal protective barrier, decreases gastric acid secretion, and helps to maintain good mucosal blood flow. The risk of gastroduodenal ulcers and ulcer complications is significantly lower in patients taking COX-2 inhibitors compared with nonselective NSAIDs. However, in high-risk individuals, such as those with previous PUD, a COX-2 inhibitor alone is no better than a nonselective NSAID coadministered with a PPI in preventing ulcer complications. Moreover, the beneficial effect of COX-2 inhibitors is lost when taken concomitantly with low-dose aspirin. There is also evidence that COX-2 inhibitors and nonselective NSAIDs, with the possible exception of naproxen, increase the risk of cardiovascular complications. Therefore, the decision to use a COX-2 inhibitor requires a risk-benefit analysis that weighs the gastrointestinal risks of an NSAID with the potential cardiovascular risks of a COX-2 inhibitor.

KEY POINT

- Proton pump inhibitors are the preferred agent for treatment and prophylaxis of NSAID- and aspirin-related gastrointestinal injury.

Gastroparesis

Diagnosis

Gastroparesis is a heterogeneous clinical syndrome that is diagnosed based on the presence of specific symptoms and objective documentation of delayed delivery of the stomach contents into the proximal small bowel in the absence of a

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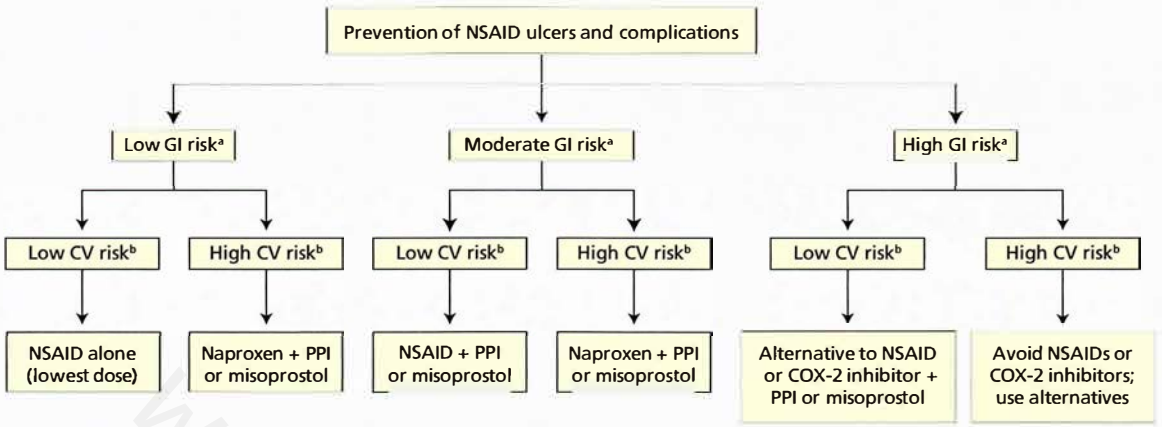

FIGURE 13. Prevention of NSAID-induced ulcers and complications. CV = cardiovascular; COX-2 = cyclooxygenase-2; GI = gastrointestinal; PPI = proton pump inhibitor.

[a]Gastrointestinal risk is stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors or previous ulcer complications or concomitant use of glucocorticoids or anticoagulants).

[b]High CV risk = need for aspirin to prevent cardiovascular events. Low-dose aspirin is indicated in patients with high CV risk.

Adapted by permission from Macmillan Publishers Ltd: American Journal of Gastroenterology (Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. 104(3):728-38. [PMID: 19240698]), copyright 2009.

mechanical obstruction. Commonly reported symptoms include early satiety, postprandial fullness, nausea, vomiting, upper abdominal pain, bloating, and weight loss. These symptoms correlate poorly with the findings on objective gastric emptying tests. For example, patients with accelerated gastric emptying may report similar symptoms to those with delayed gastric emptying. A variety of other upper gastrointestinal disorders, including PUD, partial gastric or small-bowel obstruction, functional dyspepsia, gastric cancer, *H. pylori* infection, and pancreaticobiliary disorders, can present with similar symptoms. Exclusion of other upper gastrointestinal disorders, objective documentation of delayed gastric emptying, and an attempt to identify the cause of the gastroparesis are essential prior to treatment.

KEY POINT

- Commonly reported symptoms of gastroparesis include early satiety, postprandial fullness, nausea, vomiting, upper abdominal pain, bloating, and weight loss.

Testing

A structural assessment of the upper gastrointestinal tract must be performed before pursuing a gastric emptying study. Upper endoscopy is the most accurate test for this initial assessment; however, upper gastrointestinal barium radiography is a reasonable alternative when upper endoscopy is not available or noninvasive testing is desired. The standard test for assessment of gastric emptying is the scintigraphic gastric emptying of solids. A 4-hour emptying study is more accurate than a 2-hour study. A wireless motility capsule is also available to assess gastric emptying and offers the advantage of also providing small-bowel and colon transit information. Drugs that affect gastric emptying (**Table 8**) should be stopped a minimum of 48 hours before testing. Patients with diabetes mellitus should have a plasma glucose level less than 275 mg/dL (15.3 mmol/L) during testing because marked hyperglycemia can acutely impair gastric emptying.

TABLE 8. Medications that Impair Gastric Emptying

Opioid analgesics
Anticholinergic agents
Tricyclic antidepressants
Calcium channel blockers
Progesterone
Octreotide
Proton pump inhibitors
H_2 blockers
Sucralfate
Aluminum hydroxide
Interferon alfa
L-dopa
Fiber
β-Agonists
Glucagon
Calcitonin
Dexfenfluramine
Diphenhydramine
Nicotine
Tetrahydrocannabinol

Patients diagnosed with gastroparesis should be assessed for diabetes, thyroid dysfunction, neurologic disease, previous gastric or bariatric surgery, and autoimmune disorders.

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Patients should be asked about viral illness prior to symptom onset to identify a postviral gastroparesis.

KEY POINT

- Diagnostic testing for gastroparesis consists of an initial assessment with upper endoscopy to exclude mechanical obstruction, followed by a gastric emptying study.

Management

Initial management consists of the prompt identification and treatment of dehydration, electrolyte disturbances, and micronutrient deficiencies, as these can worsen symptoms associated with gastroparesis. Dietary modification and optimization of glycemic control in patients with diabetes should be the first treatment intervention. Specific diet recommendations include small, low-fat meals consumed four to five times per day. Insoluble fiber (found in fresh fruits, fresh vegetables, and bran) should be avoided. High-calorie liquids can be used to increase the liquid nutrient component of meals. Carbonated beverages, alcohol, and tobacco smoking should be minimized or ideally avoided.

On-demand use of antiemetic agents is effective in addressing nausea and vomiting associated with gastroparesis; however, these agents have no effect on gastric emptying. Prokinetic agents can be used in conjunction with dietary management and aggressive glycemic control to improve gastric emptying. Metoclopramide is the only prokinetic agent approved by the FDA for the treatment of gastroparesis. Given the risk of side effects, including dystonia, parkinsonism-type movements, and tardive dyskinesia, the lowest dose should be used (starting at 5 mg three times daily), should be taken with meals, and should be advanced slowly to a maximum total dose of 40 mg a day (10 mg four times daily). Patients should be informed of the potential for neurologic side effects and should be instructed to stop therapy if they occur. Erythromycin also improves gastric emptying; however, it is generally reserved for short-term intravenous use in patients hospitalized for gastroparesis exacerbations. Low-dose tricyclic antidepressants can also be considered to address refractory nausea and vomiting, but these agents may further slow gastric emptying. If symptoms persist despite these interventions, patients should be referred to a gastroenterologist.

Gastric Polyps and Subepithelial Lesions

Gastric Polyps

Gastric polyps are found on up to 5% of upper endoscopies; 90% are either hyperplastic or fundic gland polyps (FGPs). Sporadic FGPs have been associated with PPI use and do not require excision or surveillance. They are usually 1 to 5 mm in size and fewer than 10 in number. FGPs related to familial adenomatous polyposis (FAP) or *MYH*-associated polyposis are usually numerous (>30 polyps), frequently harbor dysplasia, and warrant excision if they are 10 mm or larger. Colonoscopy to rule out FAP and *MYH*-associated polyposis is recommended in patients younger than 40 years with dysplastic or numerous FGPs. Adenomatous and hyperplastic polyps are associated with atrophic gastritis, intestinal metaplasia, and *H. pylori* infection. Adenomas are dysplastic and warrant excision, whereas only 20% of hyperplastic polyps harbor dysplasia. Polypectomy of lesions larger than 5 mm is recommended. Less common gastric polyps include inflammatory fibroid polyps, hamartomas, pancreatic rests, and carcinoids.

KEY POINT

- Colonoscopy to rule out familial adenomatous polyposis or *MYH*-associated polyposis is recommended in patients younger than 40 years with dysplastic or numerous fundic gland polyps.

Gastric Subepithelial Lesions

Lesions arising beneath the gastric epithelium are frequently asymptomatic and are often found incidentally during upper endoscopy or radiologic imaging of the gastrointestinal tract. The differential diagnosis of gastric subepithelial lesions (SELs) is broad and includes a variety of intramural lesions as well as compression from extraluminal organs or lesions. Benign SELs include lipoma, leiomyoma, pancreatic rests, inflammatory fibroid polyps, and duplication cysts. The malignant and potentially malignant SELs include gastrointestinal stromal tumors (GISTs), lymphoma, carcinoid, glomus tumors, and rarely metastases. Because endoscopic biopsy is often unable to provide a diagnosis, endoscopic ultrasound (EUS) is the imaging modality of choice for the evaluation of SELs. EUS ascertains characteristic features suggestive of the diagnosis by identification of the layer of origin of the lesion. Because benign and malignant lesions may not always be differentiated by sonographic features, EUS-guided fine-needle aspiration may be performed for cytopathologic specimen analysis.

Gastrointestinal Stromal Tumors

GISTs represent less than 1% of tumors of the gastrointestinal tract and are most commonly found in the stomach. Most are discovered incidentally, but large tumors may cause pain, obstruction, or hemorrhage. GISTs are mesenchymal tumors believed to arise from the interstitial cells of Cajal (ICC). Approximately 95% of GISTs have evidence of a *KIT* oncogene mutation, which stains positive for the CD117 antigen, a marker expressed by ICC. GISTs may range from indolent to aggressive. The prognosis is based upon mitotic index (mitoses per 50 high-power fields), tumor size, and location.

See MKSAP 17 Hematology and Oncology for staging and treatment of GISTs.

Gastric Carcinoid Tumors

Carcinoid tumors, known as neuroendocrine tumors (NETs), represent 1% of gastric neoplasms. They are derived from

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enterochromaffin cells of the gastric mucosa. Three subtypes of gastric NETs exist. Type I accounts for 80% and is associated with autoimmune atrophic gastritis and hypergastrinemia. Type II is associated with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. Endoscopic polypectomy is curative for type I and II NETs that are smaller than 1 cm. Type III lesions account for 15% of gastric NETs; they are gastrin independent and have the poorest prognosis. Gastric NETs secrete 5-hydroxytryptophan rather than serotonin; therefore, classic carcinoid syndrome is rare, while wheezing, lacrimation, swelling, flushing, and carcinoid heart and valvular disease may be seen owing to high systemic amine concentrations.

See MKSAP 17 Hematology and Oncology for treatment of gastric NETs.

KEY POINT

- Endoscopic ultrasound is the imaging modality of choice for evaluation of gastric subepithelial lesions.

Gastric Adenocarcinoma

Epidemiology and Risk Factors

Gastric cancer is the fourth most common cancer worldwide. The highest rates are seen in developing countries, including those in Asia (particularly China), South America, and Eastern Europe. Gastric cancer rates have decreased in most parts of the world owing to a reduction in risk factors (**Table 9**). The rate of stomach cancer in white women in the United States is 4 per 100,000, which is lower than the rate in white men (8.4 per 100,000). The incidence is higher in nonwhites, with the highest rates in black patients. Overall 5-year survival is approximately 28%. Gastric adenocarcinoma accounts for more than 90% of gastric cancers and is subdivided into intestinal and diffuse histology. Intestinal type predominates and is often related to environmental factors. Diffuse gastric cancer is more often seen in women and young patients. Germline mutations in the gene *E-cadherin* cause hereditary diffuse gastric cancer, which is associated with an 80% lifetime risk of gastric cancer. Prophylactic gastrectomy is recommended in gene carriers who are 20 years of age or older. Other genetic syndromes associated with an increased risk for gastric cancer include Lynch syndrome, FAP, *MYH*-associated polyposis, Li-Fraumeni syndrome, hyperplastic gastric polyposis, juvenile polyposis syndrome, and Peutz-Jeghers syndrome.

TABLE 9. Risk Factors Associated with Gastric Adenocarcinoma

Type	Risk Factor
Environmental factors	*Helicobacter pylori* infection
	Diet low in fresh fruits and vegetables
	Diet high in salted and preserved foods
	Smoking
Underlying conditions	Chronic atrophic gastritis and intestinal metaplasia
	Previous gastric surgery
	Gastric adenomas
Genetic factors	Familial adenomatous polyposis
	MYH-associated polyposis
	Lynch syndrome
	Li-Fraumeni syndrome
	Juvenile polyposis syndrome
	Peutz-Jeghers syndrome
	Gastric hyperplastic polyposis
	Hereditary diffuse gastric cancer

Screening and Surveillance

Gastric cancer screening for average-risk patients is not recommended in the United States. Patients with a genetic gastric cancer predisposition should undergo syndrome-specific surveillance. Surveillance upper endoscopy is recommended 1 year after adenomatous gastric polyp removal and, if negative, every 3 to 5 years. There is insufficient evidence to support surveillance for individuals with gastric intestinal metaplasia; however, surveillance can be considered in patients who have intestinal metaplasia as well as an increased risk owing to ethnicity or family history. Surveillance in intestinal metaplasia should incorporate a biopsy protocol that maps the entire stomach. Patients with low-grade dysplasia should undergo biopsy every 3 months for the first year, and surveillance should cease when two consecutive endoscopies are negative. The presence of high-grade dysplasia warrants surgical resection. Surveillance after early gastric cancer treatment should be individualized.

KEY POINT

- Gastric cancer screening for average-risk patients is not recommended in the United States; patients with a genetic gastric cancer predisposition should undergo syndrome-specific surveillance.

Clinical Manifestations and Diagnosis

Gastric cancer symptoms are nonspecific and may include anorexia, weight loss, abdominal discomfort, early satiety, gastrointestinal bleeding, or nausea and vomiting. Upper endoscopy with biopsy is the diagnostic test of choice.

For staging and treatment of gastric cancer, see MKSAP 17 Hematology and Oncology.

KEY POINT

- Upper endoscopy with biopsy is the diagnostic test of choice for gastric cancer.

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Complications of Gastric Surgical Procedures

Bariatric Surgery Complications

For a general discussion of bariatric surgery, see MKSAP 17 General Internal Medicine.

Postoperative Mortality

In general, mortality rates are low for bariatric surgery and are reported to be 0.3% to 0.4% at 30 days and 0.8% at 2 years. Laparoscopic and restrictive procedures (gastric banding, sleeve gastrectomy) are associated with lower mortality than open and malabsorptive/restrictive procedures (Roux-en-Y gastric bypass, biliopancreatic diversion with duodenal switch). Several clinical factors that increase mortality are a history of deep venous thrombosis or pulmonary embolism, obstructive sleep apnea, impaired functional status, advanced age, and a surgeon and/or hospital with lower volumes of bariatric surgery. The major causes of perioperative mortality are anastomotic leaks, pulmonary embolism, bleeding, and cardiovascular complications.

Restrictive Procedure Complications

Complications unique to gastric banding include slippage of the gastric band resulting in pouch dilatation, intragastric band erosion with the potential for gastric perforation and/or abscess formation, and esophageal dilatation. Less frequent complications include tube migration, tube disconnection, and port-site infection. Tubing-related small-bowel obstruction is a relatively rare yet serious complication that carries the risk of closed-loop bowel obstruction.

Complications unique to sleeve gastrectomy include staple-line bleeding, stenosis, and staple-line leakage; leaks are the most concerning complication. Stenosis is typically due to angulation or kinking of the stomach resulting in functional obstruction; it presents as dysphagia to solids and liquids with nausea and vomiting.

The most common complication associated with vertical banding gastroplasty is stenosis at the site of the band placement. Other less common complications include esophagitis, band migration, and staple-line disruption.

Malabsorptive Procedure Complications

Complications following Roux-en-Y gastric bypass include cholelithiasis, nephrolithiasis (due to increased urine oxalate excretion), dumping syndrome, anastomotic stricture, anastomotic ulceration, small-bowel obstruction from internal hernias, and gastrogastric fistula. Although small intestinal bacterial overgrowth can occur following any bariatric procedure, it occurs most often with Roux-en-Y gastric bypass. Similar complications are seen following biliopancreatic diversion with duodenal switch, although most concerning are the nutritional deficiencies.

Nutritional and Endocrine-Related Complications

Protein-calorie malnutrition can occur 1 to 2 years after malabsorptive procedures (Roux-en-Y gastric bypass or biliopancreatic diversion), typically presenting as rapid weight loss, generalized edema, muscle wasting, and hypoalbuminemia. Micronutrient deficiencies can also develop following bariatric surgery and are more common with malabsorptive procedures (**Table 10**). Deficiencies may include thiamine (vitamin B_1); pyridoxine (vitamin B_6); folate; cobalamin (vitamin B_{12}); vitamins C, A, D, E, and K; iron; zinc; selenium; magnesium; and copper. Acceleration in loss of bone mineral density also

TABLE 10. Possible Micronutrient Deficiency Following Bariatric Surgery

Nutrient	Features of Deficiency
Calcium	Short term: muscle contractions, pain, spasms, paresthesia
	Long term: decrease in bone density, osteopenia/osteoporosis
Cobalamin (vitamin B_{12})	Macrocytic anemia, neurocognitive impairment, peripheral neuropathy, proprioceptive loss, spasticity, weakness, glossitis, cheilosis, angular stomatitis
Copper	Microcytic anemia, leukopenia, myelopathy (weakness, numbness, spasticity, hyperreflexia, painful paresthesia), poor wound healing
Folate	Macrocytic anemia, glossitis, cheilosis, palpitations, fatigue
Iron	Microcytic anemia, fatigue, white fingernail beds
Magnesium	Muscle spasm and pain
Selenium	Dilated cardiomyopathy, myopathy, myositis, connective tissue abnormalities (hair, nails, skin)
Thiamine (vitamin B_1)	Cerebellar ataxia, nystagmus, ophthalmoplegia, confusion, confabulation (Wernicke-Korsakoff syndrome), heart failure, edema, ascites, peripheral neuropathy, weakness
Vitamin A	Night vision impairment, Bitot spots, corneal ulceration, blindness, itching, dry hair, loss of immunity
Vitamin D	Osteomalacia, osteoporosis, myalgia, arthralgia, depression, fasciculations
Zinc	Dermatitis, poor wound healing, blunting of taste sense, hair loss, glossitis

Data from: Stein J, Stier C, Raab H, Weiner R. Review article: The nutritional and pharmacological consequences of obesity surgery. Aliment Pharmacol Ther. 2014 Sep;40(6):582-609. [PMID: 25078533]

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occurs, primarily with malabsorptive procedures, due to calcium and vitamin D deficiency leading to secondary hyperparathyroidism.

In patients undergoing malabsorptive procedures, Endocrine Society guidelines recommend testing for albumin/prealbumin, iron/ferritin, vitamin B_{12}, folate, serum calcium, parathyroid hormone, and 25-hydroxyvitamin D every 6 months postoperatively for the first 2 years and then annually thereafter; measurement of vitamins A, vitamin B_1, and zinc is considered optional. Bone mineral density measurement is also recommended annually after the procedure until stable.

Postprandial hypoglycemia can occur in some patients following Roux-en-Y gastric bypass secondary to maladaptive secretion of insulin, dumping syndrome, or nesidioblastosis, which is characterized by hyperplasia of pancreatic islet cells. Ingestion of small, frequent meals along with avoidance of simple carbohydrates can decrease the frequency and improve the symptoms of postprandial hypoglycemia. In severe cases, partial pancreatectomy can be utilized for hypoglycemic symptoms associated with nesidioblastosis.

Other Gastric Resection Complications

Total and partial gastrectomy for the treatment of PUD, gastric malignancy, and pancreatic tumors can result in a variety of short- and long-term complications. Complications following gastrectomy include intraluminal bleeding, anastomotic leaks, and anastomotic strictures. Delayed gastric emptying, dumping syndrome, and/or fat malabsorption may also develop following partial gastrectomy with or without vagotomy, resulting in symptoms of nausea and vomiting, loss of appetite, bloating and fullness, or early satiety. Pancreaticoduodenectomy (Whipple resection) entails removal of the pancreatic head, duodenum, common bile duct, gallbladder, and distal stomach. Common complications are weight loss, reflux, dumping syndrome, and bacterial overgrowth.

Disorders of the Pancreas

Acute Pancreatitis

Acute pancreatitis is the leading gastrointestinal cause of hospitalization in the United States. Acute pancreatitis is an acute inflammatory process involving the pancreas and is typically associated with severe upper abdominal pain. Inflammation may be localized to the pancreas or, through a number of pathophysiologic mechanisms, may also be systemic. Systemic inflammation is characterized by involvement of distant organs as part of a capillary leak syndrome known as the systemic inflammatory response. Multiple factors contribute to the disease pathogenesis, one of which is premature intracellular activation of digestive enzymes that cause pancreatic "autodigestion."

Eighty percent of patients with acute pancreatitis experience mild disease, characterized by an uncomplicated, reversible course of interstitial pancreatitis leading to recovery within several days. Twenty percent develop moderate or severe disease and may have a protracted hospital course. Moderate severity is characterized by development of local pancreatic complications (pancreatic necrosis, acute fluid collections) or transient organ system failure (circulatory, renal, respiratory). Severe pancreatitis is defined by persistent organ system failure for 3 consecutive days; persistent failure is the strongest predictor of death. Median overall mortality rate from acute pancreatitis is 5% (range 2%-9%).

Gallstones and alcohol use are the most common causes of acute pancreatitis, accounting for 80% of cases in the United States (**Table 11**).

TABLE 11. Causes of Acute Pancreatitis

Common
Biliary disease
Gallstones
Microlithiasis (1- to 2-mm stones that are not detected by imaging studies)
Alcohol use
Occasional
Medications
Furosemide
Didanosine
Asparaginase
Mesalamine
Hydrochlorothiazide
6-Mercaptopurine/azathioprine
Simvastatin
Hypertriglyceridemia
Hypercalcemia
Pancreas divisum (controversial)
Choledochocele
Post-ERCP
Rare
Autoimmune
Infectious
Viral (mumps, coxsackie B virus, cytomegalovirus)
Parasitic (*Toxoplasma* species, *Ascaris lumbricoides*)
Ischemia
Trauma
Neoplasia
Celiac disease
Genetic (only if attacks are recurrent)

ERCP = endoscopic retrograde cholangiopancreatography.

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KEY POINT

- Gallstones and alcohol use are the most common causes of acute pancreatitis, accounting for 80% of cases in the United States.

Clinical Presentation and Diagnosis

Diagnosis of acute pancreatitis requires two of three criteria: (1) acute onset of upper abdominal pain, (2) serum amylase or lipase level increased by at least three times the upper limit of normal, and (3) characteristic findings on cross-sectional imaging (contrast CT, MRI, or ultrasound).

Sudden onset of severe epigastric abdominal pain is a hallmark feature of acute pancreatitis. Pain often radiates to the back, diminishes by sitting or leaning forward, and is associated with nausea, vomiting, and fever. Dyspnea is typically a manifestation of the systemic inflammatory response, and associated ventilation-perfusion mismatch may develop from a symptomatic pleural effusion, which is thought to impair diaphragmatic and chest-wall motion during respiration. Acute liver enzyme elevation at the time of presentation with acute pancreatitis is strongly suggestive of obstruction of the common bile duct by gallstones.

Both amylase and lipase levels increase within hours of disease onset. Lipase is the preferred test owing to its longer half-life than amylase and greater sensitivity and specificity. Amylase can be elevated in other settings, such as parotitis, peptic ulcer disease, acute cholecystitis, and diabetic ketoacidosis. Benign pancreatic hyperenzymemia is a rare cause of asymptomatic amylase and lipase elevations without significant imaging abnormalities. Macroamylasemia, a cause of isolated hyperamylasemia, is due to poor excretion of large amylase multimers from the blood and is diagnosed by serum protein electrophoresis.

In most patients, the diagnosis of acute pancreatitis may be made based on a consistent clinical picture with an elevation of the serum lipase (or amylase) level. Because gallstones are the most common cause of pancreatitis, all patients should be evaluated with a transabdominal ultrasound unless another obvious cause of pancreatitis is present; transabdominal ultrasound has excellent sensitivity for detecting cholelithiasis and evidence of biliary obstruction. It is also cost effective. Contrast-enhanced CT is not usually required to diagnose acute pancreatitis; it tends to be less sensitive than ultrasound for gallstones, exposes patients to the risk of contrast-medium–induced nephropathy (particularly in underresuscitated patients), and is expensive. CT imaging is indicated, however, when the diagnosis is uncertain (abdominal pain but minimal pancreatic enzyme elevations), the patient's presentation is severe and concerning for an undiagnosed intraabdominal complication, or the patient does not improve within 48 to 72 hours of hospital admission. Imaging features and complications of acute pancreatitis seen on CT scanning include pancreatic or peripancreatic edema, inflammatory stranding, fluid collections, pancreatic necrosis, or splenic vein thrombosis (**Figure 14**).

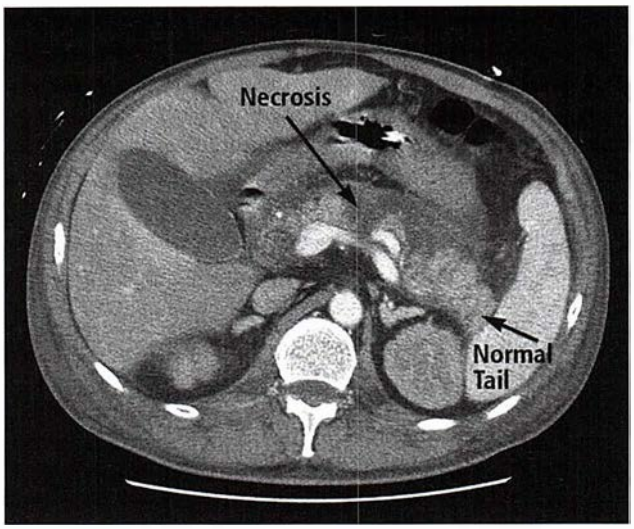

FIGURE 14. CT scan demonstrating acute pancreatitis, with hypoperfusion of the pancreatic body indicating necrosis. Note that the distal tail is perfusing normally.

KEY POINTS

- Diagnosis of acute pancreatitis requires two of three criteria: (1) acute onset of upper abdominal pain, (2) serum amylase or lipase level increased by at least three times the upper limit of normal, and (3) characteristic findings on cross-sectional imaging.
- Because gallstones are the most common cause of pancreatitis, all patients should be evaluated with a transabdominal ultrasound unless another obvious cause of pancreatitis is present.
- Contrast-enhanced CT is not usually required to diagnose acute pancreatitis; it is less sensitive than ultrasound for gallstones, exposes patients to the risk of contrast-medium–induced nephropathy (particularly in underresuscitated patients), and is expensive. HVC

Prognostic Criteria

Acute pancreatitis guidelines recommend assessment of all patients into high- and low-risk categories. Implementation of this recommendation is sometimes lacking, owing perhaps in part to poor familiarity with both the recommendations and available risk stratification tools. Multiple clinical scoring systems are available to stratify risk of developing severe disease; this can help determine the appropriate level of care and enable key early management decisions. All scoring systems have modest accuracy, but some of the more recent systems (Glasgow, Japanese scoring system, Systemic Inflammatory Response Syndrome [SIRS] score) are simpler to use compared with older criteria, such as the Ranson criteria and the Acute Physiology and Chronic Health Evaluation (APACHE) II score. Laboratory findings that are associated with a severe course are an elevated serum blood urea nitrogen level greater than

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CONT. 20 mg/dL (7.1 mmol/L), a hematocrit greater than 44%, or an elevated serum creatinine level. Similarly, a rising blood urea nitrogen level or hematocrit early in the course of acute pancreatitis portends a severe course. Patient characteristics that predispose to more severe disease or longer hospital stay include the presence of multiple comorbid illnesses, age greater than 70 years, and BMI greater than 30.

KEY POINT

HVC
- Poor prognostic indicators for acute pancreatitis are elevated serum blood urea nitrogen level greater than 20 mg/dL (7.1 mmol/L), a hematocrit greater than 44%, or an elevated serum creatinine level.

Management

Most patients with acute pancreatitis require hospitalization for hydration, brief bowel rest, pain control, and antiemetics. Intravascular fluid volume falls in response to inflammation and capillary leak syndrome. Therefore, aggressive fluid resuscitation (250-500 mL/h) with isotonic crystalloid should be administered on presentation. Similar to the sepsis paradigm of an early therapeutic window, this intervention appears to be most beneficial within the first 12 to 24 hours and may have a limited impact thereafter. In patients with evidence of developing organ system failure, careful monitoring and treatment at higher levels of care are appropriate.

In patients with severe acute pancreatitis, enteral feeding should begin approximately 72 hours after presentation. This evidence-based intervention reduces infectious complications, organ failure, and mortality compared with total parenteral nutrition. Enteral feeding prevents infections by promoting gut mucosal health and barrier function necessary for preventing leakage or translocation of bacteria that can infect other tissues. Both nasogastric and nasojejunal enteral feeding are safe and have comparable effectiveness. Total parenteral nutrition should be avoided when possible. In mild acute pancreatitis, oral feeding may start when nausea, vomiting, and abdominal pain resolve (or are absent) but should not be withheld on the basis of persistent elevations in pancreatic enzyme levels.

Pain control is not standardized but typically requires opiates, which may be administered by a nurse or a patient-controlled analgesia pump.

In patients with uncomplicated gallstone pancreatitis, a cholecystectomy should be performed prior to discharge. In those with gallstone pancreatitis who have ascending cholangitis, endoscopic retrograde cholangiopancreatography (ERCP) should be performed within 24 hours of presentation. ERCP is probably beneficial for patients with biliary pancreatitis and nonresolving bile duct obstruction (without cholangitis), but the timing of ERCP (24-72 hours) is less certain. In the absence of gallstone pancreatitis and/or a significant history of alcohol abuse, investigation is necessary to identify a cause of pancreatitis to reduce the risk of a recurrent, more devastating attack. Typical hospital evaluation includes testing for hypertriglyceridemia, hypercalcemia, drug-induced pancreatitis, infectious exposures and triggers, and abdominal trauma. In patients who are aged 40 years or older with unexplained pancreatitis, assessment for a benign or malignant pancreatic tumor may also be part of the evaluation. Consultation with a specialist is appropriate, particularly for idiopathic pancreatitis. Because of autodigestion, areas of pancreatic necrosis are frequently identified on imaging. Patients with uninfected pancreatic necrosis do not benefit from antibiotic use, which can unnecessarily increase the risk of intra-abdominal fungal infections. Therefore, patients with pancreatic necrosis should not routinely receive antibiotic agents; antibiotics should be reserved for those with proven infection. Patients whose condition does not improve or deteriorates 7 to 10 days after presentation may have infected necrosis. CT-guided fine-needle aspiration helps guide treatment decisions regarding antibiotic use, drainage, and continued supportive care. In stable patients with infected necrosis, the preferred approach is to initiate antibiotics and to ideally delay drainage procedures for at least 4 weeks to allow the collection to become encapsulated, which facilitates drainage.

KEY POINT

HVC
- In patients with uncomplicated gallstone pancreatitis, a cholecystectomy should be performed prior to discharge.

Complications

In interstitial pancreatitis, fluid collections arise from disruption of the pancreatic ductal system. They are known as acute peripancreatic fluid collections for the first 4 weeks after presentation and are subsequently called pancreatic pseudocysts when the collection becomes encapsulated. Most resolve and do not require treatment; however, in patients who are symptomatic from the effects of these fluid collections, transgastric or transduodenal drainage can be performed. Persistent leaks manifest as enlarging fluid collections and are often accompanied by ongoing symptoms; they warrant treatment with bowel rest or mid-distal jejunal feeding, pancreatic enzymes, octreotide, and pancreatic duct stenting.

In patients with pancreatic necrosis, fluid collections are known as acute necrotic collections for the first 4 weeks after presentation and involve pancreatic and/or peripancreatic tissues. They are subsequently known as walled-off necrosis, when the collection becomes encapsulated (**Figure 15**). Many resolve spontaneously, but some persist, enlarge, have a mass effect, and/or cause symptoms. They may require decompression or debridement if symptomatic. Diabetes mellitus may develop from extensive pancreatic necrosis.

Nonpancreatic local complications include gastric outlet dysfunction, splenic vein thrombosis, gastric variceal bleeding, and colonic necrosis.

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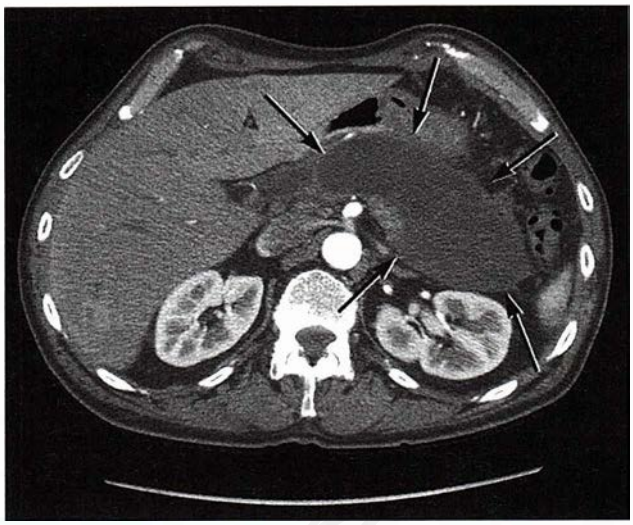

FIGURE 15. CT scan demonstrating walled-off pancreatic necrosis (*arrows*) virtually replacing the entire pancreatic body and tail.

Chronic Pancreatitis

Chronic pancreatitis affects approximately 5 in 100,000 persons in the United States. It is an inflammatory disease that results in irreversible pancreatic injury, which leads to varying degrees of abdominal pain, reduced pancreatic exocrine function, diabetes mellitus, and pancreatic calcifications.

Alcohol is the most common historical cause of chronic pancreatitis (**Table 12**), but it should be considered a disease cofactor because only 3% of patients with alcoholism develop chronic pancreatitis. Most patients with alcohol-related chronic pancreatitis are heavy users (>50-80 g/d) for more than 5 to 10 years. A standard "drink" contains approximately 14 g of alcohol. Tobacco is an independent risk factor for chronic pancreatitis.

KEY POINT

- Alcohol is the most common historical cause of chronic pancreatitis.

Clinical Presentation and Diagnosis

The hallmark symptom of chronic pancreatitis is abdominal pain that often radiates to the back; however, pain can be absent. Pain is typically intermittent, with attacks interrupted by varying pain-free intervals. Constant pain may occur from local anatomic causes (compressing pseudocyst, biliary or pancreatic duct stricture) or from visceral hyperalgesia (increased sensation in response to stimuli) from chronic narcotic use and centralization of pain. Other hallmark clinical features, particularly in severe disease, are (1) exocrine pancreatic insufficiency with bulky and greasy stools, fat-soluble vitamin deficiencies, and weight loss; (2) diabetes; and (3) pancreatic calcifications.

Chronic pancreatitis is classified anatomically as either large- or small-duct (also known as minimal change) disease.

TABLE 12. Causes of Chronic Pancreatitis

Toxic
Alcohol
Tobacco
Hypercalcemia (controversial)
Idiopathic
Early onset (commonly associated with genetic mutations)
Late onset
Genetic Mutations
Cationic trypsinogen gene
Cystic fibrosis transmembrane conductance regulator gene
Serine protease inhibitor, Kazal type I gene
Chymotrypsinogen C gene
Calcium-sensing receptor gene
Claudin-2 gene
Obstructive
Pancreatic solid tumor
Intraductal papillary mucinous neoplasm
Trauma (with pancreatic duct stricture)
Recurrent or Severe Acute Pancreatitis
Postnecrotic
Recurrent acute pancreatitis from any cause
Vascular diseases/ischemia
Postirradiation
Other
Celiac disease
Autoimmune pancreatitis

Small-duct disease is characterized by attacks of pain with normal or minimally abnormal pancreatic imaging.

The diagnosis of chronic pancreatitis remains challenging. Serum amylase and lipase levels are often not elevated and are unreliable for diagnosing chronic pancreatitis or an exacerbation of the disease. Common criteria employ a combination of clinical features (pain, recurrent attacks of pancreatitis, weight loss) with objective findings of calcifications, imaging features of ductal dilatation or inflammatory masses (**Figure 16**), exocrine pancreatic insufficiency, diabetes, and rarely histologic findings. Disease onset in older patients requires exclusion of autoimmune pancreatitis and pancreatic cancer.

An abdominal radiograph should be performed to detect pancreatic calcifications. If calcifications are absent, a dedicated pancreas-protocol CT or magnetic resonance cholangiopancreatography should be done to detect abnormalities of the main and side-branch pancreatic ducts. A gastroenterologist

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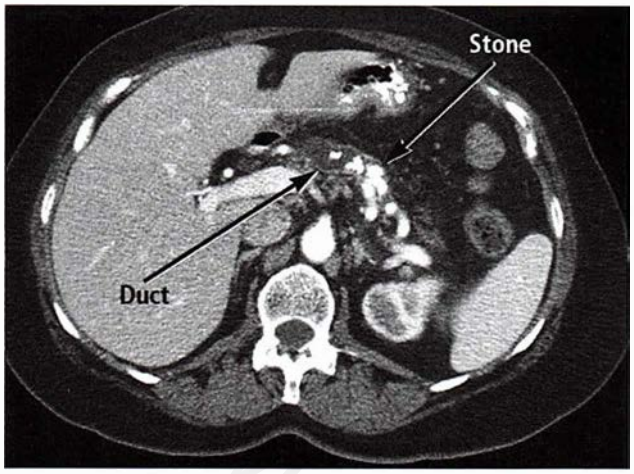

FIGURE 16. CT scan demonstrating chronic pancreatitis including pancreatic ductal dilatation and parenchymal stones.

may perform endoscopic ultrasound (EUS), which can allow application of EUS-based criteria to aid in making the diagnosis in cases where cross-sectional imaging is unremarkable. Endoscopic retrograde cholangiopancreatography should be reserved for patients requiring therapeutic interventions.

Pancreatic malabsorption, measured by quantitative 72-hour fecal fat testing, occurs when residual pancreatic enzyme secretion is only 5% to 10% of normal.

Diagnosis of chronic pancreatitis is difficult and may lack firm data, such as when imaging abnormalities are absent or minor. In this situation, clinicians may follow patients prospectively to detect more obvious manifestations of the disease or consider referring patients to specialized centers that perform direct cholecystokinin or secretin stimulation tests, the most sensitive and specific tests for detecting mild to moderate reductions in pancreatic function and aiding diagnosis of early or small-duct chronic pancreatitis.

KEY POINTS

- The hallmark symptom of chronic pancreatitis is abdominal pain, often radiating to the back.
- The common diagnostic criteria for chronic pancreatitis include clinical features (pain, recurrent attacks of pancreatitis, weight loss) with objective findings of calcifications, imaging features of ductal dilatation or inflammatory masses, exocrine pancreatic insufficiency, diabetes mellitus, and histologic findings.

Management

Patients with chronic pancreatitis should be counseled to stop smoking and drinking alcohol.

Management focuses on reducing pain and detecting and treating complications. Recognizing the pain pattern is central to pain management for patients with chronic pancreatitis.

Acute intermittent attacks of pain are treated with supportive care, acetaminophen, and ibuprofen in combination with tramadol, a nonopioid with opiate action. Tramadol has been shown to provide analgesia comparable to other opioid analgesics in patients with chronic pancreatitis and causes fewer gastrointestinal side effects. If the pain pattern changes or becomes constant, further evaluation is necessary to exclude other causes (for example, pseudocyst, mass, ductal obstruction or stones, and peptic ulcers).

Persistent pain is treated in a stepwise approach beginning with simple analgesics, tramadol, low-dose tricyclic antidepressants, and gabapentinoids (gabapentin and pregabalin). Initiating opioids other than tramadol is reasonable while developing a pain management program, but an important goal is to control pain with opioid-sparing adjunctive agents to minimize chronic narcotic use, owing to concerns of opioid dependence and gastrointestinal side effects. Pancreatic enzymes help relieve symptoms of steatorrhea, and immediate-release (non-enteric-coated) enzymes may help reduce pain in patients with nonalcoholic chronic pancreatitis by decreasing pancreatic stimulation. The use of antioxidants for pain relief is controversial. Percutaneous or EUS-guided celiac plexus blockade using glucocorticoids provides only short-term pain relief in 50% of patients, but it helps guide therapy by classifying pain as visceral or nonvisceral (central).

In persistent or refractory pain, several treatment options are available based on anatomic location. In patients with a dilated pancreatic duct and intraductal calcifications, options include endoscopic stenting, lithotripsy, and surgical drainage (pancreaticojejunostomy). Pancreaticojejunostomy provides superior short- and long-term pain relief. Disease limited to a specific segment of the pancreas may warrant localized resection, such as a pancreaticoduodenectomy for symptomatic obstruction or concern for cancer within the pancreatic head, versus a distal pancreatectomy for disease limited to the pancreatic tail. In patients with a nondilated pancreatic duct ("small-duct" disease), there is no established medical or surgical treatment for pain, but some patients are offered partial or total pancreatectomy.

Exocrine pancreatic insufficiency is treated with enzymes containing 90,000 United States Pharmacopeia (USP) units of lipase (equivalent to 30,000 international units [IU]) with meals, and a half dose with snacks. Patients should be screened and treated for fat-soluble vitamin deficiencies. Diabetes associated with chronic pancreatitis is typically labile and may be difficult to manage.

KEY POINT

- Patients with chronic pancreatitis should be counseled to stop smoking and drinking alcohol.

Pancreatic Adenocarcinoma

The 5-year survival rate for pancreatic adenocarcinoma remains low at 5%. Diagnoses exceed 45,000 annually, and more than 80% of patients die owing to unresectable disease at presentation and ineffective treatments except curative surgical resection.

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Strong risk factors for pancreatic cancer are age greater than 50 years, family history of pancreatic cancer (present in 16%), cigarette smoking, chronic pancreatitis, obesity, diabetes, and intraductal papillary mucinous neoplasms. Hereditary pancreatitis is a rare condition associated with a 40% to 55% lifetime risk of pancreatic cancer; the diagnosis is usually made by recognizing an autosomal dominant pattern of inheritance and by commercially available genetic screening to detect cationic trypsinogen (*PRSS1*) gene mutations.

KEY POINTS

- The 5-year survival rate for pancreatic adenocarcinoma remains low at 5%.
- Strong risk factors for pancreatic cancer are age greater than 50 years, family history of pancreatic cancer, cigarette smoking, chronic pancreatitis, obesity, diabetes mellitus, and intraductal papillary mucinous neoplasms.

Clinical Presentation

The most common presenting symptoms of pancreatic cancer are weight loss, abdominal pain, and jaundice. Jaundice is characteristic of tumors located in the pancreatic head (the most common location). Back pain is characteristic of tumors that are located in the body or tail of the pancreas and affect the celiac ganglia. Patients rarely present with acute pancreatitis. Most patients have abnormal glucose tolerance, and approximately 50% have diabetes. Two thirds of patients have new-onset diabetes within the 36 months prior to the cancer diagnosis.

Patients with pancreatic cancer and jaundice occasionally have Courvoisier sign (palpable gallbladder due to distal bile duct compression) and rarely paraneoplastic manifestations, such as pancreatic panniculitis (tender red-purple ulcerated subcutaneous nodules) or Trousseau syndrome (migratory thrombophlebitis). Signs of advanced disease include an abdominal mass, ascites, and supraclavicular lymphadenopathy (Virchow node).

KEY POINT

- The most common presenting symptoms of pancreatic cancer are weight loss, abdominal pain, and jaundice.

Diagnosis and Staging

Screening tests for pancreatic cancer do not improve survival but are recommended for (1) patients aged 50 years or older with idiopathic pancreatitis or with abdominal symptoms and new-onset diabetes; (2) patients older than 40 to 50 years with a family history or hereditary syndrome conferring more than 5% lifetime risk (such as selected patients with Peutz-Jeghers syndrome, familial atypical multiple mole melanoma syndrome, Lynch syndrome, hereditary pancreatitis, or germline mutations in the *BRCA2* gene); and (3) patients with pancreatic cancer precursors, intraductal papillary mucinous neoplasm, and high-grade pancreatic intraepithelial neoplasia. Recommended screening and surveillance tests are EUS or MRI/magnetic resonance cholangiopancreatography, but there is a lack of consensus of how often to screen patients and when to refer to surgery for many high-risk groups.

In patients in whom pancreatic cancer is suspected, contrast-enhanced multidetector CT has 90% sensitivity for detecting malignancy (**Figure 17**). CT also provides staging information. EUS does not significantly affect staging but has greater sensitivity in detecting tumors smaller than 2 cm and allows tissue diagnosis by fine-needle aspiration (FNA) when required.

The need for EUS-FNA is variable. It may be indicated to establish a diagnosis prior to neoadjuvant or palliative radiochemotherapy and to exclude unusual tumors or pseudotumors that would not benefit from surgery. FNA is usually unnecessary in surgical candidates with potentially resectable tumors because negative results (with a relatively low negative predictive value) do not affect management.

For staging and treatment of pancreatic adenocarcinoma, see MKSAP 17 Hematology and Oncology.

KEY POINT

- Contrast-enhanced multidetector CT has 90% sensitivity for detecting pancreatic malignancy.

Ampullary Adenocarcinoma

Ampullary adenocarcinoma is rare and develops from premalignant adenomas. Compared with pancreatic adenocarcinoma, the 5-year survival rate is much higher, ranging from 37% to 68%. Tumors causing obstructive jaundice lead to diagnosis at an earlier stage. Up to 50% of adenomas contain a focus of adenocarcinoma. Reliable differentiation between adenoma and adenocarcinoma often requires EUS. Whereas endoscopic mucosal biopsies have a high false-negative rate (25%-50%), EUS-directed biopsy has 90% diagnostic accuracy. EUS is superior to MRI and CT for staging.

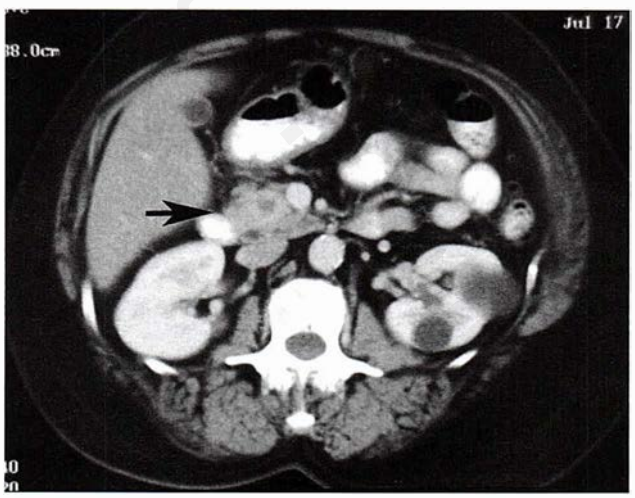

FIGURE 17. CT scan of pancreatic adenocarcinoma, with a large mass in the head of the pancreas (*arrow*).

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Only 10% of tumors are limited to the ampulla of Vater at the time of diagnosis (stage T1); these tumors are amenable to endoscopic ampullectomy. Careful staging is essential because 8% to 45% of T1 lesions have lymph node metastases that confer a 70% reduction in median survival compared with lymph node–negative T1N0 tumors. Greater T-stage tumors and/or lymph node metastases require pancreaticoduodenectomy. However, only 40% of patients undergo surgery, primarily because many patients with ampullary adenocarcinoma are older (median 65 years) and/or have a poor operative status.

Autoimmune Pancreatitis and IgG4 Disease

Autoimmune pancreatitis (AIP) is rare and has an unclear pathogenesis. Type I AIP is a systemic fibroinflammatory disease, defined as an inflammatory condition causing tissue damage and scarring. Pancreatic involvement is only one manifestation of a systemic IgG4 disease that encompasses multiple autoimmune conditions, including Sjögren syndrome, primary sclerosing cholangitis, and inflammatory bowel disease. Type II AIP is characterized by an idiopathic duct-centric chronic pancreatitis without elevated levels of IgG4 or systemic disease. Type II is frequently associated with inflammatory bowel disease (30%).

For more information on IgG4-related disease, see MKSAP 17 Rheumatology.

Clinical Presentation and Diagnosis

Patients with AIP typically have painless obstructive jaundice and cross-sectional imaging evidence of focal or diffuse "sausage-shaped" pancreatic enlargement with a featureless border (**Figure 18**). Pancreatic adenocarcinoma must be excluded. AIP presents rarely with acute pancreatitis.

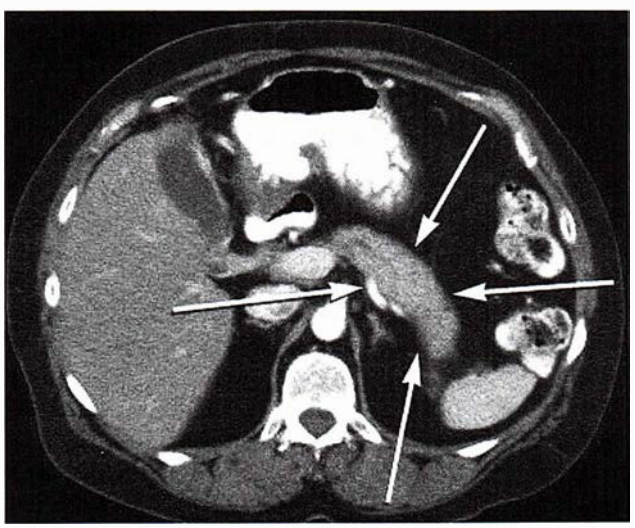

FIGURE 18. CT scan demonstrating autoimmune pancreatitis with the classic "sausage-shaped" pancreas (*arrows*).

Type I AIP typically presents in older men (mean age of onset in the fifth decade of life). Biliary involvement is common and is known as IgG4-associated cholangitis. Diagnosis is fulfilled by a combination of five criteria: (1) cross-sectional imaging abnormalities as described in the previous paragraph and pancreatography showing duct narrowing without upstream dilation, (2) increased serum IgG4 level, (3) extrapancreatic organ involvement, (4) compatible histopathology, and (5) response to glucocorticoid therapy.

Type II AIP has an equal gender distribution and an age of onset in the fourth decade of life. Definitive diagnosis requires histology because imaging findings and response to glucocorticoids are similar to type I, but serologic abnormalities and extrapancreatic organ involvement are absent.

KEY POINT

- Autoimmune pancreatitis is typically characterized by painless obstructive jaundice and cross-sectional imaging evidence of focal or diffuse "sausage-shaped" pancreatic enlargement with a featureless border.

Treatment

Almost all patients (>90%) enter clinical remission in response to glucocorticoids. Those with jaundice typically require biliary stenting. Relapse is more common in type I AIP versus type II (30% versus 10%). Patients with relapse typically respond to glucocorticoid retreatment. To avoid glucocorticoid-induced complications, glucocorticoid-sparing immunomodulators (azathioprine, 6-mercaptopurine, and mycophenolate mofetil) may be offered to patients who have single or multiple relapses and cannot be weaned from glucocorticoids. Rituximab, a monoclonal antibody, has also been found to be successful in those with recurrent disease or glucocorticoid dependency.

KEY POINT

- Almost all patients with autoimmune pancreatitis enter clinical remission in response to glucocorticoids; however, relapse is common.

Cystic Neoplasms of the Pancreas

Pancreatic cysts are common, affecting 2.5% of asymptomatic individuals; prevalence is 10% in persons aged 70 years or older.

Pancreatic cysts are classified as pancreatic cystic neoplasms (the most common), nonneoplastic pancreatic cysts, and pseudocysts. The two most common pancreatic cystic neoplasms are mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) (**Figure 19**), which involve the main duct, branch ducts, or both. Most pancreatic cysts are branch-duct IPMNs.

Figure 20 summarizes the general clinical approach to pancreatic cystic lesions and a specific approach to suspected IPMNs and MCNs.

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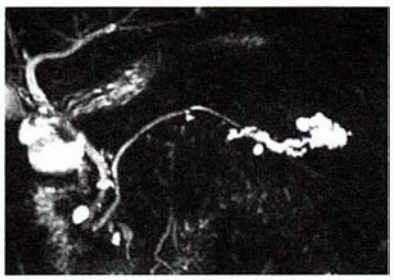
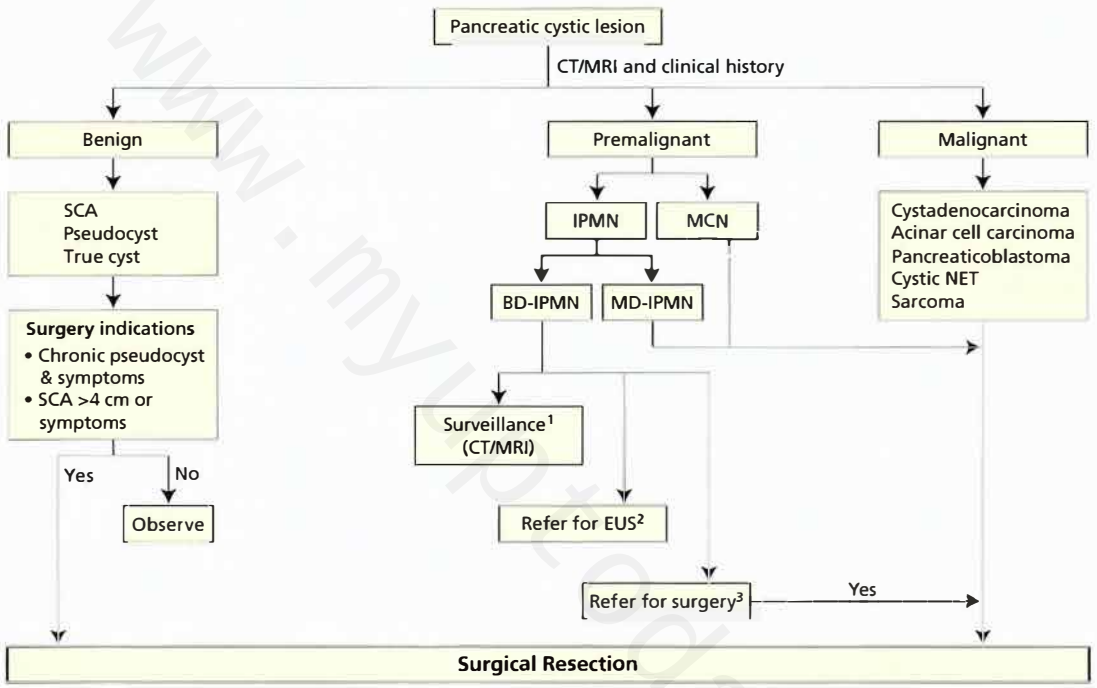


FIGURE 19. Magnetic resonance cholangiopancreatography demonstrating main-duct intraductal papillary mucinous neoplasm in the pancreatic tail.

Recent American Gastroenterological Association (AGA) guidelines recommend surveillance based on cyst characteristics (size < or ≥3 cm, presence of a solid component, pancreatic duct dilation); recommend MRI for surveillance; and provide parameters for stopping surveillance for stable cysts.

Main-duct and mixed-type IPMNs appear radiologically as a main-duct dilation often extending into branch ducts; 80% of patients have symptoms and 65% develop malignancy. Resection is recommended for surgical candidates. Branch-duct IPMNs are typically asymptomatic and have a lower incidence of malignancy (20%). Surveillance is usually indicated rather than resection.



1. Surveillance

<1 cm	CT/MRI every 2-3 years
1-2 cm	CT/MRI annually x 2 years then lengthen if stable
2-3 cm	EUS every 3-6 months. If stable lengthen interval. Alternate MRI with EUS
>3 cm	Close surveillance every 3-6 months. Alternate MRI with EUS

2. EUS indications

Symptoms/pancreatitis
Thickened/enhancing cyst wall
Nonenhancing mural nodule
Abrupt change in main pancreatic duct caliber plus pancreatic atrophy
Cyst diameter >3 cm
Main pancreatic duct diameter 5-9 mm
Lymphadenopathy

3. Surgical indications

High-risk features
Obstructive jaundice and cyst in the head of the pancreas
Cyst containing enhancing solid component
Main pancreatic duct diameter >10 mm

EUS features
Definite mural nodule & cytology suspicious/positive for malignancy

Additional indications
Consider surgery in young, fit patients with cyst 2 cm or larger

FIGURE 20. General approach to clinical evaluation of pancreatic cystic lesions and specific evaluation of suspected intraductal papillary mucinous neoplasms and mucinous cystic neoplasms. BD-IPMN = branch-duct intraductal papillary mucinous neoplasm; EUS = endoscopic ultrasound; IPMN = intraductal papillary mucinous neoplasm; MCN = mucinous cystic neoplasm; MD-IPMN = main-duct intraductal papillary mucinous neoplasm; NET = neuroendocrine tumor; SCA = serous cyst adenoma.

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MCNs most frequently occur in the body and tail of the pancreas, have ovarian stroma present on histology, and have an 18% incidence of malignancy. Resection is recommended.

Diagnosis of solitary cysts is challenging. It may require EUS-FNA to distinguish between cystic neoplasms (branch-duct IPMNs, MCNs, and serous tumors) and pseudocysts based on cytology (see Figure 20). Diagnosis may also require cyst fluid measurement; IMPNs and MCNs are high in carcinoembryonic antigen, and pseudocysts are high in amylase.

KEY POINT

- The two most common pancreatic cystic neoplasms are mucinous cystic neoplasms and intraductal papillary mucinous neoplasms, which involve the main duct, branch ducts, or both.

Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine (islet cell) tumors arise from pluripotent cells in the pancreatic ductal/acinar system and represent 3% of primary pancreatic neoplasms. Of all pancreatic neuroendocrine tumors, 75% to 90% are nonfunctional and are typically large (mean, 4 cm) and symptomatic (pancreatitis, abdominal pain, jaundice, weight loss) related to local mass effect or metastatic disease. Frequent use of abdominal imaging occasionally identifies patients with incidental, asymptomatic, and earlier-stage neoplasms. Ten percent to 25% of neuroendocrine tumors are functional and hypersecrete hormones, most commonly gastrin and insulin (**Table 13**). Most patients are older and have sporadic tumors. Younger patients may have heritable conditions. Those with von Hippel-Lindau disease typically have nonfunctional tumors, and those with multiple endocrine neoplasia type 1 typically have nonfunctional tumors or gastrinomas.

Testing focuses on determining the functional status of the tumor (see Table 13) and localizing it by cross-sectional CT or MRI imaging. Occult lesions require EUS (90% sensitivity) and pentetreotide scintigraphy (octreotide scanning). Insulinomas and gastrinomas are typically small. Insulinomas are differentiated from gastrinomas by having a typical solitary appearance and inadequate expression of somatostatin receptors to be detected by octreotide scanning. Insulinomas cause hypoglycemia, and gastrinomas produce symptoms related to oversecretion of gastric acid (diarrhea, esophagitis, peptic ulcer disease). Less common pancreatic neuroendocrine tumors are typically larger (>5 cm) and have other clinical profiles (see Table 13).

Localized tumors should be resected owing to the risk of metastases. Metastatic disease has limited treatment options. Hormone-derived symptoms are typically treated

TABLE 13. Clinical Characteristics of Pancreatic Neuroendocrine Tumors

Tumor Type	Hormone	Symptoms	Diagnostic Criteria
Nonfunctional (75%-90%)			
Nonfunctional	None	None or symptoms related to local mass effect or metastatic disease May metastasize Associated with MEN1 and VHL	Mass on imaging, typically large (mean, 4 cm) and symptomatic from mass effect (pancreatitis, abdominal pain, jaundice, weight loss) No elevated hormones
Functional (10%-25%)			
Most common			
Gastrinoma	Gastrin	Peptic ulcer disease, diarrhea, esophagitis (Zollinger-Ellison syndrome) Associated with MEN1	Elevated serum gastrin >1000 pg/mL (1000 ng/L), secretin stimulation test
Insulinoma	Insulin	Hypoglycemia Associated with MEN1	Inappropriately high insulin and C-peptide levels during hypoglycemia
Uncommon and rarely associated with MEN1			
VIPoma	Vasoactive intestinal peptide	Watery diarrhea, hypokalemia, hypochlorhydria	Elevated serum VIP level >75 pg/mL (75 ng/L)
Glucagonoma	Glucagon	Dermatitis (necrolytic migratory erythema), diabetes mellitus	Elevated serum glucagon >1000 pg/mL (1000 ng/L)
Somatostatinoma	Somatostatin	Triad of gallstones, diabetes, and diarrhea	Elevated somatostatin
GHRHoma	Growth hormone-releasing hormone	Acromegaly	Elevated GHRH

GHRH = growth hormone-releasing hormone; MEN1 = multiple endocrine neoplasia type 1; VHL = von Hippel-Lindau disease; VIP = vasoactive intestinal peptide.

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with somatostatin analogues or therapy to control symptoms of hormone secretion (for example, proton pump inhibitors for gastrinoma). Other treatments include molecularly targeted agents (everolimus or sunitinib), chemotherapy, hepatic artery embolization, and possibly radiolabeled somatostatin analogues.

KEY POINTS

- Of all pancreatic neuroendocrine tumors, 75% to 90% are nonfunctional; 10% to 25% are functional and hypersecrete hormones, most commonly gastrin and insulin.
- Localized pancreatic neuroendocrine tumors should be resected owing to the risk of metastases.

Disorders of the Small and Large Bowel

Diarrhea

Characterization

Diarrhea can be defined by high stool frequency (>3 per day) or abnormally loose stools; however, some patients use the term to describe urgency or fecal incontinence. In addition, some patients refer to an increase in stool frequency without an increase in stool liquidity as diarrhea. This phenomenon is referred to as hyperdefecation and often is seen in irritable bowel syndrome (IBS) and hyperthyroidism. However, hyperdefecation also can be seen in conditions that decrease rectal compliance, such as rectal cancer, and therefore deserves evaluation even if it is not true diarrhea. Normal stool weight should be 200 g/d or less. Stool weights above 200 g/d are sometimes used to define diarrhea, but stool weight is influenced by factors such as fiber intake. In the absence of abnormal consistency, weight alone is not an ideal indicator.

Most cases of diarrhea in developed countries are acute (<4 weeks' duration). Chronic diarrhea (>4 weeks' duration) occurs in 1% to 5% of adults in developed countries.

Chronic diarrhea is classified into five broad categories based on history, physical examination, and diagnostic tests (**Table 14**). Approaching chronic diarrhea using these subclassifications helps focus the differential diagnosis, direct the evaluation, and decrease costs of testing. However, some causes of chronic diarrhea do not fit into only one category.

Evaluation and Management

The majority of acute diarrhea in developed countries is due to viral gastroenteritis or foodborne illness and is self-limited. In these cases, the yield of testing (such as stool cultures) is low,

TABLE 14. Classification of Chronic Diarrhea

Category	Clinical Features	Examples
Secretory	Large-volume, watery stools	Medications (e.g., colchicine, NSAIDs)
	Does not stop with fasting	SIBO
		Hormone-producing tumors (e.g., gastrinoma, VIPoma, carcinoid, somatostatinoma)
		Bile acid malabsorption
		Noninvasive infections (e.g., cholera)
Osmotic	Diarrhea stops with fasting	Medications (e.g., magnesium sulfate laxative)
	Bloating, gas	Carbohydrate malabsorption
Steatorrhea	Bulky, greasy, oily, malodorous stools	Pancreatic insufficiency
	Weight loss	Small-bowel mucosal disease (e.g., celiac disease)
		SIBO
		Bile acid deficiency
		Lymphatic obstruction
Impaired motility	Bloating, nausea	Diabetes mellitus
	Features of underlying disorder	Postsurgery
		Hyperthyroidism
		Scleroderma
Inflammatory	Abdominal pain +/– fever, bleeding, weight loss	Inflammatory bowel disease
		Invasive/inflammatory infections (e.g., *Clostridium difficile*)
		Ischemia

SIBO = small intestinal bacterial overgrowth; VIP = vasoactive intestinal peptide.

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and the monetary cost per positive test is unacceptably high. In the absence of alarm features (**Table 15**), supportive care with attention to fluid balance is often sufficient. In immunocompetent patients, acute infectious diarrhea usually resolves within 1 week. Elderly patients and those with multiple or severe comorbidities require close follow-up. A careful review of medication history (including nonprescription medications and supplements) is indicated to look for drugs that cause diarrhea. If diarrhea does not resolve in 1 week, evaluation is recommended. Stool testing for common bacterial pathogens, including *Clostridium difficile*, should be performed. See MKSAP 17 Infectious Disease for further discussion of infectious diarrhea.

In patients with chronic diarrhea, clinical features help direct the evaluation (**Table 16**). A basic laboratory evaluation (complete blood count, electrolytes, creatinine) is recommended to assess for anemia (suggesting blood loss or malabsorption as part of the diarrheal process), leukocytosis (suggesting an inflammatory cause of diarrhea), electrolyte disturbances, and dehydration. Additional testing is dictated by the prioritized differential diagnosis, as discussed below.

TABLE 15. Alarm Features Requiring Evaluation in Patients with Acute Diarrhea

Severe abdominal pain
Bloody stools
Fever
Recent hospitalization or antimicrobial use
Special populations
Elderly patients
Immunocompromised patients
Patients with inflammatory bowel disease
Pregnant patients

TABLE 16. Key Clinical Features of Chronic Diarrhea

Symptoms
Diarrhea pattern and duration
Rome criteria for irritable bowel syndrome
Associated symptoms
Extraintestinal manifestations of inflammatory bowel disease
Medical history
Family history
Exposures
Changes in diet
Ingestion of nonabsorbable carbohydrates (lactose, fructose, dietary sweeteners)
Recent travel
Sick contacts
Medications
Physical examination
Rash

Infectious causes of chronic diarrhea are uncommon in immunocompetent adults in developed countries, except for infection with *Giardia lamblia* (see MKSAP 17 Infectious Disease). Giardia infection should be considered in patients with exposure to young children or potentially contaminated water such as lakes and streams.

As in acute diarrhea, a careful review of medications (including nonprescription medications and supplements) is indicated to assess for drugs that cause diarrhea.

Patients older than 50 years should undergo colonoscopy to screen for colorectal cancer. Patients younger than 50 years should also have colonoscopy if features of inflammatory bowel disease are present. Any patient undergoing colonoscopy to evaluate diarrhea should have inspection of the terminal ileum (to assess for Crohn disease) and random biopsies of the colonic mucosa (to assess for microscopic colitis). Sigmoidoscopy is not recommended in most patients because it does not evaluate the proximal colon or terminal ileum.

If this initial evaluation does not disclose an underlying diagnosis, a combination of stool tests should be performed to subclassify the type of diarrhea. A 48- to 72-hour stool collection with analysis of fat content measures the amount of diarrhea and steatorrhea. Normal fat excretion is less than 7 g/d (in patients consuming 100 g/d of fat); however, this may be increased nonspecifically by any diarrheal disorder to 12 to 14 g/d. Fat excretion above 14 g/d is diagnostic of steatorrhea. Patients with steatorrhea should undergo evaluation for small-bowel mucosal disorders (celiac disease, Whipple disease), small intestinal bacterial overgrowth (SIBO), and pancreatic insufficiency. See Malabsorption for further discussion of malabsorption syndromes, including celiac disease and SIBO. Pancreatic insufficiency may be difficult to diagnose, particularly in early disease. Abdominal imaging may show calcification, but this finding may also be absent. CT scan is more sensitive than plain radiographs in detecting pancreatic calcifications. Endoscopic ultrasound is more sensitive than CT scan or endoscopic retrograde cholangiopancreatography in diagnosing chronic pancreatitis, but it does not assess pancreatic function. Tests of pancreatic function are not widely available and have several limitations. Therefore, an empiric trial of pancreatic enzymes is often used as a diagnostic test when chronic pancreatitis is suspected.

In patients with true diarrhea but without steatorrhea, measurement of stool electrolytes can be helpful to categorize the diarrhea so that more targeted testing can later be performed. Measurement of fecal sodium and potassium allows calculation of the osmotic gap, as follows:

$$290 - 2 \times [\text{stool sodium} + \text{stool potassium}]$$

A gap greater than 100 mOsm/kg (100 mmol/kg) indicates an osmotic diarrhea, signifying that some ingested osmotic agent is promoting the diarrheal process. If the gap is

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less than 50 mOsm/kg (50 mmol/kg), the diarrhea is secretory rather than osmotic. A gap between 50 and 100 mOsm/kg (50 and 100 mmol/kg) is equivocal. Although the measured osmolality is typically not used to calculate the gap (as the stool osmolality should always be 290 mOsm/kg [290 mmol/kg]), it can be helpful if there is concern about the adequacy of the stool collection, given that the osmolality is less than 290 mOsm/kg (290 mmol/kg) when water or dilute urine has been added. Alternatively, bacterial fermentation in the stool sample can lead to falsely elevated results of the measured osmolality.

Finally, a stool test for inflammation (such as fecal leukocytes, calprotectin, or lactoferrin) should be completed if colonoscopy has not already been performed.

Based on clinical features and the results of the fecal fat study, stool electrolyte measurements, and testing for inflammation, diarrhea can often be categorized into one of the five subtypes (see Table 14), which directs further evaluation.

The evaluation of acute and chronic diarrhea is described in **Figure 21**.

KEY POINTS

HIC
- The majority of acute diarrhea in developed countries is due to viral gastroenteritis or foodborne illness and is self-limited; the yield of diagnostic testing (such as stool cultures) is low, and the monetary cost per positive test is unacceptably high.
- Patients with chronic diarrhea who are older than 50 years should undergo colonoscopy to screen for colorectal cancer.

Malabsorption

Malabsorption can be a generalized process or can involve each specific nutrient class (carbohydrate, lipid, protein) individually. For a discussion of the diagnosis and approach to fat malabsorption, see Diarrhea.

Celiac Disease

Celiac disease is a chronic inflammatory enteropathy caused by an immune-mediated reaction to gluten and gliadins, proteins that are present in wheat and other grains. Celiac disease is present in 0.5% to 1% of the population; however, many patients are undiagnosed owing to the nonspecific and variable manifestations of this disorder. The classic presentation of malabsorption (weight loss, steatorrhea, nutritional deficiencies) now occurs in a small proportion of patients owing to better recognition of earlier presentations. Chronic diarrhea and abdominal pain are common features; however, diarrhea may be absent. Other signs and symptoms include a unique, characteristic skin rash (dermatitis herpetiformis), osteopenia, iron deficiency anemia, abnormal liver chemistry studies, infertility, and a variety of neurologic symptoms. Long-standing celiac disease is associated with intestinal lymphoma and adenocarcinoma. Although these associations are strong, the absolute risk of a malignant complication is low, especially in patients who respond to a gluten-free diet.

The diagnosis of celiac disease requires positive serologic markers and a compatible small-bowel biopsy.

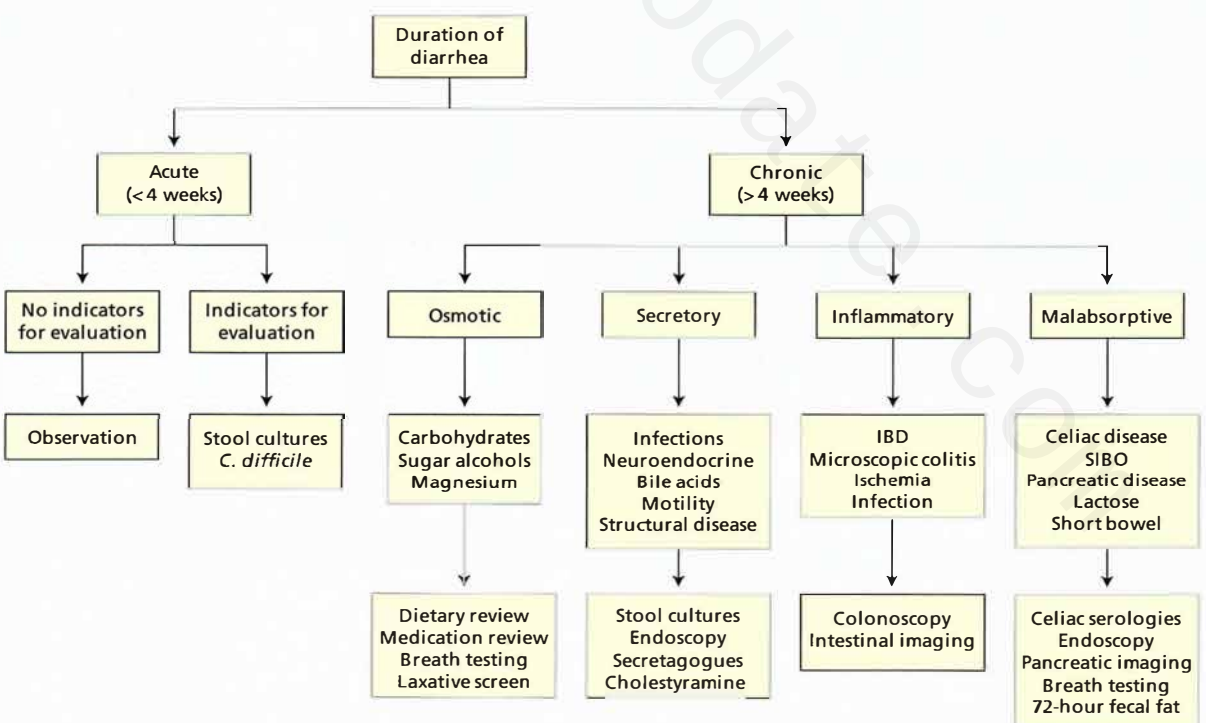

FIGURE 21. Evaluation of diarrhea. *C. difficile* = *Clostridium difficile*; IBD = inflammatory bowel disease; SIBO = small intestinal bacterial overgrowth.

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IgA tissue transglutaminase (tTG) antibodies and endomysial antibodies (EMA) are sensitive and specific serologic markers; testing for these should be done while the patient is consuming gluten. Celiac serologic studies may be negative in patients with IgA deficiency, in those with mild disease and limited small-bowel damage, and in those who have restricted dietary gluten. Other serologic studies, such as gliadin antibodies, have poor sensitivity and specificity and should not be used. Newer serologic studies for deaminated gliadin peptides (DGPs) have superior test characteristics compared with traditional gliadin antibodies, which are no longer recommended in clinical practice. Although serologic testing for anti-DGPs has not proved to be superior to tTG antibody testing (IgA tTG remains the serologic screening test of choice), studies for anti-DGPs could be performed in patients with borderline tTG results or discordant serologic and histologic findings to help ascertain the diagnosis.

The classic findings on small-bowel histology are intraepithelial lymphocytosis, crypt elongation, and villous blunting (**Figure 22**). Mild cases may show only lymphocytosis (stage 1) or hyperplasia (stage 2). Villous blunting can be partial (stage 3) or complete (stage 4). However, these changes are not specific for celiac disease (**Table 17**); therefore, the diagnosis also relies on positive serologic tests.

If the diagnosis is unclear (such as in patients with equivocal or conflicting biopsies or serologies) or if a patient is following a gluten-free diet when serologic studies are performed, *HLA* haplotyping may be helpful.

The treatment of celiac disease is with a strict gluten-free diet. Symptom improvement often occurs within a few weeks, but histologic remission may take several months or years. Patients whose symptoms do not respond to the diet or who relapse while on it should be assessed for gluten exposure, microscopic colitis, collagenous or refractory sprue, small-bowel lymphoma or adenocarcinoma, and other causes of diarrhea as discussed previously. Risk factors for a malignant complication include advanced age and long-standing, poorly controlled disease.

Repeat small-bowel biopsies are no longer required to show healing if there is a clear response to a gluten-free diet; however, patients with atypical features at disease onset may benefit from follow-up histology to ensure mucosal healing. Mucosal healing may take years in adults despite strict adherence to a gluten-free diet and may never be complete.

TABLE 17. Differential Diagnosis of Small-Bowel Villous Blunting

Celiac disease
Tropical sprue
Radiation enteropathy
Severe giardiasis
SIBO
Chronic ischemia
Chemotherapy
Graft-versus-host disease
Crohn disease
Autoimmune enteropathy
Enteropathy-associated T-cell lymphoma
Common variable immunodeficiency
Cow's milk or other dietary protein allergy
Medications (olmesartan)

SIBO = small intestinal bacterial overgrowth.

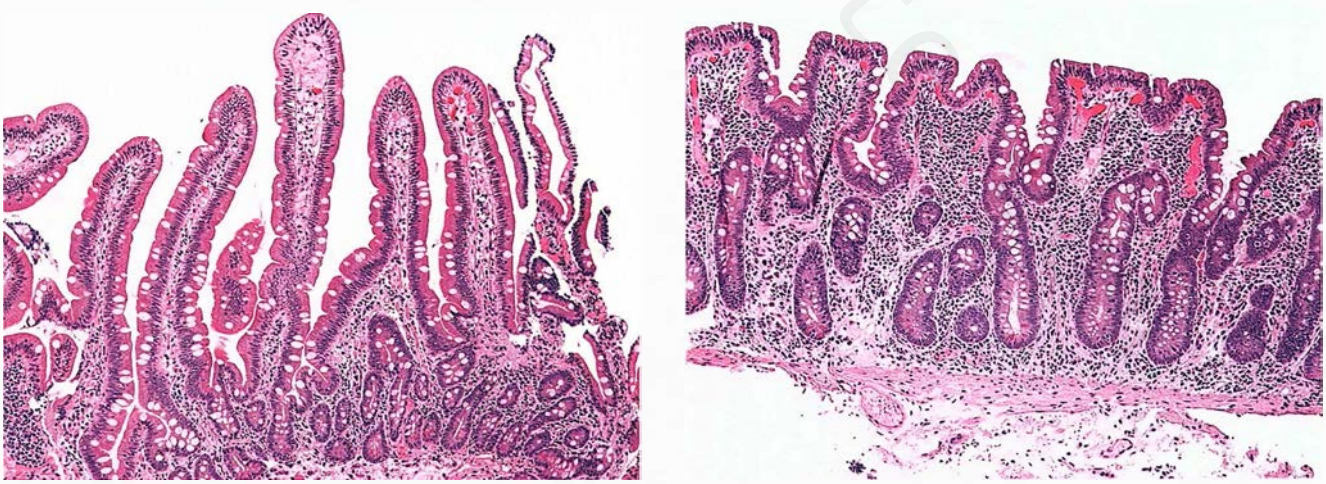

FIGURE 22. *Left panel:* Histologic findings in a normal duodenum. *Right panel:* Histologic findings of celiac disease, with villous atrophy, crypt hyperplasia, and increased inflammatory infiltration of the lamina propria.

Courtesy of Thomas C. Smyrk, MD, Division of Anatomic Pathology, Mayo Clinic.

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KEY POINTS

- The diagnosis of celiac disease requires positive serologic markers (IgA tissue transglutaminase antibodies or endomysial antibodies) and a compatible small-bowel biopsy.
- The treatment of celiac disease is with a strict gluten-free diet.

Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth (SIBO) causes diarrhea, often with bloating, flatulence, and weight loss. A clue to the diagnosis of SIBO is the combination of vitamin B_{12} deficiency (due to bacterial consumption) and an elevated serum folate level (due to bacterial production). Several conditions can predispose patients to SIBO, owing to effects on stomach acid, intestinal transit, or disruption of normal antibacterial defense mechanisms (**Table 18**). Gastric bypass surgery is an increasingly common cause of SIBO owing to the obesity epidemic and more frequent use of bariatric surgery as a treatment.

The small intestine normally has very few bacteria, with proximal jejunal bacterial counts less than 10^4/mL. SIBO is therefore typically defined as a bacterial count greater than 10^5/mL; however, in practice it is difficult to obtain cultures from the proximal jejunum. Furthermore, this practice is expensive because endoscopy is required to obtain the sample. Although not without shortcomings (low sensitivity and specificity), hydrogen breath testing provides the simplest and most widely available diagnostic modality for suspected SIBO. Alternatively, and in areas where hydrogen breath testing is not available, SIBO has been diagnosed based on a response to a trial of antimicrobial therapy. However, this practice may lead to inappropriate use of antibiotics in patients who do not have SIBO (for example, those with IBS). Therefore, empiric antibiotics should only be considered in patients with symptoms compatible with SIBO and one or more risk factors (see Table 18).

TABLE 18. Conditions Associated with Small Intestinal Bacterial Overgrowth

Disorders of Acid Secretion
Achlorhydria
Antrectomy/vagotomy
Prolonged used of high-dose acid suppressive medications
Disorders of Bowel Transit
Blind limbs
Small-bowel diverticula
Small-bowel strictures
Dysmotility (diabetic enteropathy, systemic sclerosis, pseudo-obstruction)
Disruption of Normal Antibacterial Mechanisms
Resection of ileocecal valve
Immunoglobulin deficiency (for example, CVID, IgA deficiency)
Loss of biliary or pancreatic secretions

CVID = common variable immunodeficiency.

A variety of antimicrobial agents are effective for the treatment of SIBO. Because many conditions that predispose to SIBO are irreversible, patients often need repeat courses of antimicrobial agents. In these cases, many clinicians use rotating antimicrobial agents (cycling between three to four different classes) to avoid the development of bacterial resistance. Patients with SIBO may also have lactose intolerance, perhaps owing to the effect of small-bowel inflammation on brush border enzymes. Therefore, a lactose-free diet should be considered if the response to antimicrobial agents is incomplete.

KEY POINT

- Small intestinal bacterial overgrowth may be characterized by diarrhea, bloating, flatulence, weight loss, vitamin B_{12} deficiency, and an elevated serum folate level.

Short-Bowel Syndrome

Short-bowel syndrome (SBS) arises when a large portion of the small intestine is resected or diseased. Causes of SBS are massive resection or bowel dysfunction related to ischemia, radiation enteropathy, Crohn disease, or trauma. SBS typically does not occur until less than 200 cm of healthy small intestine remains. However, the risk for SBS is lower if the colon is intact. The colon can adapt to increase fluid and electrolyte absorption, and colonic bacteria can salvage malabsorbed nutrients through fermentation to short-chain fatty acids. When SBS is present, the remaining bowel has insufficient absorptive area to meet minimal nutrient, fluid, and/or electrolyte needs. Patients with SBS present with voluminous diarrhea, weight loss, and evidence of malnutrition. Treatment focuses on ensuring adequate caloric, electrolyte, and fluid balance through the oral, enteral, and/or parenteral routes.

KEY POINT

- Short-bowel syndrome arises when a large portion of the small intestine is resected or diseased; it typically does not occur until less than 200 cm of healthy small intestine remains.

Carbohydrate Malabsorption

Carbohydrate malabsorption is relatively common but is often overlooked. Malabsorbed carbohydrates are fermented by colonic bacteria and produce osmotically active substances that cause diarrhea and gas, which causes bloating, discomfort, and flatulence. A careful dietary history is essential in the evaluation of a patient with chronic diarrhea.

Lactose, the primary carbohydrate in cow's milk and other dairy products, is the most commonly malabsorbed carbohydrate. Lactose must be cleaved to glucose and galactose by the enzyme lactase in the brush border of the small intestine in order to be absorbed. In many adults, the amount of lactase present may be marginal or its expression is lost, leading to lactose intolerance. The prevalence of lactose intolerance shows geographic and racial

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variation. For example, it is lowest in northern Europeans (approximately 10%), more common in southern European and Middle Eastern populations (approximately 40%), and most common in Asian populations (up to 90%). Lactose intolerance is not absolute; patients are usually able to tolerate variable amounts of lactose.

Lactose malabsorption often is diagnosed by history (bloating, cramps, and/or diarrhea related to dairy intake) and confirmed by resolution of symptoms with lactose avoidance. In equivocal cases, the diagnosis can be made with hydrogen breath testing. Treatment includes avoidance of lactose-containing products or administration of lactase whenever dairy products are consumed.

Fructose malabsorption is also relatively common. It is often overlooked because clinicians and patients do not recognize the presence of fructose in many processed foods, typically in the form of high-fructose corn syrup. Fresh fruits and fruit juices can also cause diarrhea if ingested in excess because the absorption of fructose has a maximum threshold. Fructose intolerance also may be diagnosed by careful history, including resolution of symptoms with dietary avoidance. In equivocal cases, hydrogen breath testing can be helpful.

Sugar alcohols (sorbitol, xylitol, maltitol, and others) are used as artificial sweeteners in sugar-free diet foods, candies, gums, and drinks. These carbohydrates have little or no absorption in the small intestine and, when taken in excess, cause symptoms of carbohydrate malabsorption. Breath tests exist for some sugar alcohols, but the diagnosis is generally made by a careful history.

KEY POINTS

- Lactose, the primary carbohydrate in cow's milk and other dairy products, is the most commonly malabsorbed carbohydrate.
- Fructose malabsorption is often overlooked because clinicians and patients do not recognize the presence of fructose in many processed foods, typically in the form of high-fructose corn syrup.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is characterized by idiopathic gastrointestinal inflammation and is divided primarily into Crohn disease (CD) and ulcerative colitis (UC). A subset of patients has indeterminate colitis, which is characterized by clinical features and test results that do not allow a definitive classification.

Risk Factors

IBD is believed to be related to interplay between genetic and environmental factors. There is an increased risk of IBD in family members, which provides evidence for a genetic component. Monozygotic twins have a higher risk than dizygotic twins or siblings. The risk of IBD in an offspring is higher if both parents are affected. Certain ethnic groups (for example, Jewish patients) are at a higher risk than others (for example, black patients). Genes associated with IBD have been identified in recent years, but the contribution of each individual gene to the overall population with IBD is small.

Environmental risk factors have also been recognized. Cigarette smoking is a risk factor for the development of CD, whereas it is a protective factor for UC. A variety of dietary factors have been proposed, but the results of studies in this area have been inconsistent. IBD is more common in developed countries, which suggests that environmental factors in developed countries are causative or that factors in underdeveloped countries are protective. For example, the hygiene hypothesis suggests that exposure to infectious or other environmental factors in underdeveloped countries may promote immune tolerance and a lower risk of autoimmune diseases like IBD. A north-south gradient (with a higher risk of IBD in northern climates) has been identified, suggesting that a factor such as vitamin D may be involved.

Clinical Manifestations

Symptoms in an individual patient with IBD are related to the location and severity of inflammation and the presence of complications or extraintestinal manifestations. These factors are nonspecific and variable between patients, which may lead to diagnostic difficulty.

Ulcerative Colitis

UC typically presents with bloody diarrhea and abdominal discomfort, the severity of which is related to the extent and severity of inflammation. The distribution of UC is generally divided into proctitis (involving the rectum only), left-sided colitis (inflammation does not extend beyond the splenic flexure), and pancolitis (inflammation extends above the splenic flexure). Some patients with distal inflammation can present with constipation owing to rectal spasm and stasis of stool. Because UC typically involves the rectum, tenesmus, urgency, rectal pain, and fecal incontinence are common. Fever and weight loss are uncommon and suggest severe disease.

With mild disease, the physical examination may be normal. Severe disease may be characterized by fever, tachycardia, dehydration, abdominal tenderness, or pallor. Abdominal distention, hypoactive bowel sounds, and rebound tenderness suggest perforation or megacolon. Laboratory findings, such as significant anemia, leukocytosis, hypoalbuminemia, and electrolyte abnormalities, also reflect the severity of disease.

KEY POINT

- Ulcerative colitis typically presents with bloody diarrhea and abdominal discomfort; tenesmus, urgency, rectal pain, and fecal incontinence are common.

Crohn Disease

Common symptoms of CD are abdominal pain, diarrhea, and weight loss; fever and overt gastrointestinal bleeding are less common than is typically seen in UC. Additionally, unlike UC, the transmural inflammation seen in CD may predispose to fistula formation. Given the variable distribution of inflammation in CD, the symptoms can vary considerably between patients. Thirty percent of patients have isolated small-bowel disease, 40% have ileocolonic inflammation, and 25% have isolated colonic disease. The other 5% of patients have isolated upper gastrointestinal or

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perianal manifestations. Symptoms correlate with disease location. Disease involving primarily the small bowel usually presents with abdominal pain with or without diarrhea; overt gastrointestinal bleeding is uncommon. In ileocolonic disease, right lower quadrant pain is common, and diarrhea and bleeding are less common. Colonic disease is more likely to present with bloody diarrhea; it is also associated with perianal disease, which causes perineal pain and seepage of stool or mucus from fistulas. Small-volume diarrhea with urgency and tenesmus suggests proctitis. Upper gastrointestinal disease presents with epigastric pain, nausea, vomiting, and occasionally gastric outlet obstruction.

Physical examination findings can range from normal to significantly abnormal depending on disease location and severity. Patients may appear pale, malnourished, or chronically ill. Fever may be present; if high it suggests an abscess or peritonitis. Abdominal tenderness, sometimes with a mass or fullness, is often located in the right lower quadrant. Perianal examination may reveal skin tags, induration, or fistulas.

As in UC, laboratory findings correlate with disease severity. Leukocytosis, anemia, hypoalbuminemia, and vitamin deficiencies indicate more severe disease. The erythrocyte sedimentation rate and C-reactive protein levels are often elevated; if so, these levels can be monitored as signs of response to therapy and subsequent disease flare.

KEY POINT

- Common symptoms of Crohn disease are abdominal pain, diarrhea, and weight loss; however, given the variable distribution of inflammation in Crohn disease, the symptoms can vary considerably between patients.

Extraintestinal Manifestations

Extraintestinal manifestations (EIMs) are found in approximately 10% of patients with IBD. The most common EIMs are oral aphthous ulcers, arthralgia, and back pain (indicating ankylosing spondylitis or sacroiliitis). Eye symptoms (redness, pain, swelling) may be due to uveitis, scleritis, or other causes of ocular inflammation and warrant immediate examination by an ophthalmologist. Skin manifestations are common and include pyoderma gangrenosum and erythema nodosum (see MKSAP 17 Dermatology). Liver involvement can also be seen, most commonly in the form of primary sclerosing cholangitis.

In CD, EIMs are more common with colitis than small-bowel disease. In either CD or UC, EIMs may precede gastrointestinal symptoms. Some EIMs correlate with IBD activity, whereas others do not.

KEY POINT

- Common extraintestinal manifestations of inflammatory bowel disease are oral aphthous ulcers, arthralgia, back pain, eye symptoms, and skin manifestations.

Diagnosis

Because the symptoms of IBD are nonspecific, visualization of the gastrointestinal tract, often by colonoscopy and biopsy of the colon and ileum, is required to make the diagnosis. All patients suspected of having IBD should undergo stool examination to exclude infectious colitis, including *C. difficile*.

In UC, inflammation typically begins in the rectum and extends proximally in a circumferential manner. At presentation, 25% of patients have only proctitis, 25% have disease up to the splenic flexure (left-sided colitis), and 50% have extensive colonic involvement. Some patients with pancolitis have inflammation extending into the ileum for a few centimeters, known as backwash ileitis. This finding alone is not indicative of CD. Mild UC is characterized by mucosal edema, erythema, and loss of the normal vascular pattern. More significant disease produces granularity, friability, ulceration, and bleeding (**Figure 23**). Histology shows altered crypt architecture with shortened, branched crypts, as well as acute and chronic inflammation of the lamina propria.

In CD, endoscopic findings vary from superficial aphthous ulcers to discrete, deep ulcers that can be linear, stellate, or serpiginous and that may coalesce into a "cobblestone" appearance (**Figure 24**). Rectal sparing is typical, as are areas of inflammation separated by normal mucosa (known as skip lesions). The ileum should be inspected during colonoscopy to detect ileal inflammation characteristic of CD. Histology may show patchy transmural inflammation, but more superficial inflammation does not rule out CD. Aphthous ulcers and granulomas are characteristic findings but are often not seen.

CD can affect any part of the gastrointestinal tract, and in some patients inflammation is beyond the reach of colonoscopy. In these patients, supportive evidence can be obtained with CT or magnetic resonance (MR) enterography, capsule endoscopy, or directly by deep enteroscopy. These tests may not only assist in confirming the diagnosis but may also determine the extent and severity of involvement. Enterography also rules out complications such as obstruction, perforation, fistulas, and



FIGURE 23. Typical endoscopic findings of ulcerative colitis are a continuous pattern of inflammation with varying severity of mucosal granularity, edema, loss of the normal vascular pattern, friability, and ulceration. A diffuse pattern of microulcerations is commonly seen, and frank ulcers are atypical.

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FIGURE 24. Endoscopic view of Crohn colitis demonstrating deep, geographic ulcerations on a background of diffuse mucosal inflammation.

abscesses. Radiographs are more often used in CD than UC owing to the frequent involvement of the small intestine. Plain films can evaluate bowel obstruction and dilatation. Small-bowel barium radiographs were often used in the past to evaluate the small bowel, but these examinations have largely been replaced by the more sensitive CT or MR enterography. Patients with CD often need repeat imaging, raising concern about cumulative doses of diagnostic ionizing radiation. Therefore, imaging should be used only when the results affect management, and modalities that do not use radiation (ultrasound, MRI) should be used in place of CT scanning whenever possible.

A subset of patients (10%-15%) has IBD that cannot be categorized; this is known as indeterminate colitis. In these patients, serologic tests have been proposed as a way to distinguish UC from CD. However, these tests are expensive, are relatively insensitive or nonspecific, and often do not add useful information to standard diagnostic tests such as colonoscopy and enterography. Therefore, they should be used only sparingly when the diagnosis remains unclear. In particular, these tests should not be used as initial tests in patients with nonspecific symptoms such as diarrhea; their operating characteristics are particularly poor in these circumstances.

KEY POINTS

- Because the symptoms of inflammatory bowel disease are nonspecific, visualization of the gastrointestinal tract, often by colonoscopy and biopsy of the colon and ileum, is required to make the diagnosis.
- Patients with Crohn disease often need repeat imaging, raising concern about cumulative doses of diagnostic ionizing radiation; therefore, imaging should be used only when the results affect management, and modalities that do not use radiation (ultrasound, MRI) should be used in place of CT scanning whenever possible.

Treatment

Many therapies are available for patients with IBD, including 5-aminosalicylate (5-ASA) drugs, antimicrobial agents, glucocorticoids, immunosuppressive medications (such as azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate, and cyclosporine), and biologic drugs (such as anti–tumor necrosis factor [TNF] agents and leukocyte trafficking inhibitors). Some of these medications deliver the drug to specific areas of the bowel, whereas others act systemically. For the former, an understanding of the distribution of inflammation is required to choose the optimal drug formulation. Many of these treatments can be used for both UC and CD, with some exceptions. The side effects of these medications are listed in **Table 19**. The

TABLE 19. Side Effects of Medications for Inflammatory Bowel Disease

Medication	Side Effects
Mesalamine, balsalazide	More common: dyspepsia, headache, nausea, alopecia
	Less common: interstitial nephritis, pericarditis, pancreatitis, hypersensitivity colitis
Sulfasalazine	In addition to side effects noted for mesalamine, autoimmune hemolytic anemia, bone marrow toxicity, reversible male infertility
Olsalazine	In addition to side effects noted for mesalamine, secretory diarrhea
Glucocorticoids	Hypertension, hyperglycemia, edema, redistribution of body fat, striae, cataracts, osteopenia
Azathioprine and 6-mercaptopurine	Fever, nausea, allergic reactions, pancreatitis, bone marrow suppression, hepatitis, infections, increased risk of lymphoma and skin cancer
Methotrexate	Liver toxicity, stomatitis, pneumonitis, bone marrow toxicity, infections, fetal toxicity; possibly lymphoma and skin cancers
Cyclosporine	Headache, paresthesias, seizures, kidney disease, hypertension, infections
Anti-TNF biologic agents	Infusion or injection site reactions, delayed hypersensitivity reaction, autoimmune disorders (such as drug-induced lupus), infections (including in particular tuberculosis and fungal infections), psoriasis; possibly lymphoma and skin cancers
Natalizumab	Headache, rash, nausea, infections (including PML), infusion reaction

PML = progressive multifocal leukoencephalopathy; TNF = tumor necrosis factor.

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treatment of IBD has become increasingly complex, and most of the medications are immune suppressing. Most patients with CD and patients with UC who require more than 5-ASA products should be referred to a gastroenterologist with expertise in managing these medications.

Ulcerative Colitis

Treatment of UC is based on disease severity (**Table 20**). For mild to moderate UC, the 5-ASA drugs are first-line therapy for inducing and maintaining remission. With these agents, 5-ASA is delivered topically to the bowel lumen, primarily to the colon, with the exception of the time-release formulation of mesalamine, which is able to deliver the drug throughout the small bowel as well as the colon (**Table 21**). Sulfasalazine may cause folate deficiency, and supplementation is recommended.

More severe UC is often treated with oral glucocorticoids such as prednisone, 40 to 60 mg/d. Doses above 60 mg provide little if any additional efficacy with more side effects. Budesonide is a glucocorticoid with high first-pass metabolism available in a controlled ileal-release formulation frequently used in CD. However, another formulation (multi-matrix [MMX] system) provides release of the drug throughout the colon and may be useful in treating UC. It has similar efficacy as prednisone but has fewer glucocorticoid-related side effects owing to its high first-pass metabolism. However, this benefit must be balanced against the high cost of this new medication. Patients whose disease does not respond to oral glucocorticoids should be hospitalized and given intravenous glucocorticoids or should be treated with a biologic agent. Glucocorticoids are not effective for maintaining remission in UC. Therefore, in patients whose disease responds to glucocorticoids, the dose should be tapered over 2 to 4 months while transitioning to a maintenance medication (AZA, 6-MP, or a biologic agent).

Patients with glucocorticoid-responsive disease are often treated with AZA or 6-MP for maintenance. AZA is converted in the body to 6-MP, which is then either inactivated (by xanthine oxidase or thiopurine methyltransferase [TPMT]) or activated to 6-thioguanine nucleotide. The level of TPMT should be checked before starting AZA or 6-MP; 1 in 300 patients (0.3%) lack enzyme activity and are at high risk of toxicity, and AZA and 6-MP should not be used in these patients. Intermediate TPMT activity is present in 10% of patients, whose increased risk of toxicity can be minimized by dose reduction and careful follow-up; 90% of patients have normal enzyme activity and can be treated with full-dose AZA or 6-MP.

AZA at daily doses between 1.5 and 2.5 mg/kg is effective for glucocorticoid sparing and maintaining remission in UC. However, the onset of action is slow, and consequently AZA is typically not used for induction.

Patients whose symptoms do not respond to glucocorticoids are treated with cyclosporine, a biologic agent, or colectomy. Cyclosporine is effective for avoiding colectomy in the short term in most patients. However, many patients eventually require colectomy, and many clinicians do not believe the risks (see Table 19) are worth the long-term benefit. The three anti-TNF antibodies approved for inducing and maintaining remission in UC are infliximab, adalimumab, and golimumab. The integrin-blocking antibody vedolizumab blocks leukocyte trafficking and is also approved for the treatment of UC.

TABLE 20. Ulcerative Colitis Severity

Variable	Mild	Severe
Stools (number per day)	<4	>6
Blood in stool	Intermittent	Frequent
Temperature	Normal	>37.5 °C (99.5 °F)
Pulse (beats per minute)	Normal	>90
Hemoglobin	Normal	<75% of normal
Erythrocyte sedimentation rate (mm/h)	<30	>30

Data from: Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955 Oct 29;2(4947):1041-8. [PMID: 13260656]

TABLE 21. 5-Aminosalicylate Preparations for Treatment of Ulcerative Colitis

Generic Name	Proprietary Name	Formulation	Sites of Delivery
Mesalamine	Canasa®	Suppository	Rectum
	Rowasa®	Enema	Left colon
	Pentasa®	Controlled-release granules	Small bowel and colon
	Asacol®, Delzicol®	Tablets with pH-dependent coating (pH ≥7)	Terminal ileum, colon
	Apriso®	Capsule with pH-dependent coating (pH ≥6) around polymer matrix	Terminal ileum, colon
	Lialda®	Tablet with pH-dependent coating (pH ≥7) around polymer matrix	Terminal ileum, colon
Olsalazine	Dipentum®	5-ASA dimer linked by azo bond	Colon
Sulfasalazine	Azulfidine®	5-ASA linked to sulfapyridine by azo bond	Colon
Balsalazide	Colazal®, Giazo®	5-ASA linked to inert carrier by azo bond	Colon

ASA = aminosalicylate.

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Crohn Disease

In contrast to UC, the role of 5-ASA drugs in CD is less clear, with meta-analyses showing little or no benefit. Antimicrobial agents are important in patients with fistulas or abscesses, but they have no role in treating luminal disease. Therefore, patients with mild to moderate inflammatory CD are often treated initially with glucocorticoids. Prednisone is often used, with the same dosing comments as noted above for UC. For patients with ileocolonic CD, controlled-release budesonide is an alternative to prednisone, with fewer side effects but higher cost.

As in UC, glucocorticoids are not effective for maintaining remission in CD. Therefore, patients whose disease responds to glucocorticoids should be transitioned to an immunomodulator while the glucocorticoid is tapered. In addition to AZA and 6-MP, methotrexate is an option in CD. Trials have demonstrated that AZA, 2 to 3 mg/kg/d; 6-MP, 1.5 mg/kg/d; and methotrexate, 25 mg/week, are effective for inducing and maintaining remission in CD. In addition, AZA and 6-MP are effective for closing fistulas. Some adverse events from methotrexate can be minimized by the use of folic acid. Methotrexate should not be used in pregnant or lactating women.

Patients with more severe disease are treated with a biologic agent. The three anti-TNF agents that are FDA approved for CD are infliximab, adalimumab, and certolizumab. These medications are effective for inducing and maintaining remission and closing fistulas, and are generally considered to be safe in pregnancy (FDA pregnancy category B). Recent evidence indicates that efficacy is better when an anti-TNF agent is used together with an immunomodulator. In addition, the risk of developing antibodies against the anti-TNF agent is lower with combination therapy. Patients whose disease does not respond to one anti-TNF agent are often switched to a second or third anti-TNF agent. Those with no response to or intolerance of anti-TNF agents should be treated with either surgery or a leukocyte trafficking blocker (natalizumab or vedolizumab).

Natalizumab is a monoclonal antibody that interferes with leukocyte migration out of the bloodstream by blocking $\alpha 4$ integrin. It is effective for induction and maintenance of remission in CD that has failed to respond to other medications. Natalizumab increases the risk of infections, including progressive multifocal leukoencephalopathy (PML). Interest in natalizumab has been renewed owing to the availability of testing for exposure to the JC virus that causes PML; patients who are seronegative have very low risk of PML. In those who are seropositive, the risk is unacceptably high with natalizumab and it should not be used. Vedolizumab is another leukocyte trafficking blocker that is specific to the gastrointestinal tract owing to its inhibition of $\alpha 4\beta 7$-integrin. It is approved for the treatment of CD. Because vedolizumab does not affect leukocyte trafficking in the brain, it should not be associated with PML.

Health Maintenance for the Patient with Inflammatory Bowel Disease

Patients with IBD have health risks related to their disease or its treatment. Patients with long-standing colitis are at increased risk for colon cancer and should undergo surveillance colonoscopy every 1 to 2 years beginning after 8 to 10 years of disease. This recommendation applies to patients with UC involving more than the rectum and those with Crohn colitis involving at least one third of the colon. Patients with severely active disease, particularly CD, are at risk for malnutrition and various vitamin deficiencies and should undergo screening for these conditions. In particular, distal ileal disease is associated with vitamin B_{12} malabsorption. Other health risks in IBD are related to immunosuppressive medications. Cumulative glucocorticoid use for longer than 3 months is a risk factor for osteoporosis and is an indication to assess bone density. Patients who will be treated with immunosuppressive medications are at risk for various infections, and vaccinations can decrease this risk. In addition to routine adult vaccines, these patients should receive annual vaccination against influenza with the killed vaccine and not the attenuated intranasal vaccine, hepatitis A and B virus (if not already immune), and pneumococcus. College students should receive meningococcal vaccine. Before starting an anti-TNF agent, patients should be assessed for exposure to tuberculosis (with a skin antigen test or interferon-γ release assay) and for immunity to hepatitis A and B viruses.

KEY POINT

- Patients with long-standing colitis associated with inflammatory bowel disease are at increased risk for colon cancer and should undergo surveillance colonoscopy every 1 to 2 years beginning after 8 to 10 years of disease.

Microscopic Colitis

Microscopic colitis (MC) accounts for 10% to 15% of patients with chronic, watery diarrhea. In contrast to IBD, MC is more common in older persons and does not cause endoscopically visible inflammation. The symptoms of MC are similar to other chronic causes of nonbloody diarrhea, such as celiac disease and IBS; therefore, colonic mucosal biopsies are required for diagnosis. Lymphocytic and collagenous colitis are the two subtypes of MC, and they are distinguishable only by histology. The pathophysiology of MC is not well known. In some patients, certain medications (such as NSAIDs and proton pump inhibitors) have been implicated as causative agents. MC is associated with other autoimmune diseases such as diabetes mellitus and psoriasis. The association with celiac disease is of particular clinical importance because the symptoms of these conditions are similar. Therefore, in patients with celiac disease or MC whose symptoms do not respond to appropriate therapy, the other condition must be ruled out.

The diagnosis of MC is made by histologic evaluation of colonic biopsies; the classic finding is intraepithelial lymphocytosis (>20 intraepithelial lymphocytes per 100 epithelial cells). In collagenous colitis, the increase in intraepithelial lymphocytes may be less pronounced than in lymphocytic colitis, and the main histologic feature is thickening of the subepithelial collagen band (usually >10 μm).

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Therapy for MC is based on symptom severity. Any potentially causative medication should be stopped if possible. In mild disease, antidiarrheal therapy such as loperamide or diphenoxylate can be used. In moderate disease, bismuth subsalicylate may be beneficial. In severe cases or those that do not respond to antidiarrheal agents or bismuth, budesonide is the treatment of choice. It is highly effective (response rates of ≥80%), but the risk of relapse is high once budesonide is stopped (70%-80%); many patients require long-term maintenance therapy with low-dose budesonide or an immunomodulator such as AZA. The 5-ASA medications are not very effective for MC. For patients who do not respond to or do not tolerate budesonide, treatment with a bile salt binder such as cholestyramine may be effective. In severe cases, treatment with an anti-TNF agent may be needed.

KEY POINTS

- Microscopic colitis accounts for 10% to 15% of patients with chronic, watery diarrhea.
- In contrast to inflammatory bowel disease, microscopic colitis is more common in older persons and does not cause endoscopically visible inflammation.

Constipation

Definition

The clinical definition of constipation (as defined by the Rome III international working group) is a symptom complex that includes at least two of the following: straining during defecation, passage of lumpy or hard stool, sensation of incomplete defecation, use of manual maneuvers to facilitate a bowel movement, and/or frequency of less than three bowel movements per week. Accompanying symptoms may include abdominal cramping, abdominal pain, bloating, abdominal distention, nausea, passage of mucus, and diarrhea (overflow diarrhea). Patients at particular risk for overflow diarrhea are the elderly, especially those who are institutionalized or hospitalized or have altered mental status. An abdominal radiograph can confirm the suspicion of excessive fecal loading.

Constipation has an estimated prevalence of 15% to 30% in the general population and is more common in women, the elderly, and institutionalized patients. Prevalence approaches 50% in nursing homes, with 74% of residents using daily laxative therapy.

KEY POINT

- The Rome III criteria define constipation as a symptom complex that includes at least two of the following: straining during defecation, passage of lumpy or hard stool, sensation of incomplete defecation, use of manual maneuvers to facilitate a bowel movement, and/or frequency of less than three bowel movements per week.

Classification

Constipation is classified as acute or chronic; it is also classified as secondary or functional. Chronic constipation is characterized by the regular presence of symptoms for a minimum of 3 months, with symptom onset at least 6 months prior to diagnosis. If secondary causes of constipation (**Table 22**) are excluded based on history, structural testing, and biochemical testing, constipation is classified as functional. Functional constipation is then further categorized as normal-transit constipation, slow-transit constipation, or dyssynergic defecation based on results of physiologic testing. Dyssynergic defecation represents a functional outlet obstruction that arises from the inability to coordinate the relaxation of the puborectalis and/or external anal sphincter muscles while increasing intraabdominal pressure that results in normal evacuation of stool. Dyssynergic defecation is believed to be an acquired behavioral disorder, resulting from causes such as sexual abuse, obstetric trauma, pelvic/abdominal surgery, or traumatic injury to the pelvis/abdomen. The causes of constipation are frequently multifactorial; medications (particularly narcotic analgesics) are the most common cause.

Evaluation

A careful history and physical examination, including rectal examination, can identify alarm features (**Table 23**) that necessitate colonoscopy, CT scan, and/or further biochemical evaluation. If a secondary cause is identified following an initial clinical assessment (such as a comorbidity, medication(s), or a biochemical or structural cause), it should be addressed, and laxative therapy should be used as needed. If no secondary cause is identified, a positive diagnosis of functional constipation can be made. The diagnosis should be explained to the patient, and therapy should be initiated.

For persistent constipation symptoms despite lifestyle changes, dietary measures, and laxative use, further physiologic evaluation and/or referral to a gastroenterologist should be pursued. Physiologic tests to consider include balloon expulsion testing, anorectal manometry, defecography, and colonic transit testing.

Treatment

Initial lifestyle and dietary measures that should be pursued are increased physical activity and increased dietary fiber. Over-the-counter laxative therapy includes fiber supplements, surfactants, and osmotic and stimulant laxatives. Soluble fibers such as psyllium, methylcellulose, calcium polycarbophil, inulin, and wheat dextrin are better tolerated and more effective than insoluble fiber supplements such as bran, flax seed, and rye. Fiber should be introduced at a low dose, ingested with adequate fluids, and increased gradually as tolerated to a maximum daily ingestion of 25 grams. Surfactants such as docusate sodium or docusate calcium are weak laxatives with an excellent safety profile. As such, they are most appropriate for very mild, intermittent constipation. Osmotic laxatives include magnesium hydroxide, lactulose, sorbitol, and polyethylene glycol (PEG) 3350; clinical trials have demonstrated the superiority and safety of PEG. Stimulant laxatives include anthraquinone, senna, and the diphenylmethanes bisacodyl and sodium

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TABLE 22. Secondary Causes of Constipation

Mechanical
Colorectal cancer
Rectocele
Sigmoidocele
Enterocele
Anastomotic stricture
Anal stenosis/stricture
Extrinsic compression from pelvic/abdominal process
Metabolic
Diabetes mellitus
Hypothyroidism
Hypercalcemia
Hypokalemia
Pregnancy
Porphyria
Panhypopituitarism
Pheochromocytoma
Glucagonoma
Heavy metal poisoning (arsenic, lead, mercury)
Neuropathic/Myopathic
Parkinson disease
Systemic sclerosis
Multiple system atrophy
Cerebrovascular accident
Spinal cord injury/spinal cord lesions
Multiple sclerosis
Amyloidosis
Myotonic dystrophy
Dermatomyositis
Shy-Drager syndrome
Autonomic neuropathy
Chagas disease
Intestinal pseudo-obstruction (myopathy and neuropathy)
Hirschsprung disease
Ganglioneuromatosis
Hypoganglionosis
Medications
Narcotic-containing analgesics
Anticholinergic agents (antispasmodics, tricyclic antidepressants, antipsychotics, antiparkinsonian drugs)
Antacids (aluminum and calcium based)
Iron supplements
Antihypertensive agents (calcium channel blockers, β-blockers, diuretics)
NSAIDs
Antidiarrheal agents

TABLE 23. Alarm Features Warranting Immediate Structural Evaluation in Patients with Constipation

Age >50 years (or >45 years in black patients)
New-onset constipation in elderly patients
Severe constipation symptoms
Rectal bleeding
Unexplained weight loss
Family history of colon cancer
History of colonic resection
History of abdominal or pelvic cancer
History of abdominal or pelvic irradiation
Palpable rectal or abdominal mass on examination

picosulfate. The stimulants are the fastest-acting agents (8-12 hours) and are most effective for acute exacerbations of constipation as well as slow-transit constipation. Chronic senna use can lead to benign pigmentation of the colon, known as melanosis coli. Theoretical concerns about the development of cathartic colon with long-term stimulant use remain unproved; recent randomized controlled trials (RCTs) demonstrate safety and efficacy of long-term stimulants with chronic use.

When constipation symptoms do not respond to fiber supplementation or osmotic and stimulatory laxative therapy, prosecretory agents, including the chloride channel activator lubiprostone and the guanylate cyclase-C activator linaclotide, are available by prescription. High-quality RCTs have demonstrated efficacy and safety for both agents. Lubiprostone can cause headache, nausea, diarrhea, and shortness of breath. Linaclotide can cause diarrhea. Agents in development include serotonin receptor activators, bile salt analogues, and bile acid transporter inhibitors. Complementary therapies include probiotics, such as *Bifidobacterium lactis*, *Bifidobacterium animalis*, and *Lactobacillus rhamnosus*, as well as food supplements such as hemp seed and dried plums/prunes. Physical therapy with biofeedback is utilized for the treatment of dyssynergia.

KEY POINT

- Initial lifestyle and dietary measures that should be pursued to improve constipation are increased physical activity and increased dietary fiber.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a heterogeneous symptom complex characterized by abdominal pain and altered bowel habits. This chronic condition affects 10% to 15% of the general population and lacks a single unifying pathophysiology and disease-defining biomarker. As a result, the diagnosis is made by the fulfillment of symptom-based criteria created by the Rome III international working group (**Table 24**). IBS is further subtyped based on the predominant stool pattern as IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), or mixed IBS

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TABLE 24. Rome III Diagnostic Criteria[a] for Irritable Bowel Syndrome and Its Subtypes

IBS
Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following:
Improvement with defecation
Onset associated with a change in frequency of stool
Onset associated with a change in form (appearance) of stool
IBS with Constipation (IBS-C)
Hard or lumpy stools for >25% of bowel movements
Loose (mushy) or watery stools for <25% of bowel movements
IBS with Diarrhea (IBS-D)
Loose (mushy) or watery stools for >25% of bowel movements
Hard or lumpy stools for <25% of bowel movements
Mixed IBS (IBS-M)
Hard or lumpy stools for >25% of bowel movements
Loose (mushy) or watery stools for >25% of bowel movements

C = constipation; D = diarrhea; IBS = irritable bowel syndrome; M = mixed-type.

[a]Diagnostic criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

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TABLE 25. Conditions Associated with Irritable Bowel Syndrome

Functional dyspepsia
Nonerosive gastroesophageal reflux disease
Cyclic vomiting syndrome
Gastroparesis
Anxiety disorder
Depression
Somatoform disorders
Posttraumatic stress disorder
Fibromyalgia and other chronic musculoskeletal pain syndromes
Migraines and nonmigrainous headaches
Chronic pelvic pain
Interstitial cystitis
Dysmenorrhea
Sexual dysfunction

(IBS-M). Additional symptoms that are not part of the diagnostic criteria but are frequently reported in IBS include fewer than three bowel movements per week, more than three bowel movements per day, abnormal stool form, straining, rectal urgency, sensation of incomplete emptying, passage of mucus, and bloating. A variety of other conditions occur in association with IBS, adding to the symptom profile (**Table 25**). IBS occurs in patients of all ages and racial/ethnic groups, but it is more common in women (67% more likely than men) and in younger adults (25% more likely than in those age ≥50 years).

Evaluation

IBS was previously considered a diagnosis of exclusion after eliminating organic causes; however, an accurate diagnosis of IBS can now be made with fulfillment of the diagnostic criteria without further testing in the absence of alarm features (anemia; weight loss; and family history of colorectal cancer, IBD, or celiac disease). Rectal bleeding and nocturnal abdominal pain are poor predictors of organic disease. Therefore, a confident diagnosis of IBS can be made in the absence of alarm symptoms. The routine pursuit of a complete blood count, serum chemistry studies, thyroid function studies, stool studies for ova and parasites, and abdominal imaging is unnecessary in this setting. Testing for celiac disease with serum IgA-based tTG should be considered in patients with IBS-D or IBS-M symptoms. Breath testing for lactase deficiency or SIBO can be considered based on initial treatment response and/or presence of risk factors. Colonoscopy should be pursued only in patients who meet criteria for colon cancer screening based on age, race, and family history. Random colon biopsies should be obtained at the time of colonoscopy to screen for microscopic colitis in patients with IBS-D. There is no established role for food allergy testing in IBS.

KEY POINT

- Irritable bowel syndrome was previously considered a diagnosis of exclusion after eliminating organic causes; however, an accurate diagnosis can now be made with fulfillment of the diagnostic criteria without further testing in the absence of alarm features (anemia; weight loss; and family history of colorectal cancer, inflammatory bowel disease, or celiac disease). HVC

Management

An essential initial step in management of IBS is the clear establishment of the diagnosis with explanation of and reassurance regarding the patient's symptoms. A strong clinician-patient relationship should be established using a patient-centered approach that is focused on effective patient and clinician communication. This can be achieved by using open-ended questions, actively listening to the patient, and showing empathy during patient encounters.

Given the growing role of presumed food intolerances in IBS symptoms (more than half of patients report symptom onset following meals), dietary interventions are growing in popularity. Although RCTs are lacking, dietary interventions may include the avoidance of trigger foods (caffeine, carbonated beverages, or fatty foods), increased dietary fiber, and various elimination diets that restrict gluten, lactose, fructose, or FODMAPs (Fermentable Oligosaccharides, Disaccharides,

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Monosaccharides, And Polyols). It is best to involve a dietitian when pursuing elimination diets to ensure safety and improve efficacy. These initial management steps may lead to symptom improvement in patients with mild symptoms. For persistent symptoms, directed pharmacologic therapy should be pursued based on the predominant stool pattern.

KEY POINTS

- An essential initial step in managing irritable bowel syndrome is the clear establishment of the diagnosis with explanation of and reassurance regarding the patient's symptoms.
- Given the growing role of presumed food intolerances in irritable bowel syndrome symptoms, dietary interventions are growing in popularity.

Therapy for Irritable Bowel Syndrome with Constipation

The soluble fiber supplement psyllium has demonstrated limited efficacy in IBS, primarily addressing stool frequency and consistency. Insoluble fiber supplements such as bran appear to worsen IBS-C symptoms. Although a variety of surfactant, osmotic, and stimulant laxatives can be used for the constipation symptoms associated with IBS-C, only the osmotic laxative PEG has been tested in IBS. Lubiprostone and linaclotide have demonstrated safety and efficacy in treating the global symptoms of IBS-C in high-quality RCTs. Lubiprostone is FDA approved for women with IBS-C, and linaclotide is FDA approved for the treatment of IBS-C in adults. There is also considerable cost associated with lubiprostone and linaclotide.

Therapy for Irritable Bowel Syndrome with Diarrhea

The antispasmodic agents hyoscyamine and dicyclomine are used for the short-term treatment of abdominal pain in IBS-D or IBS-C, although they can cause constipation. The antidiarrheal agent loperamide is safe and is only effective for the bowel symptoms associated with IBS-D. The nonabsorbable antimicrobial agent rifaximin can be effective for global symptoms and bloating associated with IBS-D, presumably by altering the colonic microbial flora; however, it is not FDA approved for this use. The 5-HT_3 antagonist alosetron is available for women with IBS-D whose symptoms have not responded to conventional therapy; however, owing to an increased risk of severe constipation and ischemic colitis with its use, it is restricted by a mandatory prescribing program.

Other Therapies

When the previously mentioned therapies are unsuccessful, central-acting agents such as tricyclic antidepressants and selective serotonin reuptake inhibitors are effective, primarily for overall symptoms and abdominal pain. The use of tricyclic antidepressants is preferred in IBS-D given their constipating side effects, and selective serotonin reuptake inhibitors are preferred in IBS-C.

Complementary Therapy

If pharmacologic therapies are not effective or not desired by the patient, a variety of complementary interventions can be considered. Although RCTs are lacking in most cases, limited clinical evidence supports the use of prebiotics (nondigestible nutrients intended to encourage desirable bacterial growth), probiotics, herbal medicine, cognitive behavioral therapy, hypnotherapy, and acupuncture in IBS.

Diverticular Disease

Diverticulosis is the presence of asymptomatic colonic mucosal outpouchings, known as diverticula. They are usually located in the sigmoid colon, but any part of the colon may be involved. These mucosal protrusions occur through weak areas where the vasa recta penetrate and are facilitated by increased intraluminal pressure, such as with chronic constipation. The prevalence of diverticulosis increases with age; it is present in 10% of patients older than 45 years and in 80% of those older than 85 years.

If a diverticulum becomes blocked, trapped bacteria proliferate, inflaming the diverticulum and surrounding tissues and resulting in diverticulitis. The inflamed diverticulum may perforate, which results in an abscess. The abscess may decompress into adjacent structures and cause fistulas to the bladder, vagina, or skin. It may also decompress into the peritoneum, resulting in peritonitis.

Approximately 20% of patients with diverticula have an episode of diverticulitis. Symptoms include abdominal pain, fever, and altered bowel habits (typically diarrhea). Although the stool may contain some blood, significant bleeding from diverticulitis is very uncommon. Dysuria, urinary frequency, and urinary urgency may reflect bladder irritation. Pneumaturia, fecaluria, or recurrent/polymicrobial urinary tract infections suggest a colovesical fistula. Physical examination findings include fever, left lower quadrant tenderness, and/or a lower abdominal or rectal mass.

The therapeutic approach to diverticulitis is dictated by patient-related factors, the severity of clinical features, and the ability to tolerate oral intake. In a healthy, immunocompetent patient with mild symptoms, outpatient therapy is appropriate and should consist of a liquid diet and oral antimicrobial agents that cover colonic organisms and include anaerobic coverage (such as ciprofloxacin and metronidazole). Close follow-up is warranted to detect any deterioration as soon as possible. For older, frail, sicker patients, hospitalization is recommended for administration of intravenous antimicrobial agents and observation.

If clinical features are highly suggestive of diverticulitis, imaging studies are unnecessary. If the diagnosis is not clear or if an abscess is suspected (severe pain, high fever, palpable mass), CT imaging is indicated. A small abscess may resolve with antimicrobial therapy alone. For larger abscesses, CT-guided drainage can facilitate nonsurgical management and decrease the chance of sepsis. Emergent surgery is

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required for generalized peritonitis, uncontrolled sepsis, or perforation. Elective surgery is indicated for fistulas and recurrent diverticulitis.

After an acute attack has resolved, a high-fiber diet is generally recommended to facilitate stool passage and decrease intracolonic pressure. When inflammation and the resulting edema have completely resolved, colonoscopy should be performed to exclude cancer or IBD.

Another major complication of diverticulosis is diverticular hemorrhage, which occurs more commonly in the right colon (but can occur anywhere in the colon) and typically resolves spontaneously. For a discussion of diverticular bleeding, see Gastrointestinal Bleeding.

KEY POINTS

- Approximately 20% of patients with diverticula have an episode of diverticulitis.
- Symptoms of diverticulitis include abdominal pain, fever, and altered bowel habits (typically diarrhea).

HVC

- If clinical features are highly suggestive of diverticulitis, imaging studies are unnecessary.

Ischemic Bowel Disease

Acute or chronic alteration of arterial or venous intestinal blood flow may result in intestinal ischemia. The intestinal insult may be mild and reversible, requiring only supportive care, or it may be severe and life threatening, requiring surgery or culminating in intestinal gangrene, sepsis, and death. The most important factor predicting outcome is the presence of bowel infarction.

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Acute Mesenteric Ischemia

Clinical Features and Diagnosis

Acute mesenteric ischemia (AMI) is an uncommon vascular emergency that accounts for less than 1 in 1000 hospital admissions and has a mortality rate of 60%.

Embolism to the mesenteric arteries causes 50% of cases of AMI and usually involves the superior mesenteric artery (SMA). Emboli are usually of cardiac origin and are due to atrial fibrillation or left ventricle thrombus. Arterial thrombosis is more common than venous thrombosis and accounts for one third of cases of AMI. Thrombosis within the mesenteric arteries is usually due to superimposed atherosclerotic disease. Symptoms of chronic mesenteric insufficiency due to atherosclerosis may be elicited in up to 25% of patients before they experience SMA occlusion. Mesenteric vein thrombosis may also lead to AMI and may result from other systemic conditions such as malignancy, hypercoagulable states, abdominal or cardiac surgery, or pancreatitis. It may also result from the use of contraceptive and estrogen-containing medications.

Nonocclusive mesenteric ischemia is caused by decreased mesenteric perfusion in low-flow states such as heart failure, sepsis, profound hypotension, or hypovolemia. It may also occur with use of vasoactive medications (vasopressors, ergots, triptans, cocaine, digitalis).

Patients typically present in the seventh decade of life and often have associated comorbidities (for example, atrial fibrillation, recent myocardial infarction, or heart failure in the case of embolism; mesenteric atherosclerosis in the case of thrombosis). The classic presentation of early AMI is abdominal pain out of proportion to the physical examination findings; however, symptoms may vary depending on the timing of presentation and cause of ischemia.

Early in AMI, laboratory studies may be normal. Leukocytosis, hemoconcentration, anion gap metabolic acidosis, and elevations in lactate dehydrogenase and/or amylase levels may be seen as disease progresses. Abdominal plain radiographs can be used to exclude other causes of pain, and they may detect bowel wall edema or pneumatosis later in the disease course. The usefulness of vascular ultrasound is limited to visualization of the proximal origin of vessels. Splanchnic angiography, once considered the standard for diagnosis and potential treatment of AMI, is increasingly being reserved for patients with nonocclusive mesenteric ischemia in whom medical management is unsuccessful, those who require intra-arterial papaverine infusion, or those who are candidates for a primary percutaneous endovascular approach in the setting of thromboembolic occlusion when peritoneal signs have not yet developed. Endovascular intervention for AMI requires careful patient selection and interventional radiology or vascular surgical expertise. When a patient has signs of peritonitis or a bowel infarction is suspected, experts favor immediate surgery.

CT angiography is considered the standard for diagnosis of AMI because it is fast, noninvasive, widely available, and has a high sensitivity and specificity for diagnosing AMI and excluding other causes of pain. It provides an accurate assessment of mesenteric vessel patency and bowel injury but offers no therapeutic role. Although MR angiography has high accuracy for detecting high-grade stenosis and occlusions in the origin of the celiac artery and SMA, it is a long test, is not quickly available, and has limited ability to detect distal arterial thrombi or emboli and nonocclusive mesenteric ischemia.

KEY POINT

- The classic presentation of early acute mesenteric ischemia is abdominal pain out of proportion to the physical examination findings.

Treatment

Treatment consists of volume resuscitation, correction of acidosis and electrolyte imbalances, broad-spectrum antimicrobial agents, nasogastric decompression, and discontinuation of medications associated with vasoconstriction. Surgery is indicated for patients with peritoneal signs or for those in whom there is a high index of concern for AMI despite negative imaging studies. Necrotic bowel should be resected. Embolectomy or, in the case of thrombosis, thrombectomy

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CONT. and surgical revascularization or endovascular stenting of the underlying atherosclerotic lesion should be performed. Intra-arterial papaverine is often used as an adjunct to surgery to minimize vasoconstriction, and it is the definitive treatment for nonocclusive mesenteric ischemia. In patients without peritonitis, endovascular or open embolectomy should be performed. Local thrombolysis is recommended in cases of incomplete endovascular embolectomy or distal artery embolization. Thrombosis should be managed with open or endovascular revascularization. Anticoagulants are the appropriate treatment for mesenteric vein thrombosis.

Chronic Mesenteric Ischemia

Clinical Features and Diagnosis

Chronic mesenteric ischemia is estimated to affect 1 in 100,000 individuals. It is almost always associated with atherosclerotic disease. Rare causes include fibromuscular dysplasia, compression of the celiac artery by the median arcuate ligament (also known as median arcuate ligament syndrome), vasculitis, and chronic mesenteric venous thrombosis. Symptoms consist of postprandial pain within 60 minutes after meals, which results in fear of eating and weight loss. Symptoms usually develop when two or more arteries have hemodynamically significant stenoses. Single-vessel involvement may be causative when collateral flow is inadequate. Vascular Doppler ultrasound is a useful screening test for chronic mesenteric ischemia but is limited by the presence of intestinal gas or obesity. Peak systolic velocities greater than 275 cm/s in the SMA and greater than 200 cm/s in the celiac artery correlate to stenoses of greater than 70% in each vessel. CT and MR angiography have high sensitivity and specificity for detecting mesenteric stenosis, but MR angiography may not be as effective for detecting distal stenosis. Conventional angiography may be used to confirm the diagnosis and plan endovascular or open surgical therapy.

KEY POINTS

- Chronic mesenteric ischemia is almost always associated with atherosclerotic disease.
- Symptoms of chronic mesenteric ischemia consist of postprandial pain within 60 minutes after meals, which results in fear of eating and weight loss.

Treatment

Surgical revascularization is the most durable treatment for chronic mesenteric ischemia. Periprocedural morbidity and mortality are lower with endovascular stenting, which may be indicated for select patients.

Colonic Ischemia

Clinical Features and Diagnosis

Ischemic colitis is the most common form of intestinal ischemic injury, accounting for 1 in 1000 hospitalizations. Approximately 90% of cases occur in patients older than 60 years. It is most often due to transient alterations in systemic circulation or local mesenteric vasculature, which decreases intestinal blood flow. Conditions that can alter circulation include hypotension, dehydration, strenuous physical activity, medications and illicit drugs, thrombophilia, aortic or cardiac bypass, vasculitis, or an obstructing colon lesion. Symptoms include sudden abdominal pain and diarrhea followed later by rectal bleeding. The diagnosis is based on clinical history. There is no role for angiography. Left colon inflammatory changes may be detected by colonoscopy or abdominal CT.

KEY POINT

- Ischemic colitis is the most common form of intestinal ischemic injury; symptoms include sudden abdominal pain and diarrhea followed later by rectal bleeding.

Treatment

Treatment depends on the severity of symptoms. Most patients have mild and transient disease and can receive outpatient management. Patients with more severe symptoms require hospitalization for supportive care with bowel rest, intravenous fluids, antimicrobial therapy, and close observation. Most cases resolve; however, up to 20% of patients require colectomy for necrotic bowel or stricturing complications.

Anorectal Disorders

Perianal Disorders

Perianal disorders affect men and women of all ages and range from benign conditions such as hemorrhoids to potentially life-threatening diseases such as anorectal cancer. A thorough history and detailed physical examination (including inspection of the anus, digital rectal examination, and direct visualization with anoscopy or proctoscopy) allow a diagnosis to be made. Patients with alarm features (such as unexplained weight loss, change in bowel movements, iron deficiency anemia, age older than 50 years, or personal or family history of colorectal cancer or IBD) warrant colonoscopy.

Hemorrhoids

Hemorrhoids are arteriovenous communications covered by cushions of connective tissue in the anal canal. Hemorrhoids above the dentate line are internal, and those below it are external. External hemorrhoids produce pain and an acutely tender nodule when thrombosed. Internal hemorrhoids cause most hemorrhoidal symptoms (painless, bright red blood dripping in the toilet bowl or noted on toilet paper; a protrusion of tissue; itching; and pain).

Initial treatment of internal and external hemorrhoids consists of dietary and lifestyle modifications to soften bowel movements and avoid constipation, straining, and prolonged time on the toilet. Increased fiber intake has been shown to reduce symptomatic prolapse and bleeding. Local therapy such as topical anesthetics and glucocorticoids may relieve pain and itching, but data to support their use are scant. Oral

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micronized, purified flavonoid fraction, a preparation that increases venous vascular tone, has been shown in some studies to improve hemorrhoidal symptoms. Office-based nonoperative therapy with sclerotherapy, rubber band ligation, infrared coagulation, radiofrequency ablation, and cryotherapy is recommended for most symptomatic hemorrhoids. Band ligation has the most durable response. Surgical excision is indicated for patients in whom nonoperative therapy is unsuccessful and in those with large or acutely thrombosed external hemorrhoids.

KEY POINT

- Initial treatment of hemorrhoids consists of dietary and lifestyle modifications to soften bowel movements and avoid constipation, straining, and prolonged time on the toilet.

Anal Fissure

Anal fissures are tears in the anoderm below the dentate line that can be seen on inspection of the perianal area, often unaided by the use of an anoscope. They are usually in the posterior position and are less often in the anterior midline. Lateral fissures should raise suspicion for IBD and infectious or neoplastic causes. The classic symptom is pain with and after defecation, which may be associated with bright red blood on the toilet tissue. Most acute fissures heal spontaneously. Sitz baths, fiber or stool softeners, topical anesthetics, or anti-inflammatory ointments may provide symptomatic relief. Chronic fissures may heal with use of topical calcium channel blockers or 0.2% nitroglycerin, although headache often limits use of nitroglycerin. The evidence to support botulinum toxin injections is limited. Lateral internal sphincterotomy is the treatment of choice for refractory fissures.

KEY POINT

- Most acute anal fissures heal spontaneously; sitz baths, fiber or stool softeners, topical anesthetics, or anti-inflammatory ointments may provide symptomatic relief.

Fecal Incontinence

Fecal incontinence is the involuntary loss of stool. Prevalence increases with age and is 16% in adults older than 70 years. Urinary incontinence, obesity, neurologic disorders, pelvic surgery, or obstetric trauma are additional risk factors. Lifestyle and dietary modification should be initiated using specific toileting regimens, fiber and antidiarrheal medications to normalize stool consistency, and biofeedback if other therapies are unsuccessful. Endoanal ultrasound is used to identify sphincter defects, and anorectal manometry assesses sphincter function, rectal sensation, and compliance. If conservative measures are unsuccessful, submucosal injection of a bulking agent in the anal canal or implantation of a device for electrostimulation of the sacral nerves have been shown to decrease fecal incontinence in patients with weak sphincters. Either sacral nerve stimulation or surgery is indicated for patients with sphincter defects.

KEY POINT

- Prevalence of fecal incontinence increases with age and is 16% in adults older than 70 years.

Anal Cancer

Anal carcinoma is a rare but increasing cause of cancer and accounts for approximately 2% of gastrointestinal cancers. Most anal cancers are squamous cell carcinomas and are associated with human papillomavirus (HPV) infection, particularly HPV 16 and HPV 18. HPV vaccine is approved for and has been shown to prevent anal HPV infection and anal intraepithelial neoplasia, precursors of anal cancer.

Risk factors for anal cancer include HPV infection; sexually transmitted infections; multiple sex partners; men having sex with men; receptive anal intercourse; history of vaginal, cervical, or vulvar cancer; smoking; immunosuppression due to hematologic malignancy; solid organ transplantation; or HIV infection.

Most patients present with a perianal lesion or mass associated with rectal bleeding or anal discomfort. Twenty percent of patients may be asymptomatic.

When anal carcinoma is suspected, biopsy is essential to establish the diagnosis. Once confirmed, the clinical examination is critical for staging. Staging is based on lesion size, local invasion, and status of regional lymph nodes. Digital rectal examination, anoscopy, inguinal lymph node palpation (with biopsy or fine-needle aspiration if enlarged), and CT scan of the pelvis, abdomen, and chest are recommended.

For treatment, follow-up, and prognosis of anal cancer, see MKSAP 17 Hematology and Oncology.

KEY POINTS

- Anal carcinoma is a rare but increasing cause of cancer and accounts for approximately 2% of gastrointestinal cancers.
- Most patients with anal cancer present with a perianal lesion or mass associated with rectal bleeding or anal discomfort.

Colorectal Neoplasia

Epidemiology

Colorectal cancer is the second most common cause of cancer and cancer-related mortality in men and women in the United States. The cumulative lifetime risk of developing colorectal cancer is 1 in 19 in men and 1 in 20 in women. More than 50% of patients are diagnosed with stage III and IV cancer, which is associated with 5-year survival rates of approximately 65% and 10%, respectively. The incidence of colorectal cancer has steadily declined over the past 30 years. The annual rate of decline

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between 1998 and 2009 was 2.6% in men and 2.1% in women. Since 1975, a decrease in mortality of more than 30% has been noted; this is attributable largely to the use of colorectal cancer screening. Despite this evidence, 35% of eligible Americans have not been screened for colorectal cancer with fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy.

KEY POINTS

- Colorectal cancer is the second most common cause of cancer and cancer-related mortality in men and women in the United States.
- HVC Despite a decrease in colorectal cancer mortality that is largely attributable to the use of screening, 35% of eligible Americans have not been screened for colorectal cancer with fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy.

Pathogenesis

Colorectal cancer is a heterogeneous genetic disease that arises from three well-characterized molecular pathways: chromosomal instability (CIN), microsatellite instability (MSI), and the CpG island methylator phenotype (CIMP).

CIN results from gains or losses of whole or portions of chromosomes, which can result in an imbalance in chromosome number (aneuploidy) or loss of paired genomic regions on complementary chromosomes (heterozygosity), leaving only one copy of certain genes. Progressive accumulation of mutations in tumor suppressor genes and oncogenes leads to subsequent development of malignancy. Seventy percent of colorectal cancers arise from adenomatous polyps through the CIN pathway.

Microsatellites are repetitive noncoding nucleotide sequences scattered throughout the human genome. The fidelity of microsatellites during DNA replication is maintained by the enzyme products of the mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Alterations in MMR gene function are associated with defective replication error repair and resultant changes in length of microsatellite sequences in a tumor; when present in a tumor, this is known as MSI. Five percent of colon cancers arise from adenomas in patients with a germline mutation in the MMR genes, which are an essential component of Lynch syndrome. These tumors are characterized by high levels of MSI (MSI-H).

A third genetic molecular pathway involved in colorectal neoplasia does not involve disruption of the genetic sequence but instead involves disruption of normal gene function by the addition of a methyl group (methylation) within the promoter region of specific genes (most commonly at the 5′-CG-3′ [CpG] dinucleotide) and silences their function (known as an epigenetic change). Patients with a tendency to excessively methylate (hypermethylate) certain genes are designated as having CIMP. When hypermethylation occurs with different genes that normally suppress tumor development, colorectal neoplasia may result. These tumors tend to be poorly differentiated and have a high degree of MSI and other genetic abnormalities. Clinically, the precursor lesions for CIMP-associated tumors are sessile serrated polyps; up to 30% of colon cancers develop from this type of polyp.

Risk Factors

Modifiable Factors

Modifiable factors associated with colorectal polyps and cancer include high dietary fat or red meat, low dietary fiber, smoking, excess alcohol ingestion, obesity, type 2 diabetes mellitus, and low physical activity.

KEY POINT

- Modifiable factors associated with colorectal polyps and cancer include high dietary fat or red meat, low dietary fiber, smoking, excess alcohol ingestion, obesity, type 2 diabetes mellitus, and low physical activity.

Predisposing Factors

Nonmodifiable risk factors include male gender, acromegaly, older age (with a peak incidence of cancer after the eighth decade of life), and black ethnicity (which is associated with a higher cancer incidence and stage-adjusted mortality compared with other ethnicities).

The risk for colorectal cancer is elevated in the presence of chronic colorectal inflammation from ulcerative colitis or Crohn disease of the colon. This increased risk is dependent on the proximal extent of mucosal involvement; patients with pancolitis are at highest risk, whereas risk is negligible in patients with proctitis. Risk is also increased with longer duration of disease, greater severity of inflammation, and the presence of coexistent primary sclerosing cholangitis. After a decade of disease, the cancer risk increases yearly by 0.5% to 1%.

Ureterosigmoidostomy also increases the risk for colon cancer. The mechanism is unknown but may be related to chronic colonic inflammation.

A personal history of adenomatous polyps or colorectal cancer increases the risk for metachronous colorectal cancer (multiple primary tumors developing at different time intervals).

KEY POINT

- Predisposing factors for colorectal cancer include male gender, acromegaly, older age, black ethnicity, ulcerative colitis or Crohn disease of the colon, ureterosigmoidostomy, and history of adenomatous polyps or colorectal cancer.

Nonsyndromic Family History

Individuals with a first-degree relative with colorectal cancer have a two- to threefold increased risk for colorectal cancer. The risk is increased with a greater number of relatives affected and an earlier age of cancer onset (defined as younger than age 60 years).

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KEY POINT

- Individuals with a first-degree relative with colorectal cancer have a two- to threefold increased risk for colorectal cancer.

Hereditary Colon Cancer Syndromes

Patients with the highest risk of colorectal cancer are those who have a hereditary colorectal cancer syndrome (**Table 26**). Recognition of a hereditary colon cancer syndrome requires an accurate and comprehensive family history, which should include the ages and causes of death of relatives in three generations, any diagnosis of cancer and age of onset, birth defects, and other inherited conditions. The family history should be confirmed with medical records when possible and should be updated periodically to ensure proper surveillance recommendations.

KEY POINT

- Patients with the highest risk of colorectal cancer are those who have a hereditary colorectal cancer syndrome.

Hereditary Nonpolyposis Colon Cancer

Hereditary nonpolyposis colon cancer (HNPCC) is the term that describes families that satisfy the Amsterdam I or II criteria. The Amsterdam I and II criteria are similar with one notable exception: Amsterdam I criteria include only colorectal cancer. The Amsterdam II criteria are as follows:

- Three or more relatives with HNPCC-related cancers (colorectal cancer or cancer of the endometrium, small intestine, ureter, or renal pelvis)
- One relative a first-degree relative of the other two
- At least two successive generations affected
- One cancer diagnosed before age 50 years
- Familial adenomatous polyposis excluded
- Tumors verified histologically

Lynch syndrome is the term used to describe patients who meet the Amsterdam II criteria for HNPCC and have an identified germline mutation in one of the four MMR genes or the epithelial cell adhesion molecule (*EPCAM*) gene (which codes for a transmembrane glycoprotein that plays a role in tumorigenesis and metastasis). Colon cancer occurs in up to 80% of individuals with Lynch syndrome, usually at a mean age of 44 years. The colon cancer is often right-sided and has particular pathologic features that include tumor-infiltrating lymphocytes, a Crohn-like lymphocytic reaction, and mucin or signet cell histology. Lynch syndrome is associated with an increased risk for extracolonic tumors (endometrial [40%-60%], followed much less commonly by ovarian, urothelial, gastric, brain, small bowel, hepatobiliary tract, sebaceous, and pancreatic). The cumulative lifetime cancer risk and age of cancer onset vary according to the specific germline mutation present.

Familial colorectal cancer type X is the term used to identify patients and families who meet the Amsterdam criteria for HPNCC but have no molecular evidence of a MMR deficiency. Patients with familial colorectal cancer type X have a much lower lifetime risk of colon cancer, later age of onset, and no increased risk of extracolonic cancers compared with patients with Lynch syndrome. Recommendations state that patients with colorectal cancer should undergo molecular testing of their tumor to determine if it has evidence of defective MMR (also known as universal testing). This can be done by MSI testing or immunohistochemistry for expression of the MMR proteins in the tumor.

KEY POINT

- Colon cancer occurs in up to 80% of individuals with Lynch syndrome, usually at a mean age of 44 years.

Adenomatous Polyposis Syndromes

The adenomatous polyposis syndromes include familial adenomatous polyposis (FAP) and *MYH*-associated polyposis (MAP).

FAP is caused by a mutation of the adenomatous polyposis coli (*APC*) gene, a tumor suppressor gene that normally attenuates cell proliferation. Classic FAP results in the development of hundreds to thousands of colorectal adenomas that

TABLE 26. Hereditary Colorectal Cancer Syndromes

Syndrome	Prevalence	Inheritance	Polyp Type
Lynch syndrome	1 in 440	AD	Adenoma
Familial adenomatous polyposis	1 in 10,000	AD	Adenoma
MYH-associated polyposis	1 in 20,000	AR	Adenoma
Peutz-Jeghers syndrome	1 in 120,000	AD	Hamartoma
Juvenile polyposis syndrome	1 in 100,000	AD	Hamartoma
PTEN hamartoma tumor syndrome	1 in 200,000	AD	Hamartoma, adenoma, ganglioneuroma, serrated
Serrated polyposis syndrome	1 in 3000	Familial	Serrated

AD = autosomal dominant; AR = autosomal recessive.

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often manifest by the second decade of life. Without treatment, colorectal cancer typically develops in all patients by the age of 40 years. Gastric fundic gland polyposis and duodenal adenomas are also present in most patients. Gastric cancer is rare, but duodenal and periampullary cancers are the second leading cause of cancer death in this group (2.5%-30%, depending on duodenal polyposis stage). Papillary carcinoma of the thyroid is increasingly recognized as accompanying FAP.

A milder form of FAP has also been identified and is known as attenuated FAP (AFAP); patients with AFAP have fewer colorectal polyps, generally less than 100. AFAP has a later age of onset and a lower cumulative lifetime risk of colorectal cancer than classic FAP. The colorectal polyps are often right-sided.

Gardner syndrome is a phenotypic variant of FAP that is characterized by colonic polyposis, benign soft tissue tumors (including sebaceous cysts and lipomas), osteomas, supernumerary teeth, desmoid tumors, and congenital hypertrophy of the retinal pigment epithelium. Turcot syndrome is another variant of FAP that includes polyposis associated with brain tumors, including cerebellar medulloblastoma, astrocytoma, and ependymoma.

Biallelic mutations in the base excision repair gene *MYH* cause MAP. MAP is an autosomal recessive syndrome that has similar colonic and extraintestinal features as AFAP, at least a 50% lifetime risk of cancer, and a mean age of cancer onset of 52 years.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is caused by a mutation in a gene that encodes for threonine kinase (*STK11*) gene. PJS results in development of diffuse intestinal hamartomatous polyps (which often cause small-bowel obstruction by the age of 20 years) and mucocutaneous pigmentation that is most obvious on the vermilion border of the lips. Diagnostic criteria for PJS consist of two or more of the following: two or more small-bowel hamartomas, mucocutaneous pigmentation, or a family history of PJS. There is a 90% cumulative lifetime risk for intestinal and extraintestinal cancer in PJS. The cumulative lifetime risk for specific sites is as follows: breast, 55%; colon, 38%; pancreas, 38%; gastric, nearly 30%; ovary, 20%; lung, 18%; small intestine, 12%; uterus and cervix, 10%; unusual gonadal neoplasms of the ovary, 20%; and unusual gonadal neoplasms of the testes, 10%.

Juvenile Polyposis Syndrome

Patients with juvenile polyposis syndrome (JPS) develop numerous hamartomatous polyps, known as juvenile polyps, in the colon. Germline mutations are detected in 50% of patients with JPS and are either in the *BMPR1A* or *SMAD4* gene. Although most patients develop symptoms by the age of 20 years, the name "juvenile" refers to the histology of the polyp, not the age of the affected individual. The clinical criteria for this syndrome consist of (1) more than three juvenile polyps of the colon, (2) juvenile polyps throughout the gastrointestinal tract, or (3) one or more juvenile polyps combined with a family history of juvenile polyposis syndrome. Juvenile polyposis syndrome usually presents with gastrointestinal bleeding, diarrhea, gastric outlet obstruction, or protein-losing enteropathy from massive gastric polyposis. There is an increased risk for colon cancer (39%), gastric cancer (25%), and more rarely small-bowel and pancreatic cancer.

Solitary juvenile polyps are one of the most commonly found colorectal polyps, particularly in children under the age of 10 years; they confer no future health risk once the polyp is removed, and follow-up surveillance colonoscopy is not required.

PTEN Hamartoma Tumor Syndrome

PTEN hamartoma tumor syndrome (including Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome) is caused by a mutation in the *PTEN* gene, which functions as a tumor suppressor gene. Macrocephaly and intestinal polyposis are primary features. There is an increased risk of thyroid, breast, endometrial, colon, and renal cell cancers.

Serrated Polyposis Syndrome

Serrated polyposis syndrome is a familial polyposis syndrome characterized by multiple, large, proximal hyperplastic polyps or serrated adenomas without a known genetic cause. It is diagnosed using the World Health Organization criteria of (1) five or more serrated polyps proximal to the sigmoid colon, two or more of which are 10 mm in diameter or greater; (2) any number of serrated polyps proximal to the sigmoid colon in an individual with a first-degree relative who has serrated polyposis syndrome; or (3) more than 20 serrated polyps distributed throughout the colon. Serrated polyposis syndrome is associated with an increased risk of colorectal but not extraintestinal cancer. The mean age of colon cancer diagnosis is 56 years, and metachronous colon cancer occurs in up to 7% of patients at 5 years of follow-up. Surveillance is recommended.

Screening

For a discussion of screening in patients at average risk for colorectal cancer, see MKSAP 17 General Internal Medicine.

Patients with a greater-than-average risk for colorectal cancer should undergo colonoscopic surveillance, which should be customized according to the patient's risk factors.

Patients with a family history of an adenoma or colorectal cancer in a first-degree relative prior to age 60 years, or in two or more first-degree relatives at any age, should undergo colonoscopy every 5 years beginning at age 40 years (or at an age 10 years younger than the earliest age of the case in the immediate family). Patients with a family history of an adenoma or colorectal cancer in a first-degree relative age 60 years or older or with two second-degree relatives with colorectal cancer at any age should undergo colorectal cancer screening with any average-risk strategy; however,

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colonoscopy every 10 years is recommended by some experts. For these patients, the U.S. Multi-Society Task Force (MSTF) on Colorectal Cancer recommends starting screening at age 40 years, whereas the American College of Gastroenterology recommends beginning at age 50 years. The MSTF recommends stopping colonoscopy surveillance when the risk of the procedure outweighs the benefit to the high-risk patient. At ages 75 to 85 years, the potential benefit of surveillance is higher than for average-risk patients. At ages older than 85 years, patients with high-risk adenomas are at higher risk for metachronous advanced neoplasia than average-risk patients; continued surveillance should be individualized based on medical comorbidities and life expectancy, but routine screening should not be continued.

KEY POINTS

- Patients with a greater-than-average risk for colorectal cancer should undergo colonoscopic surveillance, which should be customized according to the patient's risk factors.
- Patients with a family history of an adenoma or colorectal cancer in a first-degree relative prior to age 60 years, or in two or more first-degree relatives at any age, should undergo colonoscopy every 5 years beginning at age 40 years (or at an age 10 years younger than the earliest age of the case in the immediate family).

Chemoprevention

Epidemiologic studies have demonstrated an association between high consumption of folate, fruits, vegetables, and fiber with a lower risk of colorectal neoplasia; however, these findings have not been confirmed in randomized controlled trials.

Chemoprevention is not indicated for patients at average risk for colorectal neoplasia. However, there is increasing evidence that a number of agents, particularly NSAIDs, may be beneficial in preventing colorectal neoplasia. Long-term aspirin use substantially reduces the risk of benign and malignant colorectal neoplasms and colorectal cancer deaths by up to 60%. These results have been confirmed in cohort, case control, and randomized controlled trials in low- and very-high-risk populations, including patients with Lynch syndrome. Strong data demonstrate that celecoxib, rofecoxib, and sulindac (in combination with difluoromethylornithine) effectively reduce recurrent adenomas in patients who have undergone polypectomy. Celecoxib promotes the regression of adenomas in adult and pediatric patients with FAP. Additionally, a significant decrease in metachronous adenomas was observed in patients taking 1200 mg of calcium carbonate daily. However, routine use of these agents for chemoprevention is not recommended owing to the increased risk of vascular and bleeding complications with NSAIDs, the cardiovascular risk associated with exogenous calcium supplementation, the lack of consensus on the optimal dosing of these agents, and the balance of risks and benefits of aspirin use, especially in patients at low risk.

KEY POINT

- Chemoprevention is not indicated for patients at average risk for colorectal neoplasia, and it is not routinely recommended for patients at high or very high risk for colorectal neoplasia.

Clinical Presentation

The majority of colon polyps and colon cancers are asymptomatic until they are advanced. Gastrointestinal bleeding is the most common sign and may be revealed by positive fecal occult blood testing, iron deficiency anemia, or hematochezia. Unexplained anorexia, change in bowel habits, abdominal pain, weight loss, or symptoms of bowel obstruction may occur when tumors are advanced.

Diagnosis and Staging

The diagnosis of colorectal neoplasia is most often made by colonoscopy performed for gastrointestinal symptoms, screening, or surveillance.

Polyps are typically described by their appearance: sessile (in which the entire base is attached to the colonic wall), flat (in which the diameter of the lesion is at least twice as great as the height), or pedunculated (where a mucosal stalk exists between the colonic wall and the polyp).

The histologic types of polyps are noted in **Table 27**. Screening colonoscopy studies demonstrate that polyps are detected in approximately 60% of average-risk individuals. The prevalence of polyps on average-risk screening colonoscopy is 22% to 25% for adenomas, 12% for hyperplastic polyps, and 0.6% for sessile serrated polyps. The degree of dysplasia in a polyp is also reported as high, intermediate, or low.

TABLE 27. Classification of Colorectal Polyps

Adenomatous Polyps[a]
Tubular adenoma
Tubulovillous adenoma
Villous adenoma
Serrated Polyps
Hyperplastic polyp
Sessile serrated polyp with or without cytologic dysplasia
Traditional serrated adenoma
Other
Hamartomatous polyp
Inflammatory polyp

[a]With or without high-grade dysplasia.

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Adenomatous polyps are neoplastic lesions and therefore have malignant potential; most colorectal cancers arise from adenomatous polyps. Adenomatous polyps are further defined by their glandular architecture: tubular, villous, or a combination of both. The most common pattern is tubular, then tubulovillous, and the least common pattern is primarily villous.

Serrated polyps are classified into three histologic types: hyperplastic polyps, sessile serrated polyps, and traditional serrated adenomas. Hyperplastic polyps are the most common type of serrated polyp. They are non-neoplastic and are composed of normal mucosal elements; small hyperplastic polyps, often found in the rectosigmoid colon, are believed to have no clinical significance. Sessile serrated polyps (also known as sessile serrated adenomas) and traditional serrated adenomas are both neoplastic and are precursors to colorectal cancer; they should be completely excised. Substantial variability has been demonstrated in the ability of a pathologist to differentiate a hyperplastic polyp from a sessile serrated polyp; therefore, some experts recommend managing large (>10 mm) hyperplastic polyps as if they are sessile serrated polyps.

If colorectal cancer is diagnosed, staging provides a uniform description of the depth of tumor invasion into the colon wall and other structures, as well as the spread to lymph nodes and distant organs. There are two types of staging for colorectal cancer: a clinical stage and a pathologic stage. Clinical staging includes findings on physical examination, results of colonoscopic biopsy, and pretreatment CT imaging of the chest, abdomen, and pelvis. If an indeterminate liver mass is detected, MRI of the abdomen with and without gadolinium-based contrast enhancement is suggested. MRI of the pelvis is recommended for patients with rectal cancer. Pathologic staging is performed after the tumor is removed and reports the tumor type and differentiation, depth of invasion, lymph node involvement, distant metastasis, margin status, perineural and angiolymphatic invasion, and many other clinically validated factors.

For treatment of colorectal cancer, see MKSAP 17 Hematology and Oncology.

Surveillance

History of Adenomatous and Serrated Polyps

After neoplastic polyps (adenomas, sessile serrated polyps, or traditional serrated adenomas) are removed, postpolypectomy colonoscopy should be performed; the surveillance interval depends on the size, number, and pathology of the polyps (**Table 28**). Colonoscopy intervals are as short as 3 to 6 months in patients with removal of large (>2 cm) sessile polyps, more than 10 adenomas, piecemeal removal of adenomas or sessile serrated polyps, or adenomas with invasive cancer and favorable prognostic features.

Invasive adenocarcinoma arising in a pedunculated or sessile polyp may be adequately treated by endoscopic polypectomy alone if the lesion is removed en bloc, invades only the submucosa, possesses no adverse histologic features (poorly differentiated, lymphovascular invasion), and has clear margins. These polyps containing invasive cancer should be followed up with colonoscopy 3 to 6 months after removal.

TABLE 28. Postpolypectomy Surveillance

Adenomatous Polyps	Interval to Next Colonoscopy
1-2 <10-mm tubular adenomas	5-10 years
3-10 adenomas, ≥10 mm, villous histology, or high-grade dysplasia	3 years
≥10 adenomas on single examination	<3 years; a genetic cause of disease should be investigated
Serrated Polyps	
<10-mm rectosigmoid hyperplastic polyps	10 years
SSP <10 mm	5 years
SSP ≥10 mm or SSP with dysplasia or TSA	3 years
Serrated polyposis syndrome	1 year

SSP = sessile serrated polyps; TSA = traditional serrated adenomas.

KEY POINT

- After neoplastic polyps (adenomas, sessile serrated polyps, or traditional serrated adenomas) are removed, postpolypectomy colonoscopy should be performed; the surveillance interval depends on the size, number, and pathology of the polyps.

History of Colorectal Cancer

Patients who undergo a complete perioperative colonoscopy with clearing of synchronous neoplasia and curative surgical resection for colon cancer should have a subsequent surveillance colonoscopy within 1 year. If the colonoscopy is normal, a repeat examination is recommended at 3 years, and, if normal, every 5 years thereafter. If neoplasms are detected during any follow-up examination, then the surveillance interval should be adjusted based on polyp size, number, and histology (see Table 28). Owing to the heightened risk of early local recurrence after rectal cancer therapy, patients with rectal cancer should undergo a flexible sigmoidoscopy evaluation of the anastomosis every 3 to 6 months for the first 3 years.

KEY POINT

- Patients who undergo a complete perioperative colonoscopy with clearing of synchronous neoplasia and curative surgical resection for colon cancer should have a subsequent surveillance colonoscopy within 1 year.

Hereditary Nonpolyposis Colon Cancer

Patients who meet the Amsterdam criteria for HNPCC should receive genetic counseling and should be offered genetic testing.

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Individuals who have or are at risk for Lynch syndrome should undergo colonoscopy every 1 to 2 years beginning at age 20 to 25 years, or 2 to 5 years earlier than the youngest age at diagnosis of colorectal cancer if the affected relative was less than 25 years old. Although the evidence is low, consideration should be given to yearly urinalysis (to check for microscopic hematuria) or upper endoscopy every 2 to 3 years beginning at age 30 to 35 years (to screen for upper gastrointestinal cancer). Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option that should be considered in women who have completed childbearing. Annual endometrial sampling and transvaginal ultrasonography may be considered in women with Lynch syndrome who are older than 25 years.

Familial Adenomatous Polyposis and *MYH*-Associated Polyposis

Patients with FAP and MAP should receive genetic counseling and should be offered genetic testing. Because MAP is autosomal recessive, both parents must be carriers of an *MYH* mutation in order for a child to inherit the syndrome.

Beginning at age 10 to 15 years, *APC* gene carriers or those with indeterminate status for FAP should undergo yearly flexible sigmoidoscopy or colonoscopy. Individuals who have or who are at risk for MAP should undergo colonoscopy every 2 to 3 years beginning at age 25 to 30 years. After colectomy is performed, lifelong yearly surveillance of the rectum or ileal pouch is required to manage recurrent polyposis and decrease the risk of rectal or pouch adenocarcinoma. Upper endoscopy for surveillance of duodenal cancer is indicated every 1 to 5 years at an interval based on the stage of the duodenal polyposis.

Ulcerative or Crohn Colitis

Patients with long-standing colitis are at increased risk for colon cancer and should undergo surveillance colonoscopy every 1 to 2 years beginning after 8 to 10 years of disease. This recommendation applies to patients with ulcerative colitis involving more than the rectum and those with Crohn colitis involving at least one third of the colon.

KEY POINT

- Patients with ulcerative colitis or Crohn colitis should receive surveillance colonoscopy every 1 to 2 years beginning after 8 to 10 years of disease.

Peutz-Jeghers Syndrome

For patients with Peutz-Jeghers syndrome, surveillance of the small bowel with capsule endoscopy or CT or magnetic resonance enterography is recommended every 2 to 3 years starting at age 8 to 10 years. Colonoscopy and upper endoscopy should be performed every 2 to 3 years beginning in the late teenage years. MRI or endoscopic ultrasound of the pancreas should be performed every 1 to 2 years beginning at age 30 to 35 years. Patients should also receive early and aggressive surveillance for cancer of the breast, ovary, cervix, uterus, and testis.

Other Syndromes

For patients with juvenile polyposis syndrome, colonoscopy and upper endoscopy are recommended every 2 to 3 years beginning at age 15 years.

For patients with *PTEN* hamartoma tumor syndrome, colonoscopy is recommended every 5 years beginning at age 35 years. Annual surveillance of the breasts and thyroid should begin at age 25 and 18 years, respectively.

Patients with serrated polyposis syndrome should undergo colonoscopy yearly.

Disorders of the Liver

Approach to the Patient with Abnormal Liver Chemistry Studies

Approximately 13% of patients undergoing medical evaluation have abnormal liver test results; 5% of patients have persistent abnormalities of one or more liver enzyme levels.

Typical serum elevations and clinical features of common liver diseases are shown in **Table 29**.

Disorders that cause liver disease are considered hepatocellular when the predominant elevation is of the serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Disorders are considered cholestatic when the predominant elevation is of serum alkaline phosphatase (ALP). Elevations in ALT are more specific for liver injury than AST elevations; however, severe muscle injury can produce elevations of both enzymes. An elevated ALP level accompanied by elevations in other liver enzymes is nearly always due to liver or biliary disease; an isolated elevation in the ALP can be secondary to an elevation in bone fraction. Measurement of γ-glutamyl transpeptidase may be used to confirm a liver origin of an elevated ALP level.

Liver function is assessed by measuring prothrombin time and serum albumin level, which depend on the liver's synthetic ability.

Bilirubin is also a useful marker of liver function for hepatocellular diseases. Liver diseases generally cause an increase in both conjugated (direct) and unconjugated (indirect) bilirubin. Gilbert syndrome is a benign condition characterized by mild unconjugated hyperbilirubinemia, which is caused by a congenital decrease in hepatic uridine diphosphate glucuronyl transferase.

Imaging of the liver with ultrasound, CT, and MRI can assess for parenchymal changes and vascular flows. Ultrasound is useful because it does not require intravenous access, but its usefulness may be limited in obese patients and it has the lowest sensitivity for the detection of liver masses. MRI is useful because it does not expose the patient to radiation and allows for assessment of the biliary tree using magnetic resonance cholangiopancreatography (MRCP). Histologic assessment will often require a liver biopsy; however, serologic markers and ultrasound- or

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TABLE 29. Typical Liver Chemistry Studies in Common Hepatobiliary Disorders

Disease	AST	ALT	ALP	Bilirubin	Other Features
Acute viral hepatitis	↑↑↑	↑↑↑	Normal to ↑	Normal to ↑↑↑	Exposure history, fatigue, nausea
Chronic viral hepatitis	↑	↑↑	Normal to ↑	↑ if advanced	History of exposure to infected blood or body fluids
Nonalcoholic steatohepatitis	↑	↑	Normal to ↑	Normal	Metabolic syndrome
Alcoholic hepatitis	↑↑	Normal or ↑	↑	Normal to ↑↑↑	Excess alcohol intake
Acute autoimmune hepatitis	↑↑↑	↑↑↑	Normal to ↑	Normal to ↑↑	Autoantibodies
Chronic autoimmune hepatitis	↑	↑↑	Normal to ↑	Normal	Autoantibodies
Wilson disease	↑	↑	Low	↑ and often unconjugated	Hemolysis if acute, neurologic symptoms if chronic
α_1-Antitrypsin deficiency	↑	↑	Normal	↑ if advanced	May have pulmonary disease
Hemochromatosis	Normal	Normal	Normal	Normal	Joint symptoms, family history, other organ involvement
Primary biliary cirrhosis	↑	↑	↑↑↑	↑ if advanced	Female, sicca symptoms, antimitochondrial antibody
Primary sclerosing cholangitis	↑	↑	↑↑↑	↑ if advanced or dominant stricture is present	Ulcerative colitis, abnormal cholangiogram
Large duct obstruction	↑ (↑↑ if acute)	↑ (↑↑ if acute)	↑↑	↑↑	Pain if acute, dilated ducts on imaging
Infiltrative liver disease	↑	↑	↑↑↑	Normal	Features of malignancy, sarcoid, amyloid, or mycobacterial or fungal infection
Hepatic ischemia	↑↑↑	↑↑↑	Normal	Normal	AST >5000 U/L, history of hypotension
Celiac disease	Normal or ↑	Normal or ↑	Normal or ↑	Normal	Usually other features of celiac disease

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

magnetic resonance–based elastography are increasingly used to assess for fibrosis. Elastography uses the velocity at which waves pass through the liver to provide an assessment of liver tissue stiffness, which correlates with fibrosis. For patients with obvious clinical features of cirrhosis, such as splenomegaly or other complications of portal hypertension, liver biopsy is unnecessary.

KEY POINT

- Disorders that cause liver disease are considered hepatocellular when the predominant elevation is of the serum alanine aminotransferase and aspartate aminotransferase levels; disorders are considered cholestatic when the predominant elevation is of serum alkaline phosphatase.

Viral Hepatitis

Hepatitis A

The burden of hepatitis A virus (HAV) infection correlates with socioeconomic indicators, especially income levels and quality of sanitation. In areas with lower incomes and poorly developed sanitation systems, more than 90% of children have evidence of previous HAV infection by the age of 10 years. Areas with relatively higher incomes and better-developed sanitation systems such as the United States have a lower prevalence of HAV infection.

The incubation period of HAV is 2 to 6 weeks. Symptoms of acute HAV are jaundice, fatigue, mild abdominal pain, fever, and diarrhea. Patients older than 30 years are more likely than younger individuals to have jaundice with an acute HAV infection, and acute liver failure (ALF) may rarely occur. Transmission from an infected patient occurs during the incubation period or within 1 week after jaundice develops. Acute HAV is diagnosed with detection of serum IgM antibodies to HAV. The presence of IgG antibodies to HAV is a marker of immunity due to either previous exposure or vaccination.

The majority of patients with acute HAV infection have resolution of symptoms and liver test abnormalities within 3 months. A relapsing or prolonged course can occur in up to 10% of individuals, but chronic infection does not occur. The

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clinical course of relapsing HAV is characterized by clinical recovery with near normalization of the serum liver tests, followed several weeks later by biochemical and sometimes clinical relapse. No specific treatment is available for HAV.

HAV infection is prevented by administration of hepatitis A vaccine (see MKSAP 17 General Internal Medicine). Postexposure prophylaxis with hepatitis A vaccine is effective in preventing infection and obviates the need for administration of immune globulin in most patients. The administration of immune globulin can be considered for postexposure prophylaxis in patients who are immunocompromised (such as those who have undergone organ transplantation) or were previously unvaccinated and are traveling to an endemic area if departure is within 2 weeks.

KEY POINT

- The majority of patients with acute hepatitis A virus infection have resolution of symptoms and liver test abnormalities within 3 months.

Hepatitis B

Hepatitis B virus (HBV) is a DNA virus that can cause both acute and chronic hepatitis. Worldwide, chronic infection with HBV is common, with about 350 million persons infected. Transmission occurs following exposure to blood or body fluids from an infected patient. Because resolution of infection is less common when infection is acquired at a young age, as opposed to an older age, most chronically infected patients were infected perinatally or in early childhood. The incubation period of HBV infection is 4 to 24 weeks. In the United States, chronic HBV infection is encountered clinically much more frequently than acute infection. Extrahepatic manifestations of HBV infection, such as arthritis, polyarteritis nodosa, and kidney disease, are rarely encountered in clinical practice.

Relatively simple blood tests are widely available to diagnose HBV and help determine disease activity (**Table 30**).

Acute HBV infection will resolve (defined as clearance of hepatitis B surface antigen within 6 months) in 90% of adult patients. Serial monitoring of liver enzymes and markers of liver synthetic function is the most appropriate management strategy. Antiviral therapy can be considered for prolonged and severe cases.

Chronic HBV infection is characteristically divided into phases of disease (**Figure 25**). Not all patients go through each phase. Patients who acquire HBV infection at birth (vertical transmission) often go through the immune tolerant phase, which is characterized by a normal ALT level despite a positive hepatitis B e antigen (HBeAg) and very high HBV DNA level. This phase may persist until the age of 30 years. Liver biopsy will show little injury, presumably owing to an absence of immunologic damage to the infected hepatocytes. In cross-sectional studies, approximately 60% of patients with chronic HBV infection are in the inactive carrier, or "immune control," phase that is characterized by a normal ALT level and an HBV DNA level less than 10,000 IU/mL. Patients in the HBeAg-positive ("immune active") or HBeAg-negative ("reactivation") chronic HBV phases have an elevated ALT level and an HBV DNA level above 10,000 IU/mL. When liver biopsy is performed, lymphocytic inflammation and variable degrees of fibrosis are identified.

HBV treatment is not advised in patients in the immune tolerant or inactive carrier (immune control) phases; however,

TABLE 30. Interpretation of Hepatitis B Test Results

Clinical Scenario	HBsAg	Anti-HBs	IgM anti-HBc	IgG anti-HBc	HBeAg	Anti-HBe	HBV DNA (IU/mL)
Acute hepatitis B; occasionally reactivation of chronic hepatitis B	+	–	+	–	+	–	>20,000
Resolved previous infection	–	+	–	+	–	+/–	Undetected
Immunity due to previous vaccination	–	+	–	–	–	–	Undetected
False positive anti-HBc or resolved previous infection	–	–	–	+	–	–	Undetected
Immune tolerant (HBeAg-positive chronic hepatitis B) (perinatally acquired, age <30 years)	+	–	–	+	+	–	>1 million
Immune control (chronic hepatitis B inactive carrier)	+	–	–	+	–	+	<10,000
Immune active (HBeAg-positive chronic hepatitis B)	+	–	–	+	+	–	>10,000
Reactivation (HBeAg-negative chronic hepatitis B)	+	–	–	+	–	+	>10,000

Anti-HBc = hepatitis B core antibody; anti-HBe = hepatitis B e antibody; anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

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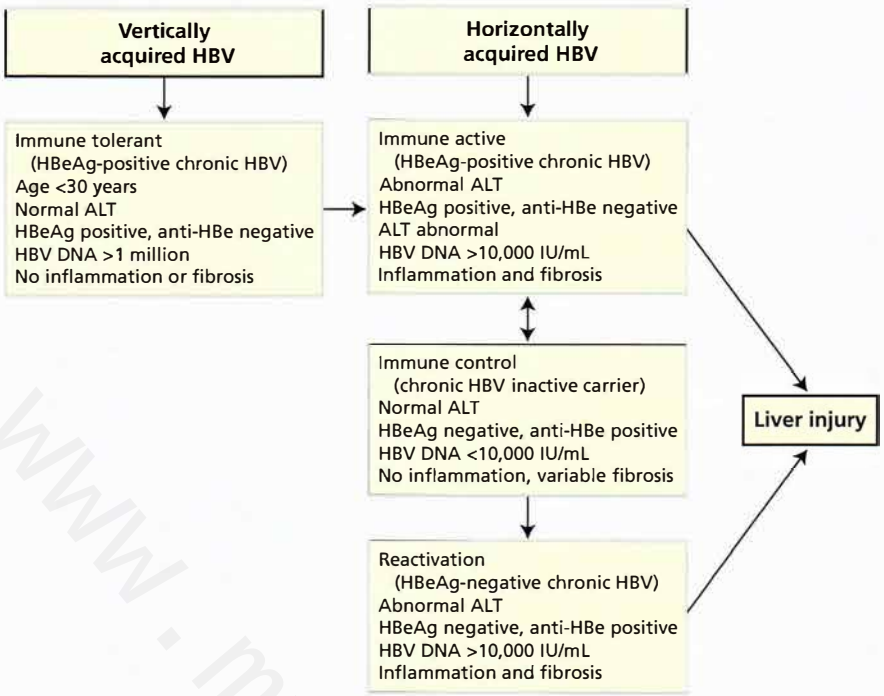

FIGURE 25. Phases of chronic hepatitis B infection. It is assumed that patients progress through the phases in sequence, although not all patients will develop HBeAg-negative chronic hepatitis B, and only patients with vertical transmission of hepatitis B will have a clinically recognized immune tolerant phase. All phases have positive HBsAg, negative anti-HBs, and positive IgG anti-HBc. ALT = alanine aminotransferase; anti-HBc = hepatitis B core antibody; anti-HBe = hepatitis B e antibody; anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HBV DNA = hepatitis B virus DNA.

monitoring with ALT measurement is necessary to detect transitions to other phases. For patients with HBV, treatment is recommended for those who (1) have ALF, (2) have chronic infection with an elevated ALT level and an HBV DNA level greater than 10,000 IU/mL, or (3) are receiving immunosuppressive therapy. Treatment usually consists of entecavir or tenofovir. For most patients, chronic treatment is necessary unless seroconversion of HBeAg or hepatitis B surface antigen (HBsAg) is observed. Lamivudine, adefovir, and telbivudine are used less often because of development of resistance with chronic use. Pegylated interferon may be used for patients without cirrhosis who have high ALT levels, relatively low HBV DNA levels, and ability to tolerate the side effects of pegylated interferon. The treatment goal is normalization of the ALT level and a decline in HBV DNA level to <50 IU/mL. Only a few patients will become HBsAg negative with treatment; therefore, cure of HBV is an unrealistic goal for most chronically infected patients.

In approximately 50% of untreated patients with chronic HBV infection in the United States, HBV will contribute to the cause of death (from hepatocellular carcinoma [HCC] or other complications of end-stage liver disease, such as cirrhosis). Patients who respond to treatment have a decreased risk of liver-related complications of HBV. The following characteristics are associated with an increased risk for HCC in patients with HBV and are indications for surveillance with ultrasound or other imaging every 6 months: (1) patients with cirrhosis, (2) Asian men older than 40 years, (3) Asian women older than 50 years, (4) African patients older than 20 years, (5) patients with persistent inflammatory activity (defined as an elevated ALT level and HBV DNA levels greater than 10,000 IU/mL for at least a few years), and (6) patients with a family history of HCC.

Population-based studies have shown that widespread use of HBV vaccination decreases the incidence and prevalence of HBV. This has also been demonstrated to result in fewer cases of HCC in endemic areas. See MKSAP 17 General Internal Medicine for a discussion of vaccinations.

KEY POINTS

- Treatment is recommended for patients with hepatitis B virus infection who (1) have acute liver failure, (2) have chronic infection with an elevated alanine aminotransferase level and a hepatitis B virus DNA level greater than 10,000 IU/mL, or (3) are receiving immunosuppressive therapy.
- Population-based studies have shown that widespread use of hepatitis B virus vaccination decreases the incidence and prevalence of hepatitis B virus infection.

Hepatitis C

Hepatitis C virus (HCV) is the most common bloodborne infection in the United States, with an estimated 4 million

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patients infected. Globally, approximately 180 million patients are infected. Because patients with HCV infection are often asymptomatic and unaware of their infection, screening is recommended by the U.S. Preventive Services Task Force for individuals born between 1945 and 1965 (see MKSAP 17 General Internal Medicine). Transmission occurs with exposure to blood; most patients acquire HCV from illicit drug use. Although the risk of transmission of HCV from needle-stick exposure is low, transmission of HCV in the health care setting is well documented. Sixty percent to 85% of patients who acquire HCV infection remain chronically infected. Over a period of 25 to 30 years, approximately 30% of patients with chronic HCV infection develop cirrhosis and are at risk for liver failure or HCC. Although the number of new HCV infections in the United States is decreasing, the number of patients with liver failure and HCC continues to increase owing to the propensity of HCV to result in chronic infection and the long lag time between infection and development of liver complications. In contrast to HBV, HCV rarely causes HCC in the absence of cirrhosis.

Symptomatic acute HCV infection is unusual. Patients with chronic HCV infection are often asymptomatic, but fatigue and vague right upper quadrant pain are sometimes reported. Those with cirrhosis may present with complications of portal hypertension. Cryoglobulinemic vasculitis, membranoproliferative glomerulonephritis, and porphyria cutanea tarda are extrahepatic manifestations of HCV infection.

The diagnosis of HCV is established by the presence of HCV RNA in serum. Patients with spontaneous resolution of acute HCV or who have been treated successfully for HCV will have clearance of HCV RNA but usually remain positive for antibody to HCV. Liver biopsy findings consistent with HCV are lymphocytic portal inflammation with nodular lymphoid aggregates, steatosis, and variable fibrosis. With the advent of more successful HCV treatment and the use of less invasive ways to assess fibrosis, liver biopsy is now done in a minority of patients with HCV. HCV RNA level does not influence disease progression, and serial monitoring of HCV RNA level is not recommended (except during HCV treatment). HCV genotyping should be performed at the time of diagnosis to help choose a treatment regimen.

The goal of HCV treatment is sustained virologic response (SVR), defined as undetectable HCV RNA 6 months after completion. SVR results in improved patient outcomes, including a decrease in all-cause mortality. Patients with cirrhosis are less likely to achieve SVR than those without cirrhosis. The treatment of HCV continues to evolve rapidly. SVR rates in excess of 90% are now achieved in most patient groups. Approved options for therapy in patients with HCV genotype 1 (the most prominent genotype in the United States) include the direct-acting antivirals sofosbuvir and ledipasvir (available as a combination tablet), which has been shown to result in SVR in 95% of treated patients. Other treatment regimens for genotype 1 include the combination of the direct-acting antivirals ombitasvir and paritaprevir and the protease inhibitor ritonavir (available in a single tablet), which is packaged and coadministered with an additional tablet, the direct-acting antiviral dasabuvir; these drugs may be administered with or without concurrent ribavirin. A third option not approved by the FDA for this indication is the combination of the protease inhibitor simeprevir and the direct-acting antiviral sofosbuvir, with or without concurrent ribavirin; these agents are not available as a combined preparation. Patients with genotype 2 are usually treated with sofosbuvir and ribavirin for 12 weeks, whereas those with genotype 3 are treated with sofosbuvir and ribavirin for 24 weeks. Sofosbuvir and ledipasvir, combined with ribavirin, may have a role in the treatment of patients with genotype 3 who do not achieve SVR with other regimens. Patients with genotype 4 are currently treated with pegylated interferon, ribavirin, and sofosbuvir.

Patients with cirrhosis should undergo surveillance for HCC. Patients with HCV who have decompensated disease or localized HCC are candidates for liver transplantation. Posttransplant hepatitis C viremia occurs in nearly all patients and has a variable natural history. Treatment with antiviral agents can be effective for patients with recurrent HCV after liver transplantation.

A vaccine against HCV has not been developed, likely related to the ability of the virus to mutate. For patients exposed to HCV, prophylactic therapy to prevent disease acquisition is not yet advised. For patients with recognized acute infection, a period of monitoring for 3 months is worthwhile to document the 15% to 40% chance for spontaneous resolution prior to initiating treatment. Patients whose disease does not resolve after 3 months are generally treated.

Patients infected with HCV are advised to avoid blood exposures (includes avoidance of sharing dental and shaving appliances). For monogamous heterosexual couples, the risk of sexual transmission is 0.07% per year, and therefore condom use is not generally recommended. Men who have sex with men are likely at increased risk of transmission of HCV compared with those in heterosexual relationships.

Owing to shared risk factors, infection with HCV is seen in 15% to 30% of individuals with HIV infection. Coinfection leads to more rapid progression of liver disease than in patients with HCV alone. Treatment of patients with coinfection is similar to that for patients with HCV alone, but careful attention to potential drug interactions is necessary.

KEY POINT

- Because patients with hepatitis C virus infection are often asymptomatic and unaware of their infection, screening is recommended by the U.S. Preventive Services Task Force for individuals born between 1945 and 1965.

Hepatitis D

Hepatitis D virus (HDV) is a defective RNA virus that requires the presence of HBV to replicate. HDV infection is most common in South America and Mediterranean countries. HDV can

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be acquired simultaneously with HBV (coinfection) or subsequently in a patient already infected with HBV (superinfection). Patients with HBV infection should be tested for HDV, especially in the presence of an otherwise unexplained acute hepatitis in a patient with chronic HBV. HDV is typically diagnosed with antibody tests, but HDV RNA testing is available at specialized laboratories. Treatment for HDV is with pegylated interferon; however, response rates are only approximately 25% to 30%. Therefore, treatment is pursued only in patients with progressive liver injury despite treatment of HBV.

Hepatitis E

Hepatitis E (HEV) is an RNA virus that most commonly causes epidemics in India, parts of Asia, and Central America. The disease presents similarly to HAV and is diagnosed by the presence of an IgM antibody to HEV.

A second genotype of the virus is increasingly recognized in more developed countries, including the United States. Population-based studies suggest that up to 20% of the U.S. population has serologic evidence of a prior HEV infection; however, acute HEV is rarely encountered. HEV in developed countries may be acquired from an animal reservoir.

Other Viruses

Epstein-Barr virus (EBV), cytomegalovirus (CMV), and other herpesviruses can cause liver injury that is usually mild and self-limited.

Patients with an infectious mononucleosis syndrome due to EBV may have a serum ALT level up to ten times the upper limit of normal, but they are not usually jaundiced. Other typical symptoms of EBV infection, such as fever, fatigue, and sore throat, are usually present.

CMV infection may cause acute hepatitis, especially in immunocompromised patients. Detection of CMV in blood by polymerase chain reaction is more specific than serologic tests.

Hepatitis due to herpesviruses (either herpes simplex viruses or varicella zoster virus) may cause serum aminotransferase levels greater than 5000 U/L, but jaundice is unusual. Most patients with severe herpes hepatitis are immunocompromised or pregnant and have features of encephalitis. The typical herpetic rash is not always present. Antiviral therapy is advised in patients with herpes hepatitis.

Alcohol-Induced Liver Disease

The earliest histologic change in alcoholic liver disease is macrovesicular steatosis. Fatty liver can be caused by binge drinking or chronic alcohol abuse. Patients are usually asymptomatic and may or may not have mild elevations in ALT, AST, γ-glutamyltransferase, or mean corpuscular volume. Abstinence from alcohol results in resolution of fatty liver in 4 to 6 weeks, whereas continued alcohol consumption over many years can result in cirrhosis.

Hepatic steatosis with inflammation is called alcoholic steatohepatitis (ASH). Mild forms of ASH are common, are usually asymptomatic, and are associated with mild elevations in aminotransferase levels.

The most severe form of ASH is called alcoholic hepatitis (AH) and is distinguished from alcohol-induced steatosis and steatohepatitis by the presence of symptoms. AH is the clinical syndrome of jaundice, anorexia, and tender hepatomegaly with or without fever in patients with high-dose (>100 g/d) alcohol intake. Severe AH may be accompanied by hepatic encephalopathy (HE), variceal bleeding, ascites, or hepatorenal syndrome. Laboratory evaluation may demonstrate elevated aminotransferase levels (<300-400 U/L), an AST to ALT ratio greater than 2, conjugated hyperbilirubinemia, elevated γ-glutamyltransferase level, elevated mean corpuscular volume, leukocytosis, and coagulopathy.

Severity of AH is determined by the Maddrey discriminant function (MDF) score, which is calculated as follows:

$$\text{MDF} = 4.6\,(\text{prothrombin time [s]} - \text{control prothrombin time [s]}) + \text{total bilirubin (mg/dL)}$$

Patients with mild disease (MDF <32) should be treated with supportive measures. All patients with alcoholic liver disease should be (1) counseled about abstinence from alcohol and monitored for signs of withdrawal, (2) assessed for thiamine and fat-soluble vitamin deficiencies, and (3) monitored for ongoing malnutrition. Enteral feedings are required in patients with prolonged periods of poor caloric intake.

The presence of HE or an MDF score of 32 or greater signifies a high risk of death and warrants treatment with prednisone or pentoxifylline. Prednisone is the first-line treatment unless contraindications such as infection, variceal hemorrhage, or acute kidney injury are present. If the serum bilirubin level does not improve by day 7, then prednisone should be discontinued. Changing therapy to pentoxifylline thereafter is not beneficial. Portal hypertensive complications should be managed according to usual practice.

Cirrhosis develops in up to 25% of patients with chronic alcohol abuse. Sustained abstinence can stabilize liver function and even resolve portal hypertensive complications.

KEY POINTS

- Abstinence from alcohol results in resolution of fatty liver in 4 to 6 weeks, whereas continued alcohol consumption over many years can result in cirrhosis.
- All patients with alcoholic liver disease should receive counseling about abstinence from alcohol and should be monitored for signs of withdrawal.

Drug-Induced Liver Injury

Drug-induced liver injury (DILI) can be caused by prescription or over-the-counter medications, herbs, or supplements. Clinical manifestations range from an asymptomatic elevation in liver chemistry studies to ALF. The annual incidence of DILI is estimated to be 19 per 100,000 persons. DILI can be

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categorized as idiosyncratic or intrinsic (predictable). Intrinsic DILI has a short duration from drug ingestion to liver injury (latency), is dose related, and is most common, whereas idiosyncratic DILI is unpredictable, has longer latency, and is less common. Acetaminophen hepatotoxicity is the classic example of intrinsic DILI and is the most common cause of ALF. The following discussion refers to idiosyncratic DILI.

The most common agents that cause idiosyncratic DILI are antimicrobial agents (particularly amoxicillin-clavulanate), antiepileptic drugs (phenytoin, valproate), antituberculosis drugs (isoniazid, rifampin), NSAIDs, and azathioprine. The most common drugs that cause ALF in the United States are antituberculosis drugs, sulfa-containing antimicrobial agents, and antifungal agents. Statins can cause ALF, but this is exceedingly rare. It is safe to continue statins in most patients with mild liver test elevations if no jaundice or symptoms are present. Supplements account for approximately 10% of DILI in the United States.

Diagnosis and management of DILI are described in **Figure 26**.

Diagnosis of DILI requires a history of drug or supplement exposure within 6 to 12 months, a biochemical pattern that fits the hepatotoxicity profile of the causative agent, improvement after drug removal (dechallenge), and the absence of underlying liver or biliary diseases.

Liver biochemistry studies and clinical features can be used to help determine the causative agent, as certain drugs tend to produce typical liver test patterns. Hepatocellular liver test abnormalities (with elevated aminotransferases) are typical of liver injury caused by allopurinol, diclofenac, isoniazid, phenytoin, and valproate. A cholestatic pattern (with elevated ALP) is seen with amoxicillin-clavulanate, carbamazepine, erythromycin, and sulfonamides. A mixed pattern (with elevated aminotransferases and ALP) is typical when azathioprine, enalapril, and ibuprofen are the causative agents.

Hypersensitivity reactions may present with fever, rash, and eosinophilia. Autoimmune-like hepatitis may present with a hepatocellular profile and elevated antinuclear antibody or anti-smooth muscle antibody titers. Minocycline and nitrofurantoin are the most common causes of autoimmune-like hepatitis.

A liver biopsy is rarely necessary but is helpful in cases of uncertainty or suspected drug-induced autoimmune hepatitis. Zone 3 necrosis and eosinophilia are classic histologic findings in DILI, but other findings may include hepatitis, cholestasis, steatosis, or granulomas.

The prognosis for most forms of idiosyncratic DILI is good after removal of the drug and supportive care. However, the mortality rate is as high as 10% when jaundice develops; such patients should be referred to a hepatologist.

Patients with suspected acetaminophen-related DILI should have acetaminophen serum concentrations measured at 4 and 16 hours after ingestion. Patients with levels above 150 µg/mL (at 4 hours after ingestion) or 18.8 µg/mL (at 16 hours after ingestion) should be treated with N-acetylcysteine (NAC)

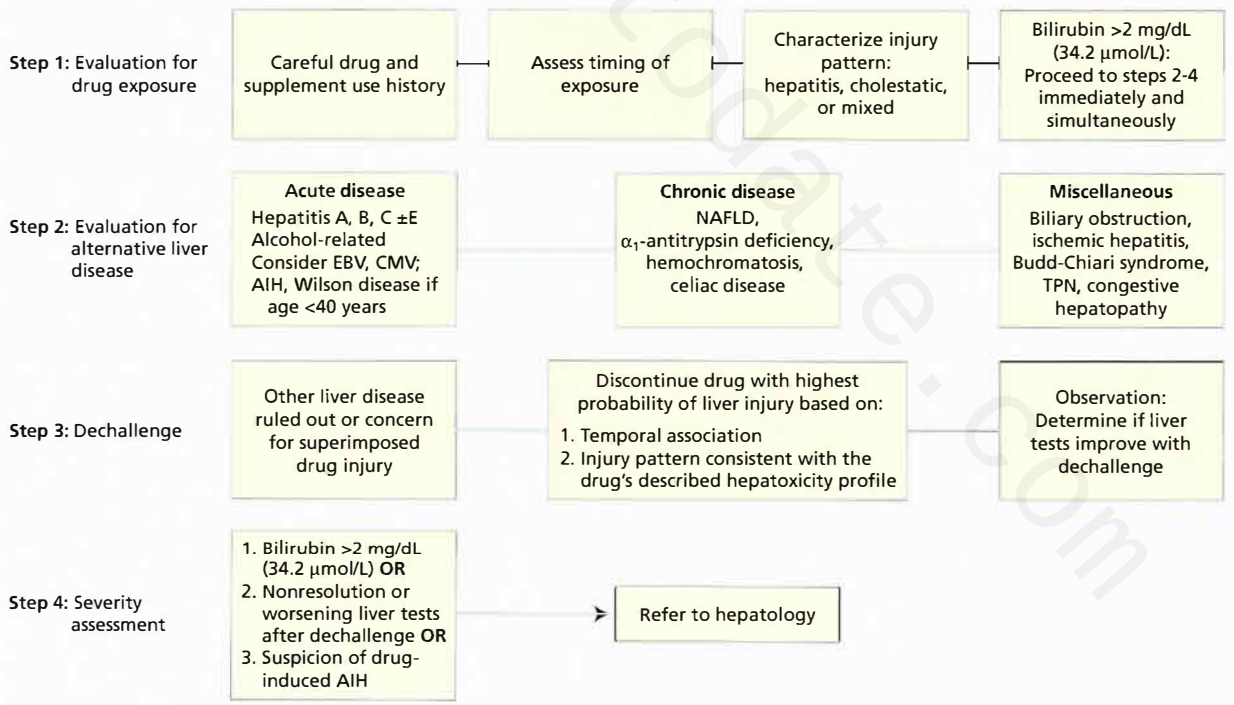

FIGURE 26. Evaluation of potential drug-induced liver injury. AIH = autoimmune hepatitis; CMV = cytomegalovirus; EBV = Epstein-Barr virus; NAFLD = nonalcoholic fatty liver disease; TPN = total parenteral nutrition.

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CONT. (Rumack-Matthews nomogram). This strategy is not effective for determining the need for treatment in at-risk patients (such as those with alcoholism or those who are malnourished) with multiple smaller overdoses. If a patient with presumed or known acetaminophen-related DILI develops HE, jaundice, and coagulopathy, this represents ALF in the absence of known chronic liver disease and should be managed accordingly. See Acute Liver Failure for a discussion of management strategies for ALF secondary to acetaminophen.

KEY POINTS

- Acetaminophen is the most common cause of intrinsic drug-induced liver injury; the most common causes of idiosyncratic drug-induced liver injury are antimicrobial agents (particularly amoxicillin-clavulanate), antiepileptic drugs (phenytoin, valproate), antituberculosis drugs (isoniazid, rifampin), NSAIDs, and azathioprine.
- The prognosis for most forms of idiosyncratic drug-induced liver injury is good after removal of the drug and supportive care.

Acute Liver Failure

Acute liver failure (ALF) is defined by the onset of HE, jaundice, and coagulopathy (INR ≥1.5) in patients without a history of chronic liver disease. Liver injury is distinct from ALF and presents with elevated liver test results and/or jaundice in the absence of evidence of liver function failure. The most common cause of ALF in the United States is acetaminophen overdose, followed by indeterminate causes, idiosyncratic DILI, and HBV infection.

A diagnosis of ALF necessitates immediate contact with a liver transplant center, regardless of the cause. Transfer is optimal early in the process when the patient has low-grade HE and can be safely transported.

Patients with ALF require frequent monitoring for hypoglycemia, hypophosphatemia, acute kidney injury, infections, and progressive HE, which can be accompanied by cerebral edema and intracranial hypertension. Patients with grade II HE (**Table 31**) should receive management in the ICU. Many patients with grade III HE and all with grade IV HE require endotracheal intubation and mechanical ventilation. The risk of cerebral edema and intracranial hypertension increases as HE worsens. Intracranial hypertension may manifest as cranial nerve palsies, papilledema, and Cushing triad, which consists of systemic hypertension, bradycardia, and irregular respiration. The initial treatment of intracranial hypertension is with mannitol, followed by hyperventilation.

Specific treatments for ALF include oral antiviral agents for HBV, penicillin G or silymarin for *Amanita* mushroom poisoning, intravenous acyclovir for herpes simplex hepatitis, and urgent delivery of the fetus in acute fatty liver of pregnancy. Other general measures include maintenance of euvolemia, close monitoring for infection, nutritional support, and peptic ulcer disease prophylaxis. In patients requiring renal replacement therapy, continuous venovenous hemofiltration is usually better tolerated than intermittent hemodialysis.

TABLE 31. Hepatic Encephalopathy Classification

Grade	Intellectual Function	Neuromuscular Abnormality
0	Normal	Normal
Minimal	Normal examination; subtle changes in driving/work	Minor abnormalities on psychometric tests
I	Personality changes, attention deficits, irritability, depressed state	Tremor and incoordination
II	Sleep-wake cycle alterations, behavioral changes, cognitive dysfunction, fatigue	Asterixis, ataxia, slow speech
III	Altered level of consciousness (somnolence), confusion, disorientation, and amnesia	Muscular rigidity, nystagmus, clonus, plantar extensor response, hyporeflexia
IV	Stupor and coma	Unresponsiveness to noxious stimuli

Adapted from Nevah MI, Fallon MB. Hepatic Encephalopathy, Hepatorenal Syndrome, Hepatopulmonary Syndrome, and Systemic Complications of Liver Disease. In: Sleisenger and Fordtran's Gastrointestinal and Liver Diseases. 9th Ed. Philadelphia, PA: Saunders; 2010. Copyright Elsevier 2010.

Patients with ALF secondary to acetaminophen toxicity typically present with aminotransferase levels in the thousands after ingestion of greater than 10 g in 24 hours. If the ingestion of acetaminophen occurred within 3 to 4 hours of presentation, activated charcoal can be administered. NAC should be given as soon as possible and is probably effective even up to 48 hours after acetaminophen ingestion. The interval from ingestion to administration of NAC is very important; mortality rates were 0.4%, 6%, 13%, and 19% when the time interval was less than 12 hours, greater than 12 hours, greater than 24 hours, and greater than 48 hours, respectively. Even in patients with non-acetaminophen-related ALF with grades I to II HE, NAC has been shown in a randomized controlled trial to improve transplant-free survival.

KEY POINTS

- The most common cause of acute liver failure in the United States is acetaminophen overdose.
- A diagnosis of acute liver failure necessitates immediate contact with a liver transplant center.

Autoimmune Hepatitis

Autoimmune hepatitis is a chronic inflammatory liver disease that is usually seen in women (female to male ratio is 4 to 1) and can be associated with other autoimmune diseases (most commonly autoimmune thyroiditis, synovitis, or ulcerative colitis) in 38% of patients. The disease presentation

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ranges from asymptomatic to ALF. Serum aminotransferase levels are elevated and range from mild elevations to greater than 1000 U/L. Serum IgG levels are also elevated. The ALP is normal to mildly elevated but may be more than two to three times the upper limit of normal in overlap syndromes with primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). There is no single test to diagnose autoimmune hepatitis; rather, diagnosis requires a constellation of clinical, biochemical, serologic, and histologic findings. Viral hepatitis, Wilson disease (especially in young adults), and alcohol- and/or drug-induced liver injury must be ruled out. Anti–smooth muscle or antinuclear antibodies are typically present; higher antibody titers strengthen the diagnosis. Liver biopsy is usually necessary to confirm the diagnosis. Classic histologic findings are interface hepatitis and lymphoplasmacytic infiltrates.

Absolute indications for treatment are: (1) an AST level greater than 10 times the upper limit of normal, (2) an AST level greater than five times the upper limit of normal with an IgG level greater than two times the upper limit of normal, or (3) bridging necrosis on liver biopsy. Treatment with glucocorticoids and azathioprine normalizes the ALT and IgG levels in most patients and should be continued for at least 24 months. Relapse occurs after stopping treatment in most patients, underscoring the need for long-term ALT/AST surveillance. The decision to stop treatment for autoimmune hepatitis should be made in conjunction with a hepatologist.

Metabolic Liver Disease

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of abnormal liver test results in the United States. Approximately 30% of individuals in the U.S. have NAFLD, some of whom have normal liver enzyme levels. Most patients with NAFLD have insulin resistance–associated obesity, hypertriglyceridemia, and/or type 2 diabetes mellitus. Approximately 20% of patients with NAFLD have nonalcoholic steatohepatitis (NASH), which is characterized by hepatic steatosis accompanied by inflammation and often fibrosis. Of patients with NASH, approximately 10% have progression to advanced fibrosis. Markers for a higher risk of advanced fibrosis include age older than 50 years, BMI greater than 28, serum triglyceride level greater than 150 mg/dL (1.7 mmol/L), and an ALT level greater than twice the upper limit of normal. Low platelet count and an AST to ALT ratio greater than 1 are clues to the presence of advanced fibrosis. Many cases of "cryptogenic" cirrhosis are likely due to NAFLD, as steatosis may regress as cirrhosis progresses. Although the risk of death from liver disease in patients with NASH is increased compared with patients without NAFLD, the more common causes of death are not liver related. The presence of NAFLD may be an independent predictor of cardiovascular disease.

Although NASH requires a liver biopsy for accurate diagnosis, a presumptive diagnosis can be made in a patient with mild abnormalities of aminotransferase levels, risk factors for NAFLD (such as diabetes, obesity, and hyperlipidemia), and imaging features consistent with hepatic steatosis. Because other liver diseases may also result in hepatic steatosis, patients with elevated liver chemistry studies suspected to have NASH should be evaluated to exclude other causes of chronic liver disease.

Treatment for NAFLD generally consists of controlling risk factors for insulin resistance. Loss of 5% of body weight improves steatosis. One randomized controlled trial showed that vitamin E results in biochemical and histologic improvement in patients without diabetes who have NASH; however, this therapy has not yet been widely accepted. Weight loss after bariatric surgery improves the histologic features of NAFLD and can also be considered if portal hypertension is not present. Statins are not contraindicated in patients with NASH.

Patients with advanced liver disease or HCC due to NAFLD represent an increasing percentage of all liver transplant recipients. NASH commonly recurs after transplantation but rarely causes significant graft dysfunction.

KEY POINTS

- Nonalcoholic fatty liver disease is the most common cause of abnormal liver test results in the United States.
- Treatment for nonalcoholic fatty liver disease generally consists of controlling risk factors for insulin resistance.

Hereditary Hemochromatosis

Hereditary hemochromatosis is often diagnosed based on abnormal iron test results detected during a presymptomatic phase. Hemochromatosis may be discovered during an evaluation for chronic liver disease. Although the serum ferritin level is often elevated in patients with acute liver disease, hemochromatosis is not a cause of acute liver disease. Patients with cirrhosis due to hereditary hemochromatosis are at increased risk for HCC.

The most appropriate initial test for hemochromatosis is a fasting serum transferrin saturation level. Ferritin is not typically used as an initial study because it is nonspecific for hereditary hemochromatosis as a cause of liver disease; it is most effective as a follow-up study for those with an elevated transferrin saturation level. Ferritin is elevated in patients with organ iron overload but can be normal in patients with early disease. Abnormal iron test results can also result from liver disease of any cause, particularly NAFLD and HCV. Patients who require multiple transfusions or have long-standing ineffective erythropoiesis can also have secondary iron overload and can develop symptoms compatible with tissue iron overload. Advanced liver disease of any cause commonly leads to an elevated serum ferritin level, but the iron saturation is usually normal.

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A definitive diagnosis of hereditary hemochromatosis is established on the basis of homozygosity for the *C282Y* polymorphism of the *HFE* gene. A liver biopsy is only rarely required to make the diagnosis. Biopsy to assess for cirrhosis is recommended (unless cirrhosis is clinically apparent) for a patient with hemochromatosis and a serum ferritin level greater than 1000 ng/mL (1000 µg/L).

Hemochromatosis is discussed further in MKSAP 17 Hematology and Oncology.

KEY POINTS

- The most appropriate initial test for hereditary hemochromatosis is a fasting serum transferrin saturation level.
- A definitive diagnosis of hereditary hemochromatosis is established on the basis of homozygosity for the *C282Y* polymorphism of the *HFE* gene.

α_1-Antitrypsin Deficiency

Patients with α_1-antitrypsin deficiency can present with lung disease and liver disease. The spectrum of liver diseases includes neonatal hepatitis, hepatomegaly with elevated aminotransferase levels, cirrhosis, and HCC. Patients with two copies of the Z allele (ZZ), which produces a deficient amount of α_1-antitrypsin, are at highest risk for developing liver disease. Patients who have a deficient allele in combination with a normal α_1-antitrypsin allele (MZ) also have an increased risk of liver disease, but usually there is another contributor such as viral hepatitis or NAFLD. Infusions of α_1-antitrypsin do not help the liver disease associated with α_1-antitrypsin deficiency because the liver disease is related to hepatic accumulation of the abnormal protein and not the loss of protease activity that contributes to lung disease. Liver transplantation is the definitive treatment for the liver consequence of the metabolic defect.

Wilson Disease

Wilson disease is a rare congenital disorder of copper excretion that affects approximately 1 in 30,000 live births. Young patients with Wilson disease tend to present with ALF; older patients present with chronic liver disease and/or neurologic manifestations. Wilson disease should be considered in all patients younger than 40 years of age who have unexplained liver disease. When Wilson disease causes an acute hepatitis, usually in young patients, the sudden release of copper from liver cells can also induce hemolytic anemia. Kayser-Fleischer rings are most common in patients with neurologic manifestations and are usually only visualized with slit-lamp examination. Biochemically, Wilson disease is generally characterized by a low or low-normal serum ALP level, relatively modest increases of aminotransferase levels, low or low-normal ceruloplasmin level, and urine copper level greater than 250 µg/24 h (3.9 µmol/d) (normal range, 15-60 µg/24 h [0.2-0.9 µmol/d]). Molecular genetic studies that test for mutations in the *ATP7B* gene can be helpful when the diagnosis is uncertain.

Treatment consists of trientine or penicillamine. Trientine is generally preferred because of the side effects associated with penicillamine. Zinc is also beneficial because it decreases intestinal absorption of copper, but it should not be used alone until copper has been depleted with a chelating agent.

Cholestatic Liver Diseases

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is a slowly progressive disorder that involves the immune-mediated destruction of the small intralobular bile ducts; it is more common in women than in men. Symptoms are generally more common in patients with advanced fibrosis and include fatigue, pruritus, jaundice, and/or complications of portal hypertension. Patients may have features of hyperpigmentation, xanthelasma, xanthomas, or hepatomegaly on physical examination.

The diagnosis of PBC is generally made on the basis of a cholestatic liver enzyme profile in the setting of a positive antimitochondrial antibody test. The predominant liver enzyme abnormality is an increase in serum ALP levels, but a mild to moderate increase in aminotransferase levels is also seen. Ten percent of patients with PBC have a negative antimitochondrial antibody test and require liver biopsy for diagnosis. Histologic changes of PBC include granulomatous inflammation centered on the septal bile duct.

Treatment of pruritus associated with PBC and other liver diseases is challenging. Antihistamines such as hydroxyzine can be helpful for sedation in patients who have itching that is most troublesome at night. Cholestyramine, rifampin, naltrexone, and sertraline may also be beneficial, but responses are widely variable. Patients with PBC should be assessed for consequences of long-term decreased bile acid secretion, including fat-soluble vitamin deficiencies and metabolic bone disease, with appropriate treatment as indicated.

Ursodiol slows disease progression and may prevent or delay advanced disease and the need for liver transplantation. Forty percent to 50% of patients with PBC treated with ursodiol continue to have a serum ALP level greater than 1.5 times the upper limit of normal and have a worse outcome than those with treatment response. Nonresponse is more common in younger patients with PBC. Outcomes with liver transplantation for PBC are excellent. Disease recurrence after transplantation occurs in 20% of patients but only rarely causes graft failure.

KEY POINTS

- Symptoms of primary biliary cirrhosis are generally more common in patients with advanced fibrosis and include fatigue, pruritus, jaundice, and/or complications of portal hypertension.
- Ursodiol slows disease progression of primary biliary cirrhosis and may prevent or delay advanced disease and the need for liver transplantation.

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Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a fibroinflammatory disorder of the bile ducts. Most patients have large-duct changes that can be identified on MRCP or endoscopic retrograde cholangiopancreatography (ERCP). Eighty percent of patients with PSC have inflammatory bowel disease, usually ulcerative colitis; however, only 4% of patients with ulcerative colitis have PSC. In patients with ulcerative colitis, the pattern of disease most highly associated with PSC is right-sided colon involvement, rectal sparing, backwash ileitis, and a quiescent clinical course. These patients also have a greater risk of colon cancer and greater risk of pouchitis after colectomy with an ileal pouch–anal anastomosis than other patients with ulcerative colitis. The risk of colon cancer in patients with PSC and inflammatory bowel disease is high enough that surveillance is recommended, regardless of duration or extent of disease.

Most patients with PSC are asymptomatic and present with a cholestatic liver enzyme profile. Diagnosis is usually established with a characteristic cholangiogram on MRCP (**Figure 27**). Patients without large-duct disease require liver biopsy for diagnosis.

There is no effective medical therapy for PSC. Endoscopic dilatation of biliary strictures and removal of stones may be necessary in patients with progressive cholestasis or symptoms of cholangitis. PSC is generally a progressive disease that often requires liver transplantation. Cholangiocarcinoma is a complication that occurs in approximately 10% of patients with PSC. Up to half of patients are diagnosed with cholangiocarcinoma within 2 years of the diagnosis of PSC. For patients with PSC, surveillance for cholangiocarcinoma is recommended by some experts using liver chemistry studies, CA 19-9 measurement, and an imaging study at 12-month intervals. A subspecialty guideline recommends an annual ultrasound of the gallbladder to screen for gallbladder cancer. Liver transplantation is effective for patients with PSC and for highly selected patients with cholangiocarcinoma.

KEY POINTS

- Eighty percent of patients with primary sclerosing cholangitis have inflammatory bowel disease, usually ulcerative colitis; however, only 4% of patients with ulcerative colitis have primary sclerosing cholangitis.
- Cholangiocarcinoma is a complication that occurs in approximately 10% of patients with primary sclerosing cholangitis.

Determining Prognosis

The Model for End-Stage Liver Disease (MELD) score predicts short-term prognosis for cirrhosis. The MELD score is used to prioritize the allocation of deceased-donor livers for transplantation. It has also demonstrated usefulness in prognosticating survival in patients with acute alcoholic hepatitis and ALF, as well as in those with cirrhosis who are undergoing surgery. A MELD score calculator and a guide to using the score for specific clinical indications may be found at www.mayoclinic.org/meld/.

The Child-Turcotte-Pugh (CTP) score is another model commonly used to classify cirrhosis (**Table 32**). The 1- and 2-year survival rates for patients with CTP class A, B, and C cirrhosis are 100% and 85%, 80% and 60%, and 45% and 35%, respectively.

Complications of Advanced Liver Disease

Chronic liver disease from a variety of causes may ultimately progress to cirrhosis if left undiagnosed or untreated. Patients

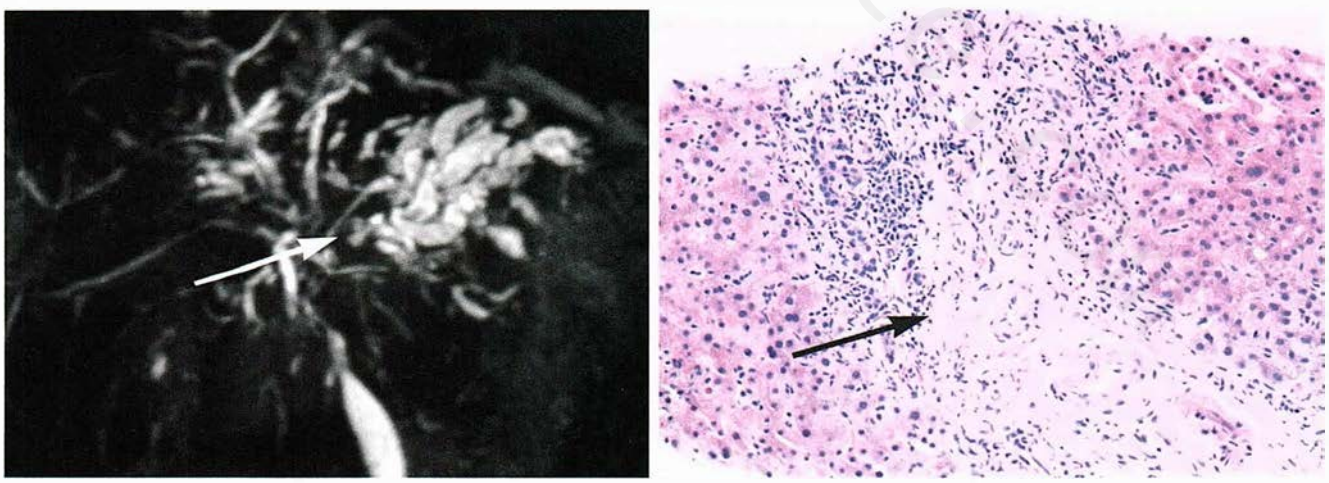

FIGURE 27. Magnetic resonance cholangiopancreatography (*left panel*) revealing upstream intrahepatic bile duct dilatation involving the left hepatic lobe (*arrow*) with stricturing of the left hepatic duct. Liver histology (*right panel*) demonstrates portal tract expansion, edema, and ductular proliferation with lymphocytic cholangitis (*arrow*) consistent with primary sclerosing cholangitis.

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TABLE 32. Child-Turcotte-Pugh Score[a]

	1 Point	2 Points	3 Points
Encephalopathy	None	Grade I-II	Grade III-IV
Ascites	None	Mild/moderate	Severe
Bilirubin	<2 mg/dL (34.2 µmol/L)	2-3 mg/dL (34.2-51.3 µmol/L)	>3 mg/dL (51.3 µmol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8-3.5 g/dL (28-35 g/L)	<2.8 g/dL (28 g/L)
Prothrombin time/INR	<4 s/<1.7	4-6 s/1.7-2.3	>6 s/>2.3

[a]5-6 points = Child-Turcotte-Pugh class A; 7-9 points = Child-Turcotte-Pugh class B; 10-15 points = Child-Turcotte-Pugh class C.

CONT. with cirrhosis but no complications are referred to as having compensated cirrhosis; they may be asymptomatic or may have nonspecific symptoms such as fatigue, poor sleep, muscle cramps, feeling cold, or itching. Patients with complications of cirrhosis (HE, variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, jaundice, or HCC) are referred to as having decompensated cirrhosis. Portal hypertension is responsible for the majority of these complications, which are a major cause of mortality. Portal hypertension also causes splenomegaly and hypersplenism with resultant consumption of platelets, which may also be accompanied by consumption of leukocytes and erythrocytes. Loss of hepatic synthetic function leads to coagulopathy and hypoalbuminemia, as the liver manufactures the majority of clotting factors and albumin.

For a discussion of HCC, see Hepatic Tumors, Cysts, and Abscesses.

Portal Hypertension

Portal hypertension can be divided into prehepatic, intrahepatic, and posthepatic causes. The most common cause of portal hypertension is cirrhosis, an intrahepatic form. Examples of pre- and posthepatic portal hypertension are portal vein thrombosis and Budd-Chiari syndrome, respectively.

Portal hypertension develops in cirrhosis owing to mechanical factors of fibrosis and regenerative liver nodules as well as increased intrahepatic vascular resistance and increased portal inflow. The high pressure in the portal vein is decompressed through collateral portosystemic shunts that occur predictably in the mucosa of the distal esophagus and proximal stomach.

Esophageal Varices

The prevalence of esophageal varices is 85% in patients with CTP class C (decompensated) cirrhosis and 40% in those with CTP class A cirrhosis. Risk factors for variceal hemorrhage are CTP class B and C cirrhosis, large varices (>5 mm), and the endoscopic finding of red markings on varices. Approximately 15% to 20% of patients die within 6 weeks of hemorrhage.

All patients with cirrhosis should undergo screening for esophageal varices with upper endoscopy. The CTP class, variceal size, and variceal appearance on endoscopy are the features that determine the need for primary prophylaxis with nonselective β-blockers (for example, nadolol, propranolol) or esophageal variceal band ligation. **Figure 28** shows a management and surveillance algorithm for patients with nonbleeding esophageal varices. Patients who receive nonselective β-blockers for primary prophylaxis do not require further upper endoscopy unless bleeding occurs. Band ligation requires indefinite endoscopic surveillance, which should be repeated every 2 to 4 weeks until varices are obliterated, then at 3 months, and every 6 to 12 months thereafter to assess for variceal recurrence. If no varices are seen on initial endoscopy, then endoscopy should be performed 3 years later, or sooner if hepatic decompensation develops.

Management of esophageal variceal bleeding includes placement of two large-bore intravenous lines, fluid resuscitation, and erythrocyte transfusion to a goal hemoglobin level of 7 g/dL (70 g/L). More liberal blood transfusion thresholds lead to increased portal pressures and risk of further bleeding. No data exist to guide specific thresholds at which fresh frozen plasma or platelets should be transfused. Up to 50% of patients with cirrhosis and gastrointestinal bleeding develop infections within 1 week, and prophylactic antimicrobial agents improve mortality rates. Oral norfloxacin or intravenous ciprofloxacin is recommended for 7 days. Ceftriaxone is preferred in patients with CTP class B and C cirrhosis, in those already receiving fluoroquinolone prophylaxis, or in geographic areas with high rates of fluoroquinolone resistance. Antimicrobial prophylaxis should be administered even if ascites is absent because it significantly reduces the risk of other infections, including urinary tract infection, pneumonia, and bacteremia; it also reduces rebleeding rates and mortality rates. A splanchnic vasoconstrictor such as octreotide is recommended for 3 to 5 days. Upper endoscopy with band ligation should be performed within 12 hours followed by addition of a nonselective β-blocker after stabilization. Upper endoscopy should be repeated every 2 to 4 weeks until varices are obliterated, then at 3 months, and every 6 to 12 months thereafter. For the 10% to 20% of patients with uncontrolled bleeding and those with early rebleeding, a transjugular intrahepatic portosystemic shunt (TIPS) should be placed.

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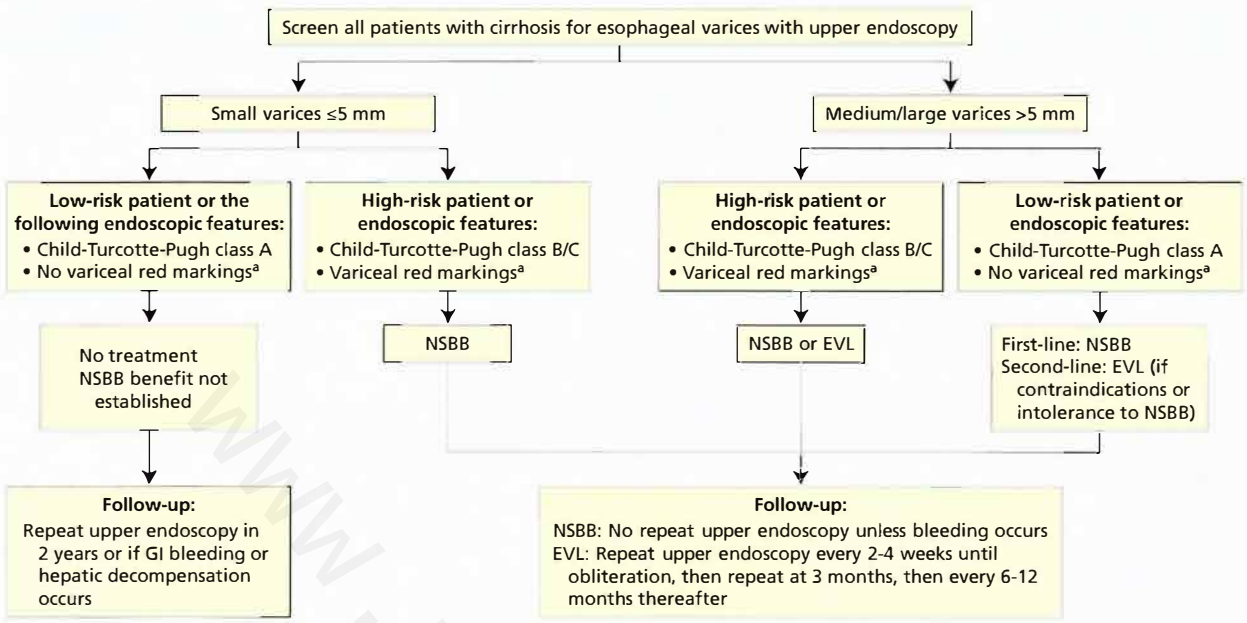

FIGURE 28. Surveillance and management of nonbleeding esophageal varices. A high-risk patient is one with Child-Turcotte-Pugh class B or C cirrhosis, whereas a low-risk patient has Child-Turcotte-Pugh class A cirrhosis. EVL = endoscopic variceal ligation; GI = gastrointestinal; NSBB = nonselective β-blockers.

[a]Variceal red markings are longitudinal red streaks on the surface of esophageal varices.

KEY POINT

HVC
- Management of esophageal variceal bleeding includes placement of two large-bore intravenous lines, fluid resuscitation, and erythrocyte transfusion to a goal hemoglobin level of 7 g/dL (70 g/L); more liberal blood transfusion thresholds lead to increased portal pressuress and risk of further bleeding.

Gastric Varices and Portal Hypertensive Gastropathy

Gastric varices are present in 20% of patients with cirrhosis. Limited data are available on the efficacy of nonselective β-blockers for primary prophylaxis of gastric varices. Hemodynamic resuscitation, antimicrobial agents, and octreotide should be initiated for bleeding gastric varices. Gastric varices that are extensions of esophageal varices into the lesser curvature of the stomach can be treated successfully with band ligation during an acute event. All other types of bleeding gastric varices respond poorly to band ligation, with high rates of rebleeding. Cyanoacrylate (glue) injection is recommended by the major societies for these other types of bleeding gastric varices. However, glue is only available in the United States under exceptional circumstances and is not FDA approved. If glue is not available, band ligation can be attempted despite its shortcomings. A TIPS should be placed for uncontrolled bleeding or rebleeding. Splenectomy is the best treatment for bleeding isolated fundic gastric varices caused by a splenic vein thrombosis in the absence of liver disease.

Portal hypertensive gastropathy (PHG) is a congestive gastropathy that occurs as a result of portal hypertension. It typically manifests as chronic gastrointestinal bleeding and rarely can result in significant acute bleeding. Despite a lack of data on efficacy, most specialists treat chronic gastrointestinal bleeding from PHG with nonselective β-blockers and iron supplementation.

Hepatic Encephalopathy

H

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome that develops in patients with hepatic dysfunction. Symptoms range from barely perceptible cognitive changes to coma. HE is graded 0 to IV according to severity (see Table 31) and can be characterized as episodic, persistent, or minimal. Because it is clinically difficult to distinguish between grade 0 (minimal) and grade I HE, new terminology has been proposed that refers to grade 0 to I as covert HE and grades II through IV as overt HE. Grade II HE is typically associated with disorientation to time and asterixis.

Diagnosis of HE is made based on the history and physical examination. The plasma ammonia level can be helpful in cases of diagnostic uncertainty; however, monitoring serial ammonia values in patients with HE is not useful. Head CT is overutilized and is warranted only in patients with unwitnessed falls or head trauma, or in cases of diagnostic uncertainty. The diagnosis of HE indicates a poor prognosis, and liver transplantation should be considered.

Management of HE depends on its acuity and severity and focuses on treatment of significant (≥grade II, also known as overt) episodes of HE followed by maintenance of remission (secondary prophylaxis). Overt episodic HE of grade II

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CONT. or greater usually requires hospitalization. Up to 80% of patients have a precipitating factor, most commonly infection or gastrointestinal bleeding. Other precipitants include opioids, benzodiazepines, electrolyte abnormalities, hypoglycemia, hypoxia, TIPS placement, inappropriate lactulose dosing, or dehydration. All patients with overt episodic HE should undergo screening for infections, including diagnostic paracentesis when ascites is present. Lactulose is first-line treatment and should be titrated to three stools per day. Rifaximin (off label) or neomycin can be added as adjunctive therapy in patients who do not respond to lactulose. Neomycin carries a risk of ototoxicity and nephrotoxicity. Rifaximin is not FDA approved for overt, episodic HE, but recent data suggest a significant benefit in patients with grades III and IV HE when added to lactulose as compared with lactulose alone. Albumin dialysis is FDA approved for medically refractory, severe HE.

Secondary prophylaxis (maintenance of remission) is warranted in most patients who recover from overt episodic HE. Lactulose is first-line maintenance therapy. Patients should receive instruction on titrating the dose to achieve three stools per day. Taking fixed doses of lactulose without monitoring stool frequency commonly precipitates overt episodes of HE. Discharging patients without secondary prophylaxis or with inadequate instructions for titrating lactulose may result in hospital readmissions. In patients with recurrent overt HE while on lactulose, the addition of rifaximin can prevent further recurrences of overt HE and hospitalizations. Dietary protein restriction is no longer recommended.

The best diagnostic test for covert HE is an active area of investigation. Historically, the diagnosis of minimal HE (now included in the term covert HE) was made by neuropsychometric testing. However, this is not widely available. Empiric treatment with lactulose is reasonable when the diagnosis is suspected, with continuation of the drug if a favorable response occurs and discontinuation if no improvement is observed.

KEY POINTS

HVC
- There is no utility in monitoring serial ammonia values in patients with hepatic encephalopathy; head CT is warranted only in patients with unwitnessed falls or head trauma, or in cases of diagnostic uncertainty.
- Lactulose is first-line treatment of overt episodic hepatic encephalopathy, and it should be titrated to three stools per day.
- In patients with recurrent overt episodes of hepatic encephalopathy while on lactulose, rifaximin should be added, as it has been shown to reduce recurrence and need for hospitalization.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) is defined by hypoxemia and intrapulmonary vascular dilatation in the presence of liver disease with portal hypertension. It is present in 4% to 32% of pretransplant patients with variable severity. Patients with HPS usually have a preexisting diagnosis of liver disease and present with shortness of breath. Classic features are platypnea (worsening shortness of breath in the upright position) and orthodeoxia (worsening arterial oxygen saturation in the upright position). The diagnosis is made by demonstrating an arterial oxygen tension less than 80 mm Hg (10.6 kPa) breathing ambient air, or an alveolar-arterial gradient of 15 mm Hg (2 kPa) or greater, along with evidence of intrapulmonary shunting on echocardiography with agitated saline or macroaggregated albumin study. Clinically significant HPS is treated with supplemental oxygen and liver transplantation.

KEY POINT

- Patients with hepatopulmonary syndrome usually have a preexisting diagnosis of liver disease and present with shortness of breath; classic features are platypnea (worsening shortness of breath in the upright position) and orthodeoxia (worsening arterial oxygen saturation in the upright position).

Portopulmonary Hypertension

Portopulmonary hypertension (PoPH) is pulmonary hypertension in the presence of chronic liver disease with portal hypertension. It is less common than HPS, with a prevalence of 5% to 9% in liver transplant candidates. The typical presentation of PoPH is dyspnea on exertion in a patient with known liver disease. Patients with typical symptoms or those being evaluated for liver transplantation should undergo transthoracic echocardiography. Those with a right ventricular systolic pressure greater than 50 mm Hg on echocardiogram require investigation for causes of pulmonary hypertension, including right heart catheterization.

Patients with moderate PoPH with a mean pulmonary artery pressure greater than 35 mm Hg at the time of diagnosis should be treated with medical therapy, which may include prostacyclin analogues, endothelin antagonists, or phosphodiesterase inhibitors. Those who respond to therapy and have satisfactory right ventricular function can benefit from liver transplantation. Survival at 1 and 3 years after liver transplantation is 83% and 76%, respectively. The effect of liver transplantation on the symptoms of pulmonary hypertension is unpredictable; 40% to 50% of patients may be weaned from medical therapy after transplantation.

KEY POINT

- Portopulmonary hypertension is pulmonary hypertension in the presence of chronic liver disease with portal hypertension.

Ascites

Ascites is the most common complication of cirrhosis and develops in approximately 50% of patients within 10 years. Ultrasound is the most cost-effective study to detect the

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CONT.

presence of ascites. Ultrasound should be followed by diagnostic paracentesis when ascites is present. Ascitic fluid analysis should include measurement of albumin and total protein; cell count and bacterial cultures should be checked when infection is suspected. The serum-ascites albumin gradient (SAAG) should be calculated by subtracting the ascitic fluid albumin level from the serum albumin level. A differential diagnosis can be formulated based on the SAAG and ascites total protein (Table 33).

In patients with ascites associated with cirrhosis, management consists of sodium restriction (<2 g/d) and spironolactone with furosemide. Spironolactone is more effective for mobilization of ascites than furosemide, and the combination allows for effective natriuresis while maintaining potassium homeostasis. Serum creatinine and electrolyte levels should be checked approximately 1 week after initiation of treatment and with dose increases. Patients who cannot tolerate diuretics (such as those with kidney dysfunction or hyponatremia) or in whom diuretics are ineffective can be treated with large-volume paracentesis. If more than 5 L of ascitic fluid is removed, 8 g of 25% albumin should be given for each liter removed; this is done to prevent postparacentesis circulatory dysfunction. A meta-analysis of 1225 patients receiving 25% albumin after large-volume paracentesis reported decreased postparacentesis circulatory dysfunction, hyponatremia, and mortality. All patients should discontinue ACE inhibitors, angiotensin receptor blockers, and NSAIDs, which can exacerbate ascites. Nonselective β-blockers should be used with caution in patients with refractory ascites because there is an association with decreased survival. Midodrine can be used as adjunctive therapy for refractory ascites, especially in patients with hypotension. A TIPS can be considered for patients with refractory ascites in the absence of HE, heart failure, and pulmonary hypertension when the serum bilirubin level is less than 4 mg/dL (68.4 µmol/L) and the MELD score is less than 15 to 18. The presence of ascites should prompt consideration for liver transplantation. H

TABLE 33. Differential Diagnosis of Ascites Based on the Serum-Ascites Albumin Gradient

Total Protein	SAAG	
	≥1.1 g/dL (11 g/L)	<1.1 g/dL (11 g/L)
<2.5 g/dL (25 g/L)	Cirrhosis	Nephrotic syndrome, myxedema
≥2.5 g/dL (25 g/L)	Cardiac ascites, Budd-Chiari syndrome	Infections, malignancy, pancreatic ascites

SAAG = serum-ascites albumin gradient.

Mayo Clinic Gastroenterology and Hepatology Board Review, 4th Edition, edited by Hauser (2011). Adapted Table 28.2 from Chapter "Ascites, Hepatorenal Syndrome and Encephalopathy" by Hay, page 318, by permission of Oxford University Press, USA.

KEY POINTS

- Ascites is the most common complication of cirrhosis and develops in approximately 50% of patients within 10 years.
- Ultrasound is the most cost-effective diagnostic test for ascites. HVC
- Management of ascites consists of sodium restriction (<2 g/d) and spironolactone with furosemide.

Spontaneous Bacterial Peritonitis H

Spontaneous bacterial peritonitis (SBP) is an infection of the ascitic fluid in patients with portal hypertension that carries a 10% to 20% risk of mortality. It can present with abdominal pain, fever, HE, or acute kidney injury. A polymorphonuclear cell count greater than 250/µL in the ascitic fluid is diagnostic of SBP. A polymorphonuclear cell count less than 250/µL with positive ascitic fluid cultures is diagnostic in symptomatic patients.

Treatment of SBP is with intravenous cefotaxime (or a similar third-generation cephalosporin), which covers the most common pathogens (*Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*). Patients who acquire SBP in the hospital or have recent exposure to β-lactams should receive broader-spectrum antimicrobial agents as determined by local microbial and resistance patterns. For culture-positive SBP, antimicrobial agents can be tailored to the susceptibility pattern. Follow-up paracentesis should be performed only in patients with nosocomial SBP, recent β-lactam exposure, infection with an atypical organism, or worsening clinical status. Patients with a serum creatinine level greater than 1 mg/dL (88.4 µmol/L), a serum bilirubin level greater than 4 mg/dL (68.4 µmol/L), or a blood urea nitrogen level greater than 30 mg/dL (10.7 mmol/L) should receive 1.5 g/kg of albumin on the day of the diagnosis of SBP and 1 g/kg of albumin on day 3; this practice has demonstrated a survival benefit.

Patients with SBP should receive indefinite prophylaxis with norfloxacin or ciprofloxacin (preferred), or trimethoprim-sulfamethoxazole. Long-term primary prophylaxis with norfloxacin is beneficial for patients at high risk for SBP. Criteria for patients at high risk for SBP include an ascitic fluid total protein level less than 1.5 g/dL (15 g/L) in conjunction with any of the following: serum sodium level less than or equal to 130 mEq/L (130 mmol/L), serum creatinine level greater than or equal to 1.2 mg/dL (106.1 µmol/L), blood urea nitrogen level greater than or equal to 25 mg/dL (8.9 mmol/L), serum bilirubin level greater than or equal to 3 mg/dL (51.3 µmol/L), or CTP class B or greater cirrhosis. H

KEY POINT

- Spontaneous bacterial peritonitis is an infection of the ascitic fluid in patients with portal hypertension that carries a 10% to 20% risk of mortality.

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Hepatorenal Syndrome

Approximately 20% of hospitalized patients with cirrhosis develop acute kidney injury. Of this group, approximately two thirds have a prerenal cause. Although most of these patients will respond to volume expansion, approximately 30% of this group will have hepatorenal syndrome. Therefore, hepatorenal syndrome accounts for a minority of patients who develop acute kidney injury.

H Hepatorenal syndrome diagnostic criteria consist of (1) an increase in the serum creatinine level to greater than 1.5 mg/dL (132.6 µmol/L) over days to weeks, (2) lack of response to an albumin challenge of 1 g/kg/d for 2 days, and (3) the absence of shock, nephrotoxic drugs, active urine sediment, proteinuria greater than 500 mg/d, and ultrasound evidence of parenchymal kidney disease or obstruction. Type 1 hepatorenal syndrome is more severe, with a doubling of the serum creatinine level in excess of 2.5 mg/dL (221 µmol/L) in less than 2 weeks. Type 2 hepatorenal syndrome is less severe, with a more gradual increase in the creatinine level; it is usually associated with diuretic-refractory ascites.

The creatinine level is one of the most important predictors of death in patients with cirrhosis. An increase in creatinine of 1.5 times baseline or the presence of acute kidney injury should increase suspicion for infections, blood loss, and fluid loss. Diuretics and any potential nephrotoxic agents should be stopped. A fluid challenge with albumin at 1 g/kg of body weight should be given over 24 hours. Patients who do not respond to these strategies and who meet criteria for hepatorenal syndrome should be treated for hepatorenal syndrome.

Patients with type 1 hepatorenal syndrome should be treated with a vasoconstrictor and albumin. Terlipressin has been shown to improve kidney outcomes but is not available in the United States. Therefore, recommendations state that patients in the ICU with type 1 hepatorenal syndrome should be treated with norepinephrine and albumin, whereas patients on the general ward should be treated with midodrine, octreotide, and albumin. Patients with type 1 hepatorenal syndrome who do not respond to medical therapy and are suitable candidates should undergo liver transplantation with or without simultaneous kidney transplantation, depending on the duration of kidney dysfunction. Patients with type 1 hepatorenal syndrome who do not receive therapy usually die within weeks. H

Health Care Maintenance of the Patient with Chronic Liver Disease

Hepatic Osteodystrophy

Hepatic osteodystrophy encompasses osteoporosis, osteopenia, and rarely osteomalacia in the context of liver disease. Diagnostic criteria for these diseases are the same as in the general population. There is a fourfold increase in risk of osteoporosis in patients with PBC. Concomitant inflammatory bowel disease increases the risk of osteoporosis in patients with PSC. Cirrhosis of any cause is a risk factor for osteoporosis, with a prevalence of approximately 25%. Women (especially those who are postmenopausal) are at higher risk than men. Standard evaluation should include measurement of serum calcium, phosphate, and vitamin D levels. Up to two thirds of patients with cirrhosis are deficient in vitamin D. Dual-energy x-ray absorptiometry is recommended for patients with cirrhosis or PBC (even if noncirrhotic) and before liver transplantation. Patients with a previous fragility fracture, postmenopausal women, and those with glucocorticoid use for longer than 3 months should also receive dual-energy x-ray absorptiometry. Osteopenia should be treated according to standard guidelines. Osteoporosis should be managed with a bisphosphonate (after vitamin D repletion), which should be an intravenous formulation in patients with esophageal varices.

KEY POINT

- Dual-energy x-ray absorptiometry is recommended for patients with cirrhosis or primary biliary cirrhosis (even if noncirrhotic) and before liver transplantation.

Immunizations

Patients with cirrhosis who develop an infection have a 30% mortality rate at 1 month, and another 30% die within 12 months; this underscores the importance of prevention of infection. Immunizations lose their effectiveness as the severity of liver disease worsens. Immunizations should ideally be provided before the patient develops cirrhosis. Inactivated vaccines are safe in patients with cirrhosis, whereas attenuated live virus vaccines should be avoided. **Table 34** describes the recommended vaccinations in patients with chronic liver disease and/or cirrhosis. Limited data exist regarding the efficacy and safety of vaccines against tetanus and diphtheria; *Haemophilus influenzae* type b; measles, mumps and rubella; herpes zoster; and human papillomavirus in patients with cirrhosis.

KEY POINT

- Inactivated vaccines are safe in patients with cirrhosis, whereas attenuated live virus vaccines should be avoided.

Avoidances

Oysters and other raw shellfish should be avoided in patients with cirrhosis because there is a risk of potentially lethal infection with *Vibrio vulnificus*. All NSAIDs should be avoided owing to the risk of precipitating acute kidney injury and gastrointestinal bleeding. Occasional doses of acetaminophen are well tolerated in patients with cirrhosis but should never be used with alcohol. Complete cessation of alcohol use is recommended in all forms of chronic liver disease. All supplements should be reviewed with a physician before initiation given the risk of DILI with some agents. Medications with significant risk of hepatoxicity, such as antituberculosis drugs

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TABLE 34. Immunizations in Patients with Cirrhosis

Immunization	Recommendation	Schedule	Notes
Inactivated influenza	Yes	Yearly	Less effective than in healthy individuals; may prevent hepatic decompensation
23-Valent pneumococcal polysaccharide vaccine (PPSV-23)	Yes	Dose 1 given at time of diagnosis if ≥19 years Dose 2 given 5 years later Dose 3 given at age 65 years (if ≥5 years or more since previous vaccination)	Probably less effective than in healthy individuals
13-Valent pneumococcal conjugate vaccine (PCV-13)	No	—	—
Hepatitis A	Yes	Dose 1 given at time zero Dose 2 given at 6-12 months	Lower rates of seroprotection in decompensated cirrhosis
Hepatitis B	Yes	Dose 1 given at time zero Dose 2 given at 1 month Dose 3 given at 6 months	Patients with cirrhosis should receive a double dose (40 μg) with the standard schedule
Herpes zoster	No	—	Limited data for safety and efficacy in cirrhosis

and antiepileptic drugs, should be reviewed by a hepatologist before initiation. Opioid pain medications and anxiolytics should be avoided in patients with cirrhosis, if possible, given the risk of precipitating HE. Patients with cirrhosis and HE are at increased risk for traffic accidents and should be advised not to drive.

Cirrhosis increases the risk of complications and decompensation from surgery. Many patients with CTP class A cirrhosis or a MELD score less than 10 can tolerate low-risk surgeries. Patients with CTP class A and B cirrhosis should be evaluated by a hepatologist before considering surgery. Patients with CTP class C cirrhosis or a MELD score greater than 15 should not undergo elective surgeries.

Nutrition

Patients with cirrhosis are catabolic and may exhibit muscle wasting. Protein consumption is crucial to maintain muscle and should not be reduced. Daily protein intake should be 1.2 g/kg/d in compensated cirrhosis and 1.5 g/kg/d in decompensated cirrhosis. Sodium restriction (<2 g/d) is necessary in patients with fluid retention. Fluid restriction is necessary in those with hypervolemic hyponatremia (serum sodium level of 125 mEq/L [125 mmol/L] or greater). Coffee may be beneficial for liver health, but data are insufficient to make any specific recommendations. Probiotics have demonstrated some efficacy in the management of HE, but further studies are necessary.

KEY POINT

- Patients with cirrhosis are catabolic and may exhibit muscle wasting; protein consumption is crucial to maintain muscle and should not be reduced.

Hepatic Tumors, Cysts, and Abscesses

Most benign liver masses are discovered incidentally on abdominal imaging and only rarely result in symptoms. Lesions that are most likely to result in symptoms include abscesses or lesions larger than 5 cm, especially if subcapsular. The diagnosis of liver lesions can usually be made using imaging, but biopsy is generally safe, even for vascular lesions.

KEY POINT

- Most benign liver masses are discovered incidentally on abdominal imaging and only rarely result in symptoms.

Hepatic Cysts

Hepatic cysts are frequently identified in patients undergoing abdominal imaging and can be multiple. Ultrasound shows an anechoic structure with smooth, thin walls and posterior shadowing. Occasionally, cysts can have thin septations or even exhibit hemorrhage. Nodular wall thickening can suggest a cystic neoplasm. Patients with autosomal dominant polycystic kidney disease may also have multiple liver cysts that can cause symptomatic hepatomegaly. Incidentally discovered cysts require no follow-up. Only large, symptomatic cysts require surgical treatment.

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is a hyperplastic reaction of the liver to long-standing aberrant arterial blood flow that is most likely congenital. On contrast-enhanced imaging, FNH usually demonstrates enhancement on the arterial phase with a central "scar." The central scar may not be identified in small lesions. The main differential diagnosis for FNH is hepatic

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adenoma. FNH rarely causes bleeding, and estrogen does not affect growth. Unless a patient is definitely symptomatic from FNH, further imaging and therapy are not required.

Hepatocellular Adenoma

Hepatocellular adenomas are generally seen in women because they can be dependent on estrogen for growth. They may be also associated with NAFLD. Adenomas may be subclassified depending on β-catenin (a proto-oncogene) nuclear reactivity on histologic specimens. Although malignant transformation of adenomas is unusual, those lesions that exhibit β-catenin nuclear reactivity are more likely to become malignant than those that are β-catenin negative. Adenomas larger than 5 cm have a risk of bleeding that can occasionally cause hemodynamic compromise. Regression of hepatic adenomas may be seen with withdrawal of estrogen therapy. Treatment with surgical resection or radiofrequency ablation is advised for lesions that are larger than 5 cm (or larger than 3 cm when pregnancy is anticipated) or that exhibit β-catenin nuclear reactivity.

Hepatic Hemangioma

Hepatic hemangiomas are identified in 5% of patients undergoing abdominal imaging. Hemangiomas of the liver generally have a characteristic enhancing pattern on contrast-enhanced CT or MRI, with peripheral nodular enhancement filling in toward the center of the lesion on later phases. These lesions are not estrogen dependent and do not have premalignant potential. Only hemangiomas larger than 10 cm cause symptoms and, if so, require surgery.

Hepatic Abscesses

Pyogenic liver abscesses are usually due to peritonitis and biliary tract infections. Most patients present with fever and symptoms owing to the underlying cause of the abscess. Liver abscesses are usually polymicrobial. Image-guided aspiration can be both diagnostic and therapeutic, in combination with antimicrobial agents, for small abscesses. Larger abscesses, especially if solitary, require percutaneous tube drainage in addition to antimicrobial agents. Surgery is only rarely required.

Amebiasis

Hepatic amebic cysts are due to portal vein spread of intestinal infection to the liver. Patients with amebic cysts have either lived in or traveled to endemic areas such as India, Africa, or Central or South America. Typical symptoms are right upper quadrant pain, fever, and sometimes cough. The diagnosis is usually established with compatible imaging and serologic testing. Treatment of the systemic infection with metronidazole or another appropriate agent should be following by a luminal agent such as paromomycin.

Hepatocellular Carcinoma

The incidence of HCC in the United States is increasing; it is currently the ninth most common cancer. The highest incidence occurs in sub-Saharan Africa, China, Taiwan, and Hong Kong. Liver diseases associated with the highest risk of HCC are HBV, HCV, and hemochromatosis. The most important preventive measure for HCC is HBV vaccination. Approximately 80% of HCC occurs in patients with cirrhosis, but it can develop in the absence of cirrhosis in patients with HBV infection. All patients with cirrhosis from any cause should undergo liver ultrasound every 6 months. Serum α-fetoprotein measurement is no longer recommended for HCC surveillance.

Hepatic lesions identified on screening that are smaller than 1 cm on ultrasound warrant a repeat ultrasound in 3 months. For lesions larger than 1 cm, a four-phase CT scan or contrast-enhanced MRI is recommended. A diagnosis of HCC can be made in lesions larger than 1 cm that enhance in the arterial phase and have washout of contrast in the venous phase. The vast majority of patients can be diagnosed by radiology and do not require a biopsy. If the imaging characteristics in a lesion larger than 1 cm are atypical, the alternative imaging modality (MRI or CT) may be used to attempt to confirm a radiologic diagnosis, or a liver biopsy can be performed. A negative liver biopsy can be falsely reassuring, and continued follow-up is recommended.

HCC should be managed according to the Barcelona Classification for Liver Cancer Treatment System (**Figure 29**). Small, singular lesions in patients with cirrhosis but without portal hypertension and hyperbilirubinemia should be managed with surgical resection. Patients with cirrhosis within the Milan criteria (2-3 tumors ≤3 cm or 1 tumor ≤5 cm without vascular invasion or extrahepatic spread) are best treated with liver transplantation. Transarterial chemoembolization should be used in patients with CTP class A and B cirrhosis who have large or multiple lesions confined to the liver without vascular invasion. Radiofrequency ablation is best suited for solitary, 2- to 3-cm lesions in patients with CTP class A and B cirrhosis. Either transarterial chemoembolization or radiofrequency ablation can be used in patients after approval for liver transplantation as a bridge to transplant. Patients with CTP class A and B cirrhosis, good performance status, and evidence of vascular, lymphatic, or extrahepatic spread have a survival benefit from sorafenib. Common side effects of sorafenib are hypertension, gastrointestinal symptoms, and hand-foot (rash) syndrome.

KEY POINTS

- Approximately 80% of hepatocellular carcinoma occurs in patients with cirrhosis, but hepatocellular carcinoma can arise in the absence of cirrhosis in patients with hepatitis B virus infection.
- All patients with cirrhosis should undergo liver ultrasound every 6 months to evaluate for hepatocellular carcinoma.
- The vast majority of hepatocellular carcinoma can be diagnosed by radiology and does not require a biopsy.

HVC

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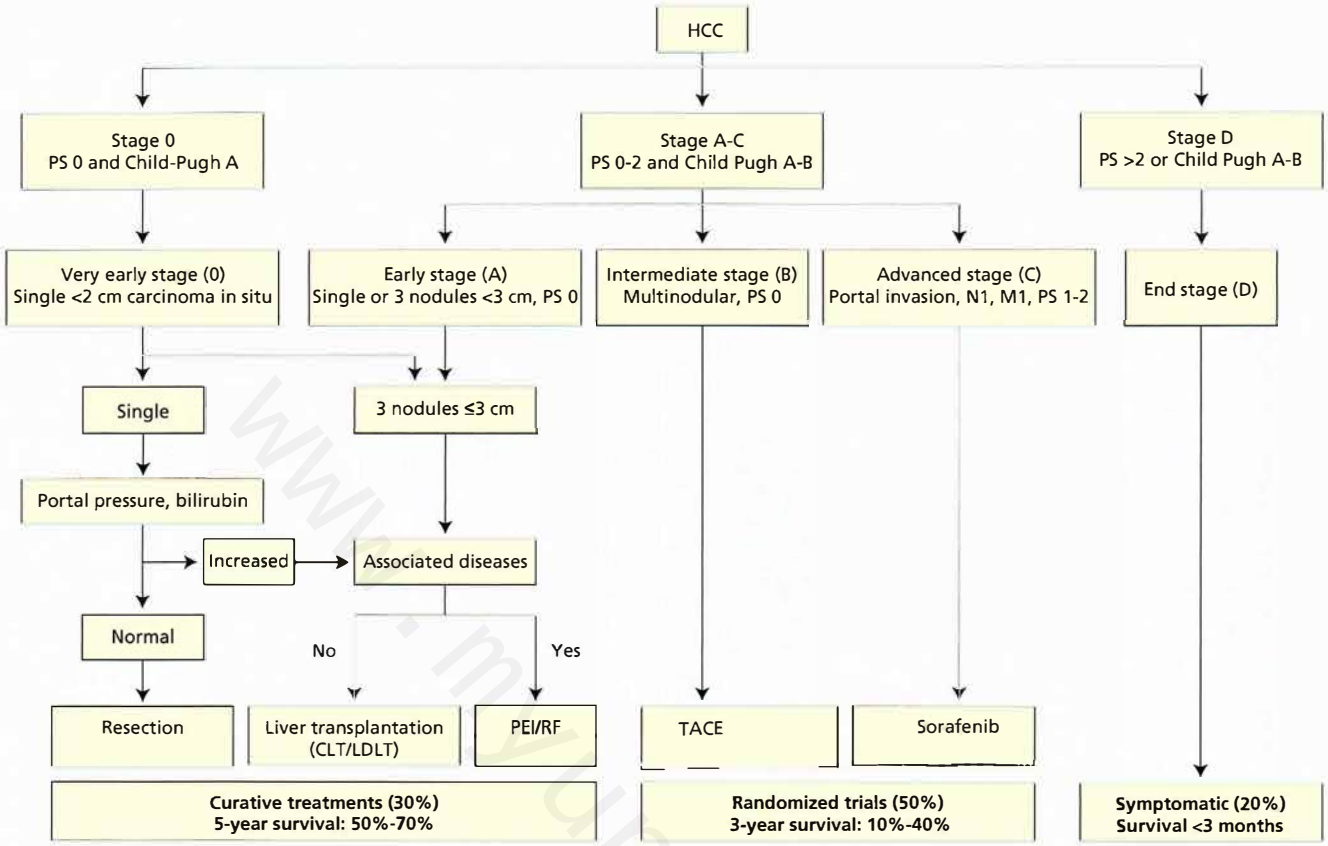

FIGURE 29. Barcelona Classification for Liver Cancer Treatment System. CLT = cadaveric liver transplantation; HCC = hepatocellular carcinoma; LDLT = living donor liver transplantation; PEI = percutaneous ethanol injection; PS = physical status; RF = radiofrequency (ablation); TACE = transarterial chemoembolization.

Llovet JM, Di Bisceglie AM, Bruix J, et al; Panel of Experts in HCC-Design Clinical Trials. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100(10):698-711. [PMID: 18477802], by permission of Oxford University Press.

Liver Transplantation

In the United States, deceased and living-donor liver transplantation are options for selected candidates. Referral to a transplant center is indicated for patients with ALF or for patients with cirrhosis with a MELD score of 15 or greater or decompensation. The MELD score accurately predicts 3-month survival and is the basis for organ allocation. Decompensation is defined by the development of HE, variceal hemorrhage, ascites, hepatorenal syndrome, or HCC.

Contraindications for liver transplantation include severe cardiopulmonary disease, uncontrolled infections, ongoing or recent history of certain extrahepatic malignancies, a severe psychiatric disorder or untreated chemical dependency, inability to comply with medical management, lack of social support, and advanced age.

Liver transplantation provides a survival advantage for patients with MELD scores of 15 or greater. One- and 5-year survival with transplantation is approximately 87% and 73%, respectively.

Most liver transplant recipients receive tacrolimus or cyclosporine, which are metabolized by CYP3A enzymes and pose a risk for drug-drug interactions (**Table 35**). Liver

TABLE 35. Drug Interactions with Calcineurin Inhibitors

Drugs that Increase Levels of CNIs		
Antimicrobials	**Calcium Channel Blockers**	**Others**
Caspofungin	Diltiazem	Danazol
Azoles	Verapamil	Grapefruit juice
Macrolides	Amlodipine (less)	Diazepam, alprazolam
Chloroquine	Felodipine (less)	Allopurinol
Protease inhibitors	Nicardipine	Sertraline
Ofloxacin		
Drugs that Decrease Levels of CNIs		
Antimicrobials	**Anticonvulsants**	**Others**
Rifampin	Carbamazepine	Orlistat
Rifabutin	Phenobarbital	St. John's wort
	Phenytoin	

CNIs = calcineurin inhibitors.

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CONT. transplant recipients are at higher risk of diabetes, hypertension, hyperlipidemia, kidney disease, and malignancy.

KEY POINTS

- Referral to a transplant center is indicated for patients with acute liver failure or for patients with cirrhosis with a Model for End-Stage Liver Disease score of 15 or greater or decompensation.
- Contraindications for liver transplantation include severe cardiopulmonary disease, uncontrolled infections, ongoing or recent history of certain extrahepatic malignancies, a severe psychiatric disorder or untreated chemical dependency, inability to comply with medical management, lack of social support, and advanced age.

Pregnancy-Related Liver Disease

Pregnancy-related liver disease can be divided into acute liver diseases that incidentally occur in a pregnant patient, liver diseases unique to pregnancy, and coincident chronic liver diseases in a pregnant patient.

Patients who are pregnant may acquire viral hepatitis in any trimester. Pregnant patients who acquire HEV have a high risk of ALF. Pregnant patients are also at increased risk for herpes hepatitis and Budd-Chiari syndrome.

The liver diseases associated with pregnancy are shown in **Table 36**. Patients with preeclampsia, HELLP (Hemolysis, Elevated Liver tests, and Low Platelets) syndrome, and acute fatty liver of pregnancy may have continuation or even worsening of their course for up to several days after delivery, so careful monitoring is necessary.

Newborns of mothers who are hepatitis B surface antigen positive should receive hepatitis B immune globulin and HBV vaccine. Patients who are not otherwise candidates for HBV treatment but have levels of HBV DNA greater than 10^8 IU/mL should be offered antiviral therapy with tenofovir during the late second or third trimester to help decrease risk of transmission to the newborn. Pregnant patients with HCV transmit infection to the newborn in less than 5% of cases; however, infants born to HCV-positive mothers should be tested for HCV at age 6 months.

Vascular Diseases of the Liver

Portal Vein Thrombosis

Portal vein thrombosis (PVT) is uncommon in patients with compensated cirrhosis, but it occurs in 8% to 25% of patients with decompensated cirrhosis. The presentation may be asymptomatic or symptomatic with variceal hemorrhage and ascites. Ultrasound with Doppler studies is the most cost-effective diagnostic test. Differentiating acute from chronic PVT is important. Chronic PVT does not require treatment. Patients with acute PVT can be considered for anticoagulation therapy after assessment and prophylaxis for esophageal varices. No formal recommendation for or against anticoagulation in acute PVT in patients with cirrhosis can be made owing to limited data. Patients with extension of PVT into the superior mesenteric vein should receive anticoagulation to prevent intestinal infarction. Evaluation for a hypercoagulable state is generally not recommended or cost effective in patients with cirrhosis. Occasionally, PVT may represent a tumor thrombus, and this should be considered in the setting of a liver mass.

KEY POINT

- Portal vein thrombosis is uncommon in patients with compensated cirrhosis, but it occurs in 8% to 25% of patients with decompensated cirrhosis; evaluation for a hypercoagulable state is not cost effective in patients with cirrhosis.

HVC

TABLE 36. Liver Diseases Unique to Pregnancy

Disease	Trimester	Clinical Features	Laboratory Studies	Bilirubin Level	Management	Recurrence
Hyperemesis gravidarum	First	Severe vomiting	ALT elevated in 50% of patients, may be 20 times ULN	Normal	Hydration	Variable
Intrahepatic cholestasis of pregnancy	Second or third	Pruritus	ALT normal to 10-fold increase, elevated serum bile acids	Usually normal	Ursodiol	45%-70%
Preeclampsia	Third	Hypertension, edema, and proteinuria	Mild increase in ALT	Normal	Delivery	5%-25%
HELLP syndrome	Third	Features of preeclampsia	Hemolysis, elevated ALT, thrombocytopenia	Usually normal	Delivery	5%-25%
Acute fatty liver of pregnancy	Third	Features of preeclampsia, features of liver failure	ALT 200-1000 U/L, hemolysis, low platelets, high ammonia	Normal unless severe	Delivery	20%-70%

ALT = alanine aminotransferase; HELLP = Hemolysis, Elevated Liver tests, Low Platelets; ULN = upper limit of normal.

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Budd-Chiari Syndrome

Budd-Chiari syndrome (BCS) refers to obstruction of the hepatic venous outflow tract by thrombus. The classic presentation is severe right upper quadrant pain, hepatomegaly, ascites, and jaundice, but BCS may present with ALF. Diagnosis can be made by ultrasound with Doppler studies of the hepatic veins and inferior vena cava; CT or MRI should be reserved for patients in whom Doppler studies are negative but suspicion remains high. BCS is associated with an underlying risk factor for thrombosis in more than 85% of patients; assessment for paroxysmal nocturnal hemoglobinuria, myeloproliferative neoplasms, and hypercoagulable disorders is appropriate. Oral contraceptives and pregnancy are also associated with BCS. Management consists of immediate and indefinite anticoagulation unless a contraindication exists. Hepatic vein angioplasty, stenting, or TIPS should be attempted in patients with acute or symptomatic BCS as determined by anatomy and local expertise. Liver transplantation is reserved for patients with ALF or those in whom attempts at hepatic vein decompression have been unsuccessful. Chronic BCS with collateral vein formation and compensated liver function may be managed with anticoagulation alone.

KEY POINTS

- Budd-Chiari syndrome refers to obstruction of the hepatic venous outflow tract by thrombus.
- The classic presentation of Budd-Chiari syndrome is severe right upper quadrant pain, hepatomegaly, ascites, and jaundice, but it may present with acute liver failure.

Disorders of the Gallbladder and Bile Ducts

Asymptomatic Gallstones

Gallstones are classified as cholesterol, pigment, or mixed types. Risk factors for cholesterol or mixed gallstones are female gender, advancing age, and North or South American Indian ethnicity. Risk factors for pigment gallstones include chronic hemolysis (such as occurs in hereditary spherocytosis), cirrhosis, and terminal ileal disease or resection (such as might accompany Crohn disease).

Eighty percent of patients with asymptomatic gallstones remain asymptomatic over a 15-year period, and most serious complications of gallbladder stone disease are preceded by an episode of biliary colic. Therefore, cholecystectomy is not generally advised in asymptomatic patients. Prophylactic cholecystectomy should be performed in asymptomatic patients with gallbladder polyps larger than 1 cm or those with polyps of any size with gallbladder stones or primary sclerosing cholangitis.

KEY POINTS

- Eighty percent of patients with asymptomatic gallstones remain asymptomatic over a 15-year period, and most serious complications of gallbladder stone disease are preceded by an episode of biliary colic.
- Cholecystectomy is not generally advised in asymptomatic patients with gallstones. HVC

Biliary Colic and Acute Cholecystitis

Clinical Manifestations

Biliary colic is the relatively acute onset of fairly severe, steady upper abdominal pain that occurs in the epigastrium or the right upper quadrant. Episodes generally last 15 minutes to several hours and are often accompanied by nausea, possibly with vomiting. Fever, leukocytosis, and elevated liver chemistry studies are only seen in the presence of acute cholecystitis or obstruction of the common bile duct. Fatty food intolerance is a nonspecific symptom that is not usually related to gallbladder disease and therefore does not warrant cholecystectomy.

Patients with acute cholecystitis have more severe and prolonged pain along with abdominal tenderness. In patients with acute cholecystitis, deep palpation of the gallbladder may cause the patient to arrest inspiration owing to contact of the gallbladder wall with the examiner's fingers (Murphy sign). Ninety percent of cases of acute cholecystitis occur in the setting of obstruction of the cystic duct by gallstones.

KEY POINT

- Ninety percent of cases of acute cholecystitis occur in the setting of obstruction of the cystic duct by gallstones.

Diagnosis

Gallbladder stones are generally diagnosed with gallbladder ultrasound. Clues to gallbladder inflammation include a thickened gallbladder wall and the presence of pericholecystic fluid. Air within the gallbladder wall suggests severe inflammation with possible necrosis.

KEY POINT

- Ultrasound is the diagnostic test of choice for gallbladder stones, and findings include a thickened gallbladder wall and the presence of pericholecystic fluid.

Management

Treatment of gallbladder disease is with laparoscopic cholecystectomy. Open cholecystectomy may be necessary for patients with unfavorable anatomy, extensive upper abdominal adhesions, or severe acute inflammation of the gallbladder and surrounding tissues. Patients with acute cholecystitis

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CONT. should be given an intravenous antibiotic such as a β-lactam/β-lactamase inhibitor or a third-generation cephalosporin plus metronidazole. Patients who improve should undergo cholecystectomy during the same hospitalization; urgent cholecystectomy can be considered for patients who do not improve with antibiotics. Percutaneous or endoscopically placed cholecystostomy tubes can be used in patients with acute cholecystitis who are not improving or who are at unacceptably high risk for cholecystectomy. Laparoscopic cholecystectomy can be safely performed during pregnancy, particularly in the second trimester.

KEY POINTS

- Treatment of acute cholecystitis includes intravenous antibiotics and a cholecystectomy during the same hospitalization; urgent cholecystectomy can be considered for patients who do not improve with antibiotics.
- Cholecystostomy tubes can be used in patients with acute cholecystitis who are not improving or who are at unacceptably high risk for cholecystectomy.

Acalculous Cholecystitis

Ill patients (generally those who are hospitalized) can have acute cholecystitis without gallbladder stones. This is known as acalculous cholecystitis and is thought to reflect either bacterial seeding of the gallbladder wall or gallbladder wall ischemia. An elevation of temperature accompanying abdominal pain in a critically ill patient should prompt assessment for cholecystitis. Diagnosis is usually made with ultrasound findings of acute cholecystitis or a radionuclide biliary scan that fails to visualize the gallbladder. Treatment for acute cholecystitis, as described above, is advised; however, these ill patients more often require percutaneous cholecystectomy or endoscopic drainage owing to contraindications to cholecystectomy.

Common Bile Duct Stones and Cholangitis

Common bile duct stones are most often due to the passage of gallbladder stones. Approximately 10% to 20% of patients with gallbladder stones will have a clinical manifestation of a common bile duct stone that could include a transient elevation of serum AST or ALT up to 1000 U/L, cholangitis, or pancreatitis. A small percentage of common bile duct stones develop in patients with biliary strictures (such as those with primary sclerosing cholangitis) or infections and are known as primary duct stones. Common bile duct stones are most reliably diagnosed with magnetic retrograde cholangiopancreatography (MRCP) or endoscopic ultrasound, but they can occasionally be seen on abdominal CT or ultrasound. Management of known common bile duct stones consists of removal, usually with endoscopic retrograde cholangiopancreatography; however, experienced surgeons may be able to remove common bile duct stones at the time of laparoscopic cholecystectomy. Open common bile duct exploration is rarely required.

Patients with common bile duct stones who have cholangitis may have Charcot triad (fever, right upper quadrant pain, and jaundice) or Reynolds pentad (Charcot triad plus hypotension and mental status change). Patients with cholangitis should receive immediate broad-spectrum antimicrobial therapy similar to that for acute cholecystitis and, if not improving rapidly, urgent endoscopic stone removal. Those who improve with antibiotics can undergo elective stone removal.

Biliary stone disease is a common cause of acute pancreatitis. It should be suspected as the cause when gallbladder stones are noted or when there is a transient rise in liver chemistry studies at presentation. Patients with acute pancreatitis presumed to be from gallbladder stones should undergo cholecystectomy.

KEY POINTS

- Common bile duct stones are most reliably diagnosed with magnetic retrograde cholangiopancreatography or endoscopic ultrasound, but they can occasionally be seen on abdominal CT or ultrasound.
- Cholangitis should be treated with immediate broad-spectrum antimicrobial therapy and, if rapid improvement is not seen, urgent endoscopic stone removal with endoscopic retrograde cholangiopancreatography.

Gallbladder Cancer

Gallbladder cancer is the most common biliary cancer in the United States, but it is rare, with less than 5000 cases yearly. Risk factors for gallbladder cancer include cholelithiasis, gallbladder polyps, porcelain gallbladder, anomalous pancreaticobiliary junction, chronic *Salmonella typhi* carriage, and obesity.

Presenting symptoms may include right upper quadrant pain, nausea, vomiting, weight loss, or jaundice for more advanced cancers and biliary colic for early cancers. The diagnosis may be suspected after cross-sectional imaging to evaluate symptoms. Early gallbladder cancer is most commonly diagnosed incidentally on pathology at the time of cholecystectomy performed for biliary colic. Less than 10% of patients with symptoms and less than 20% of patients with incidentally discovered cancer are found to have early-stage tumors. Diagnosis at a late stage contributes to the poor prognosis of gallbladder cancer.

Incidental tumors found to invade the lamina propria (stage T1a) are treated with cholecystectomy, whereas more advanced lesions require repeat surgery for extended cholecystectomy. Surgery is the treatment of choice for resectable cancers identified preoperatively. Unresectable disease without metastasis can be treated with chemotherapy, with or without radiation, or with palliative care.

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Prophylactic cholecystectomy is recommended for patients with an anomalous pancreaticobiliary duct junction, gallbladder polyps 1 cm or larger, gallbladder polyp(s) with concomitant gallstones, or polyps of any size in the setting of primary sclerosing cholangitis. Prophylactic cholecystectomy can also be considered in patients with a porcelain gallbladder or with gallstones larger than 3 cm.

KEY POINTS

- Gallbladder cancer is the most common biliary cancer in the United States, but it is rare, with less than 5000 cases yearly.
- Gallbladder cancer is commonly diagnosed at a late stage, which contributes to its poor prognosis.

Cholangiocarcinoma

Cholangiocarcinoma, or bile duct cancer, is the second most common primary malignancy of the liver after hepatocellular carcinoma. The incidence of cholangiocarcinoma is rising. Established risk factors include primary sclerosing cholangitis, choledochal cysts, the liver flukes *Clonorchis* and *Opisthorchis*, previous exposure to thorium dioxide contrast media, and hepatolithiasis.

Presenting symptoms may include right upper quadrant pain, constitutional symptoms, or jaundice.

Tumors can be broadly classified by their location on the biliary tree. Intrahepatic cholangiocarcinoma typically presents as a mass lesion within the liver, perihilar cholangiocarcinoma arises from the confluence of the right and left hepatic ducts (Klatskin tumor), and distal cholangiocarcinoma arises from the common bile duct, below the cystic duct insertion. Perihilar cholangiocarcinoma is the most common. Intrahepatic tumors are usually asymptomatic until late-stage disease, which may present with right upper quadrant pain, constitutional symptoms, or an elevated serum alkaline phosphatase level. Perihilar and distal tumors commonly present with jaundice and are associated with a mass or dilated bile ducts above the lesion on imaging.

Diagnosis of extrahepatic bile duct cancers usually requires endoscopic retrograde cholangiopancreatography with bile duct brushings or biopsy in combination with MRCP or contrast-enhanced CT. Intrahepatic cholangiocarcinoma can be evaluated with MRCP or contrast-enhanced CT, and the diagnosis can be made with percutaneous biopsy. The serum CA 19-9 level may be elevated in patients with cholangiocarcinoma. However, CA 19-9 may also be elevated in patients with bacterial cholangitis and other malignancies, and it may be negative in some patients. Therefore, its diagnostic role in possible cholangiocarcinoma is supportive only, as it is not able to confirm or exclude the diagnosis.

Surgical resection is the treatment of choice when possible. Distal cholangiocarcinoma has the highest resectability rates. Perihilar and intrahepatic cholangiocarcinoma are less likely to be resectable. Chemotherapy is reserved for patients with nonresectable cholangiocarcinoma. Some patients with hilar and distal cholangiocarcinoma require endoscopic stent placement to decompress the biliary system before chemotherapy can be given. Liver transplantation is an option for nonresectable perihilar cholangiocarcinoma that is 3 cm or smaller without extrahepatic spread. Percutaneous biopsy of perihilar cholangiocarcinoma is an exclusion criterion for liver transplantation owing to the risk of tumor seeding.

KEY POINTS

- Cholangiocarcinoma, or bile duct cancer, is the second most common primary malignancy of the liver after hepatocellular carcinoma.
- Surgical resection, when possible, is the treatment of choice for cholangiocarcinoma.

Gastrointestinal Bleeding

Overview

Gastrointestinal bleeding (GIB) is defined as upper or lower according to whether the bleeding source is proximal or distal to the ligament of Treitz, respectively. Upper GIB is more common.

Upper Gastrointestinal Bleeding

Patients with upper GIB may present with hematemesis (bright-red or "coffee-ground" emesis), melena (black, tarry-appearing stool), or hematochezia (bright red blood per rectum). Hematochezia is typically from a lower GIB source but may also be seen with a briskly bleeding upper source, the latter of which is associated with increased mortality.

KEY POINT

- Patients with upper gastrointestinal bleeding may present with hematemesis (bright-red or "coffee-ground" emesis), melena (black, tarry-appearing stool), or hematochezia (bright red blood per rectum).

Causes

Table 37 summarizes causes of upper GIB. Approximately 80% is due to four causes: peptic ulcer disease, esophagogastric varices, esophagitis, and Mallory-Weiss tear. Bleeding typically stops spontaneously; however, 20% of patients have persistent or recurrent bleeding, which increases mortality. Slow and/or chronic bleeding may be suggested by history and iron deficiency and is typical of erosive disease, tumor, esophageal ulcer, portal hypertensive gastropathy, Cameron lesion (erosions found within 5% of large hiatal hernias), and angiodysplasia.

Table 38 summarizes causes of brisk and/or severe upper GIB that increase mortality. A history of chronic alcohol abuse is a clue to the possibility of variceal bleeding. Although rare, a Dieulafoy lesion is a large, tortuous, submucosal arteriole that erodes and bleeds dramatically; it is most commonly

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TABLE 37. Causes and Prevalence of Upper Gastrointestinal Bleeding

Cause	Prevalence
Peptic ulcer	33.9%
Esophagogastric varices	32.8%
Erosive esophagitis	8.1%
Mallory-Weiss tear	6.4%
Erosion	5.1%
Tumor	5.1%
Esophageal ulcer	2.1%
Portal gastropathy	1.0%
Dieulafoy lesion	0.9%
Cameron lesion	0.7%
Other	2.7%

Adapted by permission from Lippincott Williams & Wilkins: Kim JJ, Sheibani S, Park S, Buxbaum J, Laine L. Causes of Bleeding and Outcomes in Patients Hospitalized With Upper Gastrointestinal Bleeding. J Clin Gastroenterol. 2013 May 16. [PMID: 23685847]

TABLE 38. Causes of Brisk and/or Severe Upper Gastrointestinal Bleeding

Peptic ulcer
Esophagogastric varices
Dieulafoy lesion
Aortoenteric fistula
Hemobilia
Hemosuccus pancreaticus (pseudoaneurysm/aneurysm)
Neoplasm
Esophageal
Gastric
GIST

GIST = gastrointestinal stromal tumor.

CONT. found in the gastric cardia. Hemobilia is usually due to a liver or biliary procedural complication but can also rarely be caused by gallstone complications, tumors, and angiodysplasia. Hemosuccus pancreaticus (blood emerging from the pancreas) is typically associated with pancreatic pseudocysts and pseudoaneurysm; it may also occur as a complication of endoscopic procedures, including sphincterotomy, insertion of pancreatic duct stents, endoscopic cystogastrostomy, and pancreatic fine needle aspiration or biopsy. An aortic aneurysm repair raises concerns for an aortoenteric fistula.

KEY POINT

- Approximately 80% of upper gastrointestinal bleeding is due to four causes: peptic ulcer disease (34%), esophagogastric varices (33%), esophagitis (8%), and Mallory-Weiss tear (6%).

Evaluation

Evaluation of acute GIB involves assessing severity, determining the need for interventions, and differentiating between upper and lower GIB sources. Predictors of severe GIB are hematemesis, comorbidities (such as cirrhosis or malignancy), hemodynamic instability, and a hemoglobin level less than 8 g/dL (80 g/L). Outpatient management is usually appropriate when the following criteria are met: blood urea nitrogen level less than 18.2 mg/dL (6.5 mmol/L), normal hemoglobin level, systolic blood pressure greater than 109 mm Hg, pulse rate less than or equal to 100/min, and absence of melena, syncope, liver disease, and cardiac failure.

The International Consensus Upper Gastrointestinal Bleeding Conference Group, the American College of Gastroenterology Practice Guidelines, and others recommend using risk-stratification tools to guide decisions regarding urgent endoscopy (within 12 hours), hospital admission and nonurgent endoscopy (within 24 hours), and discharge home from the emergency department. Among the tools, the best validated and most useful is the Glasgow-Blatchford score (range 0-23), which is composed of nine variables: blood urea nitrogen (0-6 points), hemoglobin (0-6 points), systolic blood pressure (0-3 points), pulse rate (0-1 point), melena (0-1 point), syncope (0-2 points), hepatic disease (0-2 points), and cardiac failure (0-2 points). The Glasgow-Blatchford score is particularly useful when the score is 0, which is present in up to 22% of patients and has a nearly 100% negative predictive value for severe GIB and the need for hospital-based intervention (defined as treatment with blood transfusion, endoscopic therapy, transcatheter arterial embolization, surgery, and in some studies identification of cancer at upper endoscopy).

By meta-analysis, upper GIB is most reliably predicted by four individual variables: melena, nasogastric lavage with blood or "coffee grounds," blood urea nitrogen to serum creatinine ratio greater than 30, and absence of blood clots in the stool. It is not established whether multiple variables confer an incremental likelihood of upper GIB, but it is likely.

KEY POINT

- Evaluation of acute gastrointestinal bleeding involves assessing severity, determining the need for interventions, and differentiating between upper and lower gastrointestinal bleeding sources.

Management

Upper GIB management involves (1) pre-endoscopic care (resuscitation, hemodynamic monitoring, proton pump inhibitor [PPI] therapy, and attention to coagulopathy); (2) early endoscopic evaluation (with excellent endoscopic vision) and treatment; and (3) postendoscopic care and risk reduction.

Pre-endoscopic Care

Patients should be resuscitated with crystalloids to reach physiologic endpoints (pulse rate <100/min, systolic blood pressure >100 mm Hg, and resolution of orthostasis). Blood transfusion

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CONT.

should be performed for patients with (1) hemodynamic instability and ongoing bleeding or susceptibility to complications from oxygen deprivation (for example, ischemic heart disease) and (2) a hemoglobin level less than 7 g/dL (70 g/L) if hemodynamically stable with no active or massive bleeding; the latter approach imparts a 6-week survival benefit (number needed to treat=25), based on a recent landmark study. Early (pre-endoscopic) PPI therapy does not improve clinical outcomes (bleeding, surgery, mortality) but is safe and reduces the likelihood of detecting ulcers with high-risk stigmata and the need for endoscopic therapy compared with treatment with H_2 blockers or placebo. Coagulopathy (defined as an INR >1.5) should be corrected with fresh frozen plasma rather than vitamin K (which has a delayed full therapeutic effect) in actively bleeding patients who are receiving anticoagulation. It remains uncertain whether uncorrected drug-induced coagulopathy (INR 1.5-2.5) adversely affects endoscopic treatment outcomes (rebleeding, surgery, mortality); consensus recommendations are to not delay endoscopy unless the INR is supratherapeutic (INR >3.0). Octreotide and antibiotics should be administered before endoscopy for suspected variceal bleeding. Nasogastric tube placement is not required for diagnosis, prognosis, visualization, or therapeutic effect. Routine use of prokinetic agents is not recommended except when patients are suspected of having large amounts of blood in the upper gastrointestinal tract; in such cases, erythromycin can be given prior to upper endoscopy.

For a discussion of variceal bleeding, see Disorders of the Liver.

Endoscopic Evaluation and Treatment

Guidelines recommend upper endoscopy within 24 hours of presentation in patients with features of upper GIB. Endoscopy within 12 hours is generally recommended only for those with suspected variceal GIB. **Table 39** summarizes peptic ulcer management based on rebleeding risk.

Low-risk ulcers are clean-based or have a nonprotuberant pigmented spot (**Figure 30**). Oral PPI therapy should be

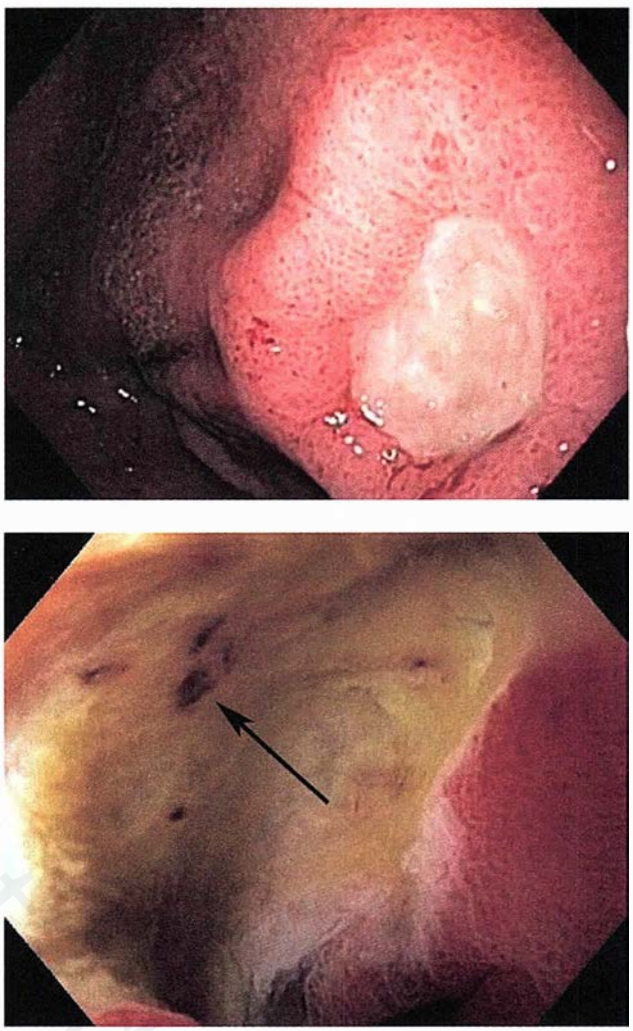

FIGURE 30. Ulcers at low risk for rebleeding; endoscopic therapy is not indicated. *Top panel:* Clean-based gastric ulcer with no blood vessels, pigmented spots/protuberances, or clots noted in the base (Forrest class III). *Bottom panel:* Gastric ulcer with nonprotuberant pigmented spot (*arrow*) in a duodenal ulcer bed (Forrest class IIc).

Courtesy of Louis M. Wong Kee Song M.D., Mayo Clinic.

TABLE 39. Forrest Classification of Peptic Ulcers by Prevalence, Rebleeding Rates, and Treatment

Category	Description	Prevalence	Rebleeding[a]	Endotherapy	PPI Therapy
Ia	Active arterial bleeding	12%	56%	Yes	IV[b]
Ib	Active oozing bleeding	12%	56%	Yes	IV[b]
IIa	Nonbleeding visible vessel	8%	43%	Yes	IV[b]
IIb	Adherent clot	8%	22%	+/–[c]	IV[b]
IIc	Flat pigmented spot	16%	10%	No	Oral
III	Clean ulcer base	55%	5%	No	Oral

IV = intravenous; PPI = proton pump inhibitor.

[a]Rebleeding without endotherapy

[b]IV PPI therapy consists of an intravenous bolus followed by continuous infusion of a high-dose PPI for 72 hours.

[c]Endotherapy of adherent clots is controversial; continuous IV PPI may be sufficient.

Adapted by permission from Macmillan Publishers Ltd: American Journal of Gastroenterology (Laine L, Jensen DM. Management of patients with ulcer bleeding. 107(3):345-60; quiz 361. [PMID: 22310222]), copyright 2012.

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CONT.

initiated, and patients should be allowed to eat. Early hospital discharge should be arranged.

Intermediate-risk ulcers have adherent clots (**Figure 31**). They should be vigorously irrigated to dislodge the clot and guide treatment. With successful dislodgment, ulcers should be treated according to recommendations for low-risk ulcers (see previous paragraph) or high-risk ulcers (see next paragraph). For persistent clots, however, the benefit of mechanically removing the clot is unclear but is possibly greater when patients have risk factors for rebleeding, as defined later. After endoscopy, patients with persistent clots should remain hospitalized and should receive continuous intravenous PPI therapy for 72 hours, as for high-risk ulcers.

High-risk ulcers have active arterial spurting or a nonbleeding visible vessel (**Figure 32**). They should be treated endoscopically with hemoclips, thermal therapy, or injection of sclerosants, which are all equally effective at achieving hemostasis. Local injection of the vasoconstrictor epinephrine may be used adjunctively to aid immediate hemostasis for optimizing visibility for subsequent and more durable endoscopic therapy; however, epinephrine injection alone is inadequate for durable hemostasis.

Following endoscopic therapy, the strongest predictors of recurrent bleeding are hemodynamic instability, active bleeding at endoscopy, ulcer size greater than 2 cm, and ulcer location (posterior duodenal or high lesser gastric curvature). Additional predictors may also include age 60 years or older, comorbid illness, and postendoscopy hemoglobin level less than 10 g/dL (100 g/L).

After endoscopic hemostasis, continuous intravenous PPI infusion for 72 hours reduces recurrent bleeding, need for surgery, and mortality. Hospital stay is generally 3 days after endoscopy, assuming clinical stability.

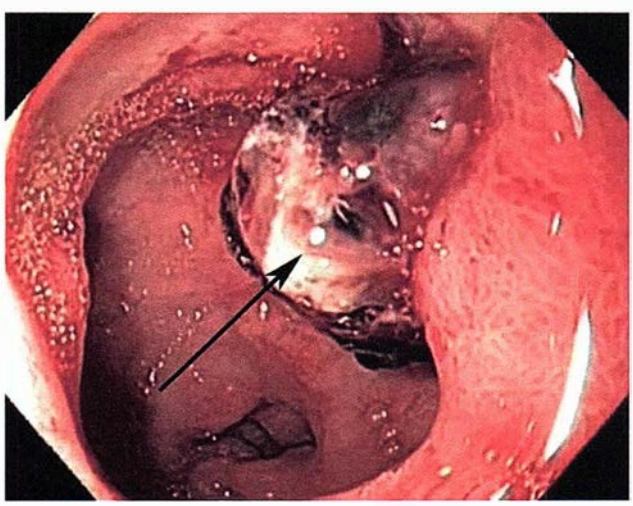
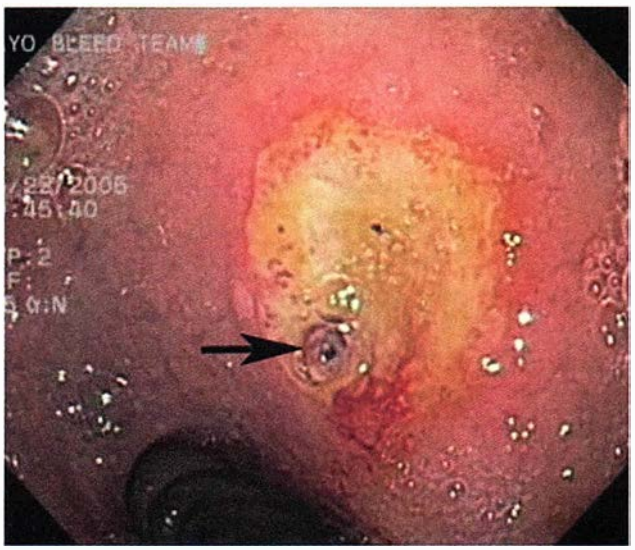


FIGURE 31. Duodenal ulcer with adherent clot (*arrow*) that is at risk for rebleeding (Forrest class IIb). This can be treated medically, or by clot removal and endoscopic therapy in addition to standard medical therapy.

Courtesy of Louis M. Wong Kee Song M.D., Mayo Clinic.



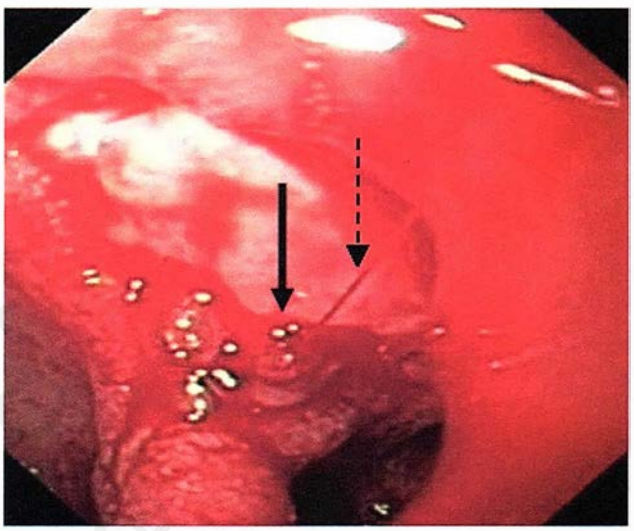


FIGURE 32. Duodenal ulcers at high risk of rebleeding that must be treated endoscopically. *Top panel:* Nonbleeding visible vessel (*arrow*) (Forrest class IIa). *Bottom panel:* Ulcer (*solid arrow*) with active arterial spurting (*dotted arrow*) (Forrest class Ia).

Courtesy of Louis M. Wong Kee Song M.D., Mayo Clinic.

Routine second-look endoscopy in all patients is not recommended, but a second attempt at endoscopic therapy is recommended for rebleeding and when the initial examination was incomplete. Repeat endoscopy can be considered for gastric ulcers after 8 to 12 weeks of PPI therapy if (1) symptoms are persistent despite therapy, (2) ulcers have an endoscopic appearance that is concerning for underlying malignancy, (3) visualization of the stomach was incomplete, or (4) biopsies were not taken at the time of the index upper endoscopy.

Consultation with surgery and interventional radiology (for embolization) may be helpful for patients with severe upper GIB, particularly with active bleeding and hemodynamic instability, and/or when endoscopic therapy fails to achieve hemostasis of a high-risk lesion.

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KEY POINTS

- Guidelines recommend upper endoscopy within 24 hours of presentation in patients with features of upper gastrointestinal bleeding; endoscopy within 12 hours is generally recommended only for patients with suspected variceal bleeding.
- Low-risk ulcers are clean-based or have a nonprotuberant pigmented spot; intermediate-risk ulcers have adherent clots and should be vigorously irrigated to dislodge the clot and reclassified based on appearance; high-risk ulcers have active arterial spurting or a nonbleeding visible vessel and require endoscopic treatment.
- HVC Routine second-look endoscopy is not required after upper gastrointestinal bleeding unless rebleeding occurs or the initial examination was incomplete.

CONT.

Postendoscopic Care and Risk Reduction

All patients with upper GIB due to peptic ulcer disease should be tested for *Helicobacter pylori* (see Disorders of the Stomach and Duodenum) in the acute setting. If testing is positive, treatment should be initiated and eradication should be confirmed. If initial testing for *H. pylori* is negative, patients should undergo retesting with an alternative modality owing to the possibility of false-negative test results in the setting of bleeding, PPI therapy, or concomitant antibiotic therapy.

The choice of whether to discontinue or withhold antiplatelet agents in patients with clear indications for treatment should balance the risk of rebleeding with the risk of thrombosis. Aspirin should be resumed within 3 to 5 days for patients with established cardiovascular disease. Aspirin reduces mortality rates tenfold over 30 days while increasing rebleeding rates only twofold. Patients taking aspirin and clopidogrel for coronary stents should continue aspirin, but clopidogrel should be temporarily withheld for high-risk ulcers. In situations in which dual antiplatelet therapy is indicated (such as following placement of a drug-eluting stent), clopidogrel should be resumed immediately for low-risk ulcers and as soon as possible for high-risk ulcers.

Long-term, daily PPI therapy should be offered to aspirin users who are *H. pylori* negative or those who use concomitant NSAIDs, anticoagulants, glucocorticoids, or other antiplatelet agents. Long-term PPI therapy may not be necessary for aspirin users who undergo *H. pylori* testing and eradication.

Patients with high thrombotic risk should receive reanticoagulation but only after evaluating thromboembolic risk against rebleeding risk. Criteria for high thrombotic risk are chronic atrial fibrillation with a previous embolic event, $CHADS_2$ score of 3 or greater, recent acute coronary syndrome, mechanical heart valve, deep venous thrombosis, pulmonary embolism, or hypercoagulable state. There are limited data for resuming anticoagulation after major GIB, particularly for patients with endoscopically treated high-risk ulcers; however, available data support beginning with (1) a bridging treatment (such as low-molecular-weight or unfractionated heparin) and careful observation or (2) beginning oral anticoagulation 7 days after the bleeding event. The latter approach, according to a retrospective study, reduces mortality and risk of thromboembolism (in patients with atrial fibrillation) without increasing GIB risk compared with withholding anticoagulation for 30 days.

Lower Gastrointestinal Bleeding

Lower gastrointestinal bleeding typically occurs in older individuals and presents as acute bright red blood per rectum or red- or maroon-colored stool (hematochezia). Hemodynamic instability is less common but, if present, raises the possibility of a briskly bleeding upper gastrointestinal source.

Causes

Hematochezia is usually from a colonic source, but in approximately 25% of patients the source is in the upper gastrointestinal tract, the small intestine, or an obscure location. **Table 40** summarizes the most common causes of lower GIB. Almost 80% of lower GIB is due to diverticulosis, colitis, hemorrhoids, and postpolypectomy bleeding. **Table 41** summarizes causes of severe lower GIB.

Diverticula represent herniation of mucosa/submucosa through the muscular layers of the colon, typically at the entry site of vasa recta (small arteries), which are a source for bleeding. Diverticula are most commonly left sided, but colonic diverticular bleeding occurs in either side of the colon. For unclear reasons, individual studies report different anatomic distributions of diverticular bleeding based on the diagnostic method: bleeding is most commonly right-sided

TABLE 40. Causes and Prevalence of Lower Gastrointestinal Bleeding

Cause	Prevalence
Diverticulosis	30%
Colitis	24%
Ischemic	12%
IBD	9%
Radiation	3%
Hemorrhoids	14%
Postpolypectomy	8%
Colon polyps or cancer	6%
Rectal ulcer	6%
Angiodysplasia	3%
Other	6%

IBD = inflammatory bowel disease.

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TABLE 41. Causes of Severe Lower Gastrointestinal Bleeding

Diverticulosis
Aortoenteric fistula
Colonic or rectal varices
Dieulafoy lesions
Neoplasm
Colitis
Ischemic
IBD
Infectious
Intussusception
Meckel diverticulum
Angiodysplasia

IBD = inflammatory bowel disease.

CONT.

when diagnosed by angiography and is most commonly left-sided when diagnosed by colonoscopy.

The presence of abdominal pain raises the possibility of neoplasia or colitis from ischemia (12%), inflammatory bowel disease (9%), radiation (3%), and less commonly infectious gastroenteritis (*Campylobacter*, *Salmonella*, *Clostridium difficile*) or drugs (NSAIDs).

Hemorrhoidal bleeding is typically small volume with bright red blood, but it is occasionally large volume. Postpolypectomy bleeding is typically associated with use of electrocautery methods for polypectomy and may have a delayed presentation. The prevalence of angiodysplasia increases with age and can be overlooked during colonoscopy if bleeding has stopped.

KEY POINT

- Almost 80% of lower gastrointestinal bleeding is due to diverticulosis (30%), colitis (24%), hemorrhoids (14%), and postpolypectomy bleeding (8%).

Evaluation

The initial steps in the evaluation of lower GIB are similar to those for upper GIB. They include assessing bleeding severity, determining the need for hospital-based interventions (defined as treatment with blood transfusion, endoscopic therapy, transcatheter arterial embolization, surgery), and differentiating between upper and lower GIB sources (see Upper Gastrointestinal Bleeding, Evaluation).

Management

Initial management of lower and upper GIB is similar in that it focuses on resuscitation and hemodynamic monitoring (see Upper Gastrointestinal Bleeding, Management). Evidence supporting a specific, initial assessment of lower GIB is limited. According to the 2008 Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/pdf/sign105.pdf), clinicians may consider nonadmission with outpatient follow-up or early hospital discharge when four criteria are present: age less than 60 years, no hemodynamic instability, no evidence of gross rectal bleeding, and identification of an obvious anorectal source of bleeding on rectal examination/sigmoidoscopy. Conversely, hospitalization should be considered in patients with any of five criteria predictive of severe bleeding, including age greater than 60 years, comorbid illnesses (particularly when two or more are present), hemodynamic instability, gross rectal bleeding (or early rebleeding), or exposure to antiplatelet drugs and anticoagulants.

Direct evidence is lacking to define a clear blood transfusion strategy for colonic bleeding. A restrictive blood transfusion strategy (based on a threshold hemoglobin level of 7 g/dL [70 g/L]) imparts a 6-week survival benefit for patients with upper GIB, but the landmark study that resulted in these findings excluded patients with colonic or massive bleeding. According to expert opinion, the blood transfusion threshold for patients with colonic bleeding is a hemoglobin value less than 9 to 10 g/dL (90 to 100 g/L); the higher cutoff should be used when cardiovascular comorbidities (including ischemic heart disease, peripheral vascular surgery, or heart failure) are present.

Lower GIB typically stops within 24 hours. Patients with suspected left-sided bleeding may undergo anoscopy or sigmoidoscopy as an initial evaluation (particularly for colitis, rectal ulcer, and postpolypectomy bleeding from polyps removed from the left colon); anoscopy or sigmoidoscopy can be performed following enemas or in an unprepped colon. Most patients require colonoscopy, however, even if a distal bleeding source is suspected. Colonoscopy identifies a source of bleeding in two thirds of patients.

Colonoscopy performed early is more likely to identify a bleeding source and allow for treatment, which may shorten length of hospitalization; however, the optimal timing of colonoscopy is not established, in part owing to time required for resuscitation and bowel cleansing. According to expert opinion, patients hospitalized for lower GIB should undergo semi-elective inpatient evaluation approximately 24 hours after initial presentation. Early rebleeding is common, however, and should prompt further resuscitation, triage to an appropriate level of care, and more urgent endoscopic evaluation within 12 to 18 hours (after a rapid purge).

Endoscopic treatments for active bleeding are similar to techniques for upper GIB and include multipolar electrocoagulation, hemoclips, and submucosal epinephrine injection. Submucosal epinephrine injection should be combined with thermal or mechanical hemostatic techniques. Data are limited for predicting outcomes based on endoscopic findings; a single center reported that diverticular bleeding associated with major stigmata of hemorrhage (active bleeding, visible vessel, and adherent clot) has a high rate of rebleeding (65%) and emergent surgery (43%) when endoscopic hemostasis is not performed.

For failed endoscopic hemostasis or recurrent bleeding, the next therapeutic step is consultation with interventional radiology for arterial embolization of the bleeding source.

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Major complications include contrast dye reactions, acute kidney injury, transient ischemic attacks, bowel ischemia, hematoma formation, and femoral artery thrombosis. Salvage therapy for recurrent bleeding may require surgery, but this is not frequently necessary because bleeding is typically self-limited and management with endoscopic or angiographic techniques may be effective. Partly because of these factors, overall mortality from colonic bleeding is low (<4%); however, mortality increases in association with age greater than 70 years, two or more comorbidities, and intestinal ischemia.

KEY POINTS

- Lower gastrointestinal bleeding typically stops within 24 hours and can be evaluated semi-electively 24 hours after initial presentation.
- Most patients with suspected lower gastrointestinal bleeding require colonoscopy, even if a distal bleeding source is suspected; colonoscopy identifies a source of bleeding in two thirds of patients.

Obscure Gastrointestinal Bleeding

Obscure gastrointestinal bleeding (OGIB) is gastrointestinal bleeding of an unknown cause. The initial evaluation includes a negative upper endoscopy and colonoscopy. Overt OGIB is defined as bleeding that is visible, such as with melena or hematochezia. Occult OGIB has no signs of gross blood, but unexplained iron deficiency anemia is present. Approximately 5% of gastrointestinal bleeding has an obscure cause occurring somewhere between the papilla and the ileocecal valve (also known as midgastrointestinal bleeding).

KEY POINTS

- Overt obscure gastrointestinal bleeding is defined as bleeding that is visible, such as with melena or hematochezia.
- Occult obscure gastrointestinal bleeding has no signs of gross blood, but unexplained iron deficiency anemia is present.

Causes

Causes of OGIB are described in **Table 42**. Angiodysplasia is the most common cause (**Figure 33**). It is responsible for up to 40% of cases and is often seen in the elderly. Other causes include NSAID enteropathy, inflammatory bowel disease, tumors (leiomyoma, carcinoid, lymphoma, and adenocarcinoma), Meckel diverticulum (typically seen in younger patients) (**Figure 34**),



FIGURE 33. Capsule endoscopy image of angiodysplasia. The lesion (*arrow*) has a fernlike pattern and is red in color. Angiodysplasia can have no bleeding or active bleeding.

Courtesy of David J. Hass, MD.

TABLE 42. Causes of Obscure Gastrointestinal Bleeding

Location	Differential Diagnosis	Patient Age (Years)	Clinical Clues
Proximal to the ligament of Treitz	Cameron erosion	20-60	Large hiatal hernia
	NSAID ulcerations	>20	Medication review
	Dieulafoy lesion	>40	Intermittent large-volume bleeding
	Crohn disease	20-60	Family history, extraintestinal manifestations; may also occur in small bowel and colon
	Gastric antral vascular ectasia	20-60	Female, autoimmune disease
Small bowel	Angiodysplasia	>60	Intermittent, usually occult bleeding; may also occur in colon
	Peutz-Jeghers syndrome	<20	Perioral pigmentation, obstructive symptoms
	Meckel diverticulum	20-60	Possible abdominal pain
	Hemangioma	<20	Possible cutaneous hemangiomas
	Malignancy	>50	Weight loss, abdominal pain
	Hereditary hemorrhagic telangiectasia	>50	Mucocutaneous telangiectasias
Colon	Diverticulosis	>50	Intermittent, painless bleeding
	Malignancy	>50	Weight loss, family history

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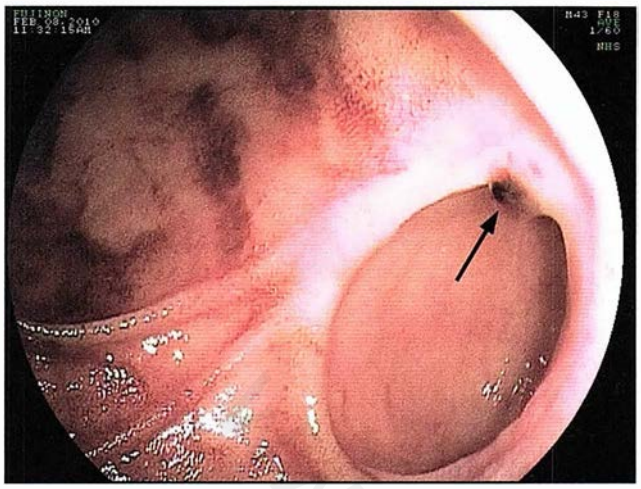

FIGURE 34. Meckel diverticulum diagnosed on balloon-assisted enteroscopy. A diverticulum is seen in the small bowel. At the top of the diverticulum is a visible vessel, which is the raised black spot at the top (*arrow*).

CONT.

radiation enteropathy, Dieulafoy lesion, hemosuccus pancreaticus, and small-bowel varices. Sources found by repeat conventional upper endoscopy and colonoscopy include Cameron ulcerations in a hiatal hernia, bleeding colonic diverticula, and vascular lesions.

KEY POINT

- Angiodysplasia is the most common cause of obscure gastrointestinal bleeding.

Evaluation

A comprehensive history and clinical examination can be useful to narrow the differential diagnosis of OGIB. Patients 50 years of age or younger are more likely to have tumors (leiomyoma, carcinoid, adenocarcinoma, or lymphoma), Dieulafoy lesion, or Crohn disease. However, older patients are more likely to have vascular lesions, such as angiodysplasia. Patients should be asked about NSAID use (NSAIDs induce small-bowel ulcers), aortic aneurysm repair (raises concern for an aortoenteric fistula), necrotizing pancreatitis (causes hemosuccus pancreaticus), or liver damage (trauma, tumor, or recent biopsy causing hemobilia). Physical examination of the skin may identify lesions associated with hereditary hemorrhagic telangiectasia (also known as Osler-Weber-Rendu syndrome) or celiac disease (associated with dermatitis herpetiformis).

Patients thought to have OGIB should be considered for repeat upper endoscopy and/or colonoscopy; studies have shown that lesions can be missed during initial examinations. Up to 50% of lesions can be identified using this strategy.

For patients with obscure active GIB, initial imaging studies may include nuclear studies followed by angiography to localize the bleeding. The next steps in patients with active bleeding are push enteroscopy, balloon-assisted enteroscopy (deep enteroscopy), or surgery and intraoperative enteroscopy as a last diagnostic option.

For patients with occult GIB, a small-bowel evaluation is indicated after endoscopy and colonoscopy are both negative. The next most appropriate test is capsule endoscopy. Other options include push or deep enteroscopy. If these tests are negative, the next step in a patient with continued bleeding is repeated endoscopic examinations (upper endoscopy, colonoscopy, capsule endoscopy, or deep enteroscopy). If the patient is stable, observation with iron replacement is a reasonable approach.

KEY POINT

- Patients thought to have obscure gastrointestinal bleeding should be considered for repeat upper endoscopy and/or colonoscopy; studies have shown that lesions can be missed during initial examinations.

Technetium-Labeled Nuclear Scan

Technetium 99m-labeled red blood cell or sulfur colloid nuclear scans may be useful in evaluating overt OGIB. They are able to detect bleeding rates between 0.1 and 0.4 mL/min, with accuracy varying from 24% to 91%. Nuclear scans can identify only a general area where bleeding is occurring; they cannot offer accuracy or intervention. Follow-up studies after a positive scan can include repeat endoscopy or angiography; both can offer more accurate localization and therapy. Nuclear scans are often done before angiography.

Angiography

Angiography can identify bleeding in overt OGIB if the bleeding rate is greater than 0.5 mL/min. It is more effective at localizing bleeding but is technically less sensitive than a nuclear bleeding scan. The diagnostic yield ranges from 27% to 77% in OGIB. Angiography allows for intervention such as selective mesenteric embolization. Complications include acute kidney injury, organ necrosis, embolism, hematoma, and vascular dissection or aneurysm.

Wireless Capsule Endoscopy

Capsule endoscopy is a wireless capsule camera (**Figure 35**) that is swallowed by the patient to take images of the small



FIGURE 35. Image of an endoscopy capsule.

Courtesy of Dr. Elizabeth Rajan, Mayo Clinic.

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bowel. These images are transmitted to a radiofrequency receiver worn by the patient. Capsule endoscopy allows visualization of the entire small bowel in up to 90% of patients and has a diagnostic yield of 83%. Limitations of capsule endoscopy include inability to perform therapeutic interventions and difficulty localizing lesions. Complications may include capsule retention in the setting of obstruction or strictures. Capsule endoscopy has become the first-line test in evaluating the small bowel after a negative endoscopy and colonoscopy in patients with OGIB. H

KEY POINT

- Capsule endoscopy has become the first-line test in evaluating the small bowel after a negative endoscopy and colonoscopy in patients with obscure gastrointestinal bleeding.

Push Enteroscopy

Push enteroscopy is performed with advancement of the endoscope beyond the ligament of Treitz into the jejunum. Depth of insertion is operator dependent but is also limited owing to looping of the scope in the stomach. The diagnostic yield is between 24% and 56%. Push enteroscopy allows for diagnostic intervention with biopsy and therapeutic intervention with cautery. The most common lesions found are angiodysplasia, which are treated with thermal cautery. This test is done after a negative upper endoscopy and colonoscopy or after a positive capsule endoscopy.

Spiral Enteroscopy

Spiral enteroscopy is performed with deep enteroscopy beyond the ligament of Treitz; it uses a spiral-shaped tube that fits over the endoscope and allows it to be advanced progressively into the small bowel. The technique involves rotary clockwise and counterclockwise maneuvers, similar to the motion of a corkscrew. Depth of insertion has been reported to be up to 260 cm beyond the ligament of Treitz. This modality allows for diagnostic intervention with tissue biopsy and therapeutic intervention (with hemostasis, polypectomy, and foreign body retrieval). The major complication of spiral enteroscopy is perforation of the small bowel, which occurs at a low rate (0.27%). This procedure is used to find a lesion seen on capsule endoscopy, such as an angiodysplasia. It can also be used to reach a lesion or abnormal area seen on a radiologic imaging study.

Single- and Double-Balloon Enteroscopy

Balloon-assisted enteroscopy allows for deep insertion of the enteroscope by using an inflatable balloon fixed on an overtube. It allows for pleating of the small intestine on the enteroscope to go deep into the small bowel beyond the reach of traditional push enteroscopy. Balloon-assisted enteroscopy can be performed with an oral or rectal approach. The diagnostic yield of balloon-assisted enteroscopy for OGIB is as high as 80%, which is superior to that of push enteroscopy. Diagnostic and therapeutic interventions similar to those of spiral enteroscopy can be performed. The complication rate of balloon-assisted enteroscopy is low; the most commonly reported complications are perforation, ileus, and pancreatitis.

Small-Bowel Radiography

The yield of radiographic imaging with small-bowel follow-through for diagnosing OGIB is very low (0%–5%). Enteroclysis (a double-contrast radiographic study of the small bowel using barium and methylcellulose) highlights the small bowel in more detail to identify inflammatory bowel disease or tumors. Either imaging modality is unable to identify angiodysplasia. Small-bowel radiography is not considered a first-line tool for OGIB because of its low diagnostic yield. Furthermore, better diagnostic tools have since been developed, such as capsule endoscopy, which allow for a better examination of the small-bowel mucosa.

Intraoperative Endoscopy

Intraoperative endoscopy should be reserved for patients with OGIB in whom all other modalities have failed to identify or control a bleeding source. It can be performed during laparotomy or laparoscopy to identify the bleeding source. The diagnostic yield has been reported to be in the range of 58% to 80%. The emergence of balloon-assisted enteroscopy has decreased the use of this technique.

Management

Therapy for OGIB is guided by the underlying source of bleeding. Angiodysplasia should be treated with electrocautery, argon plasma coagulation, injection therapy, mechanical hemostasis (hemoclips or banding), or a combination of these techniques. If endoscopic therapy has failed, medical therapy for angiodysplasia may include octreotide, hormonal therapy, or thalidomide. Patients with angiodysplasia in the setting of aortic stenosis (Heyde syndrome) may benefit from valve replacement surgery. Tumors or masses require surgical intervention. In the presence of massive bleeding, interventional radiology may temporize bleeding with localized embolization. Iron supplementation (oral or intravenous) along with blood transfusion may be needed in some patients. If a causative agent such as an NSAID is identified, it should be stopped. H

KEY POINT

- Therapy for obscure gastrointestinal bleeding is guided by the underlying source of bleeding.

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 55-year-old man is evaluated during a routine examination. He feels well other than mild knee pain. He drinks six to eight cans of beer per night. He has no personal history of liver disease, but his older brother was recently diagnosed with hereditary hemochromatosis.

On physical examination, vital signs are normal; BMI is 24. He is tanned on sun-exposed body surfaces. Cardiac examination is normal. Abdominal examination reveals hepatomegaly. Bilateral bony hypertrophy of the knees is noted.

Laboratory studies:

Alanine aminotransferase	70 U/L
Aspartate aminotransferase	160 U/L
Ferritin	592 ng/mL (592 µg/L)
Transferrin saturation	40%

Genetic testing for hemochromatosis reveals heterozygosity for *C282Y*. Abdominal ultrasound reveals a change in liver echotexture consistent with fatty changes.

Which of the following is the most appropriate treatment?

(A) Administer deferoxamine
(B) Perform phlebotomy
(C) Repeat serum iron tests now
(D) Stop alcohol intake

Item 2

A 40-year-old man is evaluated for a 6-month history of intermittent episodes of two to four loose stools per day. When he has diarrhea, he also notices crampy abdominal pain and bloating. He has not had nausea, vomiting, anorexia, fever, melena, hematochezia, recent travel, or any new medications, including antibiotics. He is overweight but has been exercising and watching his diet for the past 6 months, and he has intentionally lost 6.8 kg (15.0 lb). The main change in his diet has been switching to diet soda and using sugar-free sweeteners. He takes no medications.

On physical examination, vital signs are normal. The abdomen is obese but soft with normal bowel sounds and no distention or tenderness.

Which of the following is the most appropriate management?

(A) Abdominal CT scan
(B) Colonoscopy with biopsies
(C) Discontinuation of sugar-free sweeteners
(D) Gluten-free diet
(E) Tissue transglutaminase IgA antibody testing

Item 3

A 68-year-old man is evaluated for new-onset ascites with lower-extremity edema. Symptoms have increased gradually over the past 4 weeks. He has consumed three alcoholic beverages per day for many years. His medical history is notable for coronary artery bypass graft surgery 8 months ago and dyslipidemia. His medications are low-dose aspirin, atorvastatin, and metoprolol.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 122/84 mm Hg, pulse rate is 64/min, and respiration rate is 16/min; BMI is 28. Cardiac examination reveals an elevated jugular venous pressure, a normal S_1 and S_2, and no murmurs. Pulmonary examination findings are normal. Abdominal examination reveals hepatomegaly, distention, dullness to percussion over the flanks, and a positive fluid wave. There is 2+ pitting edema of the lower extremities.

Laboratory studies reveal a serum albumin level of 3.5 g/dL (35 g/L). Other studies, including serum alanine aminotransferase and aspartate aminotransferase levels, are normal.

Paracentesis reveals a total nucleated cell count of 120/µL with 30% polymorphonucleocytes. Ascitic fluid albumin level is 2.3 g/dL (23 g/L) and total protein is 3.5 g/dL (35 g/L).

Which of the following is the most likely cause of this patient's ascites?

(A) Alcoholic cirrhosis
(B) Constrictive pericarditis
(C) Nonalcoholic cirrhosis
(D) Tuberculous peritonitis

Item 4

A 48-year-old woman is evaluated at an urgent care center for a 2-day history of severe retrosternal chest pain. She has not had heartburn or dysphagia. She is finishing a course of treatment for Lyme disease, but she has no other medical problems and otherwise feels well. Her only medication is doxycycline.

Physical examination is unremarkable, and laboratory studies are normal.

Which of the following is the most likely diagnosis?

(A) Barrett esophagus
(B) *Candida* esophagitis
(C) Eosinophilic esophagitis
(D) Pill-induced esophagitis

Item 5

A 56-year-old woman is hospitalized for new-onset confusion. She has a history of decompensated hepatitis B cirrhosis with chronic ascites. Her medications are spironolactone, furosemide, lactulose, and entecavir.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 118/62 mm Hg, pulse rate is 88/min, and respiration rate is 20/min; BMI is 23. She is disoriented to time and date. Asterixis is noted. The abdomen is moderately distended with ascites.

Laboratory studies reveal a serum bilirubin level of 2.9 mg/dL (49.6 µmol/L), a serum creatinine level of 1.3 mg/dL

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(114.9 µmol/L), and a blood urea nitrogen level of 34 mg/dL (12.1 mmol/L).

Diagnostic paracentesis reveals a nucleated cell count of 820/µL with 70% polymorphonuclear leukocytes. Gram stain and culture results are pending.

Which of the following is the most appropriate treatment?

(A) Cefotaxime and albumin
(B) Cefotaxime and normal saline
(C) Norfloxacin
(D) Rifaximin

Item 6

A 58-year-old man is evaluated for a 6-month history of episodic epigastric abdominal pain. In addition, his wife was recently diagnosed with *Helicobacter pylori* infection, and she is concerned that he may be infected as well. His epigastric pain occurs on most days and may occur several times during the day. He characterizes it as a vague discomfort that does not affect most activities. The discomfort is not closely related to eating, but he has been eating less. The discomfort typically resolves spontaneously within 30 to 60 minutes, but it has been occurring more frequently. He has also noted occasional nausea without vomiting. His weight is 2.3 kg (5.0 lb) lower than it was 1 year ago at his last appointment. Family history is negative for gastrointestinal malignancy.

On physical examination, blood pressure is 138/79 mm Hg, and pulse rate is 80/min. Other vital signs are normal. BMI is 35. Abdominal examination reveals generalized tenderness to deep palpation but no palpable mass.

Laboratory studies reveal a hemoglobin level of 12.5 g/dL (125 g/L) and a mean corpuscular volume of 94 fL.

Which of the following is the most appropriate management?

(A) Empiric treatment of *H. pylori*
(B) Empiric trial of omeprazole
(C) *H. pylori* serologic testing
(D) Upper endoscopy

Item 7

A 28-year-old man is evaluated in follow-up for elevated liver chemistry test results, which were performed to assess a 3-month history of fatigue. He has no history of liver disease and has not had abdominal pain or fever. His medical history is significant for a 3-year history of diarrhea.

On physical examination, vital signs are normal; BMI is 24. Spider angiomata and jaundice are absent. Abdominal examination reveals hepatomegaly but no splenomegaly or ascites.

Laboratory studies:

Alanine aminotransferase	75 U/L
Aspartate aminotransferase	87 U/L
Alkaline phosphatase	456 U/L
Total bilirubin	1.2 mg/dL (20.5 µmol/L)
Direct bilirubin	0.4 mg/dL (6.8 µmol/L)

Abdominal CT shows a thickened extrahepatic bile duct but no intrahepatic biliary dilatation and no hepatic or pancreatic mass. Magnetic resonance cholangiopancreatography reveals changes consistent with primary sclerosing cholangitis.

Which of the following is the most appropriate next step in management?

(A) Colonoscopy
(B) Endoscopic retrograde cholangiopancreatography
(C) Liver biopsy
(D) Serum IgG4 measurement

Item 8

A 25-year-old woman is evaluated in the emergency department for a 3-day history of nausea with nonradiating epigastric burning. She also has had a 24-hour history of frequent black stools, fatigue, and lightheadedness. For the past 5 days she has been taking ibuprofen for migraine. She takes no other medications. There is no history of gastrointestinal bleeding, alcoholism, chronic liver disease, or bleeding disorders.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 110/65 mm Hg supine and 92/53 mm Hg standing, pulse rate is 85/min supine and 115/min standing, and respiration rate is 14/min. Abdominal examination reveals epigastric tenderness without guarding or rebound. Rectal examination is positive for melena. Laboratory studies reveal a hemoglobin level of 9.2 g/dL (92 g/L) and a blood urea nitrogen level of 28 mg/dL (10 mmol/L); all other tests are normal.

After intravenous fluid resuscitation, upper endoscopy is performed and reveals a 1.5-cm duodenal bulb ulcer with a central, nonbleeding visible vessel.

Which of the following is the most appropriate management?

(A) Endoscopic therapy
(B) Immediate surgical intervention
(C) Octreotide infusion
(D) Observation

Item 9

A 49-year-old woman is hospitalized for altered mental status. She has alcoholic cirrhosis complicated by ascites. She has not had fever, focal infection symptoms, hematemesis, hematochezia, or melena. She takes lactulose, but she is now having four to five loose stools per day. She also takes furosemide and spironolactone.

On physical examination, temperature is 36.4 °C (97.5 °F), blood pressure is 102/74 mm Hg, pulse rate is 78/min, and respiration rate is 16/min; BMI is 24. She is disoriented to time and date. Scleral icterus, spider angiomata, and asterixis are noted. The mucous membranes are dry. Ascites is present.

Laboratory studies:

INR	1.3 (normal range, 0.8–1.2)
Albumin	2.6 g/dL (26 g/L)
Total bilirubin	3.5 mg/dL (59.9 µmol/L)
Blood urea nitrogen	38 mg/dL (13.6 mmol/L)
Creatinine	2.5 mg/dL (221 µmol/L)
Urinalysis	Normal

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Blood culture results are pending. Her diuretics and lactulose are discontinued.

Which of the following is the most appropriate treatment for acute kidney injury in this patient?

(A) Midodrine
(B) Midodrine and octreotide
(C) Norepinephrine
(D) 25% albumin

Item 10

A 73-year-old woman was admitted to the hospital 12 hours ago with fever, epigastric abdominal pain, and jaundice. She was hypotensive on admission to the emergency department but improved after receiving intravenous antibiotics and fluids. One hour ago the epigastric pain recurred and she again became febrile and hypotensive. She is transferred to the ICU, and her blood pressure improves with administration of fluids. She has no history of liver or biliary disease. Her only medication is piperacillin-tazobactam.

On physical examination, temperature is 39.3 °C (102.7 °F), blood pressure is 106/60 mm Hg, pulse rate is 102/min, and respiration rate is 22/min. Oxygen saturation is 96% breathing ambient air. Jaundice is noted. Abdominal examination reveals right upper quadrant tenderness but no hepatomegaly, ascites, abdominal guarding, or tenderness to percussion.

Laboratory studies:

Hemoglobin	13 g/dL (130 g/L)
Leukocyte count	19,000/μL (19 × 10^9/L), with 80% segmented neutrophils and 15% band forms
Alanine aminotransferase	453 U/L
Total bilirubin	8.3 mg/dL (141.9 μmol/L)

Ultrasound of the right upper quadrant reveals dilated intrahepatic and extrahepatic bile ducts, gallstones, a normal gallbladder wall, and no pericholecystic fluid. The pancreas is not well visualized.

Which of the following is the most appropriate management?

(A) Abdominal CT
(B) Cholecystectomy
(C) Endoscopic retrograde cholangiopancreatography
(D) Percutaneous cholecystostomy

Item 11

A 67-year-old woman is evaluated during a routine examination. She has a history of hip and knee pain related to degenerative joint disease. The joint pain is now well controlled with diclofenac, which was started 3 months ago. A previous trial of high-dose acetaminophen was not effective. She does not have any gastrointestinal symptoms, and she takes the diclofenac with food most of the time. Her medical history is otherwise notable for type 2 diabetes mellitus, hyperlipidemia, and hypertension. Her parents both had coronary artery disease. Her medications are low-dose aspirin, metformin, chlorthalidone, simvastatin, and diclofenac.

On physical examination, vital signs are normal. Abdominal examination is unremarkable.

Which of the following is the most appropriate management?

(A) Change to enteric-coated aspirin
(B) Continue the current medication regimen
(C) Initiate omeprazole, 20 mg once daily
(D) Initiate omeprazole, 40 mg once daily

Item 12

A 66-year-old man is evaluated for a several-year history of one to three bulky, semisolid, foul-smelling bowel movements daily that are associated with excess flatulence. Associated symptoms are episodic epigastric pain, a ravenous appetite, and a 9.0-kg (19.8-lb) weight loss over the last year. Medical history is notable for alcoholism; he has not consumed alcohol since his last attack of pancreatitis 15 years ago. He has an 80-pack-year history of smoking but currently does not smoke. He takes no medications.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 133/72 mm Hg, pulse rate is 77/min, and respiration rate is 14/min; BMI is 21. He is thin with temporal wasting and poor dentition. Abdominal examination reveals mild epigastric tenderness with no masses. The liver and spleen are not enlarged. Borborygmi is audible without a stethoscope. There is no abdominal distention. No jaundice is present.

Laboratory studies reveal a serum albumin level of 3.3 g/dL (33 g/L), a serum lipase level of 46 U/L, and tissue transglutaminase serology is negative.

Abdominal ultrasound shows pancreatic calcification but no masses. Fecal fat testing reveals a stool fat of 40 g/d.

Which of the following is the most appropriate treatment?

(A) Fiber
(B) Gluten-free diet
(C) Loperamide
(D) Pancreatic enzymes

Item 13

A 23-year-old man is evaluated for chronic diarrhea. He has had intermittent loose stools over the past 2 to 3 years; however, over the past 6 months, diarrhea has become more severe (five to six bowel movements per day) and constant. Stools are described as mushy and malodorous and are accompanied by crampy abdominal pain and bloating. He has lost 2.3 kg (5.0 lb) over the past 6 months despite consuming more calories. He has not had fever or gastrointestinal bleeding and has no history of foreign travel. He has type 1 diabetes mellitus that is well controlled with insulin. He does not smoke cigarettes or drink alcohol.

On physical examination, vital signs are normal. He has evidence of muscle wasting and pedal edema. The abdomen is scaphoid but soft with increased bowel sounds. No distention or tenderness is noted.

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Laboratory studies reveal a hemoglobin level of 10.4 g/dL (104 g/L) and a mean corpuscular volume of 100 fL.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Anti-*Saccharomyces cerevisiae* antibodies
(B) Flexible sigmoidoscopy
(C) Tissue transglutaminase antibody testing
(D) Upper endoscopy with small-bowel biopsies
(E) Video capsule endoscopy

Item 14

A 25-year-old woman is evaluated for a 6-month history of constipation characterized by straining and infrequent bowel movements (once every 3 days). She has also had frequent passage of mucus, generalized abdominal discomfort, and bloating. She has not had weight loss. Symptoms began gradually and have slowly progressed. Her symptoms are severe enough to affect her appetite; she deliberately avoids some meals because eating often worsens her symptoms. Bran supplementation made her symptoms worse. There is no family history of colon cancer. Her medications are a multivitamin and an oral contraceptive agent.

On physical examination, vital signs are normal. Abdominal examination reveals generalized tenderness to light palpation but no masses. Rectal examination findings are normal.

Laboratory studies reveal a hemoglobin level of 13 g/dL (130 g/L).

In addition to starting polyethylene glycol, which of the following is the most appropriate initial management?

(A) Obtain a comprehensive metabolic panel
(B) Obtain colonoscopy
(C) Obtain tissue transglutaminase testing
(D) Reassurance and patient education

Item 15

A 35-year-old man is evaluated for a 2-month history of upper abdominal discomfort after eating. He has recently returned from working in a rural area of a developing country. He takes no medications. There is no family history of esophageal or gastric cancer.

On physical examination, vital signs are normal. BMI is 40. Centripetal obesity is noted, but abdominal examination findings are otherwise normal.

Laboratory studies reveal a hemoglobin level of 15 g/dL (150 g/L).

Which of the following is the most appropriate management?

(A) Barium esophagogram
(B) Empiric *Helicobacter pylori* eradication therapy
(C) *H. pylori* testing
(D) Upper endoscopy

Item 16

An 18-year-old woman is hospitalized for a 1-day history of confusion, which was preceded by a 1-week history of fatigue and a 2-day history of jaundice. She has not had fever or abdominal pain. She has not had liver disease previously, and she has never used injection drugs. No one else in her family is ill.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 88/58 mm Hg, pulse rate is 110/min, and respiration rate is 22/min; BMI is 24. She is oriented to person but disoriented to time and place. Jaundice and asterixis are noted. The spleen is palpable below the left costal margin, and there is no ascites.

Laboratory studies:

Hemoglobin	9 g/dL (90 g/L)
Reticulocyte count	9% of erythrocytes
INR	1.7 (normal range, 0.8-1.2)
Alanine aminotransferase	239 U/L
Aspartate aminotransferase	243 U/L
Alkaline phosphatase	34 U/L
Total bilirubin	8.4 mg/dL (143.6 µmol/L)
Direct bilirubin	2.6 mg/dL (44.5 µmol/L)

A drug screen is positive for acetaminophen. Bedside abdominal ultrasound reveals a small liver, splenomegaly, and no ascites.

Which of the following is the most likely diagnosis?

(A) Acetaminophen hepatotoxicity
(B) Budd-Chiari syndrome
(C) Herpes hepatitis
(D) Wilson disease

Item 17

A 53-year-old woman is evaluated in follow-up after a recent hospitalization for right flank pain. Ultrasound performed in the hospital showed a dilated right renal collecting system and a 12-mm gallbladder polyp. Two hours after admission, she passed a stone in the urine and the right flank pain resolved. Since her hospitalization, she has had no other episodes of pain and otherwise feels well.

On physical examination, vital signs are normal; BMI is 34. Abdominal examination reveals a normal liver and spleen, no tenderness, and a negative Murphy sign.

Laboratory studies, including a complete blood count, alkaline phosphatase, alanine aminotransferase, and bilirubin, are normal.

Which of the following is the most appropriate management?

(A) Abdominal CT
(B) Cholecystectomy
(C) Endoscopic retrograde cholangiopancreatography
(D) Magnetic resonance cholangiopancreatography
(E) Ultrasound in 1 year

Item 18

A 55-year-old man is evaluated in the emergency department for a 6-hour history of severe epigastric

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H CONT. abdominal pain, nausea, and vomiting. In the previous 6 weeks he had two episodes of postprandial right upper quadrant pain. He is otherwise healthy and takes no medications.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 130/75 mm Hg, pulse rate is 89/min, and respiration rate is 17/min; BMI is 29. Scleral icterus is present. Abdominal examination reveals epigastric abdominal tenderness without guarding or rebound. Bowel sounds are present but hypoactive, and there is abdominal distention.

He is admitted to the hospital, and fluid resuscitation is started.

Laboratory studies:

Test	On presentation	After 12 hours of fluid resuscitation
Leukocyte count	14,000/μL (14×10^9/L)	12,000/μL (12×10^9/L)
Alanine aminotransferase	350 U/L	98 U/L
Aspartate aminotransferase	310 U/L	86 U/L
Total bilirubin	4.5 mg/dL (77 μmol/L)	1.6 mg/dL (27 μmol/L)
Lipase	3250 U/L	1220 U/L

Abdominal ultrasound shows cholelithiasis with no gallbladder wall thickening or pericholecystic fluid. The common bile duct is not dilated. There is no choledocholithiasis.

Which of the following is the most appropriate management?

(A) Cholecystectomy prior to hospital discharge
(B) Cholecystokinin hepatobiliary (CCK-HIDA) scintigraphy
(C) Endoscopic retrograde cholangiopancreatography with biliary sphincterotomy
(D) Intravenous imipenem

Item 19

A 22-year-old woman is evaluated for a flare of Crohn disease. A colonoscopy performed 6 months ago showed moderate, patchy, left-sided colitis extending from the descending colon to the splenic flexure. She responded to therapy with prednisone but declined maintenance therapy in advance of conceiving. She is now 12 weeks pregnant and for the past 2 weeks has experienced bloody diarrhea and left-sided abdominal pain.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 110/66 mm Hg, and pulse rate is 76/min. Abdominal examination reveals left-sided abdominal tenderness without guarding or rebound.

Flexible sigmoidoscopy shows recurrent left-sided patchy colitis, and stool studies are negative for *Clostridium difficile* infection.

Which of the following is the most appropriate treatment?

(A) Certolizumab
(B) Ciprofloxacin and metronidazole
(C) Controlled ileal-release budesonide
(D) Mesalamine
(E) Methotrexate

Item 20

A 25-year-old woman is evaluated for an 8-month history of epigastric abdominal pain. The pain is episodic, but it is present more often than not. There do not seem to be any factors that clearly exacerbate or alleviate the pain. She notes occasional nausea and poor appetite but has not had weight loss. Her medical history is notable for gastroesophageal reflux disease. There is no family history of gastrointestinal malignancy. Her only medication is omeprazole, 20 mg/d.

On physical examination, vital signs are normal. Abdominal examination reveals generalized abdominal tenderness to light palpation but is otherwise normal.

Testing for *Helicobacter pylori* is negative. Owing to ongoing symptoms despite antisecretory therapy, upper endoscopy with gastric and small-bowel biopsies is performed; results are normal.

Which of the following is the most appropriate treatment?

(A) Increase omeprazole to twice daily
(B) Initiate hydrocodone/acetaminophen as needed
(C) Initiate metoclopramide
(D) Initiate nortriptyline
(E) Switch omeprazole to ranitidine

Item 21

A 64-year-old man is evaluated in follow-up after recent abnormal findings on intraoperative liver biopsy. Two days ago he underwent right colon resection for a large villous adenoma with high-grade dysplasia. At the time of surgery, an abnormal-appearing liver was noted and biopsy was performed. His medical history is notable for type 2 diabetes mellitus, hypertension, and obesity. Medications are metformin and lisinopril. He drinks two cans of beer daily but does not use tobacco.

On physical examination, vital signs are normal; BMI is 38. No jaundice or spider angiomata are noted. Abdominal examination reveals healing laparoscopic scars and hepatomegaly. The spleen is not palpable, and there is no ascites. No peripheral edema is seen.

Laboratory studies:

Complete blood count	Normal
INR	Normal
Alanine aminotransferase	79 U/L
Aspartate aminotransferase	68 U/L
Albumin	Normal
Alkaline phosphatase	126 U/L
Total bilirubin	Normal
Ferritin	389 ng/mL (389 μg/L)
Iron	Normal
Total iron-binding capacity	Normal
Iron saturation	Normal

Liver biopsy demonstrates a mildly active steatohepatitis without fibrosis. An iron stain is negative.

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Which of the following is the most appropriate management?

(A) Bariatric surgery
(B) Phlebotomy
(C) Surveillance for hepatocellular carcinoma
(D) Weight loss

Item 22

A 29-year-old man is evaluated during a routine examination. His medical history is significant for ulcerative colitis involving the entire colon, which was diagnosed 4 years ago. His symptoms responded to therapy with mesalamine and have remained in remission on this medication. His family history is significant for a maternal uncle who died of colon cancer at the age of 50 years.

Physical examination is unremarkable.

Serum alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels are normal.

Which of the following is the most appropriate interval at which to perform colonoscopy with biopsies in this patient?

(A) Begin now and repeat annually
(B) Begin in 4 years and repeat every 1 to 2 years
(C) Begin in 4 years and repeat every 10 years
(D) Begin at age 40 years and repeat every 5 years

Item 23

A 58-year-old woman is evaluated in the emergency department for a 2-day history of left lower abdominal discomfort. The pain began insidiously and has gradually progressed. She has felt warm but has not had shaking chills, urinary symptoms such as dysuria or urgency, change in bowel habits, or apparent blood in her stool. She is able to eat and drink normally; however, her appetite is decreased. She has never had symptoms like this before. Her medical history is unremarkable.

On physical examination, temperature is 36.6 °C (97.9 °F), blood pressure is 135/68 mm Hg, pulse rate is 94/min, and respiration rate is 18/min. She appears mildly uncomfortable. Mild left lower quadrant abdominal tenderness is noted, with no fullness or mass, guarding, or rebound tenderness.

Laboratory studies are significant for a hemoglobin level of 11.8 g/dL (118 g/L) and a leukocyte count of 10,800/μL (10.8×10^9/L). Serum electrolyte levels and kidney function studies are normal.

Abdominal CT scan shows inflammation of the sigmoid colon and mesentery consistent with acute diverticulitis; no bowel obstruction or abscess is noted.

In addition to antibiotic therapy, which of the following is the most appropriate management?

(A) Discharge home with close follow-up
(B) Laparoscopic sigmoid resection
(C) Percutaneous drainage
(D) Urgent colonoscopy

Item 24

A 57-year-old woman is evaluated after a recent screening colonoscopy. The colonoscopy disclosed a 12-mm polyp in the ascending colon, which was removed. No other lesions were noted. On pathology, the lesion was found to be a sessile serrated polyp.

Physical examination findings are unremarkable.

Which of the following is the most appropriate time to repeat colonoscopy?

(A) 1 year
(B) 3 years
(C) 5 years
(D) 10 years

Item 25

A 41-year-old woman is evaluated in follow-up after presenting to the emergency department 1 week ago for burning epigastric and chest pain. In the emergency department, a complete blood count and liver chemistry studies were normal, but a radiograph of the chest and upper abdomen demonstrated calcified gallstones. The pain resolved with administration of a liquid antacid, and omeprazole was started. The pain had been present intermittently for approximately 6 months prior to the emergency department visit. It occurred nearly every day, usually after meals and when recumbent, and had been typically burning in nature at night. The pain has not recurred since she started omeprazole. She has not had dysphagia and has a good appetite and stable weight. Her medical history is notable for obesity.

On physical examination, vital signs are normal; BMI is 36. There is no abdominal tenderness, and the liver and spleen are of normal size. Murphy sign is negative.

Which of the following is the most appropriate management for this patient's gallstones?

(A) Annual ultrasonography
(B) Laparoscopic cholecystectomy
(C) Ursodiol
(D) Clinical observation

Item 26

A 24-year-old woman is evaluated for a 1-month history of increasing pain and bleeding from a skin ulcer next to her stoma. The skin symptoms get worse each time she changes her appliance. She underwent proctocolectomy 4 years ago for medically refractory colonic Crohn disease. She has not had small-bowel involvement, and her ostomy output has been stable since surgery.

On physical examination, vital signs are normal. The skin findings are shown (see top of next page). The remainder of the skin examination is normal. The abdomen is soft with normal bowel sounds. There is no distention, tenderness, masses, or organomegaly.

Which of the following is the most likely cause of this patient's skin findings?

(A) Acrodermatitis enteropathica
(B) Erythema nodosum

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(C) Pyoderma gangrenosum
(D) Squamous cell carcinoma

Item 27

A 30-year-old woman is evaluated for a 2-month history of diarrhea with three to five loose stools per day. She has mild abdominal cramps, bloating, intermittent nausea, and mild anorexia that has resulted in the loss of 2.3 kg (5.0 lb). She has had no fever or blood in the stool. She works in a day care center and has not traveled recently or had exposure to antibiotics. She is otherwise healthy and takes no medications.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 112/74 mm Hg, and pulse rate is 70/min. The abdomen is soft with normal bowel sounds and mild distention but no tenderness.

Which of the following is the most appropriate management?

(A) Colonoscopy
(B) Stool cultures
(C) Stool testing for ova and parasites
(D) No further testing

Item 28

A 63-year-old man is evaluated for a 1-month history of painless jaundice. He has not had pancreatitis, weight loss, oily stools, or diabetes mellitus. He has never smoked cigarettes and has consumed alcohol only minimally and rarely. His medical and family history is unremarkable, and he takes no medications.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 136/78 mm Hg, pulse rate is 73/min, and respiration rate is 14/min; BMI is 27. Jaundice is noted. Abdominal examination reveals epigastric tenderness without guarding or rebound.

Laboratory studies:

Alanine aminotransferase	132 U/L
Aspartate aminotransferase	121 U/L
Alkaline phosphatase	353 U/L
Total bilirubin	4.2 mg/dL (71.8 µmol/L)
Serum IgG4	Elevated

Magnetic resonance cholangiopancreatography shows features of sclerosing cholangitis, focal enlargement of the head of the pancreas with a featureless border, and a nondilated pancreatic duct.

Which of the following is the most appropriate management?

(A) Antioxidants
(B) Biliary metal stent
(C) Prednisone
(D) Surgery

Item 29

An 80-year-old man is evaluated for gastrointestinal bleeding. His medical history is notable for a 3-month history of intermittent melena that resulted in a hospitalization 2 days ago, during which he has required fluid resuscitation and erythrocyte transfusions. Upper endoscopy and colonoscopy were normal.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 135/80 mm Hg, pulse rate is 80/min, and respiration rate is 18/min. Abdominal examination findings are normal.

Laboratory studies show a hemoglobin level of 8.2 g/dL (82 g/L). Capsule endoscopy shows fresh blood in the proximal jejunum and several angiodysplasias.

Which of the following is the most appropriate test to perform next?

(A) Intraoperative endoscopy
(B) Push enteroscopy
(C) Repeat upper endoscopy
(D) Technetium-labeled nuclear scan

Item 30

A 40-year-old man is evaluated in follow-up for irritable bowel syndrome with constipation (IBS-C), which was diagnosed 3 months ago. His IBS symptoms did not respond to a trial of psyllium, which was discontinued owing to bloating. A trial of polyethylene glycol had similar results. He has no other medical problems and takes no other medications.

On physical examination, vital signs are normal. Abdominal examination reveals generalized abdominal tenderness but is otherwise normal.

Which of the following is the most appropriate treatment?

(A) Start a bran-based dietary supplement
(B) Start bisacodyl
(C) Start linaclotide
(D) Start rifaximin

Item 31

A 55-year-old woman is evaluated during a routine examination. She underwent biliopancreatic diversion with duodenal switch 8 years ago for treatment of obesity-related complications and lost 68.0 kg (150.0 lb) in the first year

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following surgery. Her weight has been relatively stable for the last year. She has had chronic nonbloody diarrhea since her bariatric surgery. She also has had generalized fatigue, dry skin, dry and itchy eyes, and increased difficulty seeing road signs at night while driving. Her other medical problems are type 2 diabetes mellitus and hypertension. Her prescription medications are metformin and lisinopril, and she also takes an over-the-counter multivitamin with iron. Her last colonoscopy, performed 5 years ago, was normal.

On physical examination, blood pressure is 140/79 mm Hg and pulse rate is 63/min. BMI is 25. The examination is otherwise unremarkable.

Laboratory studies reveal a hemoglobin level of 10.5 g/dL (105 g/L) and a mean corpuscular volume of 95 fL.

Which of the following deficiencies best explains this patient's current findings?

(A) Copper
(B) Iron
(C) Vitamin A
(D) Vitamin B_{12}

Item 32

A 68-year-old woman is evaluated for a 3-month history of gradually progressive abdominal distention. Her medical history is notable for a 20-year history of obesity, type 2 diabetes mellitus, hyperlipidemia, and hypertension. She also has had a 10-year history of elevation of serum aminotransferase levels, which was attributed to nonalcoholic fatty liver disease. She does not consume alcohol. Her medications are metformin, lisinopril, low-dose aspirin, and simvastatin.

On physical examination, vital signs are normal; BMI is 38. Spider angiomata are present. Abdominal examination is limited by obesity, but there is mild abdominal distention consistent with ascites. There is no obvious hepatomegaly or splenomegaly.

Laboratory studies:

Platelet count	68,000/μL (68×10^9/L)
Alanine aminotransferase	54 U/L
Aspartate aminotransferase	64 U/L
Albumin	3.2 g/dL (32 g/L)
Total bilirubin	2 mg/dL (34.2 μmol/L)
Direct bilirubin	1.4 mg/dL (24 μmol/L)
Urinalysis	1+ protein

Which of the following is the most appropriate next step in management?

(A) Echocardiogram
(B) Liver biopsy
(C) Stop simvastatin
(D) Ultrasound of the liver and spleen

Item 33

A 70-year-old man is evaluated in follow-up for heartburn of 7 years' duration. He has frequent nocturnal reflux but has not had odynophagia or dysphagia, and his weight has been stable. He was recently started on once-daily omeprazole with good control of his symptoms. He has a 30-pack-year history of cigarette smoking and continues to smoke.

On physical examination, vital signs are normal; BMI is 29. The remainder of the physical examination is normal.

He is concerned about his long-term heartburn symptoms and expresses an interest in further evaluation to assess his risk of cancer because of his prolonged symptoms. Based on his risk factors and after discussing with the patient the benefits and harms of screening endoscopy for Barrett esophagus, upper endoscopy is performed. An area of salmon-colored mucosa is seen in the esophagus, and biopsies confirm Barrett esophagus without dysplasia.

Which of the following is the most appropriate next step in management?

(A) Endoscopic ablation
(B) Esophagectomy
(C) Fundoplication
(D) Repeat upper endoscopy in 3 to 5 years

Item 34

A 58-year-old woman is evaluated for a 6-month history of gradually progressive fatigue and a 1-month history of generalized pruritus without rash. She also has dry eyes and dry mouth. She has not had fever, jaundice, or weight loss. She has a 3-year history of hypercholesterolemia for which she takes simvastatin. She has no other medical problems.

On physical examination, vital signs are normal; BMI is 24. Other than excoriations on her arms, legs, and upper back, the physical examination is normal.

Laboratory studies:

Alanine aminotransferase	75 U/L
Aspartate aminotransferase	54 U/L
Alkaline phosphatase	328 U/L
Total bilirubin	1.2 mg/dL (20.5 μmol/L)
Direct bilirubin	0.6 mg/dL (10.3 μmol/L)
Antimitochondrial antibody	1:640

Ultrasound of the right upper quadrant is normal.

Which of the following is the most likely diagnosis?

(A) Autoimmune hepatitis
(B) Cholangiocarcinoma
(C) Primary biliary cirrhosis
(D) Primary sclerosing cholangitis

Item 35

A 67-year-old man is re-evaluated for a 3-month history of iron deficiency anemia due to obscure gastrointestinal bleeding. At the time of diagnosis he was evaluated with two upper endoscopies and a colonoscopy that failed to reveal the source of gastrointestinal bleeding. He has remained hemodynamically stable but requires oral iron therapy. His medical history is notable for chronic atrial fibrillation, for which he takes diltiazem and warfarin.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 130/78 mm Hg, pulse rate is 80/min, and respiration rate is 18/min. Abdominal examination findings are normal.

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Laboratory studies show a hemoglobin level of 9.2 g/dL (92 g/L) and an INR of 2.5 (normal range, 0.8-1.2). A guaiac fecal occult blood test is positive.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Angiography
(B) Capsule endoscopy
(C) Intraoperative endoscopy
(D) Technetium-labeled nuclear scan

Item 36

A 35-year-old man is evaluated in the emergency department for a 6-hour history of epigastric abdominal pain that radiates to the back. He also has nausea and occasional bilious vomiting. He has consumed between six and twelve beers daily for 10 to 15 years.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 110/65 mm Hg, pulse rate is 105/min, and respiration rate is 22/min. Abdominal examination discloses epigastric tenderness without guarding or rebound. Bowel sounds are present but hypoactive, and there is mild abdominal distention. No jaundice is noted.

Laboratory studies reveal a leukocyte count of 14,000/μL (14 × 10^9/L), a blood urea nitrogen level of 25 mg/dL (8.9 mmol/L), and a serum lipase level of 952 U/L.

Abdominal ultrasound shows a normal-appearing gallbladder and no biliary dilation. The patient is admitted to the hospital. Over the next 48 hours, he has ongoing abdominal pain, nausea, and poor appetite despite supportive therapy consisting of pain medication and aggressive intravenous fluid replacement. Subsequent contrast-enhanced CT of the abdomen shows nonenhancing areas of the head and body of the pancreas (consistent with necrosis) and several peripancreatic fluid collections.

Which of the following is the most appropriate management?

(A) Drainage of the fluid collections
(B) Endoscopic retrograde cholangiopancreatography
(C) Enteral nutrition by nasojejunal tube
(D) Total parenteral nutrition

Item 37

A 30-year-old woman is evaluated in an urgent care facility for a 1-day history of rectal bleeding and anal pain associated with a bowel movement. She has a lifelong history of constipation. She is otherwise well and her only medication is a daily laxative.

On physical examination, vital signs are normal; BMI is 27. Upon separating the buttocks, a midline posterior anal fissure is observed. There is no evidence of fresh blood or clots. Topical treatment is provided.

Which of the following is the most appropriate management?

(A) Admission to the hospital for observation
(B) Colonoscopy
(C) Outpatient follow-up
(D) Surgery

Item 38

A 42-year-old woman is evaluated after an incidental liver lesion was found during a recent CT urogram, which was performed for evaluation of kidney stones. Follow-up CT of the lesion demonstrates a well-circumscribed 6-cm lesion with peripheral enhancement on the early arterial phase, centripetal flow on the portal phase, and isodensity on the late phase. Biopsy of the lesion confirms a hepatocellular adenoma, and β-catenin activation mutation is positive. Her only medication is an estrogen and progesterone oral contraceptive.

On physical examination, vital signs are normal; BMI is 28. Abdominal examination findings are normal.

Which of the following is the most appropriate treatment?

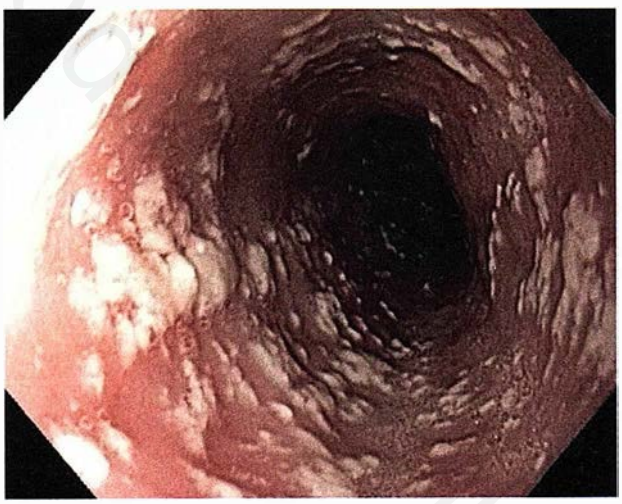
(A) Discontinuation of the oral contraceptive
(B) Resection
(C) Surveillance CT imaging every 6 months
(D) Transarterial chemoembolization

Item 39

A 60-year-old woman is evaluated for a 5-day history of painful swallowing with both liquids and solids. The pain is worse when swallowing solid foods. She otherwise feels well. She underwent liver transplantation 4 months ago. Her only medication is mycophenolate mofetil, and she recently stopped taking prednisone.

On physical examination, vital signs are normal. The oral pharynx appears normal, and abdominal examination reveals no tenderness.

Upper endoscopy findings are shown.



Which of the following is the most appropriate treatment?

(A) Acyclovir
(B) Fluconazole
(C) Ganciclovir
(D) Swallowed aerosolized fluticasone
(E) Swallowed nystatin

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Item 40

A 36-year-old woman is evaluated for a 12-year history of refractory constipation. Her symptoms began after a difficult childbirth. She has constipation marked by straining, bloating, and a constant sensation of incomplete emptying. She sometimes has 4 or more days between bowel movements. When she does have a bowel movement, the stool is soft-formed. Trials of several fiber supplements, lactulose, milk of magnesia, docusate, bisacodyl, polyethylene glycol, and lubiprostone have provided only transient relief for no more than 4 weeks before the gradual return of symptoms. There is no family history of gastrointestinal malignancies or inflammatory bowel disease. Medications are polyethylene glycol, psyllium, and bisacodyl.

On physical examination, vital signs are normal. BMI is 17. Tenderness to palpation is noted in the lower abdomen. No masses are noted. Rectal examination reveals normal resting tone, an increase in external anal sphincter tone, and poor relaxation of the pelvic floor when bearing down. Soft stool is noted in the rectal vault.

Anorectal manometry confirms paradoxical muscle contraction during the Valsalva maneuver consistent with pelvic floor dyssynergia.

Which of the following is the most appropriate management?

(A) Increase polyethylene glycol
(B) Increase psyllium
(C) Start biofeedback therapy
(D) Start enema therapy

Item 41

A 54-year-old man is evaluated for a 4-month history of intermittent, nonprogressive solid-food dysphagia. He has a long-standing history of heartburn that has been well controlled with once-daily proton pump inhibitor (PPI) therapy for the past 5 years. Results of a screening colonoscopy 4 years ago were normal. There is no family history of colorectal cancer.

Physical examination findings are unremarkable.

Upper endoscopy reveals a 3-cm hiatal hernia, an esophageal (Schatzki) ring, and approximately six polyps smaller than 4 mm in the fundus and upper body of the stomach. The duodenum is normal. The esophageal ring is dilated, and biopsy of random gastric polyps confirms fundic gland polyps without dysplasia.

Which of the following is the most appropriate next step in management?

(A) Perform *APC* gene testing
(B) Perform excision of all fundic gland polyps
(C) Repeat colonoscopy
(D) Stop PPI therapy
(E) Reassurance

Item 42

A 50-year-old man is evaluated in follow-up after hospitalization 6 months ago for a large bleeding gastric ulcer. Tests performed for *Helicobacter pylori* infection at that time were negative. However, for the 3 months before hospitalization he had been taking ibuprofen for chronic back pain. He was discharged from the hospital on omeprazole, and his ibuprofen was discontinued. Owing to the large size of the ulcer and increased suspicion for underlying malignancy, follow-up upper endoscopy was performed 3 months later and showed complete ulcer healing; the omeprazole was stopped. He has not found any other treatment as effective as ibuprofen for his back pain, and he wishes to restart the ibuprofen. He does not have cardiovascular disease and is at low risk for developing cardiovascular disease.

Physical examination is unremarkable.

Which of the following is the most appropriate management?

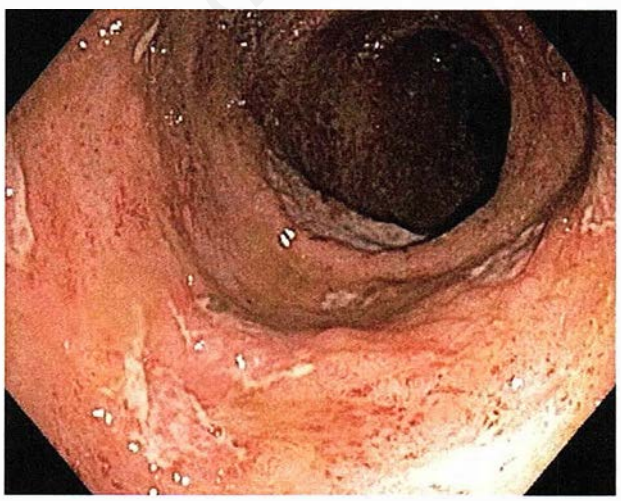
(A) Celecoxib
(B) Celecoxib and omeprazole
(C) Ibuprofen
(D) Ibuprofen and sucralfate

Item 43

A 28-year-old woman is evaluated for an 8-week history of increasing lower abdominal crampy pain and diarrhea. She now has 6 to 10 bowel movements per day with one or two nocturnal stools. Stools are loose to watery with intermittent blood streaking. The pain is in the lower abdomen and has increased to 6 to 8 out of 10 in severity over the past week. She has anorexia and nausea but no vomiting or fever. She takes no medications, including NSAIDs.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 100/54 mm Hg, and pulse rate is 96/min. She appears thin, pale, and in moderate distress. The abdomen is distended with diffuse tenderness that is most prominent in the lower quadrants. There is no rigidity, guarding, rebound tenderness, masses, or organomegaly.

Representative colonoscopy findings seen in a patchy distribution throughout the ascending, transverse, and descending colon are shown. The terminal ileum and rectum show no inflammation.



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Which of the following is the most likely diagnosis?

(A) Collagenous colitis
(B) Crohn colitis
(C) Ischemic colitis
(D) Ulcerative colitis

Item 44

A 48-year-old woman is evaluated for a 3-month history of anorexia associated with a 9.1-kg (20.0-lb) weight loss. Six months ago she began having nausea, vomiting, meal-related abdominal pain and bloating, and diarrhea. Other medical problems include dyslipidemia and hypertension treated with simvastatin, chlorthalidone, and lisinopril. She has a 25-pack-year history of smoking.

On physical examination, blood pressure is 140/85 mm Hg and pulse rate is 88/min; BMI is 17. A bruit is audible in the upper abdomen and over both femoral arteries. Dorsalis pedis and posterior tibial pulses are diminished bilaterally.

Upper endoscopy findings are normal. CT scan of the abdomen and pelvis demonstrates a dilated and debris-filled stomach and diffuse dilation of the small bowel.

Which of the following diagnostic tests should be done next?

(A) Abdominal ultrasonography
(B) Capsule endoscopy
(C) CT angiography
(D) Splanchnic angiography

Item 45

A 38-year-old woman is evaluated in follow-up after recent surgery for endometrial cancer. Her family history is significant for colon cancer in her sister (diagnosed at age 45 years) and her mother (diagnosed at age 65 years). Her maternal grandfather was diagnosed with rectal cancer at age 47 years. The patient has never had colon cancer screening with colonoscopy.

Which of the following is the most appropriate time to start colon cancer screening with colonoscopy?

(A) Now
(B) Age 40 years
(C) Age 47 years
(D) Age 50 years

Item 46

A 45-year-old man is evaluated in follow-up after a recent diagnosis of hepatitis B infection, which was discovered after a blood donation. His medical history is notable for illicit parenteral drug use 10 years ago. He has no family history of hepatitis B infection. He is otherwise well and takes no medications.

On physical examination, vital signs are normal, and he appears well. No spider angiomata are noted. The liver span is normal, and the spleen is not palpable. No ascites or edema is present.

Laboratory studies:

Alanine aminotransferase	Normal
Hepatitis B serologic studies:	
Hepatitis B surface antigen	Positive
IgM antibody to hepatitis B core antigen	Negative
IgG antibody to hepatitis B core antigen	Positive
Hepatitis B e antigen	Negative
Antibody to hepatitis B e antigen	Positive
Hepatitis B virus DNA	<20 IU/mL

Which of the following is the most appropriate management?

(A) Entecavir
(B) Lamivudine
(C) Pegylated interferon
(D) No treatment at this time

Item 47

A 23-year-old woman is evaluated for an 8-month history of alternating diarrhea and constipation, generalized abdominal discomfort, bloating, increased flatulence, nausea, and occasional passage of mucus following bowel movements. She has up to five loose, nonbloody bowel movements daily, described as oatmeal in consistency, alternating with periods of constipation. Abdominal discomfort is described as a generalized ache coming in waves and sometimes improves after a bowel movement. She has not had any improvement in her symptoms with the avoidance of milk or a short course of probiotics. Her medical history is unremarkable. There is no family history of gastrointestinal malignancies or inflammatory bowel disease. Her medications are ibuprofen and loperamide.

On physical examination, blood pressure is 130/80 mm Hg, and pulse rate is 62/min. Abdominal examination reveals generalized abdominal tenderness but is otherwise normal. Rectal examination findings are normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Colonoscopy
(B) Flexible sigmoidoscopy
(C) Lactose hydrogen breath test
(D) Thyroid-stimulating hormone level
(E) Tissue transglutaminase serology

Item 48

A 72-year-old woman is re-evaluated for iron deficiency anemia and intermittent dark-colored stools. Since the incidental discovery of iron deficiency anemia 3 months ago, she has been evaluated with upper endoscopy that showed a large hiatal hernia and specks of old blood in the stomach but no clear bleeding source. Colonoscopy was normal. Her only medication is iron sulfate.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 122/78 mm Hg, pulse rate is 72/min, and respiration rate is 18/min. Abdominal examination findings are normal.

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Laboratory studies show a hemoglobin level of 11.5 g/dL (115 g/L) and a mean corpuscular volume of 77 fL. A guaiac fecal occult blood test is positive.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Balloon enteroscopy
(B) Intraoperative endoscopy
(C) Push enteroscopy
(D) Repeat colonoscopy
(E) Repeat upper endoscopy

Item 49

A 60-year-old woman is evaluated for a 3-week history of substernal chest pain. The pain is dull, nonradiating, and unrelated to activities. Sometimes the pain is worse after eating spicy foods and can be occasionally triggered by emotional stress. She has not had shortness of breath or weakness. She is moderately active, walking a mile each day. She generally eats a "healthy heart" diet but has never had her lipid levels evaluated. She has never smoked cigarettes. There is no family history of heart disease. Other than the current problem, she is well and takes no medications.

On physical examination, blood pressure is 135/75 mm Hg, pulse rate is 70/min, and respiration rate is 12/min. The remainder of the examination is normal.

An electrocardiogram is normal.

Which of the following is the most appropriate next step in management?

(A) Ambulatory pH testing
(B) Esophageal manometry
(C) Exercise stress test
(D) Upper endoscopy

Item 50

A 34-year-old woman is evaluated in follow-up after a recent diagnosis of hepatitis C virus (HCV) infection, which was discovered after a blood donation. Her medical history is notable for injection drug use 12 years ago. Her only medication is an oral contraceptive.

Vital signs and general physical examination are normal.

Laboratory studies:

Alanine aminotransferase (ALT)	Normal
Antibody to HCV	Positive
HCV RNA	1.2 million IU/mL
Hepatitis B surface antibody	Positive
Hepatitis B surface antigen	Negative
IgG antibody to hepatitis A virus	Positive
Antibody to HIV	Negative

HCV genotyping reveals that she has HCV genotype 2. Liver biopsy demonstrates moderate portal inflammation (grade 2 of 4) and periportal fibrosis with rare portal-portal septa (stage 2 of 4).

Which of the following is the most appropriate management?

(A) Hepatitis A vaccination
(B) Hepatitis B vaccination
(C) Serial monitoring of ALT levels
(D) Testing for IgM antibody to hepatitis A virus
(E) Treatment for hepatitis C virus infection

Item 51

A 55-year-old man is evaluated in follow-up for acid reflux. He has an 8-year history of heartburn, which was previously well controlled with once-daily pantoprazole. His dosage was increased to twice daily 10 weeks ago because he was having nocturnal heartburn. Despite the increase in medication, he has had minimal improvement in symptoms. The patient verified that he is taking the medication 30 minutes before meals. He takes no other medications.

Physical examination is unremarkable.

Upper endoscopy findings are normal.

Which of the following is the most appropriate next step in management?

(A) Ambulatory pH impedance monitoring
(B) Barium esophagogram
(C) Esophageal manometry
(D) Fundoplication

Item 52

A 59-year-old woman is evaluated for a 3-month history of watery diarrhea. She has six to eight nonbloody bowel movements per day with one or two nocturnal stools. She has crampy abdominal pain that improves after a bowel movement. She has significant fecal urgency and has had three episodes of fecal incontinence. She has not had nausea or weight loss and otherwise feels well. Her only other medical problem is frequent tension-type headaches that are treated with daily over-the-counter ibuprofen.

On physical examination, vital signs are normal. Abdominal examination is unremarkable.

Colonoscopy reveals sigmoid diverticulosis but no inflammatory changes. Random colon biopsies show expansion of the lamina propria with acute and chronic inflammatory cells, increased intraepithelial lymphocytes, and no subepithelial collagen thickening.

Which of the following is the most likely diagnosis?

(A) *Clostridium difficile* colitis
(B) Collagenous colitis
(C) Ischemic colitis
(D) Lymphocytic colitis

Item 53

A 41-year-old woman is evaluated in the ICU 7 days after induction chemotherapy for acute myeloid leukemia. Twenty-four hours ago she developed fever of 39.4 °C

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CONT. (102.9 °F) and severe hypotension and was begun on intravenous fluids, broad-spectrum antibiotics, antifungal therapy, norepinephrine, and vasopressin. Last night she developed diarrhea and a 1 g/dL (10 g/L) drop in hemoglobin.

On physical examination today, temperature is 38.1 °C (100.6 °F), blood pressure is 89/47 mm Hg, pulse rate is 100/min, and respiration rate is 22/min. Oxygen saturation is 94% on a 50% rebreather mask. Palpation of the abdomen elicits left lower abdominal pain without rebound tenderness. Liquid brown stool is present.

A review of the patient's cardiac monitor recordings for the past 24 hours documents only sinus tachycardia.

Laboratory studies reveal a hemoglobin level of 8 g/dL (80 g/L), a leukocyte count of 150/μL (0.15×10^9/L), and a platelet count of 10,000/μL (10×10^9/L).

CT of the abdomen and pelvis reveals mild proximal jejunal wall thickening and dilation, mild mesenteric edema, and a trace amount of free pelvic fluid.

Which of the following is the most likely diagnosis for this patient's gastrointestinal findings?

(A) Hemorrhage into the bowel wall
(B) Ischemic colitis
(C) Nonocclusive mesenteric ischemia
(D) Superior mesenteric artery embolism

Item 54

A 58-year-old man is evaluated in follow-up for hepatitis C–related cirrhosis that is complicated by nonbleeding small esophageal varices and ascites. His ascites has recently worsened and has required large-volume paracentesis three times per month. He has been on a low-salt diet, spironolactone, and furosemide.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 98/60 mm Hg, pulse rate is 65/min, and respiration rate is 16/min; BMI is 26. He appears chronically ill. Scleral icterus, jaundice, and spider angiomata are noted. The abdomen is distended with ascites. The spleen tip is palpable.

Laboratory studies reveal a serum creatinine level of 2.2 mg/dL (194.5 μmol/L).

The Model for End-Stage Liver Disease (MELD) score is 21.

Which of the following is the most appropriate next step in management?

(A) Continuation of current medical therapy
(B) Evaluation for liver transplantation
(C) Surgical portosystemic shunt
(D) Transjugular intrahepatic portosystemic shunt

Item 55

A 28-year-old woman was hospitalized 2 days ago for gallstone pancreatitis. She is in the sixteenth week of pregnancy. She now feels well and is tolerating oral intake. Approximately 2 weeks ago she had an episode of severe right upper quadrant and shoulder pain associated with nausea that lasted 2 hours and then resolved. Her medical history is otherwise unremarkable, and her only medication is a prenatal vitamin.

On physical examination, vital signs are normal. Abdominal examination reveals an enlarged uterus consistent with pregnancy, and no hepatomegaly or abdominal tenderness is noted.

Laboratory studies, including a complete blood count, serum amylase, and serum total bilirubin, are normal.

Ultrasound of the right upper quadrant reveals gallbladder stones, no bile duct dilatation, and a normal pancreas.

Which of the following is the most appropriate management?

(A) Bile acid dissolution therapy
(B) Cholecystectomy after delivery
(C) Cholecystectomy prior to hospital discharge
(D) Endoscopic retrograde cholangiopancreatography with sphincterotomy
(E) Extracorporeal shock-wave lithotripsy

Item 56

A 45-year-old man is evaluated in the emergency department for two episodes of hematemesis and lightheadedness. He has no history of gastrointestinal bleeding, bleeding disorders, alcoholism, chronic liver disease, cardiovascular disease, or cancer. He takes no medications.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 103/62 mm Hg supine and 78/50 mm Hg standing, pulse rate is 101/min supine and 125/min standing, and respiration rate is 14/min. There is no jaundice, spider angiomata, or palmar erythema. Abdominal examination reveals no tenderness, guarding, or rebound. Rectal examination identifies melena.

Laboratory studies:

Hemoglobin	10 g/dL (100 g/L)
Platelet count	200,000/μL (200×10^9/L)
Prothrombin time	11 s
Alanine aminotransferase	28 U/L
Aspartate aminotransferase	22 U/L
Blood urea nitrogen	34 mg/dL (12.1 mmol/L)
Creatinine	0.9 mg/dL (79.6 μmol/L)

Which of the following is the most likely cause of this patient's gastrointestinal bleeding?

(A) Duodenal angiodysplasia
(B) Erosive gastritis
(C) Esophageal varices
(D) Peptic ulcer disease
(E) Portal gastropathy

Item 57

A 65-year-old man is evaluated after a recent colonoscopy, which disclosed a 2.5-cm pedunculated polyp in the sigmoid colon. The polyp was removed in its entirety in a single

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piece. Biopsy results showed a well-differentiated adenocarcinoma confined to the submucosa without evidence of lymphovascular involvement and a 1-mm margin. There is no family history of colorectal cancer.

Physical examination findings are unremarkable.

Which of the following is the most appropriate management?

(A) Colon resection
(B) CT scan of the abdomen and pelvis
(C) Radiation therapy
(D) Repeat colonoscopy in 3 months

Item 58

A 42-year-old man is evaluated in the emergency department for a 2-day history of bright red blood per rectum. He reports feeling lightheaded, which started this morning and prompted him to come to the emergency department. His medical history is otherwise unremarkable.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 95/60 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. He is clammy. Abdominal examination findings are normal. Rectal examination shows fresh blood.

He is admitted to the hospital and is stabilized with fluid resuscitation and erythrocyte transfusions.

Laboratory studies show a hemoglobin level of 8.5 g/dL (85 g/L). Upper endoscopy results are normal. Colonoscopy shows fresh blood throughout the colon and terminal ileum.

He stabilizes overnight, but the next morning he has several large bowel movements of fresh blood. He is hemodynamically unstable, and fluid resuscitation is initiated.

Which of the following is the most appropriate test to perform next?

(A) Angiography
(B) Balloon enteroscopy
(C) Repeat colonoscopy
(D) Technetium-labeled nuclear scan

Item 59

A 73-year-old man is evaluated in the hospital for a 2-day history of fever and abdominal pain. He has been on mechanical ventilation for 3 weeks owing to an exacerbation of COPD related to pneumonia. His medical history is also notable for coronary artery disease and ischemic cardiomyopathy with a left ventricular ejection fraction of 35%. His medications are piperacillin-tazobactam, albuterol, lisinopril, metoprolol, and diltiazem.

On physical examination, temperature is 38.9 °C (102.0 °F), blood pressure is 92/60 mm Hg, pulse rate is 110/min, and respiration rate is 18/min on the ventilator. BMI is 32. He is ventilated and sedated. Cardiopulmonary examination reveals a grade 3/6 holosystolic murmur at the apex and coarse breath sounds. Abdominal examination reveals right upper quadrant tenderness. No ascites or hepatosplenomegaly is noted.

Laboratory studies:

Hemoglobin	11 g/dL (110 g/L)
Leukocyte count	17,000/μL (17×10^9/L), with 92% segmented neutrophils and 5% band forms
Creatinine	1.6 mg/dL (141.4 μmol/L)
Alanine aminotransferase	Normal
Alkaline phosphatase	Normal
Bilirubin	Normal

Ultrasound of the right upper quadrant reveals an enlarged gallbladder, a thickened gallbladder wall, pericholecystic fluid, no bile duct dilatation, no gallstones, and no hydronephrosis.

Which of the following is the most appropriate management?

(A) Abdominal CT with intravenous contrast
(B) Endoscopic retrograde cholangiopancreatography with biliary sphincterotomy
(C) Laparoscopic cholecystectomy
(D) Magnetic resonance cholangiopancreatography
(E) Percutaneous cholecystostomy

Item 60

A 55-year-old man is evaluated in the emergency department for a 2-day history of mild nausea and dyspepsia that is worse with fasting and improved with eating. He has also had a 24-hour history of frequent black stools and fatigue. He has no history of gastrointestinal bleeding, alcoholism, chronic liver disease, bleeding disorders, cardiovascular disease, or cancer.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 114/66 mm Hg, pulse rate is 85/min, and respiration rate is 14/min; BMI is 27. Abdominal examination reveals epigastric tenderness without guarding or rebound. Rectal examination identifies melena. Laboratory studies are normal except for a hemoglobin level of 7.9 g/dL (79 g/L). He is admitted to the hospital and is given intravenous fluid resuscitation and intravenous proton pump inhibitor (PPI) therapy.

Upper endoscopy identifies a 1-cm clean-based gastric ulcer.

Which of the following is the most appropriate next step in management?

(A) Blood transfusion
(B) Endoscopic treatment
(C) Octreotide
(D) Substitute oral for intravenous PPI

Item 61

A 57-year-old man is evaluated during a routine examination. His medical history is notable for chronic hepatitis C infection with cirrhosis, which was diagnosed 3 years ago. He undergoes surveillance ultrasound for hepatocellular carcinoma every 6 months.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 110/82 mm Hg, pulse rate is

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65/min, and respiration rate is 18/min; BMI is 22. Muscle wasting and scleral icterus are noted. There is no flank dullness and no asterixis.

Ultrasound demonstrates three new liver masses. A four-phase CT demonstrates three lesions (1.8 cm, 2.5 cm, and 2.9 cm in size) that show arterial enhancement with venous washout. Splenomegaly and esophageal varices are also noted.

Which of the following is the most appropriate next step in management?

(A) Liver biopsy
(B) Liver transplantation evaluation
(C) Sorafenib
(D) Surgical resection
(E) Transarterial chemoembolization

Item 62

A 55-year-old man is evaluated in follow-up after a recent routine screening for antibody to hepatitis C virus (HCV) was positive. His medical history is unremarkable; he has not used illicit drugs or had any history of blood transfusions. He currently feels well and takes no medications.

Vital signs and physical examination are normal.

Laboratory studies reveal a positive HCV antibody test, but HCV RNA testing is negative. The serum alanine aminotransferase level is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Perform liver ultrasound
(B) Perform serial alanine aminotransferase monitoring
(C) Repeat HCV antibody testing
(D) Repeat HCV RNA testing
(E) No further testing

Item 63

A 46-year-old man is evaluated for intermittent rectal bleeding of 3 months' duration. He is otherwise well and takes no medications. His father had a few polyps removed from the colon when he was 71 years old, but no other details are known about his father's medical history. The patient and his wife have three children aged 8, 12, and 18 years.

On physical examination, vital signs and the remainder of the examination are normal.

Colonoscopy reveals 12 polyps ranging in size from 2 to 7 mm, all of which are removed from the colon. He undergoes genetic testing, which reveals biallelic mutations in the *MYH* gene and confirms a diagnosis of *MYH*-associated polyposis (MAP).

Genetic testing of which of the following persons will provide the most cost-effective approach to determining if the patient's children have inherited MAP?

(A) The patient's father
(B) The patient's mother
(C) The patient's 18-year-old child
(D) The patient's wife

Item 64

A 47-year-old woman is evaluated in the emergency department after vomiting bright red blood. She has alcoholic cirrhosis with ascites, which has been well controlled with diuretics. She has had jaundice and intermittent confusion for the past month. She has not consumed alcohol in the past 11 months. Her medications are spironolactone and furosemide, and octreotide was begun in the emergency department.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 72/54 mm Hg, pulse rate is 112/min, and respiration rate is 20/min; BMI is 26. She is confused. Scleral icterus, jaundice, and spider angiomata over the chest are noted. The left lobe of the liver is firm and is palpated 3 cm below the costal margin. There is no abdominal pain or flank dullness.

Laboratory studies reveal a hemoglobin level of 8.7 g/dL (87 g/L).

Ultrasound shows a coarsened liver echotexture, left lobe hypertrophy, and splenomegaly but no ascites.

Intravenous fluid resuscitation is initiated.

Which of the following is the most appropriate next step in management?

(A) Antibiotics
(B) Nonselective β-blocker
(C) Transjugular intrahepatic portosystemic shunt placement
(D) Upper endoscopy

Item 65

A 38-year-old man is evaluated for a 6-month history of fatigue. He was recently discovered to have anemia and elevated liver chemistry test results. He has had a long history of loose and occasionally malodorous stools. He has a good appetite but has unintentionally lost 2.3 kg (5.0 lb) over the past 6 weeks. He has not had blood in the stool, melena, or other obvious source of blood loss. He drinks approximately five alcoholic beverages per week and never more than two per occasion.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 108/54 mm Hg, pulse rate is 82/min, and respiration rate is 16/min; BMI is 18. He appears thin, and muscle wasting is noted. He is not in acute distress. Abdominal examination reveals a normal liver and spleen.

Laboratory studies:

Hemoglobin	11 g/dL (110 g/L)
Mean corpuscular volume	78 fL
Ferritin	8 ng/mL (8 µg/L)
Alanine aminotransferase	82 U/L
Aspartate aminotransferase	78 U/L
Alkaline phosphatase	135 U/L
Total bilirubin	Normal

Stool is negative for occult blood.

Which of the following is the most likely diagnosis?

(A) Alcohol-induced liver disease
(B) Celiac disease
(C) Chronic viral hepatitis
(D) Primary biliary cirrhosis

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Item 66

A 43-year-old woman is evaluated in the emergency department for a 4-day history of abdominal pain. She underwent laparoscopic cholecystectomy 1 week ago for symptomatic gallbladder stones. The surgery had no complications, and she left the hospital the same day. Three days after surgery she began to have episodes of epigastric pain and nausea that last 30 minutes to 2 hours. She has not had vomiting, fever, abdominal distention, jaundice, or bleeding. She is currently pain free.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 106/60 mm Hg, pulse rate is 82/min, and respiration rate is 16/min. Abdominal examination reveals well-healed laparoscopic surgery port sites. No hepatomegaly, ascites, abdominal guarding, or abdominal tenderness is noted.

Initial laboratory studies show a serum alanine aminotransferase level of 84 U/L and a serum aspartate aminotransferase level of 62 U/L. Other laboratory studies, including a complete blood count and serum alkaline phosphatase and amylase levels, are normal. Ultrasound of the right upper quadrant reveals no abdominal fluid collections; the intrahepatic and extrahepatic bile ducts are dilated, and the pancreas is not well visualized. Laboratory studies checked 24 hours later are normal.

Which of the following is the most likely diagnosis?

(A) Acute pancreatitis
(B) Bile leak
(C) Cholangitis
(D) Choledocholithiasis
(E) Sphincter of Oddi dysfunction

Item 67

A 60-year-old woman is evaluated during a routine follow-up appointment. She has gastroparesis associated with long-standing type 2 diabetes mellitus. Improved blood sugar control and efforts to eat small, frequent meals did not result in symptom improvement. In addition to these interventions, metoclopramide was started 6 months ago, after which her nausea and periodic vomiting resolved. However, she has had some restlessness at night with the urge to repeatedly cross and uncross her legs. Several weeks ago she developed a tremor in her right hand. In addition to metoclopramide, her medications are glyburide and metformin.

On physical examination, blood pressure is 125/65 mm Hg and pulse rate is 75/min. Other vital signs are normal. Tremor is noted in the lower lip and resting tremor is seen in the right hand.

In addition to dietary modification and blood glucose control, which of the following is the most appropriate management?

(A) Decrease in the metoclopramide dosage
(B) Discontinue metoclopramide and begin promethazine
(C) Gastric pacemaker placement
(D) Pyloric botulinum toxin injection

Item 68

A 38-year-old woman is hospitalized for new-onset confusion and jaundice. She noticed a yellowish discoloration of the eyes 4 days before admission. Six weeks ago she developed sinus infection symptoms that were treated with amoxicillin-clavulanate. She has no history of liver disease. She does not drink alcohol or use illicit drugs or herbal supplements. She is now taking no medications.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 118/82 mm Hg, pulse rate is 72/min, and respiration rate is 20/min; BMI is 27. She appears ill and is disoriented to time and date. Asterixis, scleral icterus, and jaundice are noted. Examination is negative for spider angiomata, palmar erythema, muscle wasting, and rash. The liver edge is palpable 2 cm below the costal margin. The spleen is not palpable.

Laboratory studies:

INR	1.9 (normal range 0.8-1.2)
Prothrombin time	28 s
Alanine aminotransferase	199 U/L
Aspartate aminotransferase	398 U/L
Total bilirubin	9.5 mg/dL (162.5 µmol/L)
Creatinine	1.2 mg/dL (106.1 µmol/L)

Serologic studies for hepatitis A IgM, hepatitis B surface antigen, hepatitis B core IgM, Epstein-Barr virus, cytomegalovirus IgM, antinuclear antibody, anti-smooth muscle antibody, and ceruloplasmin are all negative. The serum acetaminophen level is 0 µg/mL. A pregnancy test is negative.

In addition to evaluation for liver transplantation, which of the following is the most appropriate treatment?

(A) Intravenous acyclovir
(B) Intravenous glucocorticoids
(C) Intravenous *N*-acetylcysteine
(D) Oral pentoxifylline

Item 69

A 28-year-old man is evaluated in the emergency department for a piece of food stuck in his esophagus. He notes that this has happened in the past, but he was previously able to induce vomiting to relieve the blockage. He has no symptoms of gastroesophageal reflux disease, and he takes no medications.

Physical examination findings are unremarkable.

Upper endoscopy reveals a food bolus in the mid-esophagus, and gentle pressure with the endoscope passes the food bolus into the stomach. Upper endoscopy findings are shown (see top of next page).

Which of the following is the most likely diagnosis?

(A) Achalasia
(B) Barrett esophagus
(C) Diffuse esophageal spasm
(D) Eosinophilic esophagitis

Item 70

A 27-year-old woman is evaluated during a routine examination. She has a personal and family history of familial

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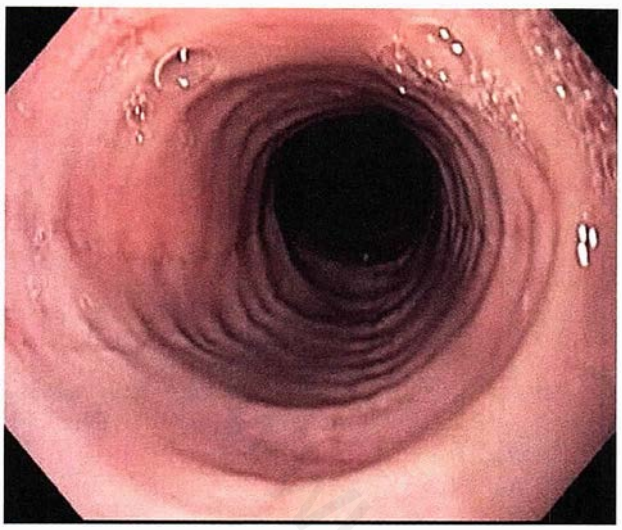

ITEM 69

adenomatous polyposis (FAP) and has undergone a total colectomy and ileorectal anastomosis.

On physical examination, vital signs are normal. The physical examination is remarkable only for a well-healed surgical scar on the abdomen.

In addition to annual sigmoidoscopy to assess for postoperative rectal polyp burden, which of the following should be recommended for FAP-related surveillance?

(A) CT of the abdomen and pelvis
(B) Ophthalmology consultation
(C) Small-bowel capsule endoscopy
(D) Upper endoscopy

Item 71

A 21-year-old man is evaluated for a 2-week history of fatigue and a 1-week history of right upper quadrant discomfort and dark urine. He drinks three alcoholic beverages per day and uses injection drugs. There is no personal or family history of liver disease or hepatocellular carcinoma.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 120/68 mm Hg, pulse rate is 112/min, and respiration rate is 20/min. He is alert and oriented. Needle marks are noted on the arms. There is no asterixis. Scleral icterus is present. There is right upper quadrant tenderness, and the liver is enlarged, soft, and tender. There is no ascites and no splenomegaly.

Laboratory studies:

INR	1.2 (normal range, 0.8-1.2)
Alanine aminotransferase	1843 U/L
Aspartate aminotransferase	1598 U/L
Total bilirubin	4.8 mg/dL (82.1 μmol/L)
Anti-hepatitis A virus IgG antibodies	Positive
Anti-hepatitis A virus IgM antibodies	Negative
Hepatitis B surface antigen	Positive
IgM antibody to hepatitis B core antigen	Positive
Hepatitis B e antigen	Positive
IgG antibody to hepatitis B core antigen	Negative
Hepatitis B surface antibody	Negative
Antibody to hepatitis B e antigen	Negative
Hepatitis B virus DNA	69,000 IU/mL

Ultrasound of the right upper quadrant reveals an enlarged liver with no masses. The spleen is normal, and there is no ascites.

Which of the following is the most appropriate management?

(A) CT of the abdomen with contrast
(B) Lamivudine
(C) Pegylated interferon
(D) Serial monitoring of liver enzymes
(E) Tenofovir

Item 72

A 31-year-old woman is evaluated for a 9-year history of episodic attacks of idiopathic pancreatitis. She previously had no pain between attacks; however, over the last 6 months, epigastric pain has become more constant and has increased in severity. The pain has not responded well to enzyme replacement, ibuprofen, and acetaminophen. She was recently started on tramadol with modest but not sufficient relief of her symptoms. Current medications are enteric-coated pancreatic enzyme replacement, ibuprofen, and tramadol.

On physical examination, vital signs are normal; BMI is 24. Abdominal examination reveals epigastric and left upper abdominal tenderness with no guarding or rebound.

Contrast-enhanced multidetector CT shows evidence of chronic pancreatitis. There is no pancreatic cyst, mass, enlargement, or pancreatic ductal dilation and no bile duct dilation or gallstones. Endoscopic ultrasonography confirms findings of chronic pancreatitis.

Which of the following is the most appropriate additional treatment?

(A) Celiac plexus blockade
(B) Extracorporeal shock wave lithotripsy
(C) Pancreaticoduodenectomy
(D) Pregabalin

Item 73

A 44-year-old man is evaluated in follow-up for symptoms of gastroesophageal reflux disease. Eight weeks ago he was evaluated for heartburn and a sour taste in his mouth and was started on once-daily pantoprazole. Despite improvement in his heartburn symptoms, he continues to wake up with an acid taste in the middle of the night. He has not had difficulty swallowing and has no reflux symptoms during the day. He confirms that he takes the medication 30 minutes before a meal.

Physical examination is unremarkable.

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Which of the following is the most appropriate next step in management?

(A) Add metoclopramide
(B) Increase pantoprazole to twice daily
(C) Perform upper endoscopy
(D) Switch to omeprazole

Item 74

A 38-year-old man is evaluated in follow-up after a diagnosis of ulcerative colitis. Ten days ago he was started on prednisone, 60 mg/d, but his symptoms have not improved. He has six to nine bloody bowel movements per day and moderate abdominal pain. He has decreased his oral intake because eating exacerbates his pain and diarrhea.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 110/56 mm Hg, and pulse rate is 96/min. He is pale but in no distress. The abdomen is diffusely tender without distention, guarding, or rebound.

Laboratory studies reveal a hemoglobin level of 9.7 g/dL (97 g/L) and a leukocyte count of 6300/μL (6.3×10^9/L).

Stool culture and *Clostridium difficile* assay are negative.

Which of the following is the most appropriate treatment?

(A) Increase prednisone to 80 mg/d
(B) Initiate adalimumab
(C) Initiate ciprofloxacin and metronidazole
(D) Initiate mesalamine
(E) Initiate sulfasalazine

Item 75

A 60-year-old man is evaluated in the emergency department for a 24-hour history of frequent black stools and fatigue without abdominal pain. His medical history is notable for a myocardial infarction 1 year ago and hypertension. He has no history of gastrointestinal bleeding, alcoholism, chronic liver disease, bleeding disorders, or cancer. His medications are aspirin, metoprolol, lisinopril, and atorvastatin.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 122/69 mm Hg, pulse rate is 87/min, and respiration rate is 14/min; BMI is 29. Abdominal examination is normal. Rectal examination identifies melena. Laboratory studies are normal except for a hemoglobin level of 10.2 g/dL (102 g/L).

He is admitted to the hospital. Aspirin is discontinued, and he is given intravenous fluid resuscitation and intravenous proton pump inhibitor (PPI) therapy (bolus followed by continuous intravenous infusion). Upper endoscopy identifies a 1-cm clean-based duodenal ulcer. Intravenous PPI is switched to an oral PPI. *Helicobacter pylori* testing is negative. He tolerates refeeding without problems and is now ready for discharge.

Which of the following adjustments should be made to this patient's medication on discharge?

(A) Change aspirin to clopidogrel
(B) Discontinue aspirin
(C) Resume aspirin before discharge
(D) Resume aspirin 4 weeks after discharge

Item 76

A 63-year-old woman is evaluated in follow-up after a colonoscopy performed last month demonstrated a 12-mm sessile serrated polyp in the transverse colon. A screening colonoscopy performed when she was 50 years old disclosed a 15-mm hyperplastic polyp in the ascending colon and two hyperplastic polyps measuring 4 and 6 mm in the transverse colon; all polyps were removed. Follow-up colonoscopy at age 55 years revealed a 5-mm sessile serrated polyp in the transverse colon and a 4-mm hyperplastic polyp in the descending colon. There is no family history of colon cancer or family members with colonic polyps.

Physical examination findings are unremarkable.

Which of the following is the most likely diagnosis?

(A) Familial adenomatous polyposis
(B) Lynch syndrome
(C) Peutz-Jeghers syndrome
(D) Serrated polyposis syndrome

Item 77

A 42-year-old man is evaluated for a 2-month history of two to four loose stools per day and abdominal cramps. He was diagnosed 1 year ago with celiac disease. Until recently, his symptoms responded to a strict gluten-free diet, with resolution of weight loss, diarrhea, abdominal pain, and iron deficiency anemia. He has not had fever, melena, or hematochezia. He has not taken any new medications.

On physical examination, vital signs are normal. The abdomen is soft with normal bowel sounds. There is no distention, tenderness, masses, or organomegaly.

Which of the following is the most appropriate management?

(A) Abdominal CT scan
(B) Careful dietary review
(C) Colonoscopy with biopsies
(D) Upper endoscopy with small-bowel biopsy

Item 78

A 45-year-old woman is evaluated in follow-up after being treated for a *Helicobacter pylori*–related duodenal ulcer 1 month ago. Despite completing a 10-day course of clarithromycin, amoxicillin, and omeprazole, urea breath testing is positive. She has no antibiotic allergies.

Physical examination is unremarkable.

Which of the following is the most appropriate treatment?

(A) Initiate a 7-day course of levofloxacin, amoxicillin, and omeprazole
(B) Initiate a 10-day course of clarithromycin, metronidazole, and omeprazole
(C) Initiate a 10-day course of levofloxacin, amoxicillin, and omeprazole

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(D) Initiate a 14-day course of clarithromycin, amoxicillin, and omeprazole
(E) Repeat the 10-day course of clarithromycin, amoxicillin, and omeprazole

Item 79

A 25-year-old man is evaluated for scleral icterus. He is a graduate student in physical chemistry; a professor noticed that he had "yellow eyes" and suggested that this finding be evaluated. The patient has no symptoms, no history of previous medical problems, and takes no medications.

On physical examination, vital signs are normal. Scleral icterus is present. The abdomen is soft and nontender. The liver and spleen are not enlarged.

Laboratory studies:

Hemoglobin	14 g/dL (140 g/L)
Reticulocyte count	1.5% of erythrocytes
Alanine aminotransferase	25 U/L
Aspartate aminotransferase	28 U/L
Alkaline phosphatase	75 U/L
Total bilirubin	2.9 mg/dL (49.6 µmol/L)
Direct bilirubin	0.2 mg/dL (3.4 µmol/L)

A blood smear is normal.

Which of the following is the most appropriate management?

(A) Direct antiglobulin (Coombs) test
(B) Hepatitis B and C serology
(C) Magnetic resonance cholangiopancreatography
(D) No further tests

Item 80

A 72-year-old man is evaluated during a routine examination. He underwent a sigmoid colectomy and adjuvant chemotherapy 4 years ago for stage III adenocarcinoma of the colon. Results of colonoscopies performed 1 year postoperatively and last year were normal.

On physical examination, he appears healthy and has no evidence of recurrent disease.

Which of the following is the most appropriate time to repeat colonoscopy?

(A) 1 year
(B) 3 years
(C) 5 years
(D) 10 years

Item 81

A 48-year-old man is evaluated for a 4-week history of heartburn that awakens him at night. The symptoms occur about three times per week. He has been taking over-the-counter antacids with incomplete relief. Food triggers include coffee and spicy foods. He has not had unintentional weight loss or difficulty swallowing.

Physical examination and laboratory studies are normal.

Which of the following is the most appropriate next step in management?

(A) Ambulatory esophageal pH monitoring
(B) Esophageal manometry
(C) Trial of a proton pump inhibitor
(D) Upper endoscopy

Item 82

A 58-year-old woman is evaluated in the emergency department for a 1-day history of nausea and pain in the left lower abdomen, which was followed by the onset of several episodes of dark-red rectal bleeding. Her bowel habits were previously normal, and she has not had tenesmus, fecal urgency, constipation, diarrhea, weight change, or previous abdominal pain. She has no history of gastrointestinal bleeding, alcoholism, chronic liver disease, bleeding disorders, or cancer. Other medical problems are hypertension, hyperlipidemia, and peripheral vascular disease. Her medications are chlorthalidone, ramipril, and simvastatin. She continues to smoke 1 pack of cigarettes daily.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 125/68 mm Hg, pulse rate is 87/min, and respiration rate is 14/min; BMI is 27. Abdominal examination reveals pain in the left lower abdomen with no guarding or rebound. No abdominal masses are noted, and the liver and spleen are not enlarged. Bowel sounds are diminished in frequency, and abdominal distention is noted. Rectal examination identifies a small amount of fresh blood and clots; no external hemorrhoids or anal fissure are noted. Femoral, popliteal, and dorsalis pedis pulses are diminished bilaterally.

Laboratory studies reveal a hemoglobin level of 10 g/dL (100 g/L), a leukocyte count of 14,000/µL (14×10^9/L), and a platelet count of 215,000/µL (215×10^9/L).

Which of the following is the most likely diagnosis?

(A) Angiodysplasia
(B) Colon cancer
(C) Diverticular bleeding
(D) Ischemic colitis
(E) Ulcerative colitis

Item 83

A 62-year-old man is evaluated after a recent screening colonoscopy. The colonoscopy disclosed a 3-mm sigmoid polyp and an 8-mm hepatic flexure polyp, both of which were removed. On pathology, the sigmoid polyp is noted to be a hyperplastic polyp, and the hepatic flexure polyp is found to be a tubulovillous adenoma with high-grade dysplasia.

Physical examination findings are unremarkable.

Which of the following is the most appropriate time to repeat colonoscopy?

(A) 3 to 6 months
(B) 1 year
(C) 3 years
(D) 5 years

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Item 84

A 72-year-old man is evaluated for a 3-month history of difficulty swallowing solid foods. He has lost 4.5 kg (10.0 lb) over the last 2 months. He has a 10-year history of heartburn, which is controlled with omeprazole once daily. His other medical problems include obesity and a 35-pack-year history of cigarette smoking. His BMI before the onset of his symptoms was 30.

On physical examination, vital signs are normal; BMI is 29. The remainder of the physical examination is unremarkable.

Laboratory studies are normal.

Which of the following is the most appropriate next step in management?

(A) CT of the chest
(B) Esophageal manometry
(C) pH study
(D) Upper endoscopy

Item 85

A 68-year-old woman undergoes upper endoscopy for evaluation of dyspepsia. She has a history of pernicious anemia. She has no other medical problems and her only medication is oral vitamin B_{12}.

On physical examination, vital signs are normal, as is the remainder of the physical examination.

Upper endoscopy discloses a 6-mm polyp in the body of the stomach, which is removed by polypectomy. Other endoscopic findings, including biopsy of the duodenum to evaluate for celiac disease, are normal. Pathologic examination of the polyp confirms a well-differentiated neuroendocrine tumor.

The fasting serum gastrin level is 1025 pg/mL (1025 ng/L).

Which of the following is the most appropriate management?

(A) CT of the abdomen and pelvis
(B) Partial gastrectomy
(C) Radiolabeled somatostatin receptor scintigraphy
(D) Observation

Item 86

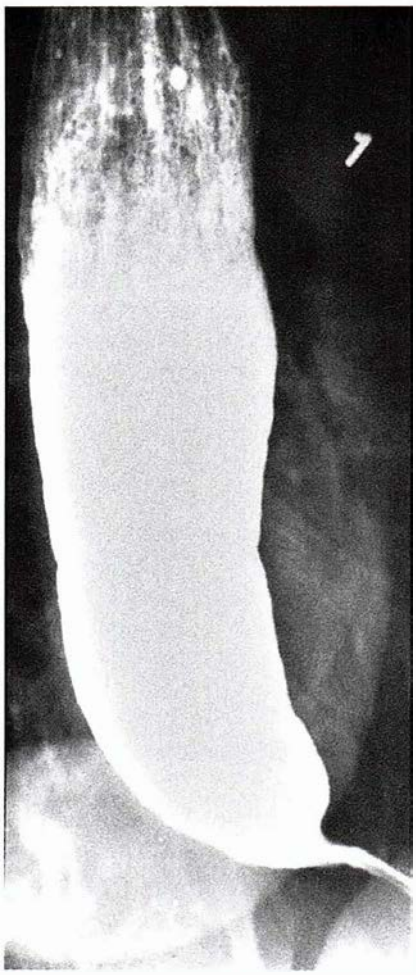
A 58-year-old man is evaluated for a 10-year history of intermittent difficulty swallowing both solids and liquids. Over the last 6 months the symptoms have worsened and now include regurgitation and weight loss of 4.5 kg (10.0 lb). He has tried antacids but has had no improvements in his symptoms.

Physical examination is unremarkable.

Laboratory studies are normal. A barium radiograph is shown (see top of next column). Upper endoscopy reveals no luminal mass. Esophageal manometry demonstrates aperistalsis and incomplete lower esophageal sphincter relaxation.

Which of the following is the most likely diagnosis?

(A) Achalasia
(B) Diffuse esophageal spasm



(C) Esophageal hypomotility
(D) Nutcracker esophagus

Item 87

A 38-year-old woman is evaluated for a 6-month history of generalized abdominal pain, nonbloody diarrhea, increased flatulence, and bloating following meals. She underwent Roux-en-Y gastric bypass with cholecystectomy 2 years ago for morbid obesity. She has no history of gastrointestinal malignancies or inflammatory bowel disease. Her medications are dicyclomine, loperamide, a multivitamin, and calcium with vitamin D.

On physical examination, vital signs are normal. BMI is 29. Abdominal examination reveals a well-healed midline incision but is otherwise normal.

Laboratory studies, including liver chemistry studies and hemoglobin level, are normal.

Which of the following is the most appropriate management?

(A) Colonoscopy
(B) Empiric treatment with antibiotics
(C) Omeprazole
(D) Right upper quadrant ultrasound
(E) Stool cultures

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Item 88

A 25-year-old woman is evaluated for a 3-day history of diarrhea with four or five loose to watery stools per day. She has had mild to moderate abdominal cramps, intermittent nausea, and muscle aches but no fever, blood in the stool, or vomiting. She has had no recent travel outside her home town and has not recently been exposed to antibiotics. She is otherwise healthy and takes no medications.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 110/70 mm Hg, and pulse rate is 85/min. She appears mildly ill. The abdomen is soft, nontender, and nondistended.

Which of the following is the most appropriate management?

(A) Colonoscopy
(B) Stool cultures
(C) Stool testing for ova and parasites
(D) Supportive care

Item 89

A 24-year-old woman is evaluated for a 2-month history of painless bright red blood per rectum that is usually associated with defecation. She has noted a protrusion of tissue from the rectum during these episodes. Her medical history is otherwise unremarkable. There is no family history of inflammatory bowel disease, colorectal polyps, or colorectal cancer.

Anoscopy discloses a rectal polyp.

Colonoscopy reveals a 14-mm pedunculated polyp in the rectum, which is removed. Colonoscopy findings are otherwise normal. Biopsy confirmed the polyp to be a juvenile polyp. Upper endoscopy is performed and is normal.

Which of the following is the most appropriate management?

(A) Genetic counseling
(B) Repeat colonoscopy in 2 years
(C) Repeat upper endoscopy in 2 years
(D) Repeat both colonoscopy and upper endoscopy in 2 years
(E) Reassurance

Item 90

A 78-year-old man is evaluated for symptoms of dysphagia that began 2 weeks ago. When he eats, he starts coughing after the first bite of food and occasionally has nasal regurgitation.

On physical examination, blood pressure is 135/90 mm Hg, pulse rate is 78/min, and respiration rate is 12/min. Left-sided weakness is noted in both extremities, upper greater than lower.

Which of the following is the most appropriate diagnostic test to evaluate this patient's dysphagia?

(A) Barium swallow
(B) Esophageal manometry
(C) Upper endoscopy
(D) Videofluoroscopy

Item 91

A 38-year-old man is evaluated in follow-up after starting therapy for ulcerative colitis. A colonoscopy performed 3 months ago showed moderate colitis extending from the rectum to the proximal transverse colon. He was initially treated with mesalamine without any improvement in his symptoms. On prednisone, 40 mg/d, his symptoms have steadily improved, with cessation of bleeding and a decrease in diarrhea. The dose of prednisone has been tapered to 20 mg/d, and he is now having one to two mostly formed stools per day.

On physical examination, vital signs are normal. Abdominal examination is unremarkable.

Laboratory studies reveal a normal complete blood count, and the serum thiopurine methyltransferase level is undetectable.

Which of the following is the most appropriate maintenance therapy?

(A) Azathioprine
(B) Infliximab
(C) 6-Mercaptopurine
(D) Methotrexate
(E) Prednisone

Item 92

A 25-year-old man is evaluated in follow-up after recently testing positive for hepatitis B surface antigen. He underwent testing as part of the immigration process from Somalia. Two other siblings also have hepatitis B virus (HBV) infection.

On physical examination, he is a young, healthy-appearing man. Vital signs are normal. No jaundice is noted, and the abdominal examination is unremarkable.

Laboratory studies:

Alanine aminotransferase	Normal
Aspartate aminotransferase	Normal
α-Fetoprotein	Normal
Hepatitis B surface antigen	Positive
Hepatitis B e antibody	Positive
Hepatitis B e antigen	Negative
HBV DNA	896 IU/mL

Ultrasound of the upper abdomen is normal.

Which of the following is the most appropriate management?

(A) Administration of hepatitis B vaccine
(B) Administration of pegylated interferon
(C) Administration of tenofovir
(D) α-Fetoprotein measurement every 12 months
(E) Ultrasound imaging of the liver every 6 months

Item 93

A 55-year-old man is hospitalized for a 3-day history of melena and a 2-week history of epigastric abdominal pain.

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His medical history is notable for degenerative arthritis of the knee, for which he takes an NSAID.

On physical examination, blood pressure is 139/65 mm Hg and pulse rate is 75/min. Other vital signs are normal. Abdominal examination reveals epigastric tenderness to light palpation.

Initial laboratory studies reveal a hemoglobin level of 12 g/dL (120 g/L). An intravenous proton pump inhibitor (PPI) and intravenous hydration are initiated.

Upper endoscopy reveals three cratered, clean-based gastric ulcers smaller than 1 cm. The esophagus, stomach, and small bowel are well visualized, and no other source of gastrointestinal bleeding is identified. Gastric biopsies are taken to test for *Helicobacter pylori*.

The patient is examined 24 hours after admission. Vital signs are stable and the abdominal examination reveals diminished tenderness to palpation. Laboratory studies reveal a hemoglobin level of 11.5 g/dL (115 g/L).

In addition to discontinuing the NSAID, which of the following is the most appropriate management?

(A) Begin oral feeding, switch to an oral PPI, and observe for 24 hours
(B) Continue intravenous PPI therapy for another 24 hours
(C) Discharge and switch to oral PPI therapy
(D) Perform repeat upper endoscopy before discharge

Item 94

A 65-year-old man is evaluated for a 4-week history of worsening reflux and heartburn. He has a 10-year history of heartburn that was previously well controlled with omeprazole. Recently he noticed that the medication is less effective, and he is experiencing heartburn in the afternoon. He has no dysphagia, nausea, vomiting, or weight loss. He takes no other medications.

On physical examination, vital signs are normal. The remainder of the examination, including abdominal examination, is unremarkable.

Upper endoscopy shows a small hiatal hernia and salmon-colored mucosa in the distal esophagus. Pathology results reveal a diagnosis of Barrett esophagus with high-grade dysplasia.

Which of the following is the most appropriate next step in management?

(A) Endoscopic ablation
(B) Esophagectomy
(C) Fundoplication
(D) Repeat upper endoscopy in 1 year

Item 95

A 51-year-old woman is evaluated in the emergency department after running her car into a stop sign several hours ago. Emergency personnel reported that she had confusion, tremulousness, and a low blood glucose level, all of which resolved after ingestion of glucose tablets. Her medical history is significant for a 1.5-year history of episodic confusion. She has no history of diabetes mellitus and has not used insulin or oral hypoglycemic agents. She has not had upper abdominal pain, pancreatitis, or weight loss. She takes no medications.

In the emergency department, vital signs and physical examination are normal.

To further investigate the hypoglycemia, she is admitted to the hospital for a 72-hour fast. Confusion is observed after 10 hours of fasting, but the neurologic examination is otherwise nonfocal. Blood samples are immediately drawn and the symptoms resolve with administration of glucose.

Laboratory studies show an elevated C-peptide level, a plasma glucose level of 45 mg/dL (2.5 mmol/L), and an elevated fasting insulin level.

Contrast-enhanced multidetector CT shows a normal-appearing pancreas.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Endoscopic retrograde cholangiopancreatography
(B) Endoscopic ultrasound
(C) Octreotide scan
(D) Transabdominal ultrasound

Item 96

A 63-year-old woman is evaluated in follow-up after a recent diagnosis of collagenous colitis. She initially presented with a 3-month history of watery diarrhea that included 7 to 10 nonbloody bowel movements per day and one or two nocturnal stools. She continues to have crampy abdominal pain and urgency but no fecal incontinence. She has been treated with loperamide, diphenoxylate, and then bismuth subsalicylate for 6 months without any improvement in her symptoms. She takes no other medications.

On physical examination, vital signs are normal. Abdominal examination is unremarkable.

Which of the following is the most appropriate treatment?

(A) Budesonide
(B) Ciprofloxacin
(C) Infliximab
(D) Mesalamine

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Answers and Critiques

Item 1 Answer: D

Educational Objective: Treat alcohol-induced liver disease with alcohol cessation.

This patient has alcohol-induced liver disease, and the most appropriate treatment is to stop alcohol intake. In alcohol-induced liver disease, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are typically elevated two to six times the upper limit of normal but AST levels above 500 U/L and ALT levels above 200 U/L are uncommon. An AST/ALT ratio above 2 to 3 is typical for alcoholic liver disease.

Hereditary hemochromatosis is an autosomal recessive disease, and homozygosity for *C282Y* is generally required to cause iron overload. The initial step in evaluating patients with suspected hemochromatosis is a serum transferrin saturation measurement, which is the most sensitive test in diagnosing this condition. Elevated serum transferrin saturations suggest hemochromatosis, and further assessment is advised, usually with serum ferritin measurement and hemochromatosis gene testing. Serum ferritin, although not usually used as an initial diagnostic study for suspected hemochromatosis, is a surrogate measure of iron stores; values greater than 1000 ng/mL (1000 µg/L) in the absence of an inflammatory state or another cause for liver disease suggest hemochromatosis. Serum ferritin measurement is therefore used as a follow-up study for elevated transferrin saturation levels. A liver biopsy specimen stained for iron confirms tissue iron overload. This patient is heterozygous for *C282Y* and has a slightly elevated serum ferritin level but a normal transferrin saturation; these findings do not support the diagnosis of hemochromatosis. Isolated elevations of serum ferritin, as seen in this patient, can be due to inflammatory states such as liver injury from another cause, including alcohol-induced liver disease. Phlebotomy (the treatment of choice for hemochromatosis) and iron chelation with deferoxamine (the typical treatment for secondary iron overload conditions) are not necessary at this time.

Repeating serum iron tests now will not add much useful information at this time; however, repeat testing should be performed later after the patient decreases his alcohol intake, as iron overload may result in some patients despite an absence of homozygosity for *C282Y*.

KEY POINT

- Isolated elevations of serum ferritin levels can be due to inflammatory states such as liver injury from another cause, including alcohol-induced liver disease.

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Item 2 Answer: C

Educational Objective: Manage chronic diarrhea caused by malabsorption of sugar-free sweeteners.

The most appropriate management is discontinuation of sugar-free sweeteners. The appearance of this patient's diarrhea coincided with healthy lifestyle changes that include the ingestion of artificial sweeteners. The temporal association between the onset of this patient's diarrhea and his dietary changes makes it highly likely that the exposure to nonabsorbable sugar alcohols ("sugar-free sweeteners") is the cause of his symptoms. The presence of bloating is also characteristic of diarrhea due to nonabsorbed carbohydrates. In this patient, further testing is not necessary before recommending the discontinuation of sugar-free sweeteners. However, if the likely diagnosis was less clear, assessment of his stool electrolytes would be helpful. In diarrhea caused by malabsorbed carbohydrates, an elevation in the osmotic gap would be expected. The osmotic gap is calculated using the following equation:

$$290 - 2 \times [\text{stool sodium} + \text{stool potassium}]$$

A gap greater than 100 mOsm/kg (100 mmol/kg) indicates an osmotic diarrhea. If the gap is less than 50 mOsm/kg (50 mmol/kg), the diarrhea is not osmotic. A gap between 50 and 100 mOsm/kg (50 and 100 mmol/kg) is equivocal. Sugar-free sweeteners are metabolized by gut bacteria, liberating gas and osmotically active substances that cause diarrhea and account for the osmotic gap.

Pancreatic cancer could present with diarrhea and weight loss, but this patient's age, absence of abdominal pain, and correlation of symptoms with dietary changes make this diagnosis less likely. Therefore, a CT scan should be deferred until a dietary cause of his symptoms is excluded.

Patients with microscopic colitis lack signs of systemic inflammation and present with painless watery diarrhea without bleeding. Diagnosis can only be made when biopsies of the colon show a predominance of intraepithelial lymphocytes in the colonic mucosa (lymphocytic colitis) or the addition of a thickened subepithelial collagen band (collagenous colitis). Colonoscopy with biopsies would be useful to exclude microscopic colitis, but this diagnosis is uncommon in younger males and would not cause an osmotic diarrhea.

Celiac disease is thought to affect nearly 0.5% to 1% of individuals in the United States. The typical features of celiac disease are diarrhea, bloating, and weight loss. Tissue transglutaminase (tTG) IgA antibody measurement would be useful to evaluate for celiac disease, but this patient's symptoms began after a dietary change, making celiac disease unlikely. In addition, the empiric use of a gluten-free diet is not recommended in the absence of a confirmed diagnosis of celiac disease.

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KEY POINT

- Artificial sweeteners have little or no absorption in the small intestine and, when taken in excess, can cause symptoms of carbohydrate malabsorption.

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Item 3 Answer: B

Educational Objective: Diagnose constrictive pericarditis as a cause of ascites.

The most likely diagnosis is constrictive pericarditis. This patient has undergone previous cardiac surgery, which is a risk factor for constrictive pericarditis. Ascitic fluid analysis should include measurement of albumin and total protein; cell count and bacterial cultures should be checked when infection is suspected. The serum-ascites albumin gradient (SAAG) should be calculated by subtracting the ascitic fluid albumin level from the serum albumin level. The main factors that distinguish a cardiac source for ascites from other sources are a SAAG of 1.1 g/dL (11 g/L) or greater and an ascitic fluid total protein level of 2.5 g/dL (25 g/L) or greater. This patient meets these criteria, making a cardiac cause for his ascites likely. In addition, over 90% of patients with constrictive pericarditis have evidence of jugular venous distention and clear lungs on auscultation. Other less commonly observed findings include Kussmaul sign (rise in jugular pressure on inspiration), paradoxical pulse, and a pericardial knock on cardiac auscultation.

Patients with cirrhosis, portal hypertension, and resultant ascites will also have a SAAG greater than 1.1 g/dL (11 g/L), but the ascitic fluid total protein level will be less than 2.5 g/dL (25 g/L). Therefore, alcoholic and nonalcoholic cirrhosis are not the likely cause of this patient's ascites.

Tuberculous peritonitis is very uncommon and is associated with a SAAG less than 1.1 g/dL (11 g/L), an ascitic fluid total protein level greater than 3 g/dL (30 g/L), and a lymphocytic predominance in the cell count with differential. Although this patient has a high ascitic fluid total protein level, the SAAG is greater than 1.1 g/dL (11 g/L) and he does not have a predominance of lymphocytes on the ascitic fluid cell count.

KEY POINT

- A serum-ascites albumin gradient (SAAG) of 1.1 g/dL (11 g/L) or greater with an ascitic fluid total protein level of 2.5 g/dL (25 g/L) or greater indicates a cardiac cause of ascites.

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Item 4 Answer: D

Educational Objective: Diagnose pill-induced esophagitis.

The most likely diagnosis is pill-induced esophagitis. This patient has retrosternal chest pain after taking doxycycline for Lyme disease. Pill-induced esophagitis has been observed with alendronate, quinidine, tetracycline, doxycycline, potassium chloride, ferrous sulfate, and mexiletine. Pills typically cause local injury at sites of anatomic narrowing of the esophagus, such as the aortic arch, gastroesophageal junction, or the esophageal indentation caused by an enlarged left atrium. Clinical symptoms include chest pain, dysphagia, and odynophagia. Symptoms may begin hours to days after starting therapy, and stopping the medication will often lead to symptom relief. Preventive strategies to decrease pill-induced esophagitis are to drink plenty of water with the medication and avoid lying down for 30 minutes after ingestion.

Barrett esophagus (BE) is present when columnar epithelium replaces the normal squamous epithelium in the distal esophagus. BE is a consequence of gastroesophageal reflux disease (GERD) and by itself is often asymptomatic. There is nothing in this patient's clinical picture to suggest BE or GERD.

Patients with infectious esophagitis may be asymptomatic or may have odynophagia or dysphagia. Infectious esophagitis is typically caused by *Candida albicans*, herpes simplex virus, and cytomegalovirus. These infections typically occur in patients who are immunosuppressed owing to medications (such as glucocorticoids, azathioprine, or tumor necrosis factor-α inhibitors) or congenital or acquired immunodeficiencies. Use of swallowed aerosolized glucocorticoids may put an immunocompetent patient at risk for some of these infections. *Candida* infection is characterized by small, white, raised plaques on upper endoscopy, and esophageal brushings confirm the diagnosis. Pill-induced esophagitis is a much more likely diagnosis for this immunocompetent patient taking doxycycline than is *Candida* esophagitis.

Eosinophilic esophagitis (EoE) is defined as esophageal squamous mucosal inflammation caused by eosinophilic infiltration. EoE is usually seen in young men who present with dysphagia and a food-bolus obstruction. This patient does not have symptoms characteristic of EoE.

KEY POINT

- Pill-induced esophagitis is characterized by chest pain, dysphagia, and odynophagia and has been associated with alendronate, quinidine, tetracycline, doxycycline, potassium chloride, ferrous sulfate, and mexiletine.

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Item 5 Answer: A

Educational Objective: Treat spontaneous bacterial peritonitis.

The most appropriate treatment is cefotaxime and albumin. This patient has been hospitalized with overt hepatic encephalopathy, which in many instances may be the sole presenting feature of spontaneous bacterial peritonitis (SBP). It is important to perform a diagnostic paracentesis in patients with ascites who are admitted to the hospital, especially those with overt hepatic encephalopathy. This patient's ascitic fluid analysis demonstrates a polymorphonuclear cell count of 820/μL, which exceeds the diagnostic threshold for SBP of 250/μL. The most important therapeutic intervention at this time is treatment of SBP, which precipitated this patient's hepatic encephalopathy. Appropriate treatment of SBP consists of a systemic antibiotic and intravenous albumin. For patients without nosocomial SBP or recent exposure to β-lactams, intravenous cefotaxime is the drug of choice. Patients with a serum creatinine level greater than 1 mg/dL (88.4 μmol/L), a serum bilirubin level greater than 4 mg/dL (68.4 μmol/L), or a blood urea nitrogen level greater than 30 mg/dL (10.7 mmol/L) should receive 1.5 g/kg of intravenous albumin (25%) on the day of diagnosis and 1 g/kg of albumin on day 3; this practice has demonstrated a survival benefit.

Cefotaxime and normal saline are not appropriate because this patient's survival will be improved with the use of intravenous albumin, whereas use of normal saline may result in worsening ascites.

Norfloxacin (or ciprofloxacin) is effective for secondary prevention of SBP and should be given to this patient indefinitely after completion of intravenous cefotaxime. However, norfloxacin is a poorly absorbed second-generation fluoroquinolone that is not appropriate for treatment of newly diagnosed SBP.

Treatment of overt hepatic encephalopathy is aimed at treating the underlying precipitant, in this case SBP. In these cases treatment consists of administering lactulose to achieve two to three, soft, formed bowel movements per day. Rifaximin is FDA approved for maintenance of remission in patients with previous episodes of overt hepatic encephalopathy, but it is not approved for initial treatment of overt hepatic encephalopathy or as treatment for SBP.

KEY POINT

- Appropriate treatment of spontaneous bacterial peritonitis consists of a third-generation cephalosporin and, in many patients, intravenous albumin.

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Item 6 Answer: D

Educational Objective: Evaluate dyspepsia with alarm features.

The most appropriate management is further investigation with upper endoscopy. Guidelines recommend upper endoscopy for patients with dyspepsia and alarm features. Alarm features include onset after age 50 years; anemia; dysphagia; odynophagia; vomiting; weight loss; family history of upper gastrointestinal malignancy; personal history of peptic ulcer disease, gastric surgery, or gastrointestinal malignancy; and abdominal mass or lymphadenopathy on examination. For patients younger than 50 years without alarm features, a test-and-treat approach for *Helicobacter pylori* is reasonable and cost effective when the patient is from an area where the prevalence of *H. pylori* is high (such as developing countries). However, a proton pump inhibitor is the most appropriate first-line strategy if the patient is from an area where the prevalence of *H. pylori* is low. Endoscopic evaluation should be reserved for those who do not respond to therapy. Cost-effective tests for *H. pylori* include urea breath testing and fecal antigen testing. This patient with uninvestigated dyspepsia has multiple alarm features, including age, progressive symptoms of recent onset, nausea, change in eating habits, weight loss, and anemia. These alarm features warrant prompt structural evaluation.

Although *H. pylori* gastritis is a possibility in this patient, empiric treatment of *H. pylori* infection is not an appropriate management strategy in patients with uninvestigated dyspepsia with alarm features.

An empiric trial of omeprazole would not be appropriate because it may mask a gastric ulcer or cancer. Given this patient's alarm features, a structural evaluation of the upper gastrointestinal tract should be performed before a trial of PPI therapy.

The serologic antibody test for *H. pylori* does not accurately identify active infection. Furthermore, treatment for a positive antibody may mask a more serious upper gastrointestinal condition such as an ulcer or gastric cancer.

KEY POINT

- Upper endoscopy is recommended for the exclusion of upper gastrointestinal structural causes of dyspepsia; it should be performed in patients who have alarm features.

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Item 7 Answer: A

Educational Objective: Evaluate for ulcerative colitis in a patient with primary sclerosing cholangitis.

The most appropriate next step in management is colonoscopy. Primary sclerosing cholangitis (PSC) is diagnosed by measuring liver enzymes and performing cholangiography.

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Serum alkaline phosphatase values are 3 to 10 times the upper limit of normal, and serum alanine aminotransferase and aspartate aminotransferase levels are two to three times the upper limit of normal. Serum total bilirubin levels may be normal in 60% of patients. Serum antinuclear and anti-smooth muscle antibodies are present in 20% to 50% of patients, but antimitochondrial antibodies are rarely found in PSC. The gold standard for diagnosis of PSC is cholangiography. Diagnostic findings consist of segmental bile duct fibrosis with saccular dilatation of normal intervening areas, resulting in the characteristic "beads on a string" appearance. Magnetic resonance cholangiopancreatography (MRCP) has been increasingly used and has an overall diagnostic accuracy rate of 90%. This patient's clinical presentation and cholangiographic findings are consistent with PSC. Eighty percent of patients with PSC have ulcerative colitis. Given this patient's 3-year history of diarrhea, colonoscopy should be performed to evaluate for ulcerative colitis. Patients with PSC and ulcerative colitis are at increased risk for colon cancer and should receive surveillance. There is no effective medical therapy for PSC. Endoscopic dilatation of biliary strictures and removal of stones may be necessary in patients with progressive cholestasis or symptoms of cholangitis. PSC is generally a progressive disease that often requires liver transplantation.

MRCP has already been performed; endoscopic retrograde cholangiopancreatography (ERCP) will not add any additional useful information to the clinical picture. ERCP will be useful in managing choledocholithiasis, occurring in 10% to 25% of symptomatic patients, and dilatation of dominant strictures, occurring in 5% to 10% of patients.

Liver biopsy is usually not necessary for the diagnosis of PSC. Liver biopsy is required for making a diagnosis of small-duct PSC when cholangiography is normal. Periductal fibrosis with inflammation, bile duct proliferation, and ductopenia are the main histologic findings.

IgG4-associated cholangitis may mimic PSC, but patients will usually have abnormalities in the pancreas on cross-sectional imaging. This patient did not have these findings, so serum IgG4 measurement is not required.

KEY POINT

- Eighty percent of patients with primary sclerosing cholangitis have ulcerative colitis.

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Item 8 Answer: A

Educational Objective: Manage upper gastrointestinal bleeding caused by a high-risk ulcer.

The most appropriate management is endoscopic therapy. Upper endoscopy should be performed at the time of an upper gastrointestinal bleed after appropriate volume resuscitation to diagnose the cause of bleeding, provide a prognosis, and provide endoscopic therapy if required. An ulcer with a visible vessel has an approximately 50% risk of rebleeding if not treated endoscopically. These ulcers can be effectively treated with injection of sclerosants, thermal coagulation via endoscopic probes, or mechanical modalities such as hemostatic clips. Clean-based ulcers rebleed in less than 5% of cases and do not require endoscopic therapy.

Prospective trials have shown a 5% to 10% rebleeding rate following endoscopic hemostasis. In these patients, endoscopic therapy may be repeated if the patient remains hemodynamically stable and if the endoscopist thinks that the bleeding lesion is amenable to endoscopic therapy. If repeat endoscopy is unsuccessful or the bleeding vessel is inaccessible or too large, surgical consultation should be obtained. However, in this patient, endoscopic intervention is the first management choice for an accessible and small visible vessel.

Octreotide may have a marginal benefit by decreasing the rate of nonvariceal bleeding, but it is inferior to intravenous proton pump inhibitors. Octreotide is most useful in patients with variceal bleeding.

Observation is not appropriate for this patient with a high-risk lesion seen on endoscopy. Without endoscopic therapy, patients with this type of lesion have a 30% to 50% chance of rebleeding.

KEY POINT

- High-risk ulcers are characterized by active arterial spurting or a nonbleeding visible vessel; they should be treated endoscopically with hemostatic clips, thermal therapy, or injection of sclerosants.

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Item 9 Answer: D

Educational Objective: Treat acute kidney injury in the context of cirrhosis with a colloid fluid challenge.

The most appropriate treatment for acute kidney injury in this patient is 25% albumin. This patient has acute kidney injury (AKI) and hepatic encephalopathy, most likely precipitated by dehydration from lactulose-induced diarrhea. AKI is common and occurs in approximately 20% of hospitalized patients with cirrhosis. In approximately 70% of patients with cirrhosis and AKI, the precipitant is prerenal, from sources such as infection, gastrointestinal bleeding, excessive diuresis, or diarrhea. This patient has dry mucous membranes, diarrhea, and no obvious signs of infection or bleeding and has been treated with diuretics. Approximately two thirds of patients with prerenal AKI are fluid responsive. After stopping diuretics and lactulose, the best initial treatment is intravenous colloid administration, usually in the form of 25% albumin, administered at 1 g/kg body weight per day in divided doses.

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CONT.

The other third of patients who are not fluid responsive generally have type 1 or type 2 hepatorenal syndrome (HRS). HRS diagnostic criteria consist of (1) an increase in the serum creatinine level to greater than 1.5 g/dL (132.6 µmol/L) over days to weeks, (2) lack of response to an albumin challenge of 1 g/kg/d for 2 days, and (3) the absence of shock, nephrotoxic drugs, active urine sediment, proteinuria greater than 500 mg/d, and ultrasound evidence of parenchymal kidney disease or obstruction. Although this patient could have evolving HRS, this cannot be diagnosed until fluid responsiveness has been evaluated. If she is not fluid responsive and does not have evidence of acute tubular necrosis on urinalysis, then treatment for type 1 HRS could begin. Norepinephrine with albumin infusion is effective for patients with type 1 HRS who are in the ICU. Midodrine, octreotide, and albumin are the appropriate treatments for type 1 HRS in patients outside of the ICU. Terlipressin is effective for type 1 HRS but is not available in the United States.

KEY POINT

- Acute kidney injury occurs in approximately 20% of hospitalized patients with cirrhosis; such patients should receive a fluid challenge (usually with 25% albumin) to evaluate fluid responsiveness before hepatorenal syndrome can be diagnosed.

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Item 10 Answer: C

Educational Objective: Manage acute cholangitis.

The most appropriate management is endoscopic retrograde cholangiopancreatography (ERCP). The presence of fever, abdominal pain, and jaundice (Charcot triad) is consistent with acute cholangitis, and ERCP is indicated. Dilation of the extrahepatic and intrahepatic bile ducts on abdominal ultrasound or noncontrast CT scan is consistent with a diagnosis of choledocholithiasis, although dilated bile ducts may not be identified in patients with acute biliary obstruction. Acute cholangitis is usually caused by *Escherichia coli*, *Klebsiella* species, *Pseudomonas* species, and enterococci and can progress to septic shock with or without liver abscess formation. Empiric antibiotics targeting these likely organisms should be administered immediately when cholangitis is suspected. If improvement is not seen rapidly, urgent ERCP should be performed to remove the common bile duct stone. When duct decompression with ERCP is not possible, percutaneous cholangiography with biliary tube placement can be performed.

Abdominal CT is not appropriate because it would delay ERCP, which is needed urgently. In addition, it would not add much useful information to this patient's ultrasound findings.

Cholecystectomy will remove the source of future gallstones, but it will not decompress this patient's obstructed common bile duct or reduce her risk of dying from sepsis. Cholecystectomy will eventually be recommended for this patient; however, it must be delayed until the cholangitis is resolved.

Percutaneous cholecystostomy could be considered if this patient had acute cholecystitis, but her clinical history suggests common bile duct obstruction rather than simple cystic duct obstruction. The pain of acute cholecystitis typically lasts longer than 3 hours and shifts to the right upper quadrant, causing localized tenderness. The pain is due to gallbladder distention, ongoing gallbladder contraction against the obstructed outlet, and occasionally bacterial infection, leading to inflammation of the gallbladder wall. Fever, nausea, and vomiting are frequent findings, but jaundice is unusual. Findings of gallbladder inflammation may include thickening of the gallbladder wall (>2 mm), intramural gas, and pericholecystic fluid. These findings are not present in this patient.

KEY POINT

- Patients with cholangitis should receive immediate broad-spectrum antimicrobial therapy; if rapid improvement is not seen, urgent endoscopic stone removal should be performed.

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Khashab MA, Tariq A, Tariq U, et al. Delayed and unsuccessful endoscopic retrograde cholangiopancreatography are associated with worse outcomes in patients with acute cholangitis. Clin Gastroenterol Hepatol. 2012 Oct;10(10):1157-61. [PMID: 22507875]

Item 11 Answer: C

Educational Objective: Provide the appropriate prevention strategy for NSAID-induced injury.

The most appropriate management is to start standard-dose omeprazole (20 mg/d). The chronic use of NSAIDs is associated with significant gastrointestinal risk. Nearly one in four chronic NSAID users will develop ulcer disease and as many as 4% will have bleeding or perforation complications. Risk factors for NSAID-related gastrointestinal complications include a history of peptic ulcer disease or other gastrointestinal bleeding event; *Helicobacter pylori* infection; age 65 years or older; concomitant use of aspirin (of any dose), anticoagulants, other NSAIDs, or glucocorticoids; high-dose NSAID use; and chronic comorbid illness. Although this patient is currently tolerating her daily NSAID well, she has several risk factors that put her at increased risk for NSAID-associated gastric injury (age older than 65 years and daily low-dose aspirin for cardiovascular risk reduction). Therefore, the most appropriate strategy for gastric protection is omeprazole, 20 mg/d. Standard-dose daily proton pump inhibitor (PPI) therapy has consistently demonstrated superiority to placebo in significantly reducing the risk of NSAID-induced gastric injury. Higher PPI doses have not demonstrated superiority to standard-dose therapy. If PPI therapy cannot be used, misoprostol, 200 µg four times daily, is an alternative; however, side effects such as abdominal cramps and diarrhea may be limiting.

Changing this patient's aspirin to an enteric-coated formulation will not reduce the risk of NSAID-induced gastrointestinal injury.

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Given this patient's risk profile, preventive measures should be pursued. Therefore, continued observation alone on the current medication regimen is not appropriate.

KEY POINT

- Standard-dose daily proton pump inhibitor therapy significantly reduces the risk of NSAID-induced gastric injury.

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Item 12 Answer: D

Educational Objective: Treat chronic pancreatitis with pancreatic enzymes.

The most appropriate treatment is pancreatic enzymes. This patient has steatorrhea and evidence of malnutrition (temporal wasting, poor dentition, hypoalbuminemia, and weight loss) that is attributable to exocrine pancreatic insufficiency from chronic pancreatitis. This diagnosis is based on established risk factors (past heavy and sustained alcohol use and cigarette smoking), clinical features (previous attacks of pancreatitis, current weight loss), and objective findings (pancreatic calcifications and steatorrhea). Exocrine insufficiency is treated using enteric-coated pancreatic enzymes. Steatorrhea that persists despite enzyme replacement may be treated by increasing the dose to 90,000 units of lipase per meal; confirming the diagnosis of pancreatic insufficiency by performing direct pancreatic function testing (if available); and excluding nonpancreatic causes, including bacterial overgrowth, celiac disease, and terminal ileal disease. Fat-soluble vitamin replacement is also important. Endocrine insufficiency can be difficult to manage because patients with chronic pancreatitis often lose counterregulatory hormones such as glucagon when their islet cells are destroyed, rendering their plasma glucose levels more labile. If diabetes mellitus occurs, it should be treated with insulin.

Loperamide and fiber are symptomatic therapies for chronic diarrhea. These are not appropriate in this patient because they do not treat the cause of steatorrhea or the associated weight loss and malnutrition.

A gluten-free diet is not appropriate because this patient's serologic testing for celiac disease was negative. Celiac disease is an established risk factor for acute and chronic pancreatitis and a cause of steatorrhea.

KEY POINT

- Common criteria for diagnosis of chronic pancreatitis consist of clinical features (pain, recurrent attacks of pancreatitis, weight loss) with objective findings of steatorrhea and pancreatic calcifications.

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Forsmark CE. Management of chronic pancreatitis. Gastroenterology. 2013 Jun;144(6):1282-91.e3. [PMID: 23622138]

Item 13 Answer: C

Educational Objective: Evaluate for celiac disease in a patient with chronic diarrhea.

The most appropriate diagnostic test to perform next is testing for serum tissue transglutaminase antibodies. This patient has chronic diarrhea with clinical evidence of steatorrhea, the differential diagnosis of which includes small-bowel mucosal diseases, pancreatic insufficiency, small intestinal bacterial overgrowth, and lymphatic obstruction. Celiac disease is a chronic inflammatory enteropathy caused by an immune-mediated reaction to gluten and gliadins and is present in 0.5% to 1% of the U.S. population. The chronic diarrhea, abdominal pain, and malabsorption present in this patient suggest this diagnosis, and the initial step is testing for serologic markers for the disease. IgA tissue transglutaminase antibody is the screening test of choice for celiac disease and is both sensitive and specific; initial testing for celiac disease should be done while the patient is consuming gluten.

While anti-*Saccharomyces cerevisiae* antibodies (ASCA) have been proposed as a serologic method for differentiating Crohn disease from ulcerative colitis, they are neither adequately sensitive nor specific and can lead to false-positive results if used as a screening test for gastrointestinal symptoms. There is no role for ASCA in the evaluation of a patient with suspected celiac disease.

Endoscopy (flexible sigmoidoscopy or colonoscopy) can be an important test in evaluating selected patients with chronic diarrhea, but it would not be the most appropriate next study in this patient with diarrhea with a high pretest probability of celiac disease given his history of type 1 diabetes mellitus with clear evidence of malabsorption. Flexible sigmoidoscopy in particular would only visualize the distal aspects of the colon, and because colonic disorders do not cause malabsorption, this test would not be diagnostic in this patient. A positive tissue transglutaminase test and confirmation of celiac disease as the cause of diarrhea in this patient would make colonoscopy unnecessary and avoid the potential risks of the procedure.

Upper endoscopy with small-bowel biopsies is performed in patients with a consistent clinical picture and positive serologic studies to confirm the diagnosis of celiac disease. Characteristic biopsy findings include intraepithelial lymphocytosis, crypt hyperplasia, and villous blunting. However, upper endoscopy with biopsies would not be indicated as an initial study in patients suspected of having celiac disease.

Video capsule endoscopy can visualize the small-bowel mucosa and might show nonspecific changes in a patient with suspected celiac disease; however, it is not indicated as an initial diagnostic study before serologic testing or for confirmation if the patient is a candidate for routine upper endoscopy with biopsy.

KEY POINT

- Serologic testing for tissue transglutaminase antibodies should be performed in patients with suspected celiac disease, which may present with weight loss, steatorrhea, and nutritional deficiencies.

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Item 14 Answer: D

Educational Objective: Diagnose irritable bowel syndrome.

The most appropriate management is reassurance and patient education that addresses the diagnosis and treatment of irritable bowel syndrome (IBS). The American College of Gastroenterology recommends a simple definition of IBS: abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least 3 months. The diagnosis of IBS is further subtyped into diarrhea predominant (IBS-D), constipation predominant (IBS-C), or mixed (IBS-M), which alternates between diarrhea and constipation. This young woman has symptoms that fulfill diagnostic criteria for IBS-C in the absence of any alarm features. A recent evidence-based review by the American College of Gastroenterology IBS task force concluded that, in such a setting, no further biochemical or structural testing is indicated given the low yield of testing. The routine pursuit of a complete blood count, serum chemistry studies, thyroid function studies, stool studies for ova and parasites, and abdominal imaging is unnecessary in this setting. An essential initial step in management of IBS is the clear establishment of the diagnosis with explanation of and reassurance regarding the patient's symptoms. In addition to reassurance, over-the-counter remedies addressing constipation or diarrheal symptoms can be recommended, as these agents are safe and potentially effective. In this patient, the osmotic laxative polyethylene glycol is likely to be well tolerated and to improve this patient's constipation symptoms.

This patient has no symptoms of diarrhea or blood in the stool, and there is no family history of colon cancer to justify a colonoscopy. The passage of mucus is commonly reported in IBS, so this symptom alone does not warrant colonoscopy.

The typical features of celiac disease are diarrhea, bloating, and weight loss. A tissue transglutaminase serologic study would be a reasonable screening test for celiac disease in a patient with IBS-D, but it is not necessary in patients with IBS-C.

KEY POINT

- Routine complete blood count, serum chemistry studies, thyroid function studies, stool studies for ova and parasites, and abdominal imaging are unnecessary in establishing the diagnosis of irritable bowel syndrome.

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Item 15 Answer: C

Educational Objective: Diagnose *Helicobacter pylori* infection in a patient at high risk using the appropriate test.

The most appropriate management is noninvasive *Helicobacter pylori* testing, followed by eradication therapy if test results are positive. Noninvasive *H. pylori* testing modalities include serology, the fecal antigen test, or the urea breath test. The recommended and most cost-effective approach for this patient is serologic testing. He is younger than 50 years of age with vague abdominal discomfort without alarm features (anemia; dysphagia; odynophagia; vomiting; weight loss; family history of upper gastrointestinal malignancy; personal history of peptic ulcer disease, gastric surgery, or gastrointestinal malignancy; and abdominal mass or lymphadenopathy on examination), and, most importantly, he has been residing in an area where the prevalence of *H. pylori* is high (a developing country). Serologic testing for *H. pylori* has limitations in that it does not test for active *H. pylori* infection and has poor positive predictive value. Therefore, positive serologic results must be interpreted with caution when performed in populations with a low background prevalence of *H. pylori*, such as those in developed countries. Fecal antigen testing and urea breath testing offer a more accurate means of noninvasive testing for *H. pylori*, as both of these test modalities assess for the presence of active infection. Therefore, these testing modalities should be used to test for *H. pylori* in individuals for whom the background prevalence of *H. pylori* is low. Although these tests are more expensive and logistically more complicated than serology, they offer greater testing accuracy. Fecal antigen and urea breath tests are equivalent in terms of their accuracy. The choice of fecal antigen testing versus urea breath testing will typically depend on test availability and patient preference.

A barium esophagogram would have limited utility in this patient with dyspepsia and no associated symptoms consistent with esophageal disease, such as acid brash, dysphagia, and odynophagia. Even with these symptoms, an empiric trial of a proton pump inhibitor could be considered consider prior to imaging with a barium esophagogram.

Empiric treatment for *H. pylori* is not appropriate because the diagnosis of *H. pylori* should be made before initiating treatment. Empiric therapy for *H. pylori* is expensive and carries the potential harm of medication side effects; therefore, it would not be indicated without first confirming active infection.

Upper endoscopy would be appropriate for patients whose symptoms do not respond to *H. pylori* treatment or PPI therapy. Patients older than 50 years or with alarm features should be evaluated with upper endoscopy. In patients without alarm features, endoscopy as an initial management intervention would be unlikely to find gastritis, peptic ulcer disease, or esophagitis.

KEY POINT

- Before pursuing *Helicobacter pylori* eradication therapy, noninvasive testing for *H. pylori* should be performed to confirm infection.

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Item 16 Answer: D

Educational Objective: Diagnose Wilson disease presenting as acute liver failure.

The most likely diagnosis is Wilson disease. Wilson disease is a rare congenital disorder of copper excretion that occurs in approximately 1 in 30,000 live births. Young patients with Wilson disease tend to present with acute liver failure; older patients present with chronic liver disease and/or neurologic manifestations. Wilson disease should be considered in all patients younger than 40 years of age who have unexplained liver disease. When Wilson disease causes acute hepatitis, usually in young patients, the sudden release of copper from liver cells can also induce hemolytic anemia. This patient's low hemoglobin level, increased reticulocyte count, and elevated indirect bilirubin level support the diagnosis of hemolytic anemia. The presence of a low alkaline phosphatase level (copper interferes with the synthesis of alkaline phosphatase enzymes), a moderate elevation of aminotransferase levels despite other evidence of liver dysfunction, and hemolytic anemia make Wilson disease likely. The most common screening test for Wilson disease is serum ceruloplasmin, which is reduced; elevated urine excretion of copper is ascertained to verify the presumptive diagnosis of Wilson disease. In a young patient with elevated liver test results, a low ceruloplasmin level, and elevated urine copper excretion, liver biopsy is typically obtained to confirm the diagnosis of Wilson disease. Liver biopsy demonstrates excessive intrahepatic copper. Kayser-Fleischer rings, noted on ophthalmologic examination, indicate copper deposition in the Descemet membrane of the iris. Patients with acute liver failure due to Wilson disease rarely recover and should be urgently referred for liver transplantation.

Acetaminophen hepatotoxicity and herpes hepatitis present with very high aminotransferase levels, often over 5000 U/L. This patient's aminotransferase levels are not compatible with these conditions.

Budd-Chiari syndrome, characterized by an obstruction of hepatic venous outflow, can occasionally present with acute liver failure but has ascites as a predominant clinical manifestation. This patient does not have ascites, which makes Budd-Chiari syndrome unlikely.

KEY POINT

- Wilson disease should be considered in all patients younger than 40 years of age who have unexplained liver disease.

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Item 17 Answer: B

Educational Objective: Manage gallbladder polyps.

The most appropriate management is cholecystectomy. The finding of a gallbladder polyp larger than 1 cm is an indication for cholecystectomy, even if the patient is asymptomatic. Gallbladder polyps are found in approximately 5% of ultrasound examinations. Although only a small percentage of gallbladder polyps are neoplastic (adenoma or adenocarcinoma), the risk for neoplasia increases as polyp size increases. In the absence of gallstones, a gallbladder polyp smaller than 1 cm can be followed with serial ultrasound examinations unless the patient is symptomatic or has primary sclerosing cholangitis. For patients with gallstones and any size polyp, cholecystectomy is usually recommended.

Further imaging with abdominal CT, endoscopic retrograde cholangiopancreatography, or magnetic resonance cholangiopancreatography is not necessary in this patient because she has an asymptomatic, incidental gallbladder polyp; however, these tests should be considered if this patient had symptoms or elevated liver chemistry tests suggesting bile duct obstruction or malignancy.

KEY POINT

- The finding of a gallbladder polyp larger than 1 cm is an indication for cholecystectomy, even if the patient is asymptomatic.

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Item 18 Answer: A

Educational Objective: Treat acute pancreatitis caused by gallstones.

The most appropriate management is to perform cholecystectomy for gallstone-induced acute pancreatitis prior to hospital discharge. In the United States, 80% of cases of acute pancreatitis are caused by gallstones or alcohol use. The pathophysiology of gallstone-induced pancreatitis is likely related to gallstone obstruction of the common channel (bile-pancreatic duct) or reflux of bile into the pancreatic duct owing to impaction of the stone at the ampulla. Elevation of the alanine aminotransferase concentration is the most clinically useful laboratory test predicting gallstone pancreatitis. In addition, this patient has evidence of gallstones on ultrasonography. Patients with gallstone pancreatitis and no complications should have a cholecystectomy prior to discharge to prevent recurrent attacks. Delaying cholecystectomy is warranted to reduce the risk of sepsis and complications in patients with severe acute pancreatitis, particularly with pancreatic necrosis and acute peripancreatic fluid collections.

Cholecystokinin hepatobiliary (CCK-HIDA) scintigraphy is most commonly used for evaluation of cholecystitis, biliary obstruction, and suspected gallbladder dysfunction.

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H CONT.

This is not appropriate for this patient because he has no ultrasound evidence of cholecystitis.

Endoscopic retrograde cholangiopancreatography (ERCP) and biliary sphincterotomy are not indicated in the absence of cholangitis or nonresolving biliary obstruction unless the patient is not a surgical candidate for cholecystectomy. Obstruction is typically indicated by a dilated bile duct and persistently elevated liver enzyme levels.

Antibiotics should be reserved for treatment of cholangitis, acute cholecystitis, or other infections, which are absent in this patient. Cholangitis typically presents with fever, jaundice, and pain in the right upper quadrant (Charcot triad). Most patients will have cholelithiasis, elevated aminotransferase levels, and hyperbilirubinemia. Ultrasonography may show a dilated common bile duct. Findings of cholecystitis may include thickening of the gallbladder wall (>2 mm), intramural gas, and pericholecystic fluid. Hepatobiliary scintigraphy is indicated to confirm or exclude the diagnosis of acute cholecystitis when the initial ultrasound is indeterminate.

KEY POINT

- Patients with uncomplicated gallstone-induced acute pancreatitis should undergo cholecystectomy prior to hospital discharge to prevent recurrent attacks.

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Item 19 Answer: A

Educational Objective: Treat Crohn disease in a pregnant patient.

The most appropriate treatment is certolizumab. The previously used treatment approach for Crohn disease (CD) was to (1) initiate therapy with 5-aminosalicylate drugs such as mesalamine at diagnosis; (2) begin thiopurine therapy with azathioprine or 6-mercaptopurine if a patient requires repeated courses of glucocorticoids; and (3) begin therapy with anti–tumor necrosis factor (anti-TNF) agents if these other therapies are unsuccessful. This paradigm has been challenged by newer studies showing that 5-aminosalicylates have only minimal, if any, efficacy in CD, and the success of treatment is significantly higher when anti-TNF therapy is begun alone or in combination with thiopurines earlier in the disease course. Many experts have abandoned the use of 5-aminosalicylates entirely for CD except perhaps for those with mild Crohn colitis. The decision to use thiopurine or anti-TNF monotherapy versus combination therapy is based on an individual patient's severity of symptoms and risk factors for developing complications of their disease balanced against the potential side effects of these treatments. This patient with new-onset CD is in her first trimester of pregnancy. Treatment with an anti-TNF agent is effective for induction and maintenance of remission in CD and is generally considered to be safe during pregnancy (FDA pregnancy category B). The three anti-TNF agents approved for CD are infliximab, adalimumab, and certolizumab. Because certolizumab is pegylated, it should have very little, if any, placental transfer and therefore is favored by some clinicians in a pregnant patient over the other two agents. Although endoscopic procedures are generally avoided in pregnant patients unless absolutely necessary, flexible sigmoidoscopy is safer than colonoscopy, and in this patient it was useful to confirm that her symptoms are due to active CD before committing her to expensive immunosuppressive medications.

Antibiotics are generally not recommended for induction of remission in CD because no particular class of drug can be endorsed based on available data. Furthermore, ciprofloxacin (pregnancy category C) should be used in pregnancy only if the potential benefits outweigh the risk to the fetus. Metronidazole is a pregnancy category B drug.

Controlled ileal-release budesonide is effective for ileocolonic CD, but it would not be effective in this patient with left-sided colitis. In addition, it is classified as category C for use during pregnancy.

Mesalamine may be used to treat ulcerative colitis, but it is not effective in most patients with CD.

Methotrexate may be effective for inducing and maintaining remission in CD, but it is contraindicated during pregnancy. Methotrexate is a classified as category X for use in pregnancy because it may cause fetal death and/or congenital abnormalities.

KEY POINT

- Treatment with an anti–tumor necrosis factor agent is effective for induction and maintenance of remission in Crohn disease and is generally considered to be safe during pregnancy (FDA pregnancy category B).

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Item 20 Answer: D

Educational Objective: Treat functional dyspepsia.

The most appropriate management is to start nortriptyline. This patient has functional dyspepsia (FD), a chronic symptom complex consisting of epigastric pain/discomfort, postprandial fullness, and/or early satiety in the absence of a structural explanation. No universally effective therapy exists, but a variety of treatments are effective in subgroups of FD. Treatment strategies must carefully weigh the therapeutic benefits with the side effects of therapy. Given the low risk of side effects, initial treatment strategies include treatment of *Helicobacter pylori* infection, proton pump inhibitor (PPI) therapy, or H_2-blocker therapy. Although generally well tolerated, these treatment strategies frequently fail to adequately alleviate symptoms. In particular, treatment for *H. pylori* is unlikely to be beneficial in this patient with negative test

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results. Clinical trials have not demonstrated an added benefit of high-dose PPI therapy compared with standard-dose therapy. Therefore, increasing omeprazole to twice daily would not be beneficial for this patient. Additionally, switching from PPI to H_2-blocker therapy is of little benefit given these agents' similar physiologic effect on gastric acid production. Tricyclic antidepressants (TCA) are generally well tolerated, with response rates as high as 70% in small, marginal-quality trials. Despite these limitations, the efficacy and side-effect profile make a trial of a low-dose TCA such as nortriptyline an attractive treatment strategy when symptoms do not respond to PPIs or H_2 blockers. Therefore, nortriptyline is the most appropriate management.

Narcotics such as hydrocodone have no role in the treatment of FD and are likely to promote side effects as well as dependence.

The prokinetic agent metoclopramide has demonstrated limited efficacy. The benefits of its use should be weighed against the substantial risk of potential neurologic side effects, which include akathisia (nervousness, restlessness, anxiety, agitation), parkinsonism (bradykinesia, resting tremor, and rigidity), and tardive dyskinesia (involuntary, repetitive, tic-like movements that involve primarily the facial muscles but also the extremities, digits, hips, or torso).

KEY POINT

- A low-dose tricyclic antidepressant may be effective in the treatment of functional dyspepsia when symptoms do not respond to proton pump inhibitor or H_2-blocker therapy.

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Lacy BE, Talley NJ, Locke GR 3rd, et al. Review article: current treatment options and management of functional dyspepsia. Aliment Pharmacol Ther. 2012 Jul;36(1):3-15. [PMID: 22591037]

Item 21 Answer: D

Educational Objective: Manage nonalcoholic fatty liver disease.

The most appropriate management is weight loss. This patient has nonalcoholic fatty liver disease (NAFLD), and weight loss should be recommended. NAFLD is the most common cause of abnormal liver test results in the United States. Approximately 30% of the U.S. population has NAFLD, some of whom have normal liver enzyme levels. Most patients with NAFLD have insulin resistance associated with obesity, hypertriglyceridemia, and/or type 2 diabetes mellitus. Approximately 20% of patients with NAFLD have nonalcoholic steatohepatitis (NASH), which is characterized by hepatic steatosis accompanied by inflammation and often fibrosis. Although NASH requires a liver biopsy for accurate diagnosis, a presumptive diagnosis can be made in a patient with mild abnormalities of aminotransferase levels, risk factors for NAFLD (such as diabetes, obesity, and hyperlipidemia), and imaging features consistent with hepatic steatosis. This patient's liver biopsy is consistent with steatohepatitis, and given his risk factors of obesity and diabetes mellitus, NAFLD is the most likely diagnosis.

Patients with NASH who have bariatric surgery and lose weight have improvement in hepatic histology, and bariatric surgery can be considered if conservative attempts at weight loss fail.

Patients with NAFLD may have abnormal iron tests, especially serum ferritin. The absence of iron on this patient's liver biopsy excludes significant iron overload, and therefore phlebotomy is unnecessary.

Patients with NASH and cirrhosis are at significant risk for hepatocellular carcinoma, and surveillance with imaging should be performed every 6 months; however, surveillance is not necessary in the absence of cirrhosis.

KEY POINT

- A presumptive diagnosis of nonalcoholic steatohepatitis can be made in a patient with mild abnormalities of aminotransferase levels, risk factors for nonalcoholic fatty liver disease (such as diabetes mellitus, obesity, and hyperlipidemia), and imaging features consistent with hepatic steatosis.

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Item 22 Answer: B

Educational Objective: Provide colon cancer surveillance in a patient with ulcerative colitis.

The most appropriate colon cancer surveillance strategy is colonoscopy with biopsies beginning in 4 years and repeated every 1 to 2 years. Patients with inflammatory bowel disease have health risks related to their disease or its treatment. Patients with long-standing colitis are at increased risk for colon cancer and should undergo surveillance colonoscopy with biopsies every 1 to 2 years beginning after 8 to 10 years of disease. This recommendation applies to patients with ulcerative colitis involving more than the rectum and those with Crohn colitis involving at least one third of the colon. This patient should begin a surveillance program in approximately 4 years, when his ulcerative colitis has been present for 8 years. He has a single second-degree relative with colon cancer, but this does not affect the surveillance recommendation. Four-quadrant surveillance biopsies should be obtained every 10 cm beginning in the cecum, resulting in approximately 32 to 36 biopsies. In patients with inflammatory bowel disease and concomitant primary sclerosing cholangitis (PSC), the risk of colon cancer is particularly high, and it is recommended that such patients begin yearly surveillance as soon as the diagnosis of PSC is made. However, this patient has normal liver chemistry studies, which makes PSC unlikely.

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For patients with Lynch syndrome (hereditary nonpolyposis colorectal cancer), recommended colorectal cancer screening is colonoscopy every 1 to 2 years beginning at age 20 to 25 years, or 2 to 5 years earlier than the youngest age at diagnosis of colorectal cancer if the affected relative was less than 25 years old.

Patients with ulcerative colitis involving the rectum are not at increased risk for colorectal cancer. In these patients, average-risk colorectal cancer screening with colonoscopy is recommended beginning at age 50 years and should be repeated every 10 years.

The 2012 American College of Physicians Guidance Statement on colorectal cancer screening recommends initiation of screening in high-risk patients (a first-degree relative with colon cancer or advanced adenoma diagnosed at age <60 years, or two first-degree relatives diagnosed at any age) at age 40 years, or 10 years younger than the earliest colon cancer diagnosis in the family, whichever is earlier. Colonoscopy is repeated every 5 years.

KEY POINT

- Patients with long-standing colitis associated with inflammatory bowel disease are at increased risk for colon cancer and should undergo surveillance colonoscopy every 1 to 2 years beginning after 8 to 10 years of disease.

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Item 23 Answer: A

Educational Objective: Manage diverticulitis.

The most appropriate management for this woman with diverticulitis is treatment with oral antibiotics with home discharge and close clinical follow-up. The therapeutic approach to diverticulitis is dictated by patient-related factors, the severity of clinical features, and the ability to tolerate oral intake. In a healthy, immunocompetent patient with mild symptoms, outpatient therapy is appropriate and should consist of a liquid diet, oral antimicrobial agents that cover colonic organisms and include anaerobic coverage (such as ciprofloxacin and metronidazole), and as-needed analgesia. Close follow-up is warranted to detect any deterioration as soon as possible. For older, frail, sicker patients, and in those with potential complications of diverticulitis (such as peritonitis or fistula formation), hospitalization is recommended for administration of intravenous antimicrobial agents and observation. This patient with diverticulitis has mild symptoms and is otherwise healthy. She is able to maintain oral intake and can therefore be managed as an outpatient with oral antibiotics and close follow-up.

Surgery is pursued acutely only in patients who have free perforation or peritonitis, or in those for whom medical therapy is unsuccessful. If indicated, both laparoscopic and open procedures are options; laparoscopic treatment is associated with a more rapid recovery time. This patient does not have a current indication for surgical intervention.

Percutaneous drainage is typically indicated in patients with diverticulitis with larger abscesses (often considered to be >3 cm) that are procedurally amenable in those without evidence of peritonitis. Smaller abscesses are usually treated with antibiotics alone and close follow-up. This patient does not have evidence of an abscess on imaging; therefore, percutaneous drainage is not indicated.

Colonoscopy is recommended after recovery because diverticulitis may be precipitated by a sigmoid cancer; however, colonoscopy during an attack is contraindicated because it would be very difficult to insert the colonoscope beyond the area of inflammation and obtain adequate mucosal inspection. In addition, it may cause peritonitis.

KEY POINT

- In a healthy, immunocompetent patient with diverticulitis and mild symptoms, outpatient therapy is appropriate and should consist of a liquid diet, oral antimicrobial agents that cover colonic organisms and include anaerobic coverage (such as ciprofloxacin and metronidazole), and as-needed analgesia.

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Item 24 Answer: B

Educational Objective: Provide colonoscopy surveillance following a diagnosis of a serrated polyp.

Colonoscopy should be repeated in 3 years. The World Health Organization has classified serrated colorectal polyps into three categories: hyperplastic polyps, sessile serrated polyps, and traditional serrated adenomas. Hyperplastic polyps are believed to have no malignant potential, whereas sessile serrated polyps and traditional serrated adenomas are neoplastic. Sessile serrated polyps are thought to be the precursor of approximately 15% of sporadic colorectal cancers. Recent guidelines have established recommendations for postpolypectomy surveillance colonoscopy intervals in patients with serrated polyps; the rationale for postpolypectomy surveillance is to detect recurrent neoplasia. Patients with large (≥10 mm) or dysplastic sessile serrated polyps or traditional serrated adenomas should undergo colonoscopy in 3 years.

A 1-year surveillance interval is recommended for patients with serrated polyposis syndrome. Serrated polyposis syndrome is a rare condition characterized by multiple or large serrated polyps, including hyperplastic polyps, sessile serrated polyps, traditional serrated adenomas, and possibly also adenomatous polyps. Patients with serrated polyposis syndrome are at increased risk of colorectal cancer.

The recommended postpolypectomy interval for patients with sessile serrated polyps smaller than 10 mm

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is 5 years. This patient's sessile serrated polyp is larger than 10 mm, so this recommendation is not appropriate.

A 10-year average-risk interval is recommended for patients with small rectosigmoid hyperplastic polyps, but it is not appropriate for this patient because her large sessile serrated polyp carries a higher cancer risk.

KEY POINT

- For patients with large (≥10 mm) or dysplastic sessile serrated polyps or traditional serrated adenomas, the recommended postpolypectomy surveillance colonoscopy interval is 3 years.

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Item 25 Answer: D

Educational Objective: Manage asymptomatic cholelithiasis.

The most appropriate management for this patient's gallstones is clinical observation. Her symptoms are consistent with gastroesophageal reflux. Gallstones were incidentally found on her evaluation but are asymptomatic. Biliary colic is the most common clinical presentation in patients with symptomatic gallstones. The usual presentation of biliary colic is episodic, severe abdominal pain typically in the epigastrium and/or right upper quadrant but occasionally in the right lower or mid-abdomen. The pain rapidly intensifies over a 15-minute interval to a steady plateau that lasts as long as 3 hours and resolves slowly. The pain is often associated with nausea or vomiting, and there is no jaundice. Pain may radiate to the interscapular region or right shoulder. An estimated 60% to 80% of gallstones are asymptomatic. Over a 20-year period, 50% of patients remain asymptomatic, 30% have biliary colic, and 20% have more serious complications. Observation is recommended for adult patients with asymptomatic gallstones. The possible exceptions to this recommendation are groups at higher risk for gallbladder carcinoma, such as patients with a calcified (porcelain) gallbladder, certain American Indians, and patients with gallstones larger than 3 cm.

Risks for symptoms or complications from silent gallstones are about 2% per year and cumulative, and risks for complications in the absence of antecedent pain are minimal. Therefore, annual ultrasonography is unlikely to alter management decisions for this patient and she can be treated expectantly, based on the occurrence of symptoms.

Laparoscopic cholecystectomy is the treatment of choice for symptomatic biliary colic and acute cholecystitis. Mortality rates following laparoscopic cholecystectomy are less than 0.7%, and complication rates (including bile duct injuries) do not differ between laparoscopic and open cholecystectomy. However, this patient's pain is inconsistent with biliary pain, and neither laparoscopic nor open cholecystectomy is indicated.

Oral administration of ursodiol for dissolution of gallstones is rarely used. It can be considered in patients with symptomatic noncalcified gallbladder stones who are at high risk for cholecystectomy.

KEY POINT

- Observation is recommended for adult patients with asymptomatic gallstones.

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Item 26 Answer: C

Educational Objective: Diagnose pyoderma gangrenosum as an extraintestinal manifestation of inflammatory bowel disease.

This patient's ulcerating lesion is characteristic of pyoderma gangrenosum (PG). PG is an uncommon skin disease characterized by intense neutrophilic inflammation and invasion of the skin. Lesions are classically ulcerated, but PG may also present with bullae, pustulonodules, and vegetative plaques. Typical lesions begin as painful pustules that rapidly ulcerate and expand, with an edematous, rolled, or undermined-appearing border that may have a violaceous hue. Annular rings are sometimes noted. As with other neutrophilic dermatoses, when the process is active, approximately 25% of patients will exhibit pathergy or induction of new lesions at sites of trauma, including ostomy, phlebotomy, and intravenous sites. Peristomal PG, occurring around ostomy sites, is common and can be challenging to manage. As PG resolves, it tends to heal with atrophic scarring in a cross-like or cribriform pattern. There are no definitive diagnostic tests, and PG is a diagnosis of exclusion. Skin biopsy may be required to exclude other diseases such as cutaneous Crohn disease but may cause worsening of the PG. Treatment can be challenging, and if there is an associated underlying disease, therapy should be directed at controlling that process. Extraintestinal manifestations such as oral aphthous ulcers, arthralgia, inflammatory eye diseases, and PG are seen in approximately 10% of patients with inflammatory bowel disease.

Acrodermatitis enteropathica (AE) is an inherited or acquired metabolic disorder characterized by perioral and acral (in the extremities) erythematous and vesiculobullous dermatitis and alopecia related to zinc deficiency. AE has been associated with Crohn disease, but this patient's stomal ulcer is not consistent with AE.

Erythema nodosum is the most common cutaneous manifestation of inflammatory bowel disease, occurring in up to 20% of patients, particularly women. The lesions of EN are tender, subcutaneous nodules presenting as barely appreciable convexities on the skin surface, with a reddish hue in the acute phase. EN is frequently bilateral

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and symmetrical, and it usually occurs on the distal lower extremities, but it may also appear on the trunk, thighs, or upper extremities.

Squamous cell carcinoma (SCC) usually appears as a scaly, crusted, well-demarcated red papule, plaque, or nodule. SCC can develop in patients with Crohn disease, most commonly at sites of chronic, long-standing inflammation such as chronic fistulas. This patient's ulcerative skin lesion with undermined and violaceous borders is not consistent with the appearance of SCC.

KEY POINT

- Pyoderma gangrenosum (PG) is characterized by painful pustules that rapidly ulcerate and expand, with edematous, rolled, or undermined borders that may have a violaceous hue; PG may be an extraintestinal manifestation of Crohn disease.

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Item 27 Answer: C

Educational Objective: Evaluate chronic diarrhea.

The most appropriate management is stool testing for ova and parasites. Infectious causes of chronic diarrhea are uncommon in immunocompetent adults in developed countries, except for infection with *Giardia lamblia*. Giardiasis should be considered in patients with exposure to young children or potentially contaminated water such as lakes and streams. Infection is asymptomatic in more than 50% of patients, and the protozoa clear spontaneously. In the remaining patients, symptoms typically occur 1 to 2 weeks after infection and include watery, foul-smelling diarrhea; bloating; flatulence; and belching. Significant weight loss is common because of anorexia and malabsorption, but fever is distinctly unusual. Gastrointestinal symptoms can persist for several weeks to months in the absence of treatment. Patients with hypogammaglobulinemia are at increased risk of developing severe or chronic infection. Given this patient's profession as a day care worker, she is at risk for exposure to a number of infectious causes of diarrhea. The duration of her diarrhea, as well as the associated bloating and weight loss, are more consistent with giardiasis than a bacterial infection. Therefore, an assessment of this patient's stools for ova and parasites would be more appropriate than stool cultures.

A colonoscopy is not indicated at this time because this patient is otherwise healthy and does not have gastrointestinal bleeding or signs suggesting inflammatory bowel disease, such as blood in the stool.

Given the chronic nature of this patient's symptoms and her associated weight loss, avoiding further testing would not be appropriate. Her symptoms warrant evaluation with stool testing.

KEY POINT

- Giardiasis should be considered in patients with chronic diarrhea and exposure to young children or potentially contaminated water such as lakes and streams.

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Item 28 Answer: C

Educational Objective: Treat autoimmune pancreatitis.

The most appropriate management is prednisone. Type I autoimmune pancreatitis (AIP) typically presents in older men, with a mean age of onset in the fifth decade of life. This patient has evidence of type 1 AIP based on the presence of three diagnostic criteria: imaging features (focal pancreatic enlargement with a featureless rim and a nondilated pancreatic duct), increased serum IgG4 level, and extrapancreatic organ involvement (sclerosing cholangitis or IgG4-associated cholangitis). Almost all patients (>90%) enter clinical remission in response to glucocorticoids, but relapse is common.

There are no data to support antioxidant treatment for AIP; however, some patients may develop nutritional deficiencies, which warrant treatment.

A biliary metal stent is generally reserved for long-term palliation of malignant biliary strictures and is not required for IgG4-associated cholangitis. IgG4-associated cholangitis typically responds to glucocorticoids, but it may not resolve completely and can relapse. Temporary plastic biliary stents may be required in patients presenting with jaundice who have a dominant stricture, which is not present in this patient.

Surgery is not indicated in this patient but should be considered when the diagnosis is uncertain and pancreatic cancer cannot be excluded.

KEY POINT

- Glucocorticoids are the cornerstone of treatment for autoimmune pancreatitis.

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Item 29 Answer: B

Educational Objective: Treat small-bowel bleeding with push enteroscopy.

The most appropriate procedure is push enteroscopy, which will allow for therapeutic intervention. Angiodysplasias are the most common cause of obscure gastrointestinal bleeding. Push enteroscopy will be able to reach the lesion and

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allow for treatment with electrocautery, argon plasma coagulation, injection therapy, mechanical hemostasis (hemoclips or banding), or a combination of these techniques. This patient had a negative upper endoscopy. Capsule endoscopy was helpful in this patient because it identified active bleeding as well as several angiodysplasias, which are causing the bleeding. Enteroscopy should be performed after a negative upper endoscopy and colonoscopy or after a positive capsule endoscopy. Complications of push enteroscopy are rare but include perforation, mucosal avulsion, and bleeding.

Intraoperative endoscopy is reserved for patients with active bleeding from the small bowel in whom both endoscopy and angiography have failed to identify the small-bowel bleeding source.

A repeat upper endoscopy would not be helpful in this situation because it will be unable to reach the lesion in the small bowel.

Technetium-labeled nuclear scans are used in patients with active bleeding (melena or hematochezia) who are transfusion dependent and hospitalized. This is a diagnostic test that will supply no additional information to what has already been provided by the results of the capsule endoscopy, and it does not allow for therapeutic intervention.

KEY POINT

- Enteroscopy should be performed after a negative upper endoscopy and colonoscopy or after a positive capsule endoscopy.

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Item 30 Answer: C

Educational Objective: Treat irritable bowel syndrome with constipation that is refractory to standard laxative therapy.

The most appropriate treatment is to start linaclotide. This patient's symptoms have not responded to initial trials of two over-the-counter laxatives for treatment of his irritable bowel syndrome with constipation (IBS-C) symptoms. Linaclotide is a synthetic peptide that acts peripherally in the gut and activates guanylate cyclase-C receptors on the enterocytes lining the small bowel and colon. Activation of the guanylate cyclase-C receptors results in increased production of cyclic guanosine monophosphate (cGMP), which in turn activates the movement of chloride ions into the intestinal lumen and promotes passive movement of sodium ions and water in the intestinal lumen. These secretory effects lead to treatment of constipation symptoms. In a multicenter randomized controlled trial (RCT) involving 804 patients with IBS-C, linaclotide significantly improved abdominal and bowel symptoms associated with IBS-C over 26 weeks of treatment. Diarrhea was the most common side effect, prompting discontinuation in 4.5% of patients. Linaclotide has an FDA indication for the treatment of adults with IBS-C and chronic constipation. Linaclotide is not a first-line agent in IBS-C, but it is appropriate for patients whose symptoms persist despite the use of fiber and standard laxatives. Lubiprostone, a chloride channel activator that increases intestinal fluid secretion, can also be used as a second-line agent in patients with IBS-C or chronic idiopathic constipation.

Bran has not shown any benefit compared with placebo in the treatment of IBS-C and is likely to worsen symptoms of bloating.

Bisacodyl has not been assessed for use in IBS-C in any RCTs. Furthermore, the side effect of abdominal cramping associated with bisacodyl is likely to exacerbate this patient's baseline abdominal pain.

Rifaximin is a nonabsorbable antibiotic under development for use in IBS with diarrhea and mixed IBS (not FDA approved). There is no established benefit for rifaximin in IBS-C.

KEY POINT

- Linaclotide is FDA approved for the treatment of irritable bowel syndrome with constipation in adults; like lubiprostone, it is second-line therapy for patients whose symptoms have not responded to standard laxative therapy.

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Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol. 2012 Nov;107(11):1702-12. [PMID: 22986437]

Item 31 Answer: C

Educational Objective: Diagnose fat-soluble vitamin deficiency following malabsorptive bariatric surgery.

Vitamin A deficiency is most likely to explain this patient's findings, and the most appropriate and important study is immediate assessment of this patient's vitamin A status with serum retinol measurement. Her ocular symptoms are very serious manifestations of vitamin A deficiency, which may be progressive and may lead to permanent visual impairment if left untreated. Symptoms associated with vitamin A deficiency include decreased vision at night or in dim light, dry eyes, corneal and/or eyelid inflammation, and rough and/or dry skin. The absorption of the fat-soluble vitamins A, D, E, and K can be severely impaired following malabsorptive bariatric surgery, including Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch. Vitamin A deficiency has been reported to occur in 11% of patients after gastric bypass despite taking a daily multivitamin. This deficiency can occur within 1 year of surgery; the reported prevalence is 10% to 50% in patients with RYGB and 61% to 69% in those with biliopancreatic diversion. Vitamin A deficiency is believed to arise from multiple factors such

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as fat malabsorption, decreased intake from reduced overall food consumption, and possible underlying fatty liver disease. Other micronutrient deficiencies (in addition to the previously mentioned fat-soluble vitamins A, D, E, and K) that can develop following RYGB include iron, folic acid, zinc, selenium, copper, magnesium, thiamine (vitamin B_1), cobalamin (vitamin B_{12}), vitamin C, and in rare cases, riboflavin (vitamin B_2) and pyridoxine (vitamin B_6).

Copper deficiency causes a chronic syndrome similar to subacute combined degeneration and is also associated with macrocytic anemia and leukopenia. Therefore, this deficiency can be difficult to differentiate from vitamin B_{12} deficiency. Less common findings include sudden bilateral visual loss.

Although iron deficiency does occur following RYGB, this patient is on iron replacement and has a normal mean corpuscular volume. Patients with iron deficiency are likely to have hypochromic, microcytic anemia and may have brittle or deformed nails, cheilitis, pica, and restless legs syndrome. Visual symptoms are not seen with iron deficiency anemia.

Although vitamin B_{12} deficiency may occur following RYGB, this is unlikely given this patient's normal mean corpuscular volume. Furthermore, a vitamin B_{12} deficiency could lead to peripheral neuropathy and gait disturbance but not the skin or visual disturbances seen in this patient.

KEY POINT

- The absorption of the fat-soluble vitamins A, D, E, and K can be severely impaired following malabsorptive bariatric surgery, including Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch.

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Item 32 Answer: D

Educational Objective: Manage advanced liver disease due to nonalcoholic fatty liver disease.

The most appropriate diagnostic test to perform next is ultrasound of the liver and spleen. This patient has a history of nonalcoholic fatty liver disease (NAFLD) and now has abdominal distention suggestive of ascites. Her low platelet count is suggestive of portal hypertension, and liver dysfunction is supported by the slightly elevated serum bilirubin and low albumin levels. The next test should be liver imaging with a test such as ultrasound to assess for changes consistent with portal hypertension. In the United States, many cases of "cryptogenic" liver disease are likely related to advanced NAFLD.

Although this patient has risk factors for cardiac disease, she does not have other signs or symptoms suggestive of heart failure. In addition, cardiac dysfunction, unless very long-standing, would not produce splenomegaly. Therefore, echocardiography is not necessary at this time.

Liver biopsy to diagnose cirrhosis is not necessary in patients with other clear manifestations of liver dysfunction and portal hypertension, such as is seen in this patient.

Simvastatin rarely produces mild liver test abnormalities but does not cause chronic liver injury or portal hypertension. Patients with NAFLD have a high prevalence of coronary artery disease; therefore, risk-factor reduction, including the use of statins where appropriate, is advised.

KEY POINT

- Liver imaging with a test such as ultrasound is useful for assessing changes consistent with portal hypertension.

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Item 33 Answer: D

Educational Objective: Provide surveillance for Barrett esophagus without dysplasia.

The most appropriate next step in management is to repeat upper endoscopy in 3 to 5 years. Although there is no evidence of the benefit of endoscopic screening of the general population, endoscopic assessment for Barrett esophagus (BE) in patients with chronic reflux symptoms may be appropriate in specific patients. It is reasonable to consider screening men older than 50 years with gastroesophageal reflux disease (GERD) symptoms for more than 5 years and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated BMI, tobacco use, and intra-abdominal distribution of fat) to detect esophageal adenocarcinoma and BE. This patient is male, older than 50 years, overweight, and is an active smoker; therefore, pursuing screening was reasonable in this patient. His endoscopy revealed BE without evidence of dysplasia. BE is thought to be a complication of GERD resulting in a change in the normal squamous lining of the distal esophagus to a specialized columnar epithelium due to the effect of refluxed gastric secretions. BE is a spectrum ranging from no dysplasia to high-grade dysplasia, and some patients progress to esophageal cancer. Recommended surveillance of patients with newly diagnosed BE is based on the presence and degree of dysplasia on biopsy. In those with no dysplasia, surveillance with upper endoscopy is recommended in 3 to 5 years. In patients with low-grade dysplasia, surveillance is more frequent, usually 6 to 12 months following confirmation by an expert pathologist. High-grade dysplasia requires either more aggressive surveillance or treatment to remove BE (such as with endoscopic ablation or esophagectomy).

Patients with BE with high-grade dysplasia are often treated with endoscopic ablation. This patient has BE with no dysplasia, so this therapy is not appropriate at this time.

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Esophagectomy should be reserved for patients in whom endoscopic ablation fails or in those with evidence of esophageal cancer.

Fundoplication is the appropriate treatment for GERD in patients who wish to stop taking medication or in those with a poor response to medical therapy. This patient's symptoms are well controlled on omeprazole, so fundoplication is not appropriate at this time. Fundoplication does not prevent the progression of BE to dysplasia or cancer.

KEY POINT

- In patients with Barrett esophagus and no dysplasia, surveillance with upper endoscopy is recommended in 3 to 5 years.

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Item 34 Answer: C

Educational Objective: Diagnose primary biliary cirrhosis.

The most likely diagnosis is primary biliary cirrhosis (PBC). PBC is a chronic cholestatic liver disease of unknown cause. PBC mainly affects middle-aged women. Most patients are asymptomatic at presentation but develop symptoms of PBC within 10 years; symptoms include fatigue, dry eyes, dry mouth, and pruritus. Hyperlipidemia is common, but jaundice, cutaneous hyperpigmentation, hepatosplenomegaly, and xanthelasmas are rarely observed at diagnosis. PBC is diagnosed by serum alkaline phosphatase levels greater than 1.5 times the upper limit of normal and typically normal serum total bilirubin levels. Serum aspartate (AST) and alanine (ALT) aminotransferase levels are typically less than five times the upper limit of normal. Serum antimitochondrial antibody is present in 90% to 95% of patients. For patients with undetectable serum antimitochondrial antibody levels, a liver biopsy is required for diagnosis. Treatment with ursodiol slows disease progression and may prevent or delay advanced disease and the need for liver transplantation.

Autoimmune hepatitis is a chronic inflammatory liver disease that is usually seen in women. The disease presentation ranges from asymptomatic to acute liver failure. Autoimmune hepatitis typically causes a predominant elevation of the serum ALT level rather than the serum alkaline phosphatase level, as was seen in this patient.

Cholangiocarcinoma is classified by location as intrahepatic and hilar/extrahepatic. Intrahepatic cholangiocarcinoma is typically asymptomatic until the tumor is advanced, at which time right upper quadrant discomfort, weight loss, and fever may be the only symptoms. An elevated serum alkaline phosphatase level may be noted. Risk factors for cholangiocarcinoma are primary sclerosing cholangitis, biliary atresia, chronic infection with liver flukes, and biliary cysts. This patient has no risk factors for cholangiocarcinoma, and that diagnosis would not explain her positive antimitochondrial antibody test.

Primary sclerosing cholangitis (PSC) is a chronic inflammatory disorder that affects the intra- and extrahepatic bile ducts. Approximately 70% to 80% of patients with PSC have inflammatory bowel disease, usually ulcerative colitis. Serum alkaline phosphatase values are 3 to 10 times the upper limit of normal, and serum ALT and AST levels are two to three times the upper limit of normal. Serum total bilirubin levels may be normal in 60% of patients. PSC is not the most likely diagnosis in this patient because she has a positive antimitochondrial antibody test and does not have ulcerative colitis.

KEY POINT

- The diagnosis of primary biliary cirrhosis is generally made on the basis of a cholestatic liver enzyme profile in the setting of a positive antimitochondrial antibody test.

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Item 35 Answer: B

Educational Objective: Evaluate obscure gastrointestinal bleeding with capsule endoscopy.

Capsule endoscopy is the most appropriate diagnostic test for this patient with obscure gastrointestinal bleeding. Obscure gastrointestinal bleeding refers to recurrent or persistent bleeding from the gastrointestinal tract without an obvious source on endoscopic studies. The evaluation of gastrointestinal bleeding of obscure origin usually begins with repeat endoscopy directed at the most likely site. Approximately 30% to 50% of lesions can be detected using this approach. If repeat endoscopy is unrevealing in a patient who is not actively bleeding, examination should focus on the small intestine, using such tests as capsule endoscopy. Wireless capsule endoscopy allows excellent visualization of the small bowel. Unlike angiography and technetium scans, wireless capsule endoscopy is effective even in the absence of active bleeding. Wireless capsule endoscopy detects the source of occult bleeding in 50% to 75% of patients. In patients with iron deficiency anemia, in whom bleeding can be episodic, capsule endoscopy is another way to investigate potential sources of blood loss after other investigations have been unrevealing. This patient, who is on anticoagulation and has heme-positive stool, is likely to have vascular lesions such as angiodysplasia in the small bowel. Angiodysplasia is the most common cause of small-bowel bleeding in older patients.

Angiography and technetium-labeled nuclear scans are used in patients with active bleeding (melena or hematochezia) who are transfusion dependent and hospitalized. This patient does not meet these criteria.

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Intraoperative endoscopy is generally employed only as a last resort for the evaluation of obscure gastrointestinal bleeding. The patient undergoes laparotomy or laparoscopy, and the bowel is evaluated with a colonoscope following surgical enterotomy. This technique should only be used if other less invasive options have been exhausted or if a patient has unexplained, life-threatening bleeding. In addition, the yield is somewhat low (approximately 25%).

KEY POINT

- Capsule endoscopy has become the first-line test in evaluating the small bowel in patients with obscure gastrointestinal bleeding after a negative upper endoscopy and colonoscopy.

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Leighton JA. The role of endoscopic imaging of the small bowel in clinical practice. Am J Gastroenterol. 2011;106(1):27-36. [PMID: 20978483]

Item 36 Answer: C

Educational Objective: Treat acute pancreatitis with enteral nutrition.

Enteral feeding is the most appropriate management. Enteral feeding has been shown to reduce infectious complications, multiple organ failure, operative interventions, and mortality compared with feeding by total parenteral nutrition in patients with severe acute pancreatitis. This patient has moderately severe acute pancreatitis based on evidence of pancreatic necrosis and peripancreatic fluid collections. He also has several risk factors for severe disease based on the presence of three of four Systemic Inflammatory Response Syndrome (SIRS) criteria (pulse rate >90/min, leukocyte count >12,000/μL [12 × 10^9/L], and respiration rate >20/min) and a blood urea nitrogen level greater than 23 mg/dL (8.2 mmol/L). Nasogastric and nasojejunal feeding appear to be comparable in safety and efficacy. The optimal time to start enteral nutrition remains under investigation, but it should commence no later than 72 hours after presentation. In mild acute pancreatitis, oral feeding may start when nausea and vomiting resolve.

Drainage of acute peripancreatic fluid collections (APFCs) is not appropriate at this time because most collections resolve without intervention. Asymptomatic APFCs require no treatment. Symptomatic APFCs can be treated medically with bowel rest, jejunal feeding, pancreatic enzymes, octreotide, and rarely pancreatic duct stenting. Rarely, APFCs persist beyond 4 weeks, when they become encapsulated and are labeled a pancreatic pseudocyst. Pseudocysts are amenable to drainage if clinically indicated based on persistent pain despite medical therapy, infected pseudocyst, or obstruction of the gastric outlet or biliary tract.

Endoscopic retrograde cholangiopancreatography in acute pancreatitis should be used only in the following clinical scenarios: (1) in a patient with ascending cholangitis (fever, right upper quadrant pain, and jaundice) concomitant with acute pancreatitis, or (2) in a patient with gallstone pancreatitis who is not improving clinically and has worsening liver chemistry test results. Patients with gallstone pancreatitis and no complications should have a cholecystectomy prior to discharge.

KEY POINT

- Enteral feeding has been shown to reduce infectious complications, multiple organ failure, operative interventions, and mortality compared with feeding by total parenteral nutrition in patients with severe acute pancreatitis.

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Item 37 Answer: C

Educational Objective: Manage lower gastrointestinal bleeding caused by an anal fissure.

The most appropriate management is outpatient follow-up. This patient meets four criteria for nonadmission with outpatient follow-up based on the 2008 Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/pdf/sign105.pdf). These criteria include age less than 60 years, no hemodynamic instability, no evidence of gross rectal bleeding, and identification of an obvious anorectal source of bleeding on rectal examination or sigmoidoscopy.

Admission to the hospital for observation is not necessary because this patient's bleeding is attributable to a specific, minor cause of lower gastrointestinal bleeding, namely an anal fissure that is appropriate for outpatient management. The diagnosis is based on physical findings and a compelling clinical history. Anal fissures are tears in the anal skin distal to the dentate line; they may therefore be exquisitely painful, particularly with defecation. They are most often caused by local trauma such as hard stools. Anoscopy or direct visualization typically reveals a small mucosal tear, most often in the posterior midline. Hospitalization should be considered in patients with any of the following five criteria that predict severe bleeding: age 60 years or older, comorbid illnesses (particularly when two or more are present), hemodynamic instability, gross rectal bleeding (or early rebleeding), or exposure to antiplatelet drugs and anticoagulants.

Colonoscopy within 12 to 18 hours is not appropriate because this patient's clinical status does not warrant urgent or emergent investigations based on the SIGN guidelines. Elective colonoscopy or sigmoidoscopy might be performed on an outpatient basis to exclude causes other than chronic constipation, such as proctitis from inflammatory bowel disease or infection (such as herpesvirus or HIV).

Surgery is not necessary because this option is typically offered for chronic rather than acute anal fissures and only after exhausting medical options.

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KEY POINT

- Patients with lower gastrointestinal bleeding do not require hospitalization when they meet four criteria (based on the 2008 Scottish Intercollegiate Guidelines Network): age less than 60 years, no hemodynamic instability, no evidence of gross rectal bleeding, and identification of an obvious anorectal source of bleeding on rectal examination or sigmoidoscopy.

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Item 38 Answer: B

Educational Objective: Treat a hepatocellular adenoma.

The most appropriate treatment is resection. This 42-year-old woman has a large hepatocellular adenoma, which has been confirmed by biopsy of the mass, and β-catenin activation mutation is positive. Hepatic adenomas can be subclassified based on genotype or immunohistochemistry, which provides information about the risk of transformation to hepatocellular carcinoma (HCC). Hepatic adenomas with positive genotyping for β-catenin activation or that are positive for the correlating immunohistochemistry study for glutamine synthetase have a higher risk of transformation to liver cancer. It is generally best to resect hepatic adenomas that are larger than 5 cm, arise in males (because they carry a higher risk of transformation to HCC), exhibit hemorrhage, or are positive for β-catenin activation/glutamine synthetase antibody. Low-risk hepatocellular adenomas are those smaller than 5 cm that arise in young women on oral contraceptives (reversible cause), as well as steatotic hepatocellular adenomas that are positive for the *HNF-1α* inactivation mutation. These low-risk hepatocellular adenomas require CT imaging surveillance at 6- to 12-month intervals.

Oral contraceptives are associated with the development and growth of hepatocellular adenomas, and cessation of oral contraceptives may lead to shrinkage and/or resolution. However, stopping oral contraceptives is not by itself sufficient treatment for this patient because her hepatic adenoma is larger than 5 cm and is β-catenin positive.

CT imaging surveillance is not appropriate given the high-risk characteristics of this patient's adenoma.

Transarterial chemoembolization is not an established treatment modality for hepatocellular adenomas. This therapy may be appropriate in a patient with cirrhosis and large or multiple hepatocellular carcinoma lesions that are unresectable.

KEY POINT

- Hepatocellular adenomas that are larger than 5 cm or that exhibit β-catenin nuclear reactivity should be treated with surgical resection.

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Item 39 Answer: B

Educational Objective: Treat *Candida* esophagitis.

The most appropriate treatment is fluconazole. This patient has a clinical presentation and findings characteristic of *Candida albicans* esophagitis. Infectious esophagitis can be caused by bacterial (uncommon), fungal, viral, and parasitic pathogens. Patients may be asymptomatic, but common symptoms are odynophagia or dysphagia. *C. albicans* is the most common cause of infectious esophagitis in immunocompromised patients and is often associated with oropharyngeal candidiasis. It often presents with dysphagia, odynophagia, and curdy white esophageal plaques seen on upper endoscopy, which is confirmed with esophageal brushings. This patient's immunocompromised status after liver transplantation puts her at risk for *Candida* esophagitis; however, *Candida* infection can occur in immunocompetent patients as well. *Candida* esophagitis should be treated with fluconazole.

The differential diagnosis also includes possible viral causes. Cytomegalovirus often presents with a single ulcer in the esophagus. The diagnosis is established with biopsies from the ulcer base, and treatment should be with ganciclovir. Herpes simplex virus is also characterized by ulcers, typically multiple, found on upper endoscopy. The diagnosis is established with biopsy of the ulcer edge, and treatment should be with acyclovir.

Swallowed aerosolized glucocorticoids such as fluticasone are often used as a treatment for eosinophilic esophagitis. Patients who respond typically do so quickly, but symptoms often relapse when the treatment is discontinued. Esophageal candidiasis is a side effect of this therapy. Treatment with swallowed aerosolized fluticasone is likely to exacerbate, not improve, this patient's symptoms.

Fluconazole is the first-line therapy for *Candida* esophagitis and is a more effective therapy than swallowed nystatin.

KEY POINT

- *Candida albicans* is the most common cause of infectious esophagitis in immunocompromised patients and is often associated with oropharyngeal candidiasis.

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Item 40 Answer: C

Educational Objective: Treat constipation due to dyssynergic defecation with biofeedback therapy.

The most appropriate management is to refer for biofeedback therapy. The cause of this patient's refractory constipation is

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dyssynergic defecation. Dyssynergic defecation is characterized by the inability to coordinate the relaxation of the puborectalis and external anal sphincter muscles while increasing intraabdominal pressure that results in normal evacuation of stool. Dyssynergic defecation is believed to be an acquired behavioral disorder, resulting from causes such as sexual abuse, obstetric trauma, pelvic/abdominal surgery, or traumatic injury to the pelvis/abdomen. The mechanisms underlying this condition can include some combination of the following factors: inability to contract the abdominal wall musculature, deficient relaxation or paradoxical contraction of the puborectalis muscle, impaired rectal contraction, paradoxical anal contraction, and/or inadequate anal relaxation. These abnormal muscle actions of the pelvic floor and anorectum can be detected by asking the patient to bear down during a digital rectal examination (DRE). The inability to relax the puborectalis and external anal sphincter when instructed or with bearing down is indicative of dyssynergia. The positive predictive value of such findings on DRE is 97%. Dyssynergia generally responds poorly to laxative therapy. Biofeedback therapy, also termed neuromuscular re-education, entails a program of neuromuscular training utilizing visual and verbal feedback to restore coordinated muscle activity involved with defecation and improve rectal sensory function. Biofeedback therapy is commonly provided by a physical therapist with this specialized training. Biofeedback therapy is superior to all forms of laxative therapy because it corrects the underlying pathologic mechanisms responsible for dyssynergic defecation.

This patient's stool is already soft, so further softening with more polyethylene glycol is unlikely to be of any sustained benefit.

Psyllium bulks the stool, which is likely to worsen symptoms in the presence of an underlying problem with stool evacuation.

Enema therapy may promote further dyssynergia by providing an artificial means of emptying the rectal vault, leading to progressive pelvic floor weakness and dysfunction.

KEY POINT

- Biofeedback therapy is superior to all forms of laxative therapy for dyssynergic defecation because it corrects the underlying pathologic mechanisms.

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Item 41 Answer: E

Educational Objective: Manage sporadic fundic gland polyps.

The most appropriate next step in management is reassurance. Fundic gland polyps (FGPs) are among the most commonly found gastric polyps and are reported to be diagnosed in up to 5% of patients undergoing upper endoscopy. Sporadic FGPs are usually 1 to 5 mm in size and fewer than 10 in number. Sporadic FGPs have been associated with proton pump inhibitor (PPI) use; the exact mechanism of this association is not known. Sporadic FGPs do not have malignant potential; therefore, this patient does not require PPI cessation, excision of the remaining polyps, or surveillance.

It is important to distinguish sporadic FGPs from those related to a hereditary colon cancer syndrome. Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary colon cancer syndrome caused by an *APC* gene mutation. It is associated with the near-universal presence of gastric fundic gland polyposis, duodenal adenomas, and a personal or family history of early-onset colonic adenomas or colorectal cancer. FAP-related FGPs frequently harbor dysplasia. *APC* gene testing is not warranted because this patient does not have dysplastic FGPs, a personal history of duodenal or colonic adenomas, or a family history of colorectal cancer.

Colonoscopy is recommended in patients with dysplastic FGPs or in those younger than 40 years of age with fundic gland polyposis; neither of these characteristics is present in this patient, so colonoscopy is not necessary at this time.

This patient's esophageal ring is an acid-related complication of gastroesophageal reflux disease that requires esophageal dilation and ongoing use of a PPI. Therefore, stopping PPI therapy is not appropriate at this time.

KEY POINT

- Sporadic fundic gland polyps have been associated with proton pump inhibitor use and do not require excision or surveillance.

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Item 42 Answer: B

Educational Objective: Provide long-term prevention of recurrent NSAID-induced peptic ulcer disease.

The most appropriate management is celecoxib and omeprazole. Patients such as this with a history of an NSAID-associated bleeding ulcer have a substantial risk for developing recurrent ulcer bleeding. A series of randomized clinical trials in a Hong Kong population illustrated the relative effectiveness of the various treatment strategies in the secondary prevention of NSAID-induced bleeding ulcer disease. Despite endoscopic documentation of complete ulcer healing, the reinitiation of NSAID therapy without a proton pump inhibitor (PPI) resulted in a recurrent ulcer bleeding rate of nearly 20% over a 6-month time frame. The addition of a PPI along with the NSAID lowered the recurrent ulcer bleeding rate to nearly 5% in the same 6-month time frame. Use of the cyclooxygenase-2 (COX-2) selective NSAID celecoxib resulted

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in a similar 6-month bleeding rate of nearly 5%. Additionally, co-therapy with sucralfate is ineffective in preventing NSAID- or aspirin-related gastric or duodenal ulceration. The most effective treatment strategy in the prevention of recurrent ulcer bleeding was use of celecoxib plus twice-daily PPI therapy, which had a 12-month rebleeding rate of 0%. Therefore, patients with a previous NSAID-associated bleeding ulcer who must remain on NSAIDs should receive a COX-2 selective NSAID plus PPI therapy to maximize risk reduction for a recurrent ulcer bleed.

KEY POINT

- A series of randomized clinical trials showed that the most effective treatment strategy in the prevention of recurrent ulcer bleeding was the use of celecoxib plus twice-daily proton pump inhibitor therapy.

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Item 43 Answer: B

Educational Objective: Diagnose Crohn colitis.

The most likely diagnosis is Crohn colitis. This patient has severe, patchy colitis with some large, deep ulcers and rectal sparing, which is consistent with Crohn colitis. In Crohn disease, endoscopic findings vary from superficial aphthous ulcers to discrete, deep ulcers that can be linear, stellate, or serpiginous and that may coalesce into a "cobblestone" appearance. Rectal sparing is typical, as are areas of inflammation separated by normal mucosa (known as skip lesions). The ileum is inspected during colonoscopy to detect ileal inflammation characteristic of Crohn disease. Histology may show patchy submucosal inflammation, but more superficial inflammation does not rule out Crohn disease.

Collagenous colitis is a form of microscopic colitis. Microscopic colitis accounts for 10% to 15% of patients with chronic, watery diarrhea. In contrast to inflammatory bowel disease, microscopic colitis is more common in older persons and does not cause endoscopically visible inflammation, as was seen in this patient.

Ischemic colitis is the most common form of intestinal ischemic injury. Approximately 90% of cases occur in patients older than 60 years. Symptoms include sudden abdominal pain and diarrhea followed by rectal bleeding. Ischemic colitis can result in segmental colitis, but it is typically not patchy and would be unusual in a 28-year-old patient.

In ulcerative colitis, inflammation typically begins in the rectum and extends proximally in a circumferential manner. Mild ulcerative colitis is characterized by mucosal edema, erythema, and loss of the normal vascular pattern. More significant disease produces granularity, friability, ulceration, and bleeding. Ulcerative colitis would typically feature rectal involvement and continuous colitis rather than patchy colitis, as was seen in this patient.

KEY POINT

- In Crohn disease, endoscopic findings vary from superficial aphthous ulcers to discrete, deep ulcers; rectal sparing is typical, as are areas of inflammation separated by normal mucosa (known as skip lesions).

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Item 44 Answer: C

Educational Objective: Diagnose chronic mesenteric ischemia.

The most likely diagnosis is chronic mesenteric ischemia and the next diagnostic test should be CT angiography. Chronic mesenteric ischemia is typically a manifestation of mesenteric atherosclerosis and presents as abdominal pain beginning within 60 minutes after eating. The pain is believed to be due to diversion of small-bowel blood flow to the stomach as digestion begins. The blood flow to the small bowel, which is already compromised, then has even more limited oxygen supply, leading to ischemia and subsequent abdominal pain. This typical symptom leads to a fear of eating (sitophobia), which causes the weight loss that is seen in most patients with chronic mesenteric ischemia. Abdominal bruits are present in 50% of patients, and 50% of patients have peripheral vascular or coronary artery disease. The natural history is progression of mild pain with eating to food avoidance, weight loss, and eventually pain without eating. Upper endoscopy is typically normal, and a CT scan may show evidence of diffuse small-bowel dilation, which is suggestive of abnormal small-bowel motility. If progressive and left untreated, chronic mesenteric ischemia can rarely lead to intestinal infarction. Vascular surgical intervention is the treatment of choice. Both magnetic resonance angiography and CT angiography have high sensitivity and specificity for detecting mesenteric stenosis, although MR angiography may not be as good at detecting distal stenosis.

Doppler ultrasound is a useful screening test for chronic mesenteric ischemia. Peak systolic velocities greater than 275 cm/s in the superior mesenteric artery and greater than 200 cm/s in the celiac artery correlate with stenoses of greater than 70% in each vessel. Doppler ultrasound is often of limited use if patients are obese or there is overlying bowel gas. Ultrasonography without Doppler modality to assess blood flow will not help establish the diagnosis in this patient.

Capsule endoscopy is contraindicated in patients with small-bowel obstruction regardless of whether obstruction is due to a mechanical or functional cause (such as dysmotility due to underlying chronic ischemia, as in this patient).

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Splanchnic angiography is useful if the results of noninvasive testing are equivocal to confirm the diagnosis and to plan intervention; in particular, it allows for performance of endovascular procedures at the time of diagnosis. However, owing to its invasive nature it is typically not the first diagnostic test for chronic mesenteric ischemia.

KEY POINT

- The typical presentation of chronic mesenteric ischemia consists of abdominal pain within an hour of meals, fear of food ingestion, and weight loss.

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Item 45 Answer: A

Educational Objective: Screen for hereditary nonpolyposis colon cancer.

The most appropriate colon cancer screening strategy is colonoscopy beginning now. This patient's family history is consistent with hereditary nonpolyposis colorectal cancer (HNPCC). The Amsterdam II criteria include (1) three or more relatives with an HNPCC-associated cancer (including colorectal, endometrial, ovarian, urothelial, gastric, brain, small bowel, hepatobiliary, or skin), (2) two successive generations of relatives affected, (3) one affected relative a first-degree relative to two other affected relatives, and (4) one cancer diagnosed before age 50 years. Patients with HNPCC should undergo genetic counseling, and an attempt should be made to ascertain the genetic cause of cancer in the patient and family. Surveillance colonoscopy is indicated in patients who meet the clinical criteria for HNPCC, have Lynch syndrome (defined by the presence of a germline genetic mutation), or are at risk for Lynch syndrome and have not had genetic testing. The recommended surveillance interval for colonoscopy screening in patients who have or are at risk for Lynch syndrome is every 1 to 2 years beginning at age 25 years, or 2 to 5 years earlier than the youngest age at diagnosis of colorectal cancer if the affected relative was younger than 25 years old.

Colonoscopy every 5 years beginning at age 40 years (or 10 years before the earliest case in the immediate family) is the surveillance recommendation for a patient with either colorectal cancer or adenomatous polyps in a first-degree relative before age 60 years or colorectal cancer in two or more first-degree relatives at any age.

Colonoscopy every 10 years beginning at age 40 years is the U.S. Multi-Society Task Force on Colorectal Cancer recommendation for a patient with either colorectal cancer or adenomatous polyps in a first-degree relative aged 60 years or older or colorectal cancer in two second-degree relatives with colorectal cancer at any age.

Although the earliest colorectal cancer diagnosis in this patient's family was at age 47 years, she should begin screening now owing to her increased risk related to her family history consistent with HNPCC.

A 5-year interval beginning at age 50 years is not recommended for patients who have or who are at risk for Lynch syndrome; it would be appropriate for low-risk patients diagnosed with one to two tubular adenomas smaller than 10 mm.

KEY POINT

- The recommended surveillance interval for colonoscopy screening in patients who have or are at risk for Lynch syndrome is every 1 to 2 years beginning at age 25 years, or 2 to 5 years earlier than the youngest age at diagnosis of colorectal cancer if the affected relative was younger than 25 years old.

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Item 46 Answer: D

Educational Objective: Manage chronic hepatitis B infection in the inactive carrier state.

The most appropriate management is to perform no further treatment at this time. Hepatitis B virus (HBV) is diagnosed by serologic tests for HBV antigens and antibodies as well as direct HBV DNA assays. Inactive carriers of HBV have a normal alanine aminotransferase level and low levels of HBV DNA (generally less than 10,000 IU/mL) and are at low risk for progression of liver disease; therefore, initiation of medications to treat HBV in these patients is not justified. These patients remain at risk for reactivation of HBV, which may cause subsequent progression of liver disease. Monitoring for the development of chronic active HBV is therefore warranted. This patient's laboratory studies are consistent with HBV infection (positive hepatitis B surface antigen). His negative hepatitis B e antigen, low HBV DNA level, and normal serum alanine aminotransferase (ALT) level indicate that he is in the inactive carrier state. Hepatitis B treatment is not indicated; however, serum ALT levels should be monitored at 6-month intervals to detect potential transitions to other disease phases. Surveillance for hepatocellular carcinoma (HCC) is advised for patients with chronic HBV who have cirrhosis, a family history of HCC, or persistent elevation of ALT and HBV DNA levels. HCC surveillance is also advised in Asian men older than 40 years, Asian women older than 50 years, and African patients older than 20 years.

Treatment with pegylated interferon or entecavir should be considered if the patient has an elevated serum ALT level and HBV DNA level greater than 10,000 IU/mL. These features are not present in this patient, so treatment is not warranted at this time.

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Treatment with lamivudine is seldom advised owing to the high rate of resistance with chronic administration.

KEY POINT

- Patients in the inactive carrier phase of hepatitis B virus (HBV) infection, characterized by a normal serum alanine aminotransferase level and a low HBV DNA level, do not require treatment.

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Item 47 Answer: E

Educational Objective: Screen for celiac disease in a patient with symptoms of irritable bowel syndrome with diarrhea.

The most appropriate diagnostic test to perform next is tissue transglutaminase serology. This patient fulfills the criteria for irritable bowel syndrome with diarrhea (IBS-D) and has no accompanying alarm features. Therefore, the diagnosis of IBS-D can be confidently made with minimal testing. Such testing should be limited to studies assessing for organic diseases that are more prevalent in patients with IBS-D than in the general population. A meta-analysis and systematic review of 14 studies including 4204 patients (54% meeting criteria for IBS) found that patients with IBS are three to four times more likely to have positive celiac antibodies and are more than four times more likely to have biopsy-proven celiac disease than controls. Therefore, screening for celiac disease with tissue transglutaminase testing is warranted.

This patient has no alarm features to warrant a colonoscopy or sigmoidoscopy. Furthermore, a study of more than 900 adults (466 with IBS and 451 controls undergoing screening colonoscopy) found the prevalence of structural abnormalities on colonoscopy, including polyps, colorectal cancer, and inflammatory bowel disease, to be no greater in patients with IBS than in controls.

Lactose hydrogen breath testing would be a consideration only if there was a reported connection between the ingestion of milk and bowel symptoms. This patient reported no change when eliminating milk from her diet.

The prevalence of abnormal thyroid-stimulating hormone (TSH) findings is no greater in patients with IBS than in the general population. Furthermore, there is no established causality between abnormal TSH results and the symptoms reported in IBS.

KEY POINT

- Patients with irritable bowel syndrome with diarrhea (IBS-D) should undergo screening for celiac disease with serum tissue transglutaminase testing, as celiac disease has greater prevalence in patients with IBS-D than in the general population.

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Item 48 Answer: E

Educational Objective: Diagnose the cause of obscure gastrointestinal bleeding with repeat upper endoscopy.

The most appropriate diagnostic test is a repeat upper endoscopy. The underlying cause of obscure gastrointestinal bleeding can often be found by repeating upper endoscopy or colonoscopy. Approximately 30% to 50% of lesions can be detected using this approach. Bleeding sources found by these modalities include Cameron ulcerations in a hiatal hernia, bleeding colonic diverticula, and vascular lesions. This patient had an initial upper endoscopy that showed a hiatal hernia and old blood in the stomach. She also reported dark stools, which suggests an upper gastrointestinal bleeding source. She subsequently had a colonoscopy with normal results. Her large hiatal hernia and old blood in the stomach are clues that she may have chronic bleeding from within the hiatal hernia. Cameron ulcerations are linear gastric erosions found within a hiatal hernia. These erosions have been associated with both iron deficiency anemia and acute and chronic blood loss. Repeating the upper endoscopy will allow re-evaluation of the hiatal hernia and the possible diagnosis of Cameron erosions.

Push enteroscopy and balloon enteroscopy are used for evaluating and treating a small-bowel source of bleeding. The clues of a hiatal hernia and blood in the stomach support upper endoscopy as a higher-yield test to perform next.

Intraoperative endoscopy is generally employed only as a last resort for the evaluation of obscure gastrointestinal bleeding. The patient undergoes laparotomy or laparoscopy, and the bowel is evaluated with a colonoscope following surgical enterotomy. This technique should only be used if other less invasive options have been exhausted or if a patient has unexplained, life-threatening bleeding. In addition, the yield is somewhat low (approximately 25%).

A repeat colonoscopy would not be as helpful as a repeat upper endoscopy because this patient has clues to an upper gastrointestinal bleeding source (hiatal hernia, blood in the stomach, and dark stools).

KEY POINT

- After an initial negative evaluation, the underlying cause of obscure gastrointestinal bleeding can often be found by repeating either upper endoscopy or colonoscopy depending on presenting features.

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Item 49 Answer: C

Educational Objective: Evaluate chest pain with an exercise stress test in a patient with suspected gastroesophageal reflux disease.

The most appropriate next step in management is an exercise stress test. Chest pain caused by esophageal disorders can be difficult to distinguish from cardiac chest pain because of the anatomic proximity and common innervation of the esophagus and the heart. Esophageal chest pain is often prolonged, nonexertional, and associated with other esophageal symptoms such as dysphagia, odynophagia, or reflux. The most common cause of noncardiac chest pain is untreated gastroesophageal reflux disease (GERD), followed by motility disorders. Owing to the potentially life-threatening consequences of untreated cardiac chest pain, a cardiac evaluation must be performed and cardiac causes must be ruled out before attributing chest pain to an esophageal cause. In addition, the rationale for evaluating this patient for coronary artery disease is particularly compelling. She has atypical chest pain. Atypical chest pain meets two of the three diagnostic criteria for typical chest pain: substernal in location, provoked by exertion or emotional distress, relieved by rest or nitroglycerin. Taking into account the description of the chest pain, sex, and age, this patient has a 51% pretest probability of coronary artery disease and should be further evaluated with an exercise stress test. If this patient's cardiac evaluation is negative, she should receive an empiric trial of a proton pump inhibitor. If symptoms resolve, this confirms the diagnosis of GERD.

Ambulatory pH testing is used to identify patients with GERD. Esophageal manometry testing will identify an underlying motility disorder of the esophagus. Lastly, upper endoscopy is used to identify mucosal inflammation in the upper gastrointestinal tract. These tests should be performed only after a cardiac condition has been ruled out as the cause of this patient's chest pain.

KEY POINT

- Although gastroesophageal reflux disease (GERD) is the most common cause of noncardiac chest pain, a cardiac evaluation should be considered to rule out cardiac causes before initiating treatment for GERD.

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Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013 Mar; 108(3):308-28; quiz 329. Erratum in: Am J Gastroenterol. 2013 Oct;108(10): 1672. [PMID: 23419381]

Item 50 Answer: E

Educational Objective: Treat chronic hepatitis C virus infection.

The most appropriate management is to initiate treatment for hepatitis C virus (HCV) infection. Testing for HCV consists of detecting antibody to HCV and has a very high positive predictive value in patients with elevated liver test results and risk factors for HCV infection. HCV RNA by polymerase chain reaction confirms HCV infection. HCV genotyping should be performed at the time of diagnosis to help choose a treatment regimen. This patient has HCV genotype 2 with significant fibrosis on liver biopsy. Effective antiviral treatment of HCV infection can prevent or delay the development of cirrhosis and hepatocellular carcinoma. Patients with HCV genotype 2 have a very high likelihood of sustained virologic response with sofosbuvir and ribavirin, and therefore treatment should be initiated with these agents.

This patient's positive IgG antibody to hepatitis A virus test is a marker of previous infection; therefore, hepatitis A vaccination will not be useful or necessary.

Likewise, this patient has immunity to hepatitis B based on her positive hepatitis B surface antibody test, and therefore hepatitis B vaccination is not necessary.

Although this patient has a normal alanine aminotransferase level, she has evidence of active inflammation with fibrosis on liver biopsy, and antiviral treatment is indicated despite her normal aminotransferase level. The need for treatment in individuals with HCV infection and normal liver enzyme levels is generally assessed similarly to those with abnormal liver enzyme levels.

Testing for IgM antibody to hepatitis A virus is helpful in the diagnosis of acute hepatitis A; however, this patient has no clinical features of acute hepatitis.

KEY POINT

- Effective antiviral treatment of hepatitis C virus infection can prevent or delay the development of cirrhosis and hepatocellular carcinoma.

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Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009 Apr;49(4):1335-74. [PMID: 19330875]

Item 51 Answer: A

Educational Objective: Perform ambulatory pH impedance monitoring for gastroesophageal reflux disease in a patient whose symptoms did not respond to proton pump inhibitor therapy.

The most appropriate next step in management is ambulatory pH impedance monitoring. This patient has features of refractory gastroesophageal reflux disease (GERD). The first step in treating refractory GERD is to optimize proton pump inhibitor (PPI) therapy by verifying correct administration (30-60 minutes before meals) or increasing to twice-daily dosing. Despite increasing this patient's PPI therapy to twice daily, symptoms have persisted. Upper endoscopy has been performed, and the normal results have ruled out an alternative cause of symptoms such as eosinophilic esophagitis or erosive esophagitis. Ambulatory pH impedance monitoring is usually performed in patients who do not respond to antireflux medications and who have a negative upper endoscopy to make a definitive diagnosis. Ambulatory pH

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impedance testing while not taking a PPI is useful in patients who have atypical symptoms to determine if reflux is the cause of the symptoms. If pH testing is done with impedance, the PPI can be continued, as impedance can measure nonacid reflux. Testing is also helpful in patients who have had a partial response to treatment to determine if there is continued acid exposure despite the use of a PPI. The finding of continued acid exposure despite the proper dose and use of a PPI is most helpful in patients considering GERD surgery (fundoplication). Ambulatory pH impedance monitoring can be done with a pH catheter over 24 hours or with an endoscopically placed wireless transmitter over 48 hours.

A barium esophagogram would be the appropriate test for evaluation of dysphagia. Barium radiographs have low sensitivity in the evaluation of GERD and should not be performed.

Esophageal manometry measures the pressure levels in the esophagus and is useful in evaluating esophageal motility disorders such as achalasia. This patient does not have dysphagia or signs of a motility disorder, so manometry is not needed.

Fundoplication may be considered for patients with refractory GERD; however, a pH monitoring study is needed to help determine if antireflux surgery is appropriate.

KEY POINT

- Ambulatory pH impedance testing while not taking a proton pump inhibitor is useful in patients who have atypical symptoms of gastroesophageal reflux to determine if reflux is the cause of the symptoms; it is also useful in patients who are symptomatic while on a proton pump inhibitor to determine if there is continued acid exposure.

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Item 52 Answer: D

Educational Objective: Diagnose lymphocytic colitis.

The most likely diagnosis is lymphocytic colitis, a form of microscopic colitis. Microscopic colitis (MC) accounts for 10% to 15% of patients with chronic, watery diarrhea. In contrast to inflammatory bowel disease, MC is more common in older persons and does not cause endoscopically visible inflammation. The symptoms of MC are similar to other chronic causes of nonbloody diarrhea, such as celiac disease and irritable bowel syndrome; therefore, colonic mucosal biopsies are required for diagnosis. Lymphocytic and collagenous colitis are the two subtypes of MC, and they are distinguishable only by histology. The diagnosis of MC is made by histologic evaluation of colonic biopsies; the classic finding is intraepithelial lymphocytosis (>20 intraepithelial lymphocytes per 100 epithelial cells). In collagenous colitis, the increase in intraepithelial lymphocytes may be less pronounced than in lymphocytic colitis, and the main histologic feature is thickening of the subepithelial collagen band (usually >10 µm). This patient's histologic findings are pathognomonic of lymphocytic colitis. Microscopic colitis often is idiopathic, but in a small subset of patients it may be a side effect of medications. A diagnosis of microscopic colitis should prompt a careful review of prescription and over-the-counter medications such as NSAIDs, aspirin, proton pump inhibitors, and others. Celiac disease should also be considered, as it can be associated with microscopic colitis.

The hallmark of *Clostridium difficile* colitis is watery diarrhea that is frequently associated with fever and abdominal pain or cramps. Diarrhea may be absent in patients with significant ileus or toxic megacolon, leading to a delay in diagnosis. Grossly bloody stools are rare. Risk factors for *C. difficile* infection include use of antibiotics or chemotherapeutic agents in the 8 weeks preceding infection because this causes alterations in enteric flora that allow bacterial overgrowth and toxin production. Typical symptoms of ischemic colitis are the acute onset of mild, crampy abdominal pain with tenderness on examination over the affected region of colon. Bleeding may not occur early but often occurs within a few days of pain onset. This patient does not have clinical features or colonoscopic findings of either *C. difficile* colitis or ischemic colitis.

KEY POINT

- Microscopic colitis is characterized by histologic inflammation in endoscopically normal-appearing colonic mucosa; patients lack signs of systemic inflammation and present with painless watery diarrhea without bleeding.

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Pardi DS, Kelly CP. Microscopic colitis. Gastroenterology. 2011 Apr;140(4): 1155-65. [PMID: 21303675]

Item 53 Answer: C

Educational Objective: Diagnose nonocclusive mesenteric ischemia.

Nonocclusive mesenteric ischemia is the most likely cause of this patient's jejunal wall thickening and dilation, ongoing hypotension, fever, and abdominal pain. Nonocclusive mesenteric ischemia is caused by decreased mesenteric perfusion in low-flow states such as heart failure, sepsis, profound hypotension, or hypovolemia. It may also occur with use of vasoactive medications such as vasopressors, ergots, triptans, cocaine, and digitalis. This patient most likely developed sepsis following induction chemotherapy. The severe and sustained hypotension from sepsis in addition to the use of vasopressor medications results in decreased mesenteric perfusion.

Although this patient has thrombocytopenia, which can predispose to bowel-wall hemorrhage and CT scan

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findings of wall thickening, bowel-wall hemorrhage would not be associated with the clinical picture of sepsis and fever.

Ischemic colitis is the most common form of ischemic injury to the gastrointestinal tract. Although the vast majority of cases occur in patients older than 60 years of age, it can be seen in this setting owing to altered arterial flow secondary to hypotension and vasopressor medications. This patient has predisposing factors for ischemic colitis with systemic alterations in blood flow, and the typical clinical features of the disease with left lower abdominal pain and diarrhea. However, the lack of rectal bleeding and absence of left colon inflammatory changes on CT do not support ischemic colitis as the cause for this patient's life-threatening clinical scenario.

Mesenteric artery emboli account for 50% of cases of acute mesenteric ischemia. They are usually of cardiac origin owing to atrial fibrillation or left ventricle thrombus. This patient has no evidence of atrial fibrillation, and the clinical picture of severe, unresponsive hypotension before the onset of the gastrointestinal symptoms makes nonocclusive mesenteric ischemia a more likely diagnosis than mesenteric artery embolism.

KEY POINT

- Nonocclusive mesenteric ischemia is caused by decreased mesenteric perfusion in low-flow states such as heart failure, sepsis, profound hypotension, or hypovolemia.

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Brandt LJ, Boley SJ. AGA technical review on intestinal ischemia. American Gastrointestinal Association. Gastroenterology. 2000 May;118(5):954-68. [PMID: 10784596]

Item 54 Answer: B

Educational Objective: Manage decompensated cirrhosis with referral for liver transplantation.

The most appropriate next step in management is an evaluation for liver transplantation. This patient has decompensated cirrhosis as manifested by ascites and has a moderately elevated Model for End-Stage Liver Disease (MELD) score. The MELD score is an equation that incorporates the bilirubin, INR, and creatinine levels and was derived initially as a way to accurately predict 3-month and 1-year survival in patients undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure. The MELD score has also been validated as a tool for accurately predicting 3-month survival in patients with cirrhosis. This score is the basis for considering referral for liver transplantation (MELD ≥15) and organ allocation. Patients with cirrhotic-stage liver disease and a MELD score of 15 or greater have better survival with liver transplantation than without.

Diuretics have been unsuccessful in this patient owing to the development of kidney dysfunction. Further administration of diuretics may precipitate the development of hepatorenal syndrome; therefore, diuretics should be discontinued.

Patients with MELD scores greater than 10 are at risk of hepatic decompensation and mortality from any surgery, and especially with higher-risk surgeries such as a surgical portosystemic shunt. Therefore, surgical portosystemic shunt should not be performed in this patient, who has a MELD score of 21.

A TIPS can be an attractive option for patients whose ascites does not improve with medical management with a low-sodium diet (<2 g/d) and the usual diuretics (spironolactone and furosemide). However, a TIPS is contraindicated in patients with MELD scores greater than 15 to 18 or serum bilirubin levels greater than 4 mg/dL (68.4 µmol/L), owing to high risk of mortality.

KEY POINT

- Patients with cirrhotic-stage liver disease and a Model for End-Stage Liver Disease (MELD) score of 15 or greater have better survival with liver transplantation than without.

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Item 55 Answer: C

Educational Objective: Manage gallstone disease during pregnancy with surgery.

The most appropriate management is laparoscopic cholecystectomy prior to hospital discharge. This patient has uncomplicated gallstone pancreatitis in her second trimester. This is very likely her second symptomatic episode of gallstone disease, and cholecystectomy should be performed. Her risk of recurrent pancreatitis over the next 90 days is about 20%. Laparoscopic cholecystectomy can be safely performed during pregnancy, particularly in the second trimester.

Bile acid dissolution therapy for gallstones has not gained widespread acceptance because most patients, such as this one, are candidates for laparoscopic cholecystectomy and few are candidates for bile acid dissolution therapy. Bile acid dissolution therapy is expensive, requires long-term multiple daily dosing, necessitates repeated ultrasonography, and has a potential long-term risk for cancer in the remaining gallbladder. Finally, most nonsurgical therapies for gallstones are contraindicated in pregnant patients. The safety of bile acid therapy in pregnant women is largely unknown.

In a study of pregnant women who had complications related to gallstones during pregnancy, recurrent biliary symptoms, repeated visits to the emergency department, and recurrent hospitalizations were significantly more common in patients who received conservative treatment as compared with women who underwent laparoscopic cholecystectomy or endoscopic retrograde cholangiopancreatography (ERCP). Waiting until after delivery is not the best option for this patient.

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ERCP with sphincterotomy could be used, but it should be performed only if this patient had contraindications to cholecystectomy or if there was high clinical suspicion of a persistent common bile duct stone. Neither of these conditions is present in this patient.

Extracorporeal shock-wave lithotripsy (ESWL) is reserved for patients with symptomatic gallstones who are poor candidates for surgery and in those patients with bile duct stones that are refractory to removal at ERCP owing to large size. After ESWL, the gallbladder remains in place and stones recur in about 50% of patients. This patient does not have an indication for ESWL.

KEY POINT

- Laparoscopic cholecystectomy can be safely performed during pregnancy, particularly in the second trimester.

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Item 56 Answer: D

Educational Objective: Diagnose peptic ulcer disease as the cause of upper gastrointestinal bleeding.

The most likely cause of this patient's gastrointestinal bleeding (GIB) is peptic ulcer disease. This patient has upper GIB, which is predicted based on four aspects of his presentation: hematemesis, melena detected on physical examination, absence of blood clots in the stool, and an elevated blood urea nitrogen to creatinine ratio (>30). The most common causes of upper GIB are peptic ulcer disease (34%), esophageal varices (33%), esophagitis (8%), and Mallory-Weiss tear (6%). Peptic ulcer disease (PUD) can cause severe upper GIB in the absence of coagulopathy. PUD is asymptomatic in 4% to 20% of patients and is commonly diagnosed because of complications such as bleeding.

Duodenal angiodysplasia is not the most likely cause of bleeding because severe GIB is rare in the absence of a bleeding diathesis or use of medications that affect hemostasis, including NSAIDs, aspirin, and anticoagulants.

Erosive gastritis is not likely in this patient because it would not cause severe GIB; the injury does not extend deeper than the mucosa, which lacks arteries and veins.

Variceal bleeding can be responsible for severe GIB that should not be overlooked because the mortality rate is high. Variceal bleeding may be the first presentation of cirrhosis, and therefore a high index of suspicion is needed. This patient has no history or biochemical evidence of cirrhosis, making variceal bleeding unlikely.

Portal gastropathy is unlikely because it is a mucosal cause of chronic, slow GIB. It can rarely cause acute but not severe GIB. In addition, this patient has no risk factors for chronic liver disease that would raise suspicion for this condition.

KEY POINT

- Peptic ulcer disease is the most common cause of upper gastrointestinal bleeding.

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Item 57 Answer: D

Educational Objective: Manage a curable malignant polyp.

The most appropriate management is to repeat colonoscopy in 3 months. A malignant polyp was discovered during this patient's colonoscopy and was endoscopically resected. Invasive adenocarcinoma arising in a pedunculated polyp may be considered adequately treated by endoscopic en bloc polypectomy alone if the lesion is confined to the submucosa and possesses no adverse histologic features such as poor differentiation, lymphatic or vascular invasion, or involved margins. National recommendations for postpolypectomy surveillance intervals are as short as 3 to 6 months in patients with large (>2 cm) adenomas or adenomas with invasive cancer and favorable prognostic features. These shorter surveillance intervals help to ensure that no residual polyp tissue remains.

If any adverse histologic features are noted, the risk of lymph node involvement is increased substantially and surgical resection of the involved colon is required. Surgical resection should also be considered if the lesion is removed piecemeal and the adequacy of resection cannot be confirmed.

Since this tumor is endoscopically cured, neither radiation therapy nor CT scan of the abdomen or pelvis is necessary.

KEY POINT

- National recommendations for postpolypectomy surveillance intervals are as short as 3 to 6 months in patients with large (>2 cm) adenomas or adenomas with invasive cancer and favorable prognostic features.

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Item 58 Answer: A

Educational Objective: Diagnose and treat small-bowel bleeding with angiography.

The most appropriate test to perform next is angiography, which will allow for bleeding localization and embolization of the bleeding source. Angiography should only be performed in patients with active overt bleeding, as it requires a

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bleeding rate greater than 0.5 mL/min. Complications such as acute kidney injury, organ necrosis, and vascular dissection/aneurysm can occur.

Balloon enteroscopy is used to visualize the small bowel. Latex balloons are mounted on an overtube that can deliver the enteroscope into the small bowel by successive inflation and deflation. Balloon enteroscopy can deliver the enteroscope orally or rectally (retrograde) and can be used for diagnosis and therapy. Complications of balloon enteroscopy are perforation and bleeding via avulsion of the bowel. Contraindications are radiation enteritis, severe ulceration, and recent bowel surgery. Retrograde balloon enteroscopy is not necessary because blood was seen in the colon; balloon enteroscopy is reserved for evaluation of the small intestine, which is not needed in this patient.

Repeat colonoscopy could be attempted, but visualization would be limited because the colon lumen would be filled with blood.

Technetium-labeled nuclear scans are used in patients with active bleeding (melena or hematochezia) who are transfusion dependent and hospitalized. This a diagnostic test and does not allow for therapeutic intervention.

KEY POINT

- In patients with gastrointestinal bleeding, angiography can identify bleeding and allows for therapeutic intervention with embolization.

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Item 59 Answer: E

Educational Objective: Manage acalculous cholecystitis.

The most appropriate management is percutaneous cholecystostomy. This ill patient presents with symptoms, signs, and imaging studies consistent with cholecystitis. Hospitalized patients can have acute cholecystitis without gallstones. This is known as acalculous cholecystitis and is thought to reflect either bacterial seeding of the gallbladder wall or gallbladder wall ischemia. Fever accompanying abdominal pain in a critically ill patient should prompt an assessment for cholecystitis. Diagnosis is usually made with ultrasound findings of acute cholecystitis or a radionuclide biliary scan that fails to visualize the gallbladder. Approximately 50% of these high-risk patients will develop cholangitis, empyema, gangrene, or gallbladder perforation during their hospitalization. Supportive treatment with intravenous antibiotic coverage of anaerobic and gram-negative bacteria is required. Definitive therapy with cholecystectomy is preferred but may be contraindicated in severely ill patients. Therapeutic decompression can be achieved with image-guided percutaneous cholecystostomy tube placement. The mortality rate for acute acalculous cholecystitis is between 10% and 50%.

An abdominal CT with contrast will add little useful information to this patient's clinical picture, and it might worsen his kidney disease.

Endoscopic retrograde cholangiopancreatography with sphincterotomy would be a consideration if this patient had gallbladder stones and/or a common bile duct stone. However, his normal liver chemistry studies and absence of biliary dilatation on ultrasound make a common bile duct stone unlikely.

Magnetic resonance cholangiopancreatography, similarly to CT, would not add important clinical information and would be difficult to perform in this ill, ventilated patient.

KEY POINT

- Fever accompanying abdominal pain in a critically ill patient should prompt an assessment for acalculous cholecystitis (acute cholecystitis without gallstones).

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Item 60 Answer: D

Educational Objective: Manage upper gastrointestinal bleeding caused by a low-risk gastric ulcer.

The most appropriate next step in management is to switch the intravenous proton pump inhibitor (PPI) to an oral PPI because this patient's low-risk ulcer does not require prolonged intravenous treatment or observation. Low-risk gastric ulcers are clean-based or have a nonprotuberant pigmented spot and should be treated with oral PPI therapy, initiation of refeeding within 24 hours, and early hospital discharge.

Blood transfusion should be performed in patients with (1) hemodynamic instability and ongoing bleeding or susceptibility to complications from oxygen deprivation (for example, ischemic heart disease) and (2) a hemoglobin level less than 7 g/dL (70 g/L) if hemodynamically stable with no active or massive bleeding. This patient does not meet these criteria.

Endoscopic treatment of the ulcer is not appropriate because clean-based ulcers are at low risk for rebleeding and the risks of endoscopic therapy outweigh any potential benefits in this patient.

Octreotide is not a routine treatment, even for acute active bleeding, unless variceal bleeding is suspected. This patient has a low-risk ulcer and no evidence of esophageal varices, so octreotide is not indicated.

KEY POINT

- Low-risk gastric ulcers are clean-based or have a nonprotuberant pigmented spot; they should be treated with oral proton pump inhibitor therapy, initiation of refeeding within 24 hours, and early hospital discharge.

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Item 61 Answer: B

Educational Objective: Manage hepatocellular carcinoma in a patient who meets the Milan criteria.

The most appropriate next step in management is to refer this patient for liver transplantation evaluation. A diagnosis of hepatocellular carcinoma can be made in a patient with cirrhosis in the presence of lesions larger than 1 cm that enhance in the arterial phase and have washout of contrast in the venous phase. Patients who meet the Milan criteria (up to three hepatocellular carcinoma tumors ≤3 cm or one tumor ≤5 cm) have excellent 5-year survival rates after liver transplantation. Patients who meet Milan criteria and have a tumor 2 cm or larger with arterial enhancement and venous washout on CT or MRI are eligible to receive Model for End-Stage Liver Disease (MELD) exception points, placing them at a higher priority for liver transplantation.

This patient does not require a biopsy of the liver masses because the radiographic characteristics of his liver tumors meet criteria for a diagnosis of hepatocellular carcinoma. The vast majority of hepatocellular carcinomas in the context of cirrhosis can be diagnosed with radiologic criteria alone. There is also a small risk (1%-3%) of seeding the needle track with tumor cells with percutaneous biopsy of hepatocellular carcinoma.

Sorafenib, a compound that targets growth signaling and angiogenesis, should be reserved for patients with Child-Turcotte-Pugh class A or B cirrhosis, good performance status, and vascular, lymphatic, or extrahepatic spread of the tumor. This patient has no evidence of angiolymphatic or extrahepatic involvement, and the tumor sizes are within Milan criteria; therefore, he should be evaluated for liver transplantation rather than started on sorafenib.

Surgical resection is not an appropriate option in this patient with evidence of hyperbilirubinemia and portal hypertension; he would be at high risk for postsurgical hepatic decompensation.

Transarterial chemoembolization (TACE) should not be performed before referral to a transplant center. Ultimately, patients who are expected to be on the waiting list for longer than 6 months are recommended to receive locoregional therapy such as TACE to control the tumor while awaiting a transplant. However, TACE should only be performed after the liver transplant evaluation is completed.

KEY POINT

- Patients with cirrhosis who meet the Milan criteria (up to three hepatocellular carcinoma tumors ≤3 cm or one tumor ≤5 cm) are best treated with liver transplantation and have excellent 5-year survival rates.

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Item 62 Answer: E

Educational Objective: Evaluate a patient with a positive hepatitis C virus (HCV) antibody test and a negative HCV RNA test.

Patients who are hepatitis C virus (HCV) antibody positive but HCV RNA negative do not have HCV infection and require no further testing. Repeating HCV RNA testing can be considered if there are risk factors for recent HCV infection or if there is other clinical evidence of liver disease, but neither of these is present in this patient. A 2013 guideline from the U.S. Preventive Services Task Force recommended screening for hepatitis C once in all persons born between 1945 and 1965, as well as targeted screening of persons with risk factors such as illicit drug use, receipt of blood products, hemodialysis, and multiple sex partners. Screening is accomplished by testing for antibody to HCV (anti-HCV). If antibody testing is positive, the next step is to perform HCV RNA testing, which is often done by "reflex" testing in many laboratories. The test results are interpreted in the following ways: Positive anti-HCV with negative HCV RNA indicates either false-positive anti-HCV or cleared infection, and positive anti-HCV with positive HCV RNA indicates active infection. Rarely, in instances of acute HCV infection or in an immunosuppressed patient, HCV RNA may be positive despite a negative anti-HCV.

Liver ultrasound and serial alanine aminotransferase monitoring are not necessary in the absence of clinical evidence of liver disease.

KEY POINT

- Patients with a positive antibody to hepatitis C virus (HCV) but negative HCV RNA do not have HCV infection, and no further testing is required.

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Item 63 Answer: D

Educational Objective: Perform genetic testing to evaluate the inheritance pattern of *MYH*-associated polyposis.

The most important person to receive genetic testing is the patient's wife. *MYH*-associated polyposis (MAP) is the only known autosomal recessive hereditary colorectal cancer syndrome. MAP should be considered as a cause for multiple colorectal adenomas (>10) in patients with an apparent autosomal recessive inheritance of colorectal polyposis or cancer. MAP is caused by biallelic mutations in the base excision repair gene *MYH*. Because the disorder is autosomal

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recessive, both parents must be carriers of an *MYH* mutation in order for a child to inherit the syndrome. Therefore, testing the patient's wife would provide the knowledge required to make a risk assessment for the children. If the patient's wife is negative for the *MYH* mutation, the children will not be biallelic mutation carriers and do not need genetic testing. If the patient's wife has a genetic mutation in the *MYH* gene, each child has a 25% chance of inheriting both *MYH* gene mutations (and would have the disease), a 50% chance of inheriting at least one *MYH* gene mutation (and would be a carrier), and a 25% chance of inheriting no *MYH* gene mutations. In that circumstance, the children should each undergo genetic testing.

Performing genetic testing on the patient's father or mother would not provide any useful information at this time. The patient has already been diagnosed with the two mutations; therefore, both his mother and father must be positive for the mutation.

If the patient's wife was unavailable for genetic testing, it would be appropriate to perform genetic testing on the children. Genetic testing is usually done at the age at which high-risk colorectal cancer screening would begin, which is 18 years in MAP and attenuated familial adenomatous polyposis and 12 to 15 years in classic FAP.

KEY POINT

- Because *MYH*-associated polyposis is an autosomal recessive disorder, both parents must be carriers of an *MYH* mutation in order for a child to inherit the syndrome.

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Item 64 Answer: A

Educational Objective: Provide antibiotic prophylaxis for variceal hemorrhage in a patient with cirrhosis but without ascites.

The most appropriate next step in management is administration of antibiotics. This patient has decompensated cirrhosis as evidenced by previous ascites and jaundice, and she has developed hematemesis, which is most suggestive of a variceal hemorrhage. Patients with cirrhosis, especially those with decompensated cirrhosis, are at high risk for developing bacterial infections during an episode of variceal hemorrhage. A common misperception is that antibiotic prophylaxis need only be provided for patients with variceal hemorrhage and ascites (at risk for spontaneous bacterial peritonitis). A Cochrane systematic review confirmed that antibiotic prophylaxis during variceal bleeding not only helps prevent spontaneous bacterial peritonitis but also helps reduces the risk of bacteremia, pneumonia, and urinary tract infection and reduces mortality. Therefore, prophylactic antibiotics should be provided for patients with cirrhosis and variceal hemorrhage, regardless of the presence or absence of ascites. An oral fluoroquinolone such as norfloxacin or intravenous ciprofloxacin (when oral intake is not possible) are the acceptable choices. Intravenous ceftriaxone may be more effective for patients with Child-Turcotte-Pugh class B and C cirrhosis. The maximum duration of antibiotic administration is 7 days.

A nonselective β-blocker is recommended as secondary prophylaxis after recovery from a variceal bleed, but it would not be warranted in the acute setting in this patient with hypotension.

Evidence regarding the early placement (within 72 hours) of a transjugular intrahepatic portosystemic shunt (TIPS) for patients with variceal hemorrhage is evolving. Despite some evidence of improved mortality for early TIPS placement after endoscopic and pharmacologic control of variceal hemorrhage, this is not the current standard of care. In addition, variceal hemorrhage has not yet been confirmed in this patient, so this intervention is not appropriate at this time.

An upper endoscopy should be performed in this patient with presumed variceal hemorrhage within 12 hours, but only after she has been treated with standard pharmacotherapy (octreotide and antibiotics) and appropriately resuscitated to enable safe endoscopy. A blood pressure of 72/54 mm Hg is too low to be able to proceed immediately with a safe endoscopy.

KEY POINT

- Patients with variceal hemorrhage and cirrhosis are at high risk for infection and require antibiotic prophylaxis, regardless of the presence or absence of ascites.

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Item 65 Answer: B

Educational Objective: Diagnose celiac disease in a patient with abnormal liver chemistry studies.

The most likely diagnosis is celiac disease. This patient has the combination of loose stools, unintentional weight loss, elevated liver chemistry test results, and iron deficiency anemia without an obvious source of blood loss. Minor elevations of serum aminotransferase levels are found in up to 50% of patients with celiac disease and may be the only presenting feature in approximately 9% of patients. Serum aspartate aminotransferase (AST) is usually less than 80 U/L, and alanine aminotransferase (ALT) is usually less than 130 U/L. Patients with celiac disease can also have coexisting liver disease such as autoimmune hepatitis, primary sclerosing cholangitis, or primary biliary cirrhosis. Improvements in liver chemistry

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studies that are related to celiac disease occur when such patients are treated with a gluten-free diet.

Alcohol-induced liver disease (ALD) is diagnosed by a history of significant alcohol intake and clinical evidence of liver disease. Serum AST level is typically elevated two to six times the upper limit of normal in severe alcoholic hepatitis. AST levels above 500 U/L and ALT levels above 200 U/L are uncommon. An AST/ALT ratio above 2 to 3 is typical for ALD. This patient does not have significant alcohol intake or an aminotransferase profile typical of alcohol-induced liver disease.

Chronic viral hepatitis can result in modest elevations in the aminotransferase levels; typically ALT is greater than AST. The alkaline phosphatase level may be normal or slightly elevated. A diagnosis of chronic hepatitis would not account for the patient's diarrhea or iron deficiency anemia.

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease of unknown cause. PBC is diagnosed by serum alkaline phosphatase levels greater than 1.5 times the upper limit of normal and typically normal serum total bilirubin levels. Increases in serum AST and ALT levels less than five times the upper limit of normal may be seen as well. PBC is not associated with diarrhea or iron deficiency anemia.

KEY POINT

- Celiac disease is identified in 9% of patients with otherwise unexplained elevated serum aminotransferase levels.

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Item 66 Answer: D

Educational Objective: Diagnose a common bile duct stone.

The most likely diagnosis is choledocholithiasis. This patient's pain is consistent with biliary pain, and the presence of a transient elevation of serum alanine aminotransferase and the dilated bile ducts on ultrasound are consistent with intermittent biliary obstruction due to a common bile duct stone. Up to 20% of patients with symptomatic gallbladder stones will have a common bile duct stone. Although complications are more common than with symptomatic gallstones, less than 50% of patients with choledocholithiasis develop symptoms, and 20% spontaneously pass stones from the common bile duct. Assessment of the bile duct preoperatively with endoscopic ultrasound or magnetic resonance cholangiopancreatography is recommended if the clinical suspicion is high.

Acute pancreatitis could be a complication of a common bile duct stone, but the pain would not be intermittent and it would result in an elevated serum amylase level, which was not present in this patient.

A bile leak would present earlier, within a day or two after surgery. It would cause more continuous pain and would result in signs of peritonitis on examination. In addition, the bile ducts would not be dilated.

Fever suggests the development of cholangitis, which is potentially life threatening. Additional findings of cholangitis include jaundice and pain in the right upper quadrant (Charcot triad). Most patients will have cholelithiasis, elevated aminotransferase levels, and hyperbilirubinemia. Ultrasonography may show a dilated common bile duct.

Sphincter of Oddi dysfunction would produce the same symptoms as are found in this patient; however, this condition is typically diagnosed in patients with biliary-type pain without an alternative explanation. This patient's recent history of cholelithiasis, cholecystectomy, and dilated intrahepatic and extrahepatic bile ducts strongly suggests choledocholithiasis, not sphincter of Oddi dysfunction.

KEY POINT

- Biliary pain associated with dilated bile ducts on ultrasound is consistent with the diagnosis of choledocholithiasis.

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Item 67 Answer: B

Educational Objective: Manage gastroparesis.

The most appropriate management is to discontinue metoclopramide and begin promethazine. Replacing the metoclopramide with a scheduled antiemetic is the safest and most cost-effective next step in management. The initial treatment of diabetic gastroparesis should include a dietary management plan consisting of frequent small-volume meals that are low in fat and soluble fiber. Equally important is tight glycemic control because acute hyperglycemia can impair gastric emptying, often resulting in nausea, vomiting, and abdominal pain. When these initial treatment modalities are ineffective, the use of the prokinetic agent metoclopramide is indicated. Metoclopramide is the only drug approved by the FDA for the treatment of gastroparesis. Metoclopramide crosses the blood-brain barrier and potentially causes side effects such as hyperprolactinemia, galactorrhea, and a variety of neurologic symptoms such as tardive dyskinesia. The risks of neurologic side effects are increased with chronic therapy (greater than 3 months) and with use in the elderly and in women. Drug-induced movement disorders are the most concerning neurologic symptoms. Patients taking metoclopramide should receive counseling about these potential adverse effects and should notify the prescriber immediately if these symptoms develop. Symptoms are likely to progress in severity and may become permanent with continued therapy. Although metoclopramide was effective at relieving this patient's gastroparesis symptoms, her neurologic symptoms

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mandate its prompt discontinuation. Simply decreasing the dose of metoclopramide is unlikely to resolve the neurologic symptoms. Although antiemetic therapy will not improve gastric emptying, it can be very effective for symptoms of nausea and vomiting.

Gastric electrical stimulation with a gastric pacemaker may be considered for compassionate treatment in patients with refractory symptoms of nausea and vomiting in whom all other forms of more conservative therapy have failed.

Given the lack of superiority to placebo in randomized clinical trials, intrapyloric injection of botulinum toxin cannot be recommended for patients with gastroparesis.

KEY POINT

- Metoclopramide is the only drug approved by the FDA for the treatment of gastroparesis; however, metoclopramide is associated with side effects such as hyperprolactinemia, galactorrhea, and tardive dyskinesia that require discontinuation of the drug.

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Item 68 Answer: C

Educational Objective: Treat non–acetaminophen-related acute liver failure with *N*-acetylcysteine.

The most appropriate treatment is intravenous *N*-acetylcysteine (NAC). This patient has features of acute liver failure (ALF). ALF is defined by the absence of previous liver disease accompanied by new-onset hepatic encephalopathy and coagulopathy, usually in the presence of jaundice. The cause of ALF is most likely amoxicillin-clavulanate, which is the most common cause of drug-induced liver injury. Intravenous NAC was shown to be effective for non–acetaminophen-related ALF in a randomized, placebo-controlled trial (N=173). The transplant-free survival was 40% in the NAC-treated patients compared with 27% in the placebo group, and this survival benefit was seen only in early-grade (grade I to II) hepatic encephalopathy. This patient has grade II hepatic encephalopathy as evidenced by the presence of asterixis.

Intravenous acyclovir would be an appropriate treatment for herpes hepatitis. Herpes hepatitis classically presents with serum aminotransferase values in the multiple thousands and a disproportionately low serum bilirubin level, which is not the case for this patient.

Intravenous glucocorticoids are not appropriate because they are not proved to be effective in ALF related to drug-induced liver injury.

Oral pentoxifylline is a second-line treatment for alcoholic hepatitis. This patient has a non–alcohol-related cause of ALF; her drinking history does not suggest that alcoholic hepatitis is likely.

KEY POINT

- *N*-acetylcysteine has been shown in a randomized controlled trial to improve transplant-free survival in non–acetaminophen-related acute liver failure in patients with grade I or II hepatic encephalopathy.

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Item 69 Answer: D

Educational Objective: Diagnose eosinophilic esophagitis.

The most likely diagnosis is eosinophilic esophagitis (EoE). This patient has the classic presentation of EoE, which occurs in a young man with solid-food dysphagia that requires endoscopy for removal. EoE is the result of eosinophil cell infiltration of the esophageal squamous mucosa. The incidence of EoE is thought to be increasing, and it seems to parallel the increasing incidence of allergic disease and asthma. Asthma and systemic and seasonal allergies have significant prevalence in adults with EoE. EoE is diagnosed by the finding of greater than 15 eosinophils/hpf on esophageal endoscopic biopsy and by exclusion of GERD. GERD must be excluded because it can also cause esophageal eosinophilic infiltration. This can be done with a therapeutic trial of a proton pump inhibitor (PPI) for 8 weeks. Clinical response to PPI therapy should be assessed based on improvement of clinical symptoms and even repeating the upper endoscopy with biopsies to demonstrate mucosal healing. Endoscopy often reveals characteristic findings of EoE such as rings, longitudinal furrows, and sometimes strictures. Medical therapy consists of swallowed aerosolized topical glucocorticoids (fluticasone or budesonide).

Achalasia is also characterized by dysphagia; however, endoscopic findings of achalasia would include a dilated esophagus with a tight gastroesophageal junction, where the lower esophageal sphincter is located. These endoscopic findings are not present in this patient.

Barrett esophagus (BE) is the result of chronic acid reflux, but it is usually not associated with dysphagia, especially in a young person. The diagnosis of BE is suggested by endoscopic findings of salmon-colored mucosa at the gastroesophageal junction compared with the normal pearl-colored squamous mucosa and is confirmed histologically by the presence of specialized intestinal metaplasia with acid-mucin–containing goblet cells.

Diffuse esophageal spasm is usually characterized by dysphagia or chest pain but not food impaction. Manometry shows intermittent, high-amplitude, simultaneous, nonperistaltic contractions in response to swallowing. Findings of a "corkscrew esophagus" (caused by multiple simultaneous contractions) on barium swallow are typical of diffuse

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esophageal spasm. Longitudinal rings or furrows are not seen on endoscopic examination.

KEY POINT

- The classic presentation of eosinophilic esophagitis is a young man with solid-food dysphagia that requires endoscopy for removal.

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Item 70 Answer: D

Educational Objective: Recommend surveillance upper endoscopy in a patient with familial adenomatous polyposis.

The most appropriate recommendation for surveillance of a familial adenomatous polyposis (FAP)-related cancer is upper endoscopy. Once the colon is removed in a patient with FAP, duodenal and periampullary cancers are the second leading causes of cancer deaths. The cumulative lifetime risk of duodenal cancer is based on the size, number, and pathology of duodenal polyps and ranges from 2.5% for stage I to 30% for stage IV duodenal polyposis. Gastric fundic gland polyps and duodenal adenomas are almost always present in patients with FAP. Upper endoscopy is recommended for surveillance of duodenal cancer every 1 to 5 years in all patients with FAP; the exact interval is based on the stage of duodenal polyposis.

CT of the abdomen and pelvis is not a standard recommendation for patients with FAP, but it may be useful for surveillance of patients with FAP-related intra-abdominal desmoid tumors.

A phenotypic variant of FAP called Gardner syndrome is associated with extraintestinal manifestations of FAP, which include congenital hypertrophy of the retinal pigment epithelium (CHRPE). CHRPE may be an indication of underlying FAP, but it has no attendant health risks for patients with FAP and does not require ongoing surveillance if detected.

Small-bowel capsule endoscopy is not a standard surveillance recommendation for a patient with FAP because the risk for small-bowel cancer beyond the duodenum is small.

KEY POINT

- Upper endoscopy is recommended for surveillance of duodenal cancer every 1 to 5 years in all patients with familial adenomatous polyposis.

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Item 71 Answer: D

Educational Objective: Manage acute hepatitis B.

The most appropriate management is serial monitoring of liver enzymes. This patient has acute hepatitis B without evidence of marked liver dysfunction (such as markedly increased INR or hepatic encephalopathy). Typical clinical symptoms include malaise, fatigue, nausea, and right upper quadrant discomfort. Jaundice and cholestasis can develop 1 to 2 weeks after the onset of symptoms. Acute hepatitis B infection will resolve (defined as clearance of hepatitis B surface antigen within 6 months) in 90% of adult patients. Serial monitoring of liver enzymes and markers of liver synthetic function is the most appropriate management strategy.

Given this patient's essentially unremarkable ultrasound and laboratory tests consistent with acute hepatitis B, abdominal CT is not necessary at this time.

Patients with fulminant acute hepatitis B or severe protracted acute hepatitis B may be offered antiviral therapy with agents such as lamivudine, entecavir, or tenofovir. This patient does not have marked liver dysfunction. so these agents are not appropriate at this time.

Pegylated interferon is contraindicated in acute hepatitis B owing to the risk of exacerbating liver inflammation and is therefore not appropriate for this patient.

KEY POINT

- Acute hepatitis B infection will resolve (defined as clearance of hepatitis B surface antigen within 6 months) in 90% of adult patients.

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Item 72 Answer: D

Educational Objective: Manage pain in chronic pancreatitis using a gabapentinoid.

The most appropriate additional treatment is pregabalin, a gabapentinoid. Pain can be difficult to treat in patients with chronic pancreatitis. In the absence of a local anatomic cause of pain, a stepwise approach to analgesia is appropriate starting with simple analgesics such as NSAIDs or acetaminophen. Non-enteric-coated pancreatic enzymes, which theoretically limit stimulation of the pancreas by inhibiting the cholecystokinin feedback loop, can be tried for pain control. They seem to be most effective in patients with idiopathic pancreatitis. For patients with persistent pain despite the use of simple analgesics, initiating opioids is a reasonable consideration while developing a pain management program that includes adjunctive agents to minimize chronic narcotic use, which can create addiction and gastrointestinal side effects. Most experts begin with tramadol, a nonopioid with opioid actions that provides analgesia comparable to other opioid analgesics in patients with chronic pancreatitis

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but causes fewer gastrointestinal side effects. Pregabalin (or a low-dose tricyclic antidepressant) may be offered adjunctively, as part of a step-up approach to pain management, after an initial trial of acetaminophen, ibuprofen, and/or tramadol. According to a recent randomized controlled trial, the gabapentinoid pregabalin used as adjuvant treatment reduced constant pain in chronic pancreatitis but has an unclear durability of action and may cause central nervous system side effects in up to 30% of patients.

Celiac plexus blockade (using glucocorticoids) or neurolysis (using ethanol) can be performed percutaneously or via endoscopic ultrasonography, but any relief from this procedure tends to be short lived and is associated with risks of diarrhea, postural hypotension, and rarely paraplegia. Adding pregabalin as adjuvant therapy is a more reasonable and less invasive next therapeutic step for this patient.

Extracorporeal shock wave lithotripsy can be used to break up stones obstructing pancreatic ducts and improve ductal drainage and relieve pain. Extracorporeal shock wave lithotripsy is not appropriate for this patient because she does not have an intraductal pancreatic duct stone and dilated main pancreatic duct.

Surgical management of chronic pancreatitis is reserved for patients in whom conventional medical management is unsuccessful. Surgical management is categorized into operative resection (pancreaticoduodenectomy or distal pancreatectomy) and drainage procedures (lateral pancreaticojejunostomy), and the choice of surgery is dependent on the clinical situation.

KEY POINT

- For patients with persistent pain due to chronic pancreatitis, pregabalin (or a low-dose tricyclic antidepressant) may be offered adjunctively, as part of a step-up approach to pain management, after an initial trial of acetaminophen, ibuprofen, and/or tramadol.

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Item 73 Answer: B

Educational Objective: Treat gastroesophageal reflux disease in a patient with an incomplete response to once-daily proton pump inhibitor therapy.

The most appropriate next step in management is to increase the pantoprazole to twice daily. This patient has classic symptoms of gastroesophageal reflux disease (GERD), with heartburn and a sour taste in his mouth. Once-daily proton pump inhibitor (PPI) therapy has significantly improved his symptoms, but he still has breakthrough symptoms at night. Patients with no alarm symptoms (dysphagia, unintentional weight loss, hematemesis, or melena) and a partial response to PPI therapy should have their dose increased to twice daily. Genetic variation in rates of drug metabolism, including PPIs, may decrease effectiveness in some populations (especially white patients), providing a rationale for twice-daily dosing for some patients. Before drug dose escalation, adherence and correct administration (30 to 60 minutes before a meal) should be confirmed. When adequate symptom relief is obtained, it is reasonable to decrease to the lowest effective dose or even stop therapy.

Prokinetic medications such as metoclopramide have no role in the therapy of GERD. Tardive dyskinesia is a serious complication of metoclopramide therapy, is more common in women, occurs with increased frequency with prolonged use, and may be irreversible.

This patient's symptoms are improving with medical therapy, so upper endoscopy is not necessary at this point. Upper endoscopy would be warranted if this patient's symptoms do not improve with twice-daily PPI therapy.

There are no convincing data to suggest that one PPI is superior to another in the treatment of uncomplicated GERD. Increasing the dose of the current PPI is more likely to be beneficial than is switching to another PPI such as omeprazole.

KEY POINT

- Patients with gastroesophageal reflux disease with no alarm symptoms who have a partial response to once-daily proton pump inhibitor therapy should have their dose increased to twice daily.

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Item 74 Answer: B

Educational Objective: Treat refractory ulcerative colitis with an anti-tumor necrosis factor agent.

The most appropriate treatment is to initiate an anti-tumor necrosis factor (anti-TNF) agent such as adalimumab. This patient has moderate to severe ulcerative colitis that is not responding to 60 mg/d of prednisone. Moderate to severe ulcerative colitis is often treated with oral glucocorticoids such as prednisone, 40 to 60 mg/d. Patients whose disease does not respond to oral glucocorticoids should be hospitalized and given intravenous glucocorticoids or should be treated with an anti-TNF agent. Randomized controlled clinical trials have shown three anti-TNF antibodies (infliximab, adalimumab, and golimumab) to be effective for inducing and maintaining remission in patients such as this with ulcerative colitis. Indications for hospital admission include dehydration, inability to tolerate oral intake, fever, significant abdominal tenderness, and abdominal distention.

A meta-analysis of clinical trials showed that using doses of prednisone above 60 mg/d provides little if any additional efficacy and produces more side effects.

Ciprofloxacin and metronidazole should be used in patients with severe colitis associated with high fever, significant leukocytosis, peritoneal signs, or toxic megacolon.

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However, antibiotics are not indicated in a patient such as this with colitis without signs of systemic toxicity.

Patients with mild to moderate ulcerative colitis respond well to 5-aminosalicylate agents. Patients with proctitis or left-sided colitis should receive topical therapy with a 5-aminosalicylate or hydrocortisone suppositories or enemas. If patients require repeated courses of glucocorticoids or become glucocorticoid dependent, thiopurines (6-mercaptopurine or azathioprine) or an anti-TNF agent should be initiated (methotrexate has not been shown to be effective in ulcerative colitis). Anti-TNF agents should be used in patients who do not maintain remission with thiopurines or patients whose disease is refractory to glucocorticoids. It is unlikely that 5-aminosalicylates would be beneficial in this patient with more severe disease that is refractory to prednisone.

KEY POINT

- Patients with moderate to severe ulcerative colitis whose disease does not respond to oral glucocorticoids should be treated with either intravenous glucocorticoids or an anti–tumor necrosis factor agent.

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Item 75 Answer: C

Educational Objective: Manage upper gastrointestinal bleeding in a patient with cardiovascular disease.

The most appropriate postendoscopic management is to resume aspirin before discharge. This patient has upper gastrointestinal bleeding due to a low-risk (clean-based) ulcer. Aspirin should be resumed within 3 to 5 days for patients such as this with established cardiovascular disease. Aspirin reduces all-cause mortality (attributable primarily to cardiovascular, cerebrovascular, or gastrointestinal complications) tenfold over 30 days while increasing rebleeding rates only twofold. Long-term, daily proton pump inhibitor therapy should be offered to aspirin users who are *Helicobacter pylori* negative or those who use concomitant NSAIDs, anticoagulants, glucocorticoids, or other antiplatelet drugs.

This patient has no indication for changing his antiplatelet therapy from aspirin to clopidogrel. Although the relative risk for gastrointestinal bleeding is slightly lower with clopidogrel than aspirin, the absolute risk reduction from making the change is low enough that this patient's medication should not be switched; he has a low-risk ulcer and no other cardiovascular indication for clopidogrel (such as a recent drug-eluting stent). In addition, clopidogrel carries a high risk of bothersome side effects such as rash and diarrhea. It is also more expensive than aspirin.

KEY POINT

- In patients with upper gastrointestinal bleeding due to peptic ulcer disease and concomitant cardiovascular disease, aspirin should be resumed within 3 to 5 days; aspirin reduces mortality tenfold over 30 days while increasing rebleeding rates only twofold.

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Item 76 Answer: D

Educational Objective: Diagnose serrated polyposis syndrome.

The most likely diagnosis is serrated polyposis syndrome. Serrated polyposis syndrome (SPS) is a familial polyposis syndrome without a known genetic cause. It is diagnosed by the World Health Organization criteria of (1) five or more serrated polyps proximal to the sigmoid colon, two or more of which are 10 mm in diameter or greater, (2) any number of serrated polyps proximal to the sigmoid colon in an individual with a first-degree relative who has SPS, or (3) more than 20 serrated polyps distributed throughout the colon. This patient has had six serrated polyps, two of which are larger than 10 mm; therefore, she meets criteria for SPS. SPS is associated with an increased risk of colorectal but not extraintestinal cancer. The mean age of colon cancer diagnosis is 56 years, and metachronous colon cancer occurs in 7% of patients at 5 years of follow-up. Because of this, patients with SPS should undergo colonoscopy yearly. Serrated polyps are a common finding on screening colonoscopy. It is important to recognize that hyperplastic polyps are the most common type of serrated polyp and, when small and located in the rectosigmoid colon, are believed to impart no risk to the patient. However, the other two forms of serrated polyps, sessile serrated polyps and traditional serrated adenomas, are precancerous lesions that occur in 3% and less than 1%, respectively, of individuals undergoing screening colonoscopy. Approximately 30% of colon cancers develop from sessile serrated polyps. Patients with neoplastic serrated polyps should undergo colonoscopy at an interval based on the size and pathology of the lesion.

Familial adenomatous polyposis (FAP) is characterized by tens to thousands of adenomatous colorectal polyps. This patient has no adenomatous polyps and, therefore, FAP is not the most likely diagnosis.

Lynch syndrome is a hereditary colon cancer syndrome caused by a germline mutation in a mismatch repair gene. Colorectal cancers in Lynch syndrome arise from adenomatous polyps. Although patients with Lynch syndrome can have numerous adenomatous polyps, it does not appear typically as a polyposis syndrome.

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Peutz-Jeghers syndrome (PJS) is an autosomal dominant hamartomatous polyposis syndrome. The intestinal polyps in PJS are hamartomatous rather than serrated, as was seen in this patient.

KEY POINT

- Serrated polyposis syndrome is associated with an increased risk of colorectal but not extraintestinal cancer; patients with serrated polyposis syndrome should undergo colonoscopy yearly.

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Item 77 Answer: B

Educational Objective: Evaluate recurrent symptoms with a dietary history in a patient with celiac disease.

The most appropriate management is a careful dietary review. Celiac disease is an immunologic response to dietary gliadins in patients who are genetically at risk as deemed by the presence of *HLA-DQ2* or *HLA-DQ8*. All patients with celiac disease should adhere to a gluten-free diet by avoiding wheat, barley, and rye. Because of cross-contamination with other cereal grains, oats should be avoided for the first year and should only be introduced if the patient is doing well clinically. In patients whose symptoms are recurrent or do not respond to a gluten-free diet, gluten ingestion (either surreptitious or inadvertent) is the most likely explanation. In many cases, patients believe they are being compliant with a strict gluten-free diet, but careful review by an experienced dietitian reveals inadvertent gluten ingestion. Associated conditions that may account for recurrent diarrhea are microscopic colitis (70-fold increased risk), lactose malabsorption, small intestinal bacterial overgrowth, pancreatic insufficiency, inflammatory bowel disease, refractory celiac disease, or enteropathy-associated T-cell lymphoma. A careful review of diet and potential nondietary sources of gluten exposure (such as medications, lipstick, and toothpaste) should be explored before performing additional testing.

A CT scan would be helpful to exclude enteropathy-associated lymphoma or adenocarcinoma; however, these diagnoses are extremely uncommon, even in patients with celiac disease. Dietary indiscretion is a much more likely cause.

Colonoscopy with biopsies would be useful to exclude microscopic colitis, which is associated with celiac disease, but a second diagnosis should be pursued only after ruling out gluten ingestion.

Upper endoscopy with small-bowel biopsies would be helpful to evaluate for active celiac disease, but it would not determine whether gluten ingestion is the cause of this patient's symptoms.

KEY POINT

- Assessment for intentional or unintentional gluten ingestion is the first step in evaluating recurrent symptoms in a patient with celiac disease.

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Item 78 Answer: C

Educational Objective: Treat *Helicobacter pylori* infection after initial treatment failure.

The most appropriate treatment for this patient is a 10-day course of levofloxacin, amoxicillin, and omeprazole. *Helicobacter pylori* infection is closely linked with recurrent peptic ulcer disease, chronic metaplastic gastritis, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, gastric adenocarcinoma, iron deficiency anemia, and primary immune thrombocytopenia. Therefore, an effort should be made to successfully eradicate the infection once it is identified. Initial treatment regimens are effective in *H. pylori* eradication in only 70% to 80% of patients. The most common reason for treatment failure is antibiotic resistance. In the United States, *H. pylori* resistance prevalence is 37% for metronidazole and 13% for clarithromycin. Clarithromycin resistance is absolute and cannot be overcome by increasing the dose or re-treating with a longer course of therapy. Conversely, metronidazole resistance can be overcome by increasing the dose or by using metronidazole in an alternative medication regimen. If *H. pylori* infection is not eradicated with primary therapy, as in this patient, a second-line salvage therapy should contain an alternative antibiotic to clarithromycin, and the treatment should be at least 10 days in duration to maximize the likelihood of treatment success. Two universally recommended second-line therapies are (1) a 10- to 14-day course of bismuth subsalicylate, metronidazole, tetracycline, and a proton pump inhibitor (PPI), or (2) a 10-day course of levofloxacin, amoxicillin, and a PPI.

KEY POINT

- If *Helicobacter pylori* infection is not eradicated with primary therapy, a second-line salvage therapy should contain an alternative antibiotic to clarithromycin, and the treatment should be at least 10 days in duration to maximize the likelihood of treatment success.

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Item 79 Answer: D

Educational Objective: Diagnose Gilbert syndrome.

This patient requires no further tests for his scleral icterus. He has an indirect hyperbilirubinemia with normal liver enzyme

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levels, reticulocyte count, and blood smear. These findings are consistent with Gilbert syndrome, and no further tests are necessary. Gilbert syndrome is a benign condition characterized by mild unconjugated hyperbilirubinemia, which is caused by a congenital decrease in hepatic uridine diphosphate glucuronyl transferase. Patients with Gilbert syndrome have a defect in the ability to conjugate bilirubin, resulting in unconjugated hyperbilirubinemia. The bilirubin level tends to be highest when the patient is fasting or ill but is usually less than 3 mg/dL (51.3 µmol/L).

Patients with warm autoimmune hemolytic anemia (WAIHA) may present with rapid or more insidious symptoms of anemia or jaundice; mild splenomegaly is often present. Spherocytes are seen on the peripheral blood smear. The direct antiglobulin (Coombs) test is used to diagnose WAIHA and is typically positive for IgG and negative or only weakly positive for complement (C3). Hemolytic anemia is associated with a low hemoglobin level, a high reticulocyte count, and an abnormal blood smear. Because these features are not present in this patient, there is no need for further hematologic evaluation with a direct antiglobulin (Coombs) test.

Hepatitis is associated with hepatocyte inflammation and injury typically manifested as elevations of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT). This patient's laboratory abnormality is limited to unconjugated hyperbilirubinemia, which is not consistent with either hepatitis B or C; serologic screening for these conditions is unnecessary.

Primary sclerosing cholangitis (PSC) is a chronic inflammatory disorder that affects the intra- and extrahepatic bile ducts. Serum alkaline phosphatase values are 3 to 10 times the upper limit of normal, and serum ALT and AST levels are two to three times the upper limit of normal. The diagnosis is made by cholangiography. This patient's solitary finding of unconjugated hyperbilirubinemia is not compatible with the diagnosis of PSC.

KEY POINT

- The finding of predominantly unconjugated hyperbilirubinemia indicates non–liver-disease states such as hemolysis or Gilbert syndrome, which is characterized by benign defects in bilirubin conjugation.

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Ehmer U, Kalthoff S, Fakundiny B, et al. Gilbert syndrome redefined: a complex genetic haplotype influences the regulation of glucuronidation. Hepatology. 2012 Jun;55(6):1912-21. [PMID: 22213127]

Item 80 Answer: C

Educational Objective: Provide colonoscopy surveillance in a patient with a history of colorectal cancer.

The most appropriate time to repeat colonoscopy is in 5 years. Patients who undergo curative surgical resection for colon cancer should have a complete perioperative colonoscopy to remove all synchronous neoplasia. A subsequent surveillance colonoscopy is recommended within 1 year. If results of that colonoscopy are normal, repeat colonoscopy is recommended at 3 years, and, if normal, every 5 years thereafter. If colorectal polyps are detected, the surveillance interval should be based upon the number, size, and pathology of the polyps. This patient has received his 1- and 3-year follow-up colonoscopies and has had normal results; therefore, colonoscopy can now be repeated every 5 years.

A 10-year colonoscopy interval is appropriate for patients with a family history of adenoma or colorectal cancer in one first-degree relative or two second-degree relatives older than age 60 years. It is not recommended for this patient because his history of colorectal cancer requires more frequent surveillance.

KEY POINT

- Screening recommendations for patients with a history of colorectal cancer consist of follow-up colonoscopy at 1 year and 3 years after curative surgical resection; if results of these colonoscopies are normal, the surveillance interval can be extended to 5 years.

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Item 81 Answer: C

Educational Objective: Manage gastroesophageal reflux disease with an empiric trial of a proton pump inhibitor.

The most appropriate next step in management is a trial of a proton pump inhibitor (PPI). This patient has classic symptoms of gastroesophageal reflux disease (GERD) in the form of heartburn. Symptoms of heartburn and regurgitation are strong predictors for the clinical diagnosis of GERD. The most appropriate next step in a patient without alarm symptoms (dysphagia, unintentional weight loss, hematemesis, or melena) is an empiric trial of a PPI.

Although ambulatory esophageal pH monitoring is the most accurate technique to diagnose GERD, it is expensive and invasive and is therefore only indicated in patients whose symptoms have not responded to medication. This patient has never taken a PPI previously to control his symptoms, so pH testing is not needed at this point in management.

Esophageal manometry measures the pressure levels in the esophagus and is useful in evaluating esophageal motility disorders such as achalasia. However, this patient has not had dysphagia to solids and liquids, which makes an esophageal motility disorder unlikely.

This patient has not had any alarm symptoms such as difficulty swallowing or weight loss that would warrant an upper endoscopy at this time. An upper endoscopy would be necessary if this patient had alarm symptoms or if his symptoms did not respond to the empiric trial of a PPI.

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KEY POINT

- In a patient without alarm features (dysphagia, unintentional weight loss, hematemesis, or melena), symptom relief with an empiric trial of a proton pump inhibitor confirms the diagnosis of gastroesophageal reflux disease.

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Item 82 Answer: D

Educational Objective: Diagnose ischemic colitis as a cause of lower gastrointestinal bleeding.

The most likely diagnosis is ischemic colitis. The most common causes of acute, severe lower gastrointestinal (LGI) bleeding are colonic diverticula, angiodysplasia, colitis (due to inflammatory bowel disease, infection, ischemia, or radiation therapy), and colonic neoplasia. Other than colitis, LGI bleeding is typically painless. Ischemic colitis is due to a temporary interruption in mesenteric blood flow and typically occurs in older individuals with significant cardiac and peripheral vascular disease. Typical symptoms are the acute onset of mild, crampy abdominal pain with tenderness on examination over the affected region of the colon. Bleeding may occur early but often occurs within a few days of pain onset.

Angiodysplasia is most common among the elderly and usually presents as chronic or occult blood loss, but it can also cause acute painless, hemodynamically significant bleeding.

Colonic neoplasms may present with bleeding but it is typically of small volume and is not associated with abdominal pain.

Bleeding from a colonic diverticulum typically is acute and painless. Bleeding stops spontaneously in approximately 80% of patients but recurs in 10% to 40%.

Patients with ulcerative colitis almost always have a sense of bowel urgency due to rectal inflammation. Frequent watery bowel movements are typical, and bleeding occurs with more severe inflammation. The onset of ulcerative colitis is typically acute, and patients often remember when symptoms first started. Severe abdominal pain is an unusual manifestation of ulcerative colitis and suggests a complication such as toxic megacolon or perforation. Most patients with toxic megacolon related to ulcerative colitis have at least 1 week of bloody diarrhea symptoms.

KEY POINT

- The presence of abdominal pain in a patient with lower gastrointestinal bleeding raises the possibility of colitis from ischemia, inflammatory bowel disease, infection, or radiation.

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Item 83 Answer: C

Educational Objective: Provide colonoscopy surveillance following a diagnosis of adenomatous polyps.

Colonoscopy should be repeated in 3 years. Patients with adenomas are at increased risk for colon cancer. They can be stratified into low- and high-risk groups for metachronous neoplasia based on the polyp size, number, and pathology. This risk stratification has a strong evidence base and guides when the next colonoscopy should be performed. Patients with (1) an adenoma 10 mm or larger, (2) three to ten adenomas, (3) an adenoma with a villous component (such as a tubulovillous or villous adenoma), or (4) an adenoma with high-grade dysplasia are considered high risk and should undergo their next colonoscopy in 3 years. Diminutive (<5 mm) rectosigmoid (hyperplastic) polyps are not a known risk factor for colorectal cancer and do not warrant more than average-risk colorectal cancer screening.

Patients with polyps larger than 20 mm or polyps removed in pieces should undergo their next colonoscopy in 3 to 6 months to ensure that no residual polyp tissue remains.

Patients with colon cancer, not adenomas, should have their first postoperative colonoscopy examination within 1 year of the clearing colonoscopy.

Patients with one to two tubular adenomas smaller than 10 mm are considered low risk and should undergo their next colonoscopy in 5 years.

KEY POINT

- Patients with (1) an adenoma 10 mm or larger, (2) three to ten adenomas, (3) an adenoma with a villous component (such as a tubulovillous or villous adenoma), or (4) an adenoma with high-grade dysplasia are considered high risk for colon cancer and should undergo their next colonoscopy in 3 years.

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Item 84 Answer: D

Educational Objective: Diagnose esophageal cancer with upper endoscopy.

The most appropriate next step in management is upper endoscopy. Progressive solid-food dysphagia is the most common presenting symptom of esophageal cancer. Associated weight loss (as a consequence of reduced oral intake), anorexia, and anemia (from gastrointestinal bleeding) may be

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present as well. Despite the association of gastroesophageal reflux disease (GERD) with adenocarcinoma, many patients do not have frequent or severe reflux symptoms. This may be because of decreased perception of acid reflux in these patients. Endoscopy is usually diagnostic. Upper endoscopy is the preferred test to assess for esophageal cancer, as it allows for tissue biopsy. Squamous cell carcinoma usually affects the proximal esophagus, whereas adenocarcinoma usually affects the distal esophagus. Risk factors for squamous cell carcinoma include long-term exposure to alcohol and tobacco, nitrosamine exposure, corrosive injury to the esophagus, dietary deficiencies (zinc, selenium), achalasia, tylosis (keratosis of the palms and soles), and human papillomavirus infection. In addition to GERD, risk factors for the development of adenocarcinoma include tobacco use, obesity (especially central obesity), and Barrett esophagus. Staging of the tumor is critical in determining therapy and prognosis. Staging is typically done with CT (to detect distant metastases), endoscopic ultrasound (for locoregional staging), and PET (to follow up on indeterminate lesions found with other staging modalities).

A CT of the chest could be used later to assess locoregional spread of esophageal cancer (such as lymph node involvement), but upper endoscopy should be performed first to assess for esophageal cancer.

Esophageal manometry is the test of choice to evaluate an underlying motility disorder. In this patient, the concern is for an esophageal mass, which does not require manometry.

A pH study would be useful to evaluate a patient with acid reflux whose symptoms are not responding to medical therapy. This test would not be appropriate to evaluate this patient's solid-food dysphagia, and his GERD symptoms have been controlled with omeprazole.

KEY POINT

- Upper endoscopy with biopsy is the preferred initial diagnostic test for suspected esophageal cancer.

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Item 85 Answer: D

Educational Objective: Manage a gastric neuroendocrine tumor.

The most appropriate management is observation. This patient has a gastric neuroendocrine tumor (NET) that has developed in the presence of chronic autoimmune gastritis, which is characterized by pernicious anemia and hypergastrinemia due to achlorhydria or hypochlorhydria. Endoscopic polypectomy is considered curative treatment for this patient's NET. Gastric NETs are classified into three subtypes: type I, II, and III. This classification distinguishes the underlying pathogenesis and guides the appropriate management of the NET. Type I NETs account for the majority of gastric NETs, have an increased prevalence in older women, and are associated with autoimmune atrophic gastritis and hypergastrinemia. Type I gastric NETs are not associated with multiple endocrine neoplasia or Zollinger-Ellison syndrome (unlike type II gastric NETs) and rarely metastasize. Curative treatment of type I NETs is achieved with endoscopic removal of these lesions when they are small (<1 cm) and few lesions are present (<5), as is the case in this patient.

Tumor staging for type I gastric NETs (using CT of the abdomen and pelvis or radiolabeled somatostatin receptor scintigraphy) is not indicated because type I NETs rarely metastasize.

Surgical intervention is not indicated for this patient's small, type I NET that has been completely eradicated. Partial gastrectomy would be indicated if this patient's tumor was larger than 2 cm because of a risk of metastasis.

KEY POINT

- Curative treatment of type I gastric neuroendocrine tumors is achieved with endoscopic removal of these lesions when they are small (<1 cm) and few lesions are present (<5).

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Crosby DA, Donohoe CL, Fitzgerald L, et al. Gastric neuroendocrine tumours. Dig Surg. 2012;29(4):331-48. [PMID: 23075625]

Item 86 Answer: A

Educational Objective: Diagnose achalasia.

The most likely diagnosis is achalasia. This patient has dysphagia to both solids and liquids, suggesting a motility disorder. This patient's diagnostic evaluation and associated findings represent the classic presentation of achalasia, which is characterized by dysphagia to solids and liquids, regurgitation, and possibly weight loss, chest pain, and heartburn. Barium radiography shows a dilated esophagus with narrowing at the lower esophageal sphincter, described as a "bird's beak." Upper endoscopy was performed to rule out mechanical obstruction in the region of the lower esophageal sphincter as a cause of dysphagia. If obstruction is caused by a malignant lesion, the disorder is designated "pseudoachalasia." Manometry is required to confirm the diagnosis of achalasia.

Diffuse esophageal spasm is a rare hypertonic motility disorder that presents with chest pain or dysphagia. Clinical manifestations are similar to those of angina pectoris. On esophageal manometry, simultaneous high-amplitude (>30 mm Hg) esophageal contractions are seen with intermittent aperistaltic contractions. The barium esophagogram finding of a "corkscrew" esophagus is typical of diffuse esophageal spasm. This patient's manometric and barium radiography findings are not consistent with diffuse esophageal spasm.

Esophageal hypomotility disorders can involve a hypotense lower esophageal sphincter, aperistaltic contractions, or both. In most patients, the cause of the hypotensive esophageal disorder is unknown. However, secondary causes

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include smooth-muscle relaxants, anticholinergic agents, estrogen, progesterone, connective tissue disorders (such as systemic sclerosis), and pregnancy. Esophageal hypomotility disorders are characterized by low-amplitude contractions on manometry with a hypotensive lower esophageal sphincter; this differs from achalasia, which is characterized by incomplete relaxation of the lower esophageal sphincter. These manometric findings are the opposite of what was found on this patient's manometry, which was consistent with achalasia.

Nutcracker esophagus is a hypertonic motility disorder that is characterized by high-amplitude peristaltic contractions of greater than 220 mm Hg. This patient does not have these manometric findings.

KEY POINT

- The primary screening test for achalasia is a barium esophagogram, which demonstrates dilation of the esophagus and narrowing at the gastroesophageal junction, described as a "bird's beak."

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Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. Am J Gastroenterol. 2013 Aug;108(8):1238-49; quiz 1250. [PMID: 23877351]

Item 87 Answer: B

Educational Objective: Manage small intestinal bacterial overgrowth in a patient with Roux-en-Y gastric bypass.

The most appropriate management is empiric treatment for small intestinal bacterial overgrowth (SIBO) with antibiotics. Digestive enzymes and intestinal motility normally limit the growth of excessive bacteria, but SIBO can occur in conditions in which these functions are disrupted, such as the creation of a blind loop. Bacterial metabolism of carbohydrates prior to small-bowel absorption results in symptoms of SIBO (diarrhea, bloating, flatulence, and weight loss). This patient's symptoms of diarrhea, increased gas, bloating, and abdominal discomfort can collectively be explained by the bacterial fermentation of simple carbohydrates in the small bowel from SIBO. Given her presentation, the pretest probability is high enough to justify empiric therapy for SIBO and monitoring of symptoms for a response.

Because SIBO is a very plausible explanation for this patient's diarrhea, performing a colonoscopy would be premature at this time.

A potent antisecretory agent such as omeprazole is indicated for acid-related disorders, and the symptoms reported by this patient are not suggestive of an acid-related disorder. Furthermore, there is some evidence to suggest that the use of a proton pump inhibitor may promote bacterial overgrowth in the small bowel. Therefore, a trial of omeprazole is unlikely to improve this patient's symptoms.

The nature of this patient's abdominal pain is atypical for a biliary source, as it is not meal related or located in the right upper quadrant. Furthermore, this patient's liver chemistry studies were unremarkable and the gallbladder was resected during her gastric bypass surgery. Therefore, the yield of a right upper quadrant ultrasound would be low in this setting.

Stool cultures are generally not helpful in assessing a patient with chronic diarrhea, except if *Giardia* infection is suspected. In addition, stool cultures are not capable of making the diagnosis of bacterial overgrowth because the bacteria in the blind loop resemble the normal flora of the large bowel. Because this patient's surgical history supports bacterial overgrowth as the cause of diarrhea, an empiric trial of antibiotics is warranted.

KEY POINT

- Small intestinal bacterial overgrowth is common following Roux-en-Y gastric bypass; patients with typical symptoms (diarrhea, bloating, flatulence, and weight loss) should receive empiric antibiotic treatment.

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Machado JD, Campos CS, Lopes Dah Silva C, et al. Intestinal bacterial overgrowth after Roux-en-Y gastric bypass. Obes Surg. 2008 Jan;18(1):139-43. [PMID: 18080824]

Item 88 Answer: D

Educational Objective: Manage acute diarrhea.

The most appropriate management is supportive care. Most cases of acute diarrhea in developed countries are self-limited and due to a viral infection. In this otherwise healthy young woman with no alarm features (gastrointestinal bleeding, dehydration, fever, significant abdominal tenderness, recent antibiotic use), further testing is not indicated. Supportive measures, such as ensuring adequate oral fluid intake and using acetaminophen for muscle aches, are the only necessary intervention for most patients. Antimotility agents such as loperamide may be useful for patients with mild diarrhea, but they should not be used in patients with fever, significant abdominal pain, or bloody stools because they may worsen inflammatory diarrhea and increase the risk of complications such as toxic megacolon. Diarrhea in an otherwise healthy person lasting for more than 7 days suggests a parasitic or noninfectious origin and evaluation is appropriate.

Given this patient's age, absence of bleeding, and acute onset of symptoms, a colonoscopy is not indicated. A colonoscopy would be warranted if features of inflammatory bowel disease, such as blood in the stool, were present.

The diagnostic yield of bacterial stool culture for acute diarrhea is low (less than 3%); however, identification of a pathogen has important treatment and public health implications and may be useful in identifying and tracking a food-borne outbreak. Because most cases of community-acquired diarrhea are self-limited, stool cultures are not required in most patients; cultures may be indicated for symptoms

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lasting longer than 72 hours, particularly in patients with associated fever, tenesmus, or bloody stools.

Parasitic infection should be considered as a potential cause of diarrhea lasting for more than 7 days. *Giardia lamblia* and *Cryptosporidium parvum* are the most commonly identified parasitic agents definitively known to cause diarrhea in the United States. Amebiasis is relatively uncommon in the United States but can cause hemorrhagic colitis in travelers and may occur several years after return from an endemic area. Because this patient does not have a travel history and her symptoms are of short duration, stool testing for ova and parasites is not necessary at this time.

KEY POINT

- Because most cases of community-acquired diarrhea are self-limited, stool cultures or evaluation for ova and parasites are not required in most patients; studies may be indicated for symptoms lasting longer than 72 hours, particularly in patients with associated fever, tenesmus, or bloody stools.

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Item 89 Answer: E

Educational Objective: Manage a sporadic juvenile polyp.

The most appropriate management is reassurance. Solitary juvenile polyps are one of the most commonly found polyps, particularly in children under the age of 10 years; they confer no future health risk once the polyp is removed, and follow-up surveillance colonoscopy is not required. It is important to distinguish between a sporadic, nonsyndromic juvenile polyp and juvenile polyposis syndrome (JPS) because management of JPS is substantially different. The clinical criteria for diagnosis of JPS include (1) more than three juvenile polyps of the colon, (2) juvenile polyps throughout the gastrointestinal tract, or (3) one or more juvenile polyps combined with a family history of JPS. Patients with JPS have an increased risk for colon cancer (39%), gastric cancer (25%), and more rarely small-bowel and pancreatic cancer.

Patients with JPS should undergo genetic counseling and testing for the mutations known to cause the disease (*SMAD4* and *BMPR1A* genes). Surveillance guidelines for patients with JPS recommend colonoscopy and upper endoscopy every 2 to 3 years beginning at age 15 years or sooner if symptoms are present. Because this patient does not meet criteria for JPS, these interventions are not appropriate at this time.

KEY POINT

- Solitary juvenile polyps are one of the most commonly found polyps; they confer no future health risk once the polyp is removed and do not require surveillance endoscopy.

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Item 90 Answer: D

Educational Objective: Evaluate oropharyngeal dysphagia with videofluoroscopy.

The most appropriate diagnostic test to evaluate this patient's dysphagia is videofluoroscopy. Dysphagia is classified as either oropharyngeal dysphagia (also called transfer dysphagia) or esophageal dysphagia. Each of the two kinds of dysphagia has distinct epidemiology, pathophysiology, and management implications. Oropharyngeal dysphagia usually occurs immediately with deglutition. Causes of oropharyngeal dysphagia may be either neuromuscular or anatomic. Patients may have associated symptoms that provide clues, such as neurologic symptoms like dysphonia, diplopia, and muscular weakness. When this patient starts to eat he coughs, which indicates oropharyngeal impairment of the swallowing mechanism rather than an esophageal cause. Patients with oropharyngeal dysphagia typically describe coughing, choking, and nasal regurgitation. Choking occurs owing to failure to clear food from the epiglottis and may lead to aspiration. The initial test of choice for evaluation of oropharyngeal dysphagia is videofluoroscopy (also known as a modified barium swallow) in which the oropharyngeal phase of swallowing is assessed with foods of different consistencies. Oropharyngeal forms of dysphagia are often managed with dietary adjustment and incorporation of swallowing exercises with the assistance of a speech pathologist.

Barium swallow may be useful in the evaluation of esophageal dysphagia following a normal upper endoscopy when a mechanical obstruction is still suspected. For example, upper endoscopy may miss lower esophageal rings or extrinsic compression of the esophagus. A barium swallow will not be as helpful as videofluoroscopy in a patient with oropharyngeal dysphagia.

Esophageal dysphagia tends to occur after the initiation of the swallow. Esophageal manometry is useful to diagnose an esophageal motility disorder such as achalasia. However, it is not the best test in a patient with symptoms of oropharyngeal dysphagia.

Esophageal dysphagia often has an intraluminal cause, such as strictures, Schatzki rings, or masses. The diagnostic test of choice for esophageal dysphagia is upper endoscopy, which can be both diagnostic (allowing biopsy and visualization of the mucosa) and therapeutic (allowing dilation to be performed if indicated).

KEY POINT

- The initial test of choice for evaluation of oropharyngeal dysphagia is videofluoroscopy.

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Item 91 Answer: B

Educational Objective: Treat ulcerative colitis with the appropriate maintenance therapy.

The most appropriate maintenance therapy is infliximab. This patient's ulcerative colitis symptoms were refractory to mesalamine but have responded to prednisone, and he is doing well after the dose was tapered to 20 mg/d. Glucocorticoids are not effective for maintaining remission in ulcerative colitis. Therefore, in patients whose disease responds to glucocorticoids, the dose should be tapered while transitioning to a maintenance medication (azathioprine, 6-mercaptopurine, or an anti-tumor necrosis factor agent). Randomized controlled clinical trials have shown infliximab to be an effective maintenance therapy in patients such as this one.

Immunosuppression with azathioprine or 6-mercaptopurine is often used to maintain glucocorticoid-induced remission, but the data supporting this practice are scant. Moreover, this patient has a low thiopurine methyltransferase (TPMT) level, which indicates a high likelihood of severe bone marrow toxicity if exposed to azathioprine or 6-mercaptopurine. Azathioprine is converted in the body to 6-mercaptopurine, which is then either inactivated (by xanthine oxidase or TPMT) or activated to 6-thioguanine nucleotide. The level of TPMT should be checked before starting azathioprine or 6-mercaptopurine; 1 in 300 patients (0.3%) lack enzyme activity and are at high risk of toxicity. Azathioprine and 6-mercaptopurine should not be used in these patients.

Methotrexate may be used in the treatment of Crohn disease; however, there is no evidence for efficacy of methotrexate in ulcerative colitis.

Prednisone is not effective for maintenance of ulcerative colitis. In addition, long-term glucocorticoid use carries significant risk of side effects.

KEY POINT

- Glucocorticoids are not effective for maintaining remission in ulcerative colitis; the glucocorticoid dose should be tapered while transitioning to a maintenance medication (azathioprine, 6-mercaptopurine, or an anti-tumor necrosis factor agent).

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Item 92 Answer: E

Educational Objective: Provide surveillance for hepatocellular carcinoma in a patient with chronic hepatitis B infection.

The most appropriate management is ultrasound imaging of the liver every 6 months. This patient from Africa has evidence of chronic hepatitis B virus (HBV) infection. In approximately 50% of untreated patients with chronic HBV infection in the United States, HBV will contribute to the cause of death (from hepatocellular carcinoma [HCC] or other complications of end-stage liver disease, such as cirrhosis). HCC surveillance is advised in African patients over the age of 20 years with chronic HBV infection. Screening and surveillance for HCC consist of cross-sectional imaging with ultrasound, CT, or MRI. Ultrasound is the most widely available and least expensive imaging modality and is preferred. For patients with normal imaging at diagnosis, the recommended interval for surveillance imaging is 6 months. Serum α-fetoprotein measurement does not have sufficient diagnostic accuracy alone to be a valuable tool for early detection. The combination of ultrasonography and α-fetoprotein measurement increases cancer detection rates, but this comes at the expense of increased false-positive findings. Other indications for HCC surveillance in patients with chronic HBV infection are (1) patients with cirrhosis, (2) Asian men older than 40 years, (3) Asian women older than 50 years, (4) patients with a family history of HCC, and (5) patients with persistent hepatocellular inflammation (defined as elevated alanine aminotransferase [ALT] level and HBV DNA level greater than 10,000 IU/mL).

This patient has already been infected with HBV, so vaccination at this point will not be effective.

This patient's HBV infection is in the inactive carrier/immune control state, as evidenced by his normal ALT level and HBV DNA level below 10,000 IU/mL. Treatment with antiviral agents such as pegylated interferon or tenofovir is not necessary for patients in the inactive carrier state. However, surveillance for HCC is still indicated.

KEY POINT

- Screening and surveillance for hepatocellular carcinoma consist of cross-sectional imaging with ultrasound, CT, or MRI.

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Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011 Mar;53(3):1020-2. [PMID: 21374666]

Item 93 Answer: C

Educational Objective: Manage peptic ulcer bleeding.

The most appropriate management is prompt discharge on oral proton pump inhibitor (PPI) therapy. In addition, NSAIDs should be discontinued. Upper endoscopy identified several small gastric ulcers as this patient's bleeding source. Patients with low-risk stigmata (a clean-based ulcer [rebleeding risk with medical therapy 3%-5%] or a nonprotuberant pigmented spot in an ulcer bed [rebleeding risk with medical therapy 5%-10%]) can be fed within 24 hours, should receive oral PPI therapy, and can undergo early hospital discharge. This patient's ulcers did not require endoscopic therapy and are at low risk for rebleeding, especially with the daily use of an oral PPI and discontinuation of NSAIDs. Other clinical predictors that justify prompt discharge are

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this patient's stable vital signs, stable hemoglobin level, and absence of serious comorbidities.

Several studies have demonstrated similar outcomes in patients with low-risk ulcers who were discharged on the first hospital day compared with those hospitalized for longer periods of time. There is no benefit to another day of hospitalization for observation.

With a low-risk ulcer, feeding can be initiated and PPI therapy can be promptly switched from continuous intravenous infusion to an oral formulation. An additional 24 hours of an intravenous PPI therapy is unnecessary and needlessly expensive.

More than 90% of uncomplicated NSAID-induced gastric ulcers will heal with standard-dose PPI therapy if NSAID therapy is discontinued. This patient could be considered for upper endoscopy in 2 to 3 months to document healing of his gastric ulcers if dyspeptic symptoms persist despite therapy, the initial endoscopy was not complete in evaluating the stomach, gastric biopsies were not obtained on initial endoscopy, or the appearance of the gastric ulcer was suspicious for malignancy. If NSAID therapy is reinitiated in the future, co-therapy with a PPI should be employed to prevent a recurrent peptic ulcer. Misoprostol at 800 µg total daily dosing is an alternative to PPI therapy, but gastrointestinal side effects at this dose may be limiting. Twice daily H_2-blocker therapy offers some benefit, but protection is inferior to that of PPI therapy. There is no need to routinely perform second-look endoscopy during hospitalization for an acute peptic ulcer bleed. Indications for repeat endoscopy in the hospital setting would include concern for ongoing gastrointestinal bleeding or an incomplete endoscopic evaluation with concern for missing a bleeding source.

KEY POINT

- Peptic ulcers at low risk for bleeding (clean based or with a nonprotuberant pigmented spot) can be managed with oral proton pump inhibitor therapy and early hospital discharge.

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Item 94 Answer: A

Educational Objective: Treat Barrett esophagus with high-grade dysplasia with endoscopic ablation.

The most appropriate next step in management is endoscopic ablation. Barrett esophagus (BE) is a precancerous condition that can progress to esophageal cancer. Risk factors associated with BE are older age, male gender, white ethnicity, gastroesophageal reflux disease (GERD), hiatal hernia, high BMI, smoking, and an abdominal distribution of fat. This patient has high-grade dysplasia, a high-risk feature of the condition. Treatment to remove BE is recommended for patients with confirmed high-grade dysplasia and can be done with endoscopic therapies such as radiofrequency ablation, photodynamic therapy, or endoscopic mucosal resection. Choice of treatment may be influenced by local expertise and patient preference.

Esophagectomy is the treatment of choice for esophageal cancer if the patient is a surgical candidate. Esophagectomy may be required in patients with BE and high-grade dysplasia if ablation has failed or progression to cancer occurred during endoscopic treatment. Endoscopic treatment should be attempted for this patient before surgery would be appropriate.

Fundoplication would be indicated in a patient with refractory GERD. Fundoplication has not been shown to reduce the risk of progression of BE with high-grade dysplasia to cancer and is therefore not an appropriate choice.

A repeat surveillance upper endoscopy in 3 to 5 years would be appropriate in a patient with BE with no dysplasia. Because this patient has high-grade dysplasia, more aggressive management is necessary.

KEY POINT

- Treatment to remove Barrett esophagus is recommended for patients with confirmed high-grade dysplasia and can be done with endoscopic therapies that include radiofrequency ablation, photodynamic therapy, or endoscopic mucosal resection.

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Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ; American Gastroenterological Association. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology. 2011 Mar;140(3):e18-52; quiz e13. [PMID: 21376939]

Item 95 Answer: B

Educational Objective: Diagnose an insulinoma with endoscopic ultrasound.

The most appropriate diagnostic test is endoscopic ultrasound. Hypoglycemia is best diagnosed when three conditions coexist (Whipple triad): (1) hypoglycemic symptoms are present, (2) the plasma glucose level is low, and (3) resolution of symptoms occurs promptly after glucose ingestion. When Whipple triad is observed, further evaluation for the cause of pathologic hypoglycemia should include an inpatient 72-hour fast with regular measurement of simultaneous plasma glucose, insulin, and C-peptide (a measure of endogenous insulin secretion). If the results are consistent with insulinoma, only then should CT imaging of the pancreas be performed to localize the tumor and direct its surgical resection. Because insulinomas are often small, further testing (with, for example, endoscopic ultrasonography) may be necessary for localization, as is required in this patient.

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic test that allows for visualization and therapeutic interventions of the bile and pancreatic ducts. It is an invasive procedure that will not identify small solid tumors of the pancreas such as an insulinoma.

Insulinomas almost always have inadequate expression of somatostatin receptors to be detected by octreotide

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scanning; therefore, this is not a useful diagnostic test for insulinomas.

Although abdominal ultrasonography is noninvasive, it does not have the resolution to identify small pancreatic tumors, particularly tumors not detected by a higher-resolution imaging procedure such as CT scanning.

KEY POINT

- Endoscopic ultrasound is sensitive for detecting insulinomas, which are typically small and solitary and may not be detected by CT cross-sectional imaging.

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Item 96 Answer: A

Educational Objective: Treat microscopic colitis.

The most appropriate treatment is budesonide. Collagenous colitis, a form of microscopic colitis, is most often idiopathic, but in a small subset of patients it may be a side effect of medications. Drugs that have been highly associated with microscopic colitis include aspirin, acarbose, lansoprazole, NSAIDs, ranitidine, sertraline, and ticlopidine. Celiac disease is also associated with microscopic colitis. Treatment may be as simple as drug withdrawal or treatment of celiac disease. In mild persistent disease, antidiarrheal therapy such as loperamide or diphenoxylate can be used. In moderate disease, bismuth subsalicylate may be beneficial. This patient has collagenous colitis that has not responded to antidiarrheal therapy with diphenoxylate, loperamide, or bismuth subsalicylate. In patients with severe disease or in those that do not respond to antidiarrheal agents or bismuth, budesonide is the treatment of choice. It is highly effective (response rates of ≥80%). However, the risk of relapse is high once budesonide is stopped (70%-80%). Many patients require long-term maintenance therapy with low-dose budesonide or an immunomodulator such as azathioprine.

There is no evidence of benefit from antibiotics in collagenous colitis; therefore, ciprofloxacin is not appropriate for this patient.

In severe microscopic colitis, treatment with an anti–tumor necrosis factor agent such as infliximab may be effective. However, this expensive, potent immune-suppressing medication should be used only if budesonide is unsuccessful.

Open-label reports of mesalamine suggested a possible small benefit in microscopic colitis; however, a randomized trial showed no benefit compared with placebo.

KEY POINT

- Therapy for microscopic colitis is based on symptom severity and may consist of withdrawal of an offending drug or administration of loperamide or diphenoxylate for mild persistent disease, bismuth subsalicylate for moderate disease, or budesonide for severe disease.

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In these pages, you will find updated information on routine care of the healthy patient; patient safety and quality improvement; professionalism and ethics; palliative care; common symptoms, including chronic pain, cough, dizziness, and insomnia; musculoskeletal pain; dyslipidemia; obesity; men's and women's health; eye, ear, nose, mouth, and throat disorders; mental and behavioral health; geriatric medicine; perioperative medicine; and many other clinical challenges. All of these topics are uniquely focused on the needs of both generalists and those who practice subspecialty internal medicine.

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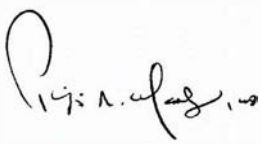

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The learning objectives of MKSAP 17 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence

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- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internists and primary care physicians
- Subspecialists who need to remain up-to-date in internal medicine and in areas outside of their own subspecialty area
- Residents preparing for the certification examination in internal medicine
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Hospital-Based Medicine

For the convenience of subscribers who provide care in hospital settings, content that is specific to the hospital setting has been highlighted in blue. Hospital icons (H) highlight where the hospital-based content begins, continues over more than one page, and ends.

High Value Care Key Points

Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon (HVC).

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General Internal Medicine High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 17 in several important ways. MKSAP 17 now includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the General Internal Medicine section of MKSAP 17.

- Statistical significance does not equal clinical importance, especially for large studies with uncommon outcomes.
- Relative risk comparisons tend to exaggerate outcomes relative to absolute risk measures; whenever possible, absolute risk should be used when explaining risk to patients (see Item 129).
- Numbers needed are estimates of the number of patients who must receive an intervention to cause one patient to experience the outcome being studied; numbers needed are useful indicators of the clinical impact of an intervention because they provide a sense of magnitude of benefit/harm expected from the intervention (see Item 162).
- Although the periodic health examination has been associated with increased delivery of preventive services, multiple studies have failed to show a beneficial effect of the periodic health examination on morbidity or mortality.
- A condition is amenable to screening if it is sufficiently common, will cause significant morbidity and mortality if left untreated, has a preclinical stage to allow for detection, and has an effective, available treatment that can improve prognosis if given early.
- Screening based on clinical guidelines needs to be individualized to account for patient circumstances; shared decision-making discussions should be documented and include the rationale for not providing screening that might otherwise be recommended.
- Although providing the appropriate preventive services is vital for optimal medical care, it is equally important to recognize what screening tests should not be performed and when screening should be discontinued.
- Women should have a life expectancy of at least 10 years to benefit from screening mammography (see Item 9).
- The U.S. Preventive Services Task Force recommends that all adults be screened for obesity, hypertension, tobacco use, alcohol misuse, and depression (if adequate resources are available to provide support and treatment for depression).
- The U.S. Preventive Services Task Force recommends against using prostate-specific antigen level to screen average-risk men for prostate cancer.
- Patients who have no genetic family history available (for example, due to adoption) should not undergo genetic testing without other reason.
- Although pharmacogenetic testing is available for many drug-metabolizing enzymes, its use has been clinically limited and is not routinely recommended.
- Providing age- and risk-appropriate vaccination is one of the most cost-effective preventive health measures available and is essential to the practice of high value care.
- Influenza vaccination is recommended for all persons aged 6 months and older unless specifically contraindicated.
- Pneumococcal vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13) is indicated for all adults aged 65 years and older and for certain high-risk persons younger than 65 years.
- Bivalent, quadrivalent, and nine-valent vaccines for human papillomavirus are approved for use in females and quadrivalent and nine-valent vaccines for males between the ages of 11 and 26 years to prevent cancer.
- Vaccination with herpes zoster vaccine is recommended for individuals aged 60 years and older, including patients with a previous episode of zoster.

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- Annual vaccination against influenza and one-time vaccination against pertussis with the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine is recommended for all health care workers.
- Smokers should receive pneumococcal vaccination and annual influenza vaccination.
- Given small potential effect, time limitations, and opportunity costs, the U.S. Preventive Services Task Force recommends offering dietary and exercise behavioral counseling based only on individual patient circumstances (grade C).
- Hospital-to-primary provider communication at discharge, predischarge patient education, medication reconciliation, and timely post-hospitalization follow-up are all necessary to improve patient safety during transitions of care.
- The Model for Improvement involves defining the goal of the project (aim), measuring the baseline to see if interventions lead to improvement (measures), determining what changes can be made to improve quality (ideas), and implementing and testing the change in a process called a Plan-Do-Study-Act cycle.
- The Lean model focuses on closely examining a system's processes and eliminating non-value-added activities, or waste, within that system (see Item 6).
- The Six Sigma model has an emphasis on reducing cost, variation, or defects within a process to make the process more effective.
- A cause-and-effect diagram, also known as a fishbone or Ishikawa diagram, is a quality improvement tool that is used to list and organize root causes of a problem (see Item 57).
- Physicians are not ethically obliged to grant patient requests for ineffective tests and treatments; they should advise patients that using an ineffective intervention does not promote patient well-being, may cause harm, and violates the profession's commitment to stewardship of health care resources.
- Palliative medicine maximizes quality of life for patients with serious illness through meticulous symptom management and by aligning comprehensive care to meet the patients' goals as much as possible.
- Palliative care may be provided concurrently with life-prolonging therapies or with therapies with curative intent; hospice is palliative care that is reserved for patients in the terminal phase of their disease.
- When bad news is communicated in a skillful and empathic manner using the SPIKES (Setting, Perception, Invitation, Knowledge, Empathy, Strategize) protocol, patient satisfaction is increased, and depression and anxiety are decreased (see Item 21).
- Studies indicate that approximately 85% of diagnoses are correctly made simply by performing a detailed history and physical examination.
- Diagnostic testing beyond the history and physical examination should be used in an intentional, logical, and stepwise fashion; nearly 30% of all health care costs are spent on unnecessary tests and treatments.
- Reasonable quality evidence refutes the commonly held belief that ordering additional, unnecessary diagnostic testing alleviates patient fears and concerns.
- Nonpharmacologic modalities that can be effective when part of a multimodal approach to pain management include exercise, ice and heat therapy, transcutaneous electric nerve stimulation, massage, acupuncture, and chiropractic manipulation.
- There is no evidence to support the efficacy of long-term opioids in managing chronic pain, and there are significant harms associated with their use.
- Evidence that further diagnostic testing helps reassure patients with medically unexplained symptoms or improves outcomes is limited; negative test results may, in fact, increase patient anxiety over a potentially missed diagnosis (see Item 95).
- In patients with medically unexplained symptoms, the point of aborting diagnostic testing and unsuccessful therapy and shifting primary attention toward symptom management (and if indicated, mental health care) requires clinical judgment on an individualized basis and patient engagement in the conversation.
- Consistent follow-up visits with brief focused history and physical examination are the cornerstone of management of patients with medically unexplained symptoms (see Item 122).
- Cognitive-behavioral therapy may be beneficial in the management of medically unexplained symptoms and should be considered in place of additional testing (see Item 16).
- Routine antibiotic treatment of uncomplicated upper respiratory tract infections and acute bronchitis in the nonelderly immunocompetent patient is not indicated because of lack of efficacy and associated harms and costs (see Item 63).
- Most cases of otitis media with effusion resolve spontaneously; observation and symptomatic treatment of conditions contributing to eustachian tube dysfunction are appropriate (see Item 11).
- The Dix-Hallpike maneuver can be used to distinguish central from peripheral causes of vertigo; for peripheral causes, the Epley maneuver is an effective and safe treatment; neuroimaging is not necessary in patients with peripheral vertigo (see Item 3).
- Management of patients with disequilibrium involves physical therapy, visual and auditory screening followed by correction of impairment, and mobility aids that stabilize ambulation; extensive imaging and testing is unnecessary (see Item 18).
- The initial treatment of insomnia is nonpharmacologic and focuses on implementing good sleep hygiene via

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patient education or brief cognitive-behavioral therapy (see Item 139).

- Although effective for short-term treatment of insomnia, the use of benzodiazepines is limited by dependence, tolerance, and the side effects of daytime somnolence, falls, cognitive impairment, and anterograde amnesia.
- The most valuable diagnostic and management test in patients with syncope is postural blood pressure measurement; extensive additional testing, including telemetry, cardiac enzyme testing, CT of the head, echocardiography, carotid ultrasonography, and electroencephalography, aided diagnosis in less than 2% of patients and altered management decisions in less than 5% of patients.
- The American College of Physicians does not recommend brain imaging, either with CT or MRI, in the evaluation of a patient with simple syncope and a normal neurologic examination.
- Most patients with syncope can be safely managed as outpatients; indications for hospital admission for patients with syncope include presence of severe traumatic injuries or a high short-term risk for adverse cardiovascular outcomes.
- Diagnostic testing for low back pain should be reserved for patients with severe or progressive neurologic deficits, patients for whom a serious underlying condition is suspected, or patients who do not have symptom improvement after 4 to 6 weeks of conservative management (see Item 109).
- Most patients with acute musculoskeletal low back pain have an excellent prognosis no matter what therapeutic intervention is used; therapeutic interventions should focus on symptom management and maintaining function.
- Massage therapy for low back pain is likely to be helpful in patients with subacute or chronic symptoms and no abnormal neurologic findings (see Item 51).
- Surgery has been shown to have definite benefits only for patients with low back pain due to disk herniation causing persistent radiculopathy, patients with painful spinal stenosis, and those with cauda equina syndrome.
- Imaging studies and laboratory testing are not needed for most patients with neck pain; patients with a history of trauma, presence of neurologic signs or symptoms, fever, weight loss, or immunosuppression may require additional testing (see Item 167).
- Most patients with neck pain recover with conservative therapy, including mobilization, exercise, analgesic agents, and physical therapy.
- Although most rotator cuff tears can be managed conservatively, immediate surgery is indicated for younger patients with an acute full-thickness tear, and surgery may be indicated for patients with partial tears who do not respond to conservative therapy.
- Imaging studies are not indicated for patients with clinical findings consistent with epicondylosis; treatment of epicondylosis should focus on avoidance of activities that cause pain (see Item 5).
- Surgery in carpal tunnel syndrome is reserved for patients who do not respond to conservative measures, have intolerable pain, have severe disease on nerve conduction testing, or have evidence of muscle wasting on examination.
- In patients with acute knee pain, plain radiographs are generally needed only if a traumatic fracture is suspected.
- Patellofemoral pain syndrome is characterized by anterior knee pain that is usually gradual in onset and worsens with running, prolonged sitting, and climbing stairs; this is a clinical diagnosis and imaging studies are not usually needed.
- The Ottawa ankle and foot rules are useful in excluding ankle fractures, with an extremely high sensitivity (>95%); if these rules are not met, obtaining radiographs is not necessary, as the probability of an ankle fracture is exceedingly low.
- Initial treatment of plantar faciitis is multimodal and consists of patient education, activity modification, application of ice, correcting improper mechanics, and heel stretches.
- There is insufficient evidence to support the routine measurement of lipoprotein(a), apolipoprotein B, and LDL particles in the evaluation or management of dyslipidemia.
- Baseline creatine kinase measurement is not routinely indicated before starting statin therapy or for monitoring therapy in the absence of symptoms of muscle disease.
- Current guidelines recommend against screening for androgen deficiency in asymptomatic men, regardless of age.
- Because pregnancy commonly causes changes in the normal bleeding pattern, pregnancy testing must be performed in all women with abnormal uterine bleeding before more extensive testing is ordered.
- Because most symptoms of cyclic mastalgia are self-limited, management usually requires only education, reassurance, and appropriate breast support (see Item 106).
- Healthy women of reproductive age generally do not require a pelvic examination or other studies before beginning hormonal contraception.
- In a patient with dysmenorrhea, if pelvic pathology is not suspected and a diagnosis of primary dysmenorrhea is made, symptomatic treatment may begin without additional evaluation.
- Hormone measurements during perimenopause are imprecise, cannot predict onset of menopause, and are therefore not recommended.
- Viral conjunctivitis is often acute, unilateral, and associated with antecedent upper respiratory tract infection

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and exposure to infected persons; treatment is supportive and should not include topical antibiotics.
- Intranasal glucocorticoids, antihistamines, and topical decongestants are all appropriate for initial treatment of acute sinusitis; antibiotics should not be used initially (see Item 55).
- In patients with symptoms of acute sinusitis, antibiotics are recommended only for those with severe symptoms (fever, purulent drainage, and facial pain) of 3 to 4 days' duration, worsening of symptoms that were initially improving, or failure to improve after 10 days of supportive therapy.
- Whispered voice test, finger rub test, hearing loss questionnaire, and hand-held audiometry are all reasonable screening tests for hearing loss.
- Interventions that decrease fall risk in community-dwelling older adults include implementing individualized exercise programs (physical therapy, tai chi), limiting polypharmacy, addressing orthostasis, assessing footwear, and adding vitamin D supplementation.
- Pelvic floor muscle training is recommended as first-line therapy for stress urinary incontinence (see Item 43).
- Behavioral therapy utilizing prompted voiding has been shown to reduce urinary incontinence in older patients with dementia (see Item 85).
- Bladder training is recommended as first-line therapy for urge urinary incontinence.
- Weight loss and exercise are recommended for obese women with urinary incontinence.
- Advanced static mattresses or overlays reduce the risk of pressure ulcers in at-risk patients (see Item 8).
- Several organizations recommend against obtaining routine preoperative laboratory studies or chest radiography in healthy, asymptomatic patients undergoing elective or low-risk surgery (see Item 34).
- Patients without coronary artery disease (CAD) or CAD risk factors with an estimated major adverse cardiac event risk of less than 1% or with a functional capacity of 4 or more metabolic equivalents do not require preoperative coronary evaluation (see Item 58).
- In asymptomatic patients at low risk for cardiovascular disease, cardiac testing is unnecessary (see Item 46).
- Preoperative coronary revascularization in asymptomatic patients has not been shown to reduce postoperative cardiac complications and should be reserved for the same indications as in the general setting.
- Preoperative spirometry should be performed only for dyspnea or hypoxia of uncertain cause (see Item 4).
- The mainstay of perioperative pulmonary risk management is lung expansion maneuvers, including deep breathing exercises and incentive spirometry.
- Conservative postoperative measures that may reduce the risk of pulmonary complications from suspected obstructive sleep apnea include nonsupine positioning, careful use of sedatives and opioids, and continuous pulse oximetry (see Item 33).
- Preoperatively, for patients with low thromboembolic risk, warfarin therapy is stopped with no bridging anticoagulation, whereas high-risk patients should receive bridging anticoagulation.
- For patients with cardiovascular disease and postoperative anemia, transfusion of red blood cells is recommended if the patient has symptoms attributable to anemia or a hemoglobin level less than 7 to 8 g/dL (70-80 g/L) (see Item 19).
- First-line therapy for erectile dysfunction includes lifestyle modification (weight loss, exercise, smoking cessation), psychotherapy as needed, and phosphodiesterase type 5 inhibitors, provided the patient has no contraindications (see Item 24).
- Older patients who present with symptoms of a mood disorder or cognitive dysfunction should be screened for hearing loss (see Item 27).
- Direct-to-consumer genetic tests have questionable clinical validity and may lead to patient misinterpretation of test results and unnecessary anxiety (see Item 29).
- Decision-making capacity exists when a patient demonstrates an ability to understand relevant information, appreciate the situation and its possible consequences, manipulate information rationally, and make a reasoned choice (see Item 41).
- When a patient lacks decision-making capacity, a surrogate who best knows the patient's health care values, goals, and preferences must make decisions (see Item 82 and Item 128).
- Men with low or low-normal testosterone levels should have confirmatory morning serum total testosterone testing before initiating testosterone therapy, and further evaluation of the cause of hypogonadism should be pursued before treatment is started (see Item 49).
- The diagnostic cognitive error of anchoring can be avoided by being willing to reconsider the initial diagnosis and act on the appearance of new clinical information; close clinical observation is often an important high value intervention (see Item 54).
- Proton pump inhibitor therapy can be initiated without 24-hour esophageal pH monitoring in patients with chronic cough who have a normal chest radiograph and symptoms suggestive of gastroesophageal reflux disease (see Item 67).
- Palpating the pulse is an effective, low-risk, and inexpensive way to screen adults aged 65 years and older for atrial fibrillation (see Item 68).
- All overweight and obese patients should be offered a comprehensive lifestyle intervention for weight loss including diet, physical activity, and behavioral therapy (see Item 73).
- Genetic testing for *BRCA* gene mutations should only be performed in patients with a family history that is suggestive of an increased genetic risk (see Item 76).
- Antipsychotic medications, individualized exercise programs, and skilled nursing facility placement have not been shown to be beneficial in reducing fall risk in cognitively impaired patients (see Item 77).

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- Inactivated influenza vaccine can be safely administered to patients with an egg allergy who have only experienced hives upon exposure to eggs (see Item 78).
- Patients with a family history suggestive of an inherited disorder should receive genetic counseling before undergoing genetic testing so that they understand the ramifications of testing; genetic testing is expensive and may impact a patient's ability to obtain health and life insurance (see Item 81).
- The diagnosis of lower extremity edema due to chronic venous insufficiency usually may be made based on a consistent clinical presentation and minimal laboratory testing (see Item 84).
- Artificial nutrition and pharmacologic agents do not improve morbidity and mortality or quality of life in cancer patients with cachexia (see Item 100).
- It is reasonable to proceed with elective noncardiac surgery without extensive additional testing in patients with asymptomatic severe aortic stenosis; these patients should undergo appropriate intraoperative and postoperative hemodynamic monitoring (see Item 104).
- Treatment of drug-induced lower extremity edema is discontinuation of the offending agent (see Item 105).
- Imaging of the shoulder is typically not needed to diagnose rotator cuff tendinitis but should be considered if a full-thickness rotator cuff tear is suspected or if there is diagnostic uncertainty (see Item 108).
- In patients with mild lower urinary tract symptoms caused by benign prostatic hyperplasia, observation with conservative therapy measures is appropriate (see Item 110).
- Vitamin supplementation, either with a multivitamin or with a single- or paired-vitamin preparation, has not been shown to reduce the risk for cardiovascular disease or cancer (see Item 114).
- Central adiposity increases risk for hypertension, type 2 diabetes mellitus, and coronary heart disease; in obese and overweight patients, measuring waist circumference is a cost-effective way to risk stratify patients (see Item 124).
- Screening for cervical cancer can be stopped in women age 65 years and older who have had three consecutive negative Pap smears or two consecutive negative Pap smears plus human papillomavirus test results within the last 10 years, with the most recent test performed within 5 years (see Item 126).
- In the absence of suspicious symptoms, physical examination findings, or family history in a patient undergoing a preparticipation sports evaluation, additional testing with either cardiovascular imaging or electrocardiography to exclude hypertrophic cardiomyopathy is not indicated (see Item 131).
- In patients with hyperlipidemia but without clinical atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus, an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher, or elevated 10-year risk for developing ASCVD, therapeutic lifestyle modification is the primary intervention for prevention of ASCVD (see Item 133).
- Intranasal glucocorticoids are first-line therapy for patients with upper airway cough syndrome due to allergic rhinitis; antibiotics should not be used without clear evidence of bacterial infection (see Item 136).
- The mainstay of obesity treatment is lifestyle modification that includes diet for weight loss, increased physical activity, and behavioral therapy (see Item 137).
- In patients with usual symptoms of benign prostatic hyperplasia (BPH), a careful history and physical examination can usually render the diagnosis; a urinalysis is also indicated in evaluating BPH to exclude infection, malignancy, or postobstructive nephropathy (see Item 138).
- Treatment of cerumen impaction is indicated only in symptomatic patients or if the tympanic membrane needs to be visualized (see Item 140).
- Palliative care that is initiated early and integrated throughout the disease trajectory results in prolonged life of higher quality in patients with serious illness when compared with patients who do not receive palliative care (see Item 143).
- In older patients who require posthospital rehabilitation but cannot tolerate active, intensive therapy (3 hours per day, 5 days per week), rehabilitation services may be performed in a skilled nursing facility (see Item 144).
- In the case of a patient who refuses life-prolonging treatment, the physician's duty is to understand the rationale for the decision and ensure that it is informed; provided that the decision meets these criteria, the physician must honor it (see Item 146).
- In patients with insomnia in whom sleep hygiene techniques are ineffective, sleep restriction may be beneficial; sleep restriction limits and then gradually increases the time in bed for sleep (see Item 151).
- Patients with intact decision-making capacity have the right to request the withdrawal of any treatment, even those that are life prolonging (see Item 155).
- There is no specific objective laboratory test to diagnose systemic exertion intolerance disease (formerly known as chronic fatigue syndrome); recommended value-based tests to rule out this disease include complete blood count, glucose level, and thyroid function tests (see Item 157).
- In patients with cardiac risk factors undergoing elevated-risk procedures, preoperative coronary evaluation is not required if the patient has a good functional capacity (≥4 metabolic equivalents) (see Item 163).
- All adults aged 50 to 75 years should be screened for colorectal cancer using high-sensitivity fecal occult blood testing every year, flexible sigmoidoscopy every 5 years, combined flexible sigmoidoscopy every 5 years with high-sensitivity fecal occult blood testing every 3 years, or colonoscopy every 10 years; discontinuation of screening should be considered in patients with life expectancy of less than 10 years (see Item 168).

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General Internal Medicine

High Value Care in Internal Medicine

An economically unsustainable amount of money is spent on health care in the United States–18% of the U.S. gross domestic product–leaving less money to pay for other essential services such as public health and safety, infrastructure, and education. Despite spending more on health care than any other country, the United States has health outcomes, including mortality, survival, and life expectancy, that rank at or near the bottom when compared with other high-income countries.

Misuse and overuse of medical interventions contribute significantly to this untenable health care spending. Physicians are uniquely positioned to take the lead in addressing these problems by partnering with patients and other health care providers to reduce the use of medical interventions (tests and treatments) that offer minimal or no benefit and may lead to unintended harm.

High value care is care that balances the clinical benefit of a given medical intervention with its harms and costs, with the goal of improving patient outcomes. High value care represents a paradigm shift away from the belief that more care is better care toward the idea that evidence-based, individualized care is better care. High value care places patients and their outcomes, values, and concerns at the center of every major clinical decision, using cost-effective and low-risk tools (for example, history and physical examination) and patient-centered communication to improve patient outcomes. This approach helps lay a foundation for dealing with the psychological burden that accompanies diagnostic uncertainty and allows both patients and physicians to be more comfortable with a conservative course of care. New drugs, devices, procedures, and tests are the primary drivers of increased health care spending; however, it is critical that physicians use testing and medical technology judiciously and selectively assess whether potential benefits justify the costs.

The Alliance for Academic Internal Medicine and the American College of Physicians (ACP) have developed a simple stepwise framework to help providers incorporate high value care into daily practice (**Table 1**). The ACP has also developed clinical recommendations and physician resources to help physicians practice high value care (available at http://hvc.acponline.org/index.html). Additionally, over 72 medical specialty societies and Consumer Reports (an independent product testing organization) have participated in the American Board of Internal Medicine Foundation's Choosing Wisely campaign, which promotes stewardship of medical resources by asking societies to create evidence-based lists of tests and procedures whose necessity should be questioned. The Choosing Wisely lists and accompanying patient educational information are available at www.choosingwisely.org.

TABLE 1. High Value Care Framework: Steps Toward High Value Care

Step 1: Understand the benefits, harms, and relative costs of the interventions that you are considering.
Step 2: Decrease or eliminate the use of interventions that provide no benefits and/or may be harmful.
Step 3: Choose interventions and care settings that maximize benefits, minimize harms, and reduce costs (using comparative effectiveness and cost-effectiveness data).
Step 4: Customize a care plan with patients that incorporates their values and addresses their concerns.
Step 5: Identify system-level opportunities to improve outcomes, minimize harms, and reduce health care waste.

Reprinted with permission from Smith CD; Alliance for Academic Internal Medicine-American College of Physicians High Value, Cost-Conscious Care Curriculum Development Committee. Teaching high-value, cost-conscious care to residents: the Alliance for Academic Internal Medicine-American College of Physicians Curriculum. Ann Intern Med. 2012 Aug 21;157(4):284-6. [PMID: 22777503]

KEY POINT

- High value care is care that balances the clinical benefit of a given medical intervention with its harms and costs, with the goal of improving patient outcomes.

Interpretation of the Medical Literature

Introduction

Physicians must be familiar with an ever-expanding knowledge base that is founded on published research. Consequently, physicians must understand the basic principles of research to be able to independently interpret the literature, remain current in their medical knowledge, and apply the results of studies to provide high value care for their patients.

Study Designs

Many research study designs exist, and it is important to recognize the strengths and weaknesses of each and the appropriate application of information derived from these studies to clinical situations.

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Experimental Studies

CONT.

In an experimental study, subjects and interventions are determined at the study outset, and investigators and subjects are often blinded to the intervention to minimize biased outcomes. In the most common type of experimental study, a randomized controlled trial (RCT), subjects are randomly assigned to either an intervention or control group to equally distribute predictive factors and minimize confounding among the groups. Although RCTs are considered the most rigorous study design and have the greatest ability to draw causal inferences, these studies usually involve detailed protocols and patients with a narrow disease spectrum—conditions that are challenging to replicate in ordinary practice settings. Consequently, RCTs often have limited generalizability. A variation of an RCT is a cluster-randomized trial, in which groups (or clusters) of study subjects are randomized to a treatment or control group; this design is helpful in evaluating interventions directed toward specific groups of people instead of individual patients. A less rigorous experimental design is the quasi-experimental study, in which investigators assign patients to intervention and control groups in a nonrandom manner. This type of design is typically used when randomization would be impractical or unethical. The different types of experimental studies and observational studies are compared in **Table 2**.

Observational Studies

An observational study does not employ interventions or patient assignment to groups; alternatively, researchers compare two or more naturally existing groups. Observational studies are often less rigorous than experimental studies, thus reducing the ability to draw causal inferences. Advantages of observational studies include the capacity to utilize natural practice settings and to involve patients with wider ranges of illnesses and exposures. A disadvantage of observational studies is that they are more subject to confounding and bias than experimental studies.

Observational designs include cohort studies, case-control studies, cross-sectional studies, and case series. A cohort study investigates the outcomes of groups (cohorts) with or without certain exposures or treatments. An example is a study that examines the rates of type 2 diabetes mellitus among patients with high socioeconomic status versus patients with low socioeconomic status. In prospective cohort studies, patients are observed for outcomes going forward in time, whereas retrospective cohort studies look at patients' histories, often after an outcome has occurred. Prospective cohort studies are more rigorous than retrospective cohort studies because they reduce bias by selecting patients and statistical methods a priori. The standard outcome measure for a cohort study is relative risk.

A case-control study, which is usually retrospective, compares the outcomes of patients with a disease (cases) to those without a disease (controls). For instance, patients with and without type 2 diabetes could be compared with respect to exposure to high-calorie, fast-food diets. Case-control studies can be particularly valuable in the study of rare diseases. To reduce bias in case-control studies, investigators carefully match selected cases to controls in terms of demographic and prognostic factors. Additionally, investigators often increase statistical power by recruiting more controls than cases. For case-control studies, the standard estimate of risk is the odds ratio.

Cross-sectional studies examine associations between diseases and exposures within a group of patients at one point in time. This study design is most commonly used to determine disease prevalence and infer causation. Survey studies are generally cross-sectional studies. Case series include only patients with the condition of interest. These patients are evaluated, either prospectively or retrospectively, to identify exposures or outcomes. Cross-sectional and case series designs are limited, based on the absence of control groups.

Systematic Reviews

Systematic reviews provide a comprehensive summary, synthesis, and analysis of the literature that pertains to a focused research question. Systematic reviews involve exhaustive literature searches, systematic data abstraction, multiple reviewers, and a narrative summary regarding the strengths and limitations of the analysis. Systematic reviews minimize error by combining results from many studies. They may also include meta-analysis, which involves the statistical analysis of pooled data from the studies identified in a systematic review meeting certain predefined criteria for adequacy. The purpose of meta-analysis is to draw conclusions using a greater amount of data than is available in each of the individual studies. The limitations of systematic reviews and meta-analysis result from variability in the identification and selection of studies and from the inclusion of weak studies. However, a systematic review with meta-analysis that is based on the rigorous selection of numerous, high-quality RCTs could be considered the highest level of evidence.

KEY POINTS

- In a randomized controlled trial, subjects are randomly allocated to an intervention or control group, and investigators and subjects are often blinded to the intervention to minimize biased outcomes.
- Observational designs include cohort studies, case-control studies, cross-sectional studies, and case series; patients are not randomly allocated to an intervention or control group, thus reducing the ability to draw causal inferences.
- A systematic review provides a comprehensive summary, synthesis, and analysis of the literature that pertains to a focused research question and may or may not include meta-analysis; systematic reviews minimize errors by combining results from many studies but may be limited by variability in the identification and selection of studies and from the inclusion of weak studies.

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TABLE 2. Types of Study Designs

Study Design	Description	Strengths	Weaknesses	Key Threats to Validity
Experimental Studies				
Randomized controlled trial (RCT)	Subjects are randomly allocated to a treatment group or a control group	Strongest design for determining causation	Expensive, time consuming, not practical for many clinical situations Limited follow-up duration Limited number of outcomes that can be assessed Limited generalizability	If randomization is ineffective If data are not analyzed according to initially assigned group If key individuals are aware of group assignment (not blinded) If follow-up is incomplete
Cluster-randomized trial	Subjects are randomized by clusters (e.g., nursing unit) rather than as individuals	Same as for RCTs Can be used if randomization of patients is not ethical or feasible	Same as for RCTs Challenging to analyze	Same as for RCTs If analysis does not account for clustering
Quasi-experimental design	Review of data collected before and after an intervention	Can be used if randomization of patients is not ethical or feasible	Patients not randomized	If no adjustment for possible confounding
Observational Studies				
Cohort study	Studies outcomes of groups using observed assignment	Able to detect associations, but these are not always cause-effect relationships Able to study multiple outcomes over a long period of time Large sample size	Requires complicated statistical techniques to minimize confounding Prospective designs can be expensive and take many years before results are available	Selection bias in cohort Bias in measurement of exposures and outcomes If important confounders not accounted for
Case-control study	Compares past exposures in patients with and without disease	Useful for rare diseases or exposures Inexpensive	High risk for bias High risk for confounding Cannot assess incidence/prevalence	Selection bias, especially in controls Measurement bias, especially recall bias
Cross-sectional study	Determines prevalence of disease (e.g., survey studies)	Can be completed quickly Inexpensive	May result in misleading information Provides information on only one point in time High risk for bias	Selection bias, response bias If sample is not representative
Case series	Describes the characteristics of a group (or series) of patients (or cases)	Hypothesis generating Observations may be useful in designing a study to evaluate possible explanations or causes for the observed findings	High risk for bias Cannot infer causation	Multiple biases related to subject selection and the characteristics observed

Validity of a Study

Validity, or the trustworthiness of a study's results, can be threatened by many factors, including errors in sampling, measurement, and data analysis. Internal validity is the extent to which a study's results are true and supported by the study. External validity is the degree to which a study's findings are generalizable to other settings.

Study errors can be random or systematic. Random error, which is due to chance, can be reduced by increasing the sample size and measurement precision. Systematic error results from bias and influences the study findings in a certain direction. Systematic error cannot be improved by increasing the sample size; it must be addressed by eliminating bias. For example, a study randomizes two groups of patients with

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diabetes to receive a new medication that lowers blood glucose levels (intervention group) or a placebo (control group), with the study outcome being self-monitored blood glucose (SMBG) measurements. If it were found that most of the intervention group patients recorded fasting morning SMBG levels and most of the control group recorded SMBG levels following the evening meal, any overall differences in glycemic control between the two study groups would be biased by the systematic, between-group differences in SMBG monitoring. When designing studies, systematic error is minimized by ensuring that the comparison groups are sampled, measured, and analyzed in the same way.

Confounding occurs when the hidden effect of an extraneous variable (the confounding variable) influences the outcome of a study. For example, early research indicated that coffee drinkers were more likely to develop pancreatic cancer. However, coffee drinkers are also more likely to be smokers. It was later demonstrated that the outcome of pancreatic cancer in these studies was attributable to smoking (confounding variable), not coffee consumption. Confounding can be decreased through the use of matching, randomization, and statistical methods such as multivariate analysis.

Statistical Analysis

Confidence Intervals and *P* Values

Every research finding reflects some amount of error, which is often expressed as a 95% confidence interval (CI). The 95% CI indicates that the researcher can be 95% certain that the value expressed in a study truly lies within that interval. The sample size of a study can influence the CI; larger samples will tend to allow more precise estimates and a narrower CI, whereas smaller sample sizes tend to yield wider CIs. Sample size is also directly proportional to a study's power, which is the probability of detecting an association between variables or a difference between groups when the association or difference truly exists. Statistical power can be used to determine the minimum sample size required for a study to demonstrate a specified effect.

The *P* value is another statistical indicator that indicates the likelihood of the study result being caused by chance alone. A *P* value of less than 0.05, which is a commonly used cut-off for statistical significance, represents a 1 in 20 chance of obtaining the observed results by chance, assuming that there is no difference between the study groups. Similarly to CIs, the *P* value is also related to the degree of difference between groups and the study's sample size; studies with large samples are more likely to produce statistically significant results. It is important not to confuse statistical significance with clinical importance, because a study that reports statistically significant *P* values may not be clinically relevant. This is particularly true for studies with large sample sizes or uncommon events of interest.

P values offer less information than CIs, because CIs can demonstrate the plausible range of an event or outcome, whereas *P* values indicate only statistical significance. Specifically, the lower and upper limits of a CI reveal, in discrete terms, the range of values around a given point, which allows readers to determine a plausible range of clinical significance and to apply study results to patients in clinical settings. For example, a study showed an association between influenza vaccination and development of Guillain-Barré syndrome (GBS), with a *P* value of 0.02 and a relative incidence of 1.45 (CI, 1.05 to 1.99). Considering the baseline GBS risk of 10 cases per million, influenza vaccination might result in 14.5 cases per million persons. However, the CI indicates that the risk of GBS from influenza vaccination ranges from only 5% increased risk to doubling of the risk. Accordingly, the worst-case risk would yield an absolute risk increase of 10 cases per million and a number needed to harm of 100,000. More strikingly, the best-case risk would yield an absolute increase of 0.5 cases per million and a number needed to harm of 2 million.

Calculations for Diagnostic Tests and Medical Therapeutics

Sensitivity, Specificity, and Predictive Values

Sensitivity is the ability of a test to detect patients with a disease when it is truly present. Specificity is the ability of a test to exclude disease in patients truly without the disease. The sensitivity and specificity are characteristics of a specific diagnostic test and do not change with the prevalence of disease in the population of patients to which they are applied (**Table 3**).

Compared with sensitivity and specificity, predictive values indicate the likelihood that a positive test result (positive predictive value [PPV]) or negative test result (negative predictive value [NPV]) truly reflects the presence or absence of disease in a specific patient population to which the test is applied. They are generated when applying tests of known sensitivity and specificity to a particular group of patients and are therefore dependent on the prevalence of the disease in that population. Because a positive test is more likely to be truly positive in a patient population with a high prevalence of disease, the PPV is directly related to prevalence. Conversely, a negative test is more likely to be truly negative when the prevalence of disease in the tested population is low; therefore, the NPV is inversely related to prevalence.

Likelihood Ratios

Likelihood ratios are a newer statistical tool that greatly simplifies applying diagnostic test results to patient care. The likelihood ratio (LR) is the ratio of the probability of a given test result (positive or negative) among patients with a disease to the probability of the same test result among patients without the disease. The posttest odds of a disease are equal to the pretest odds of the disease multiplied by the LR; the posttest odds can then be converted to a percentage to yield the more commonly recognized posttest probability. A major benefit of LRs is that they can be determined for any test for which the sensitivity and specificity are known, allowing clinicians to apply them to patients based on the clinically assessed pretest

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TABLE 3. Common Terms Used in the Interpretation of the Medical Literature for Diagnostic Tests

Term	Definition	Calculation	Notes
Prevalence (Prev)	Proportion of patients with the disease in the population	Prev = (TP + FN) / (TP + FP + FN + TN)	
Sensitivity (Sn)	Proportion of patients with the disease who have a positive test	Sn = TP / (TP + FN)	
Specificity (Sp)	Proportion of patients without the disease who have a negative test	Sp = TN / (FP + TN)	
Positive predictive value (PPV)	Proportion of patients with a positive test who have the disease	PPV = TP / (TP + FP)	Increases with *increasing* prevalence
Negative predictive value (NPV)	Proportion of patients with a negative test who do not have the disease	NPV = TN / (TN + FN)	Increases with *decreasing* prevalence
Positive likelihood ratio (LR+)	The ratio of the probability of a positive test result among patients with the disease to the probability of a positive result among patients without the disease	LR+ = Sn / (1 − Sp)	
Negative likelihood ratio (LR−)	The ratio of the probability of a negative test result among patients with the disease to the probability of a negative result in patients without the disease	LR− = (1 − Sn) / Sp	
Pretest odds	The odds that a patient has the disease before the test is performed	Pretest odds = pretest probability / (1 − pretest probability)	
Posttest odds	The odds that a patient has the disease after a test is performed	Posttest odds = pretest odds × LR	LR+ is used if result of test is positive; LR− is used if result of test is negative. A nomogram is available to calculate posttest probability using pretest probability and LR without having to convert pretest probability to odds (see Figure 1)
Pretest probability	Proportion of patients with the disease before a test is performed	Pretest probability can be estimated from population prevalence, clinical risk calculators, or clinical experience if no evidence-based tools exist	
Posttest probability	Proportion of patients with the disease after a test is performed	Posttest probability = posttest odds / (1 + posttest odds)	

FN = false negative; FP = false positive; TN = true negative; TP = true positive.

CONT.

probability of disease to generate a posttest likelihood of the presence or absence of the condition being tested. **Figure 1** shows a nomogram that may be used to estimate the posttest probability when the pretest probability and likelihood ratio are known.

Separate LRs are calculated for use when a test result is positive (LR+) or when a test result is negative (LR−). Larger positive LRs and smaller negative LRs are more apt to affect clinical decisions. For ease of clinical use, several general LR rules apply. LR+ values of 2, 5, and 10 correspond to an increase in disease probability of 15%, 30%, and 45%, respectively; LR− values of 0.5, 0.2, and 0.1 correspond to a decrease in disease probability of 15%, 30%, and 45%, respectively.

Relative and Absolute Risk

The effectiveness of different therapeutic interventions is frequently reported as relative or absolute risk differences between study groups. Relative comparisons compare the

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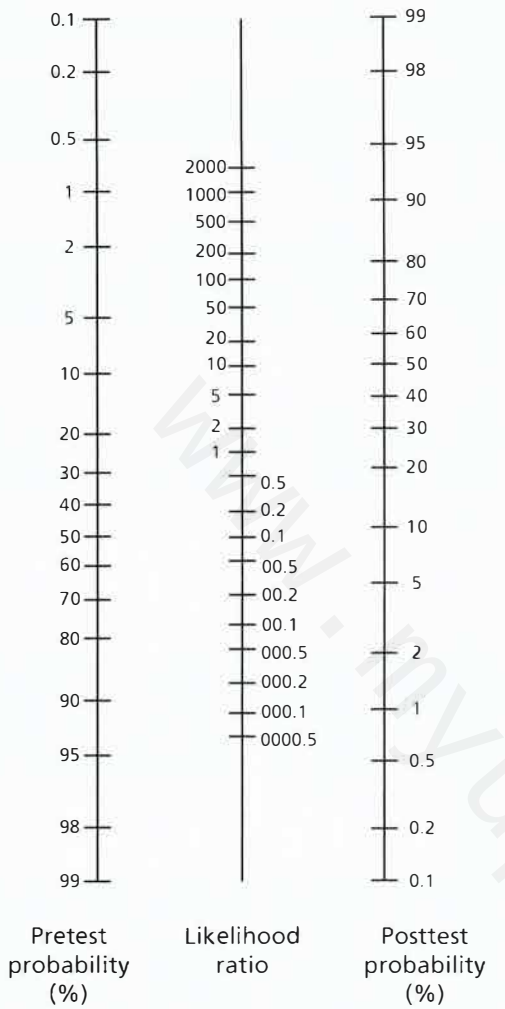

FIGURE 1. Nomogram for interpreting diagnostic test results. In this nomogram, a straight line drawn from a patient's pretest probability of disease (which is estimated from experience, local data, or published literature) through the likelihood ratio for the test result will point to the posttest probability of disease.

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rates of events, such as death or complications, in two study groups using measures that include relative risk, odds ratios, and hazard ratios (**Table 4**). Absolute comparisons, on the other hand, represent absolute (that is, total) differences in outcomes between two groups.

A disadvantage of relative comparisons is the potential for exaggerated outcomes, especially if the outcomes are uncommon. For instance, interventions that reduce the rate of a disease from 40% to 20% and 4% to 2% each have a relative risk reduction of 50%. However, the absolute risk reduction (ARR) for the first case is 20%, whereas the ARR for the second case is 2%.

Numbers Needed

Numbers needed are estimates of the number of patients who must receive an intervention to cause one patient to experience the outcome being studied; if beneficial, it is termed the number needed to treat (NNT), and if detrimental, the number needed to harm (NNH). Numbers needed are useful indicators of the clinical impact of an intervention because they provide a sense of magnitude expected from the intervention. Numbers needed are calculated by taking the reciprocal of the change in absolute risk. For example, for the two interventions previously discussed, the NNT in the first case is 5 (1/0.2) and in the second case 50 (1/0.02) (see Table 4). H

KEY POINTS

- Confidence intervals provide more information than *P* values because they reveal the plausible range of an event, allowing clinical significance to be estimated.
- Statistical significance does not equal clinical importance, especially for large studies with uncommon outcomes. HVC
- Relative risk comparisons tend to exaggerate outcomes relative to absolute risk measures; whenever possible, absolute risk should be used when explaining risk to patients. HVC
- Numbers needed are estimates of the number of patients who must receive an intervention to cause one patient to experience the outcome being studied; numbers needed are useful indicators of the clinical impact of an intervention by providing a sense of magnitude of benefit/harm expected from the intervention. HVC

Levels of Evidence and Recommendations

Physicians make clinical decisions about patients by interpreting evidence from the published literature; however, not all evidence is developed with the same rigor. Therefore, the U.S. Preventive Services Task Force has identified levels of evidence that reflect the rigor of methods used in a study (**Table 5**). Additionally, grades of recommendations for providing a clinical service were created by balancing the level of evidence with the risk versus benefit of the service (**Table 6**).

Routine Care of the Healthy Patient

History and Physical Examination

Periodic Health Examination

Although the periodic health examination has been associated with increased delivery of preventive services, multiple studies have failed to show a beneficial effect of the periodic health examination on morbidity or mortality; however, many of these trials were older, limited in scope, and assessed out-of-date interventions. Many physicians argue that the periodic health examination builds physician-patient relationships, which may promote improved adherence to physician recommendations.

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TABLE 4. Common Terms Used in the Interpretation of the Medical Literature for Therapeutics

Term	Definition	Calculation	Notes
Absolute risk (AR)	The probability of an event occurring in a group during a specified time period	AR = patients with event in group / total patients in group	Also known as event rate; can be for benefits or harms. Often, an experimental event rate (EER) is compared with a control event rate (CER)
Relative risk (RR)	The ratio of the probability of developing a disease with a risk factor present to the probability of developing the disease without the risk factor present	RR = EER / CER	Used in cohort studies and randomized controlled trials
Absolute risk reduction (ARR)	The difference in rates of events between experimental group (EER) and control group (CER)	ARR = | EER − CER |	
Relative risk reduction (RRR)	The ratio of absolute risk reduction to the event rate among controls	RRR = | EER − CER | / CER	
Number needed to treat (NNT)	Number of patients needed to receive a treatment for one additional patient to benefit	NNT = 1 / ARR	A good estimate of the effect size
Number needed to harm (NNH)	Number of patients needed to receive a treatment for one additional patient to be harmed	NNH = 1 / ARI	ARI = absolute risk increase and equals | EER − CER | when the event is an unfavorable outcome (e.g., drug side effect)

TABLE 5. U.S. Preventive Services Task Force Hierarchy of Research Design

Level	Description
I	Properly powered and conducted RCT; well-conducted systematic review or meta-analysis of homogeneous RCTs
II-1	Well-designed controlled trial without randomization
II-2	Well-designed cohort or case-control analytic study
II-3	Multiple time series with or without the intervention; dramatic results from uncontrolled experiments
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

RCT = randomized controlled trial.

Reprinted from U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Agency for Healthcare Research and Quality Publication No. 08-05118-EF. www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual. Published July 2008. Accessed June 24, 2015.

TABLE 6. U.S. Preventive Services Task Force Grade Definitions

Grade	Definition and Suggestion for Practice
A	There is high certainty that the net benefit is substantial. Offer or provide this service.
B	There is high certainty that the net benefit is moderate. Offer or provide this service.
C	There is at least moderate certainty that the net benefit is small. Offer or provide this service for selected patients depending on the individual circumstances.
D	There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Discourage use of this service.
I (Insufficient)	Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Adapted from U.S. Preventive Services Task Force. Grade definitions. www.uspreventiveservicestaskforce.org/uspstf/grades.htm. Updated February 2013. Accessed June 24, 2015.

In patients who do have regularly scheduled examinations, some aspects of preventive care are optimally addressed over several visits; thus, preventive care should be considered at every visit when feasible and an effort made to prioritize recommendations based on the patient's needs.

Routine History and Physical Examination

The history and physical examination can help identify those who are at risk for disease and who may benefit from additional screening tests or counseling. In patients who have positive findings on a detailed history, including a review of

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systems, a relevant physical examination pertinent to those concerns should be performed. The physical examination should include measurement of height and weight (to calculate BMI) and assessment of blood pressure. In persons with a BMI of 30 or more, the physician should assess for signs and symptoms of obstructive sleep apnea, as this condition is known to be underrecognized in primary care practices and has a high prevalence among obese persons. Heart rate should also be evaluated, as checking the pulse has been shown to increase detection of atrial fibrillation. The U.S. Preventive Services Task Force (USPSTF) recommends against routine abdominal and testicular examination for the purposes of cancer screening, and both the USPSTF and the American College of Physicians (ACP) recommend against screening pelvic examinations. Abdominal palpation for detection of abdominal aortic aneurysm and carotid auscultation for detection of carotid stenosis have both been shown to have poor reliability. Although all of the benefits of a comprehensive physical examination may not be clearly defined in regards to patient outcomes, the comprehensive physical examination is not directly associated with increased harm, may have less tangible benefits related to the physician-patient relationship, and is generally accepted as a standard of care. There is no evidence to support a routine panel of laboratory tests in all adult patients.

Internists are commonly asked to perform preparticipation sports examinations. The American Academy of Family Physicians (AAFP) and American Academy of Pediatrics, with several national sports medicine organizations, created a monograph on the approach to preparticipation physical evaluations, including free history and physical examination forms (available at www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Council-on-sports-medicine-and-fitness/Pages/PPE.aspx). Current American Heart Association (AHA) guidelines on preparticipation screening consist of a 12-step clinical history and physical examination focused on cardiovascular screening. The elements of this examination include evaluating the family history for evidence of heart disease or premature death, cardiac-related symptoms (such as unexplained near-syncope/syncope or exertional dyspnea or fatigue), and physical examination findings (including hypertension and murmurs). Additional testing, with either cardiovascular imaging or electrocardiography, is not indicated in the absence of suspicious symptoms, physical findings, or family history.

KEY POINT

HVC

- Although the periodic health examination has been associated with increased delivery of preventive services, multiple studies have failed to show a beneficial effect of the periodic health examination on morbidity or mortality.

Screening

Principles of Screening

Primary prevention is preventing disease or injury before it occurs, with the goal of decreasing the incidence of disease. Secondary prevention is early detection of disease in asymptomatic patients to promote early intervention and reduce complications of disease. Most screening tests fall into the category of secondary prevention. Tertiary prevention is optimizing care of patients with established disease to improve function and reduce complications.

A condition is amenable to screening if it is sufficiently common, will cause significant morbidity and mortality if left untreated, has a preclinical stage to allow for detection, and has an effective, available treatment that can improve prognosis if given early. An ideal screening test must be widely available, safe, acceptable to the patient, of reasonable cost, and highly sensitive and specific for the disease of interest or have a complementary confirmatory test that has high specificity. The screened patient should be at risk for the condition and have adequate quality of life and life expectancy to benefit from screening.

Individuals who are likely to benefit from screening are often determined by the results of randomized controlled trials, but the results of these studies can be affected by commonly encountered biases. Selection (volunteer) bias occurs when patients who volunteer or comply with screening are healthier than those who do not undergo screening. The possibility of selection bias highlights the need for screening trials to use intention-to-treat analysis, which evaluates patient outcomes based on their initial group assignment in a randomized controlled trial instead of by the intervention they ultimately received; this minimizes selection bias. Lead-time bias occurs when survival time (time from diagnosis to death) appears to be lengthened because the screened patient is diagnosed earlier during the preclinical phase but does not live longer in actuality. As a result, disease-specific mortality rates rather than survival time should be used as an outcome. Screening is also more likely to detect indolent disease, which has a long latent period, than aggressive disease, which has a short latent period and is most often detected with onset of symptoms. This causes length-time bias, in which a screen-detected cohort will have overrepresentation of indolent disease, whereas a symptom-detected cohort will have overrepresentation of aggressive disease. Consequently, the screen-detected cohort falsely appears to have a better prognosis. A drastic type of length-time bias that has been increasingly recognized, especially in prostate, breast, and thyroid cancers, is overdiagnosis. Overdiagnosis occurs when disease that would not otherwise have been clinically significant during a patient's lifespan is detected.

KEY POINT

HVC

- A condition is amenable to screening if it is sufficiently common, will cause significant morbidity and mortality if left untreated, has a preclinical stage to allow for detection, and has an effective, available treatment that can improve prognosis if given early.

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Screening Recommendations for Adults

Recommendations on which screening tests to use are frequently based on clinical practice guidelines. The USPSTF systematically reviews the available evidence and issues recommendations for clinicians and health care systems on screening, counseling, and preventive medicine based on the strength of evidence of benefit or harm of these interventions. **Table 7** provides a summary of the USPSTF screening recommendations. The ACP also publishes evidence-based clinical practice guidelines, guidance statements, and best practice advice (which recommend a clinical approach in areas where there may be insufficient or conflicting evidence). The National Guideline Clearinghouse provides a convenient online resource (www.guideline.gov) to compare clinical practice guidelines. Recommendations also change periodically as evidence emerges from large population-based trials. Therefore, clinicians should maintain awareness of these changes as they emerge, reflect upon the rationale and literature supporting the changes, and consider how to best incorporate new screening recommendations into practice.

Clinical guidelines are also sometimes used to develop quality performance measures, although this is an imperfect process given the need to individualize the appropriateness of screening in individual patient circumstances. Consequently, the medical record should reflect a shared decision-making discussion with the patient and the rationale for not providing screening that might normally be recommended.

To ensure that patients are receiving appropriate screening, many electronic health record (EHR) systems include features such as tracking and reminder systems for both providers and patients. This has been shown to improve adherence to evidence-based screening guidelines. Providing patients with electronic access to their health records may also help engaged patients facilitate appropriate screening. An additional resource for screening recommendations is the Electronic Preventive Services Selector (ePSS) developed by the Agency for Healthcare Research and Quality (AHRQ), available at http://epss.ahrq.gov/PDA/index.jsp. It is a point-of-care web- and mobile-based application that provides patient-specific clinical preventive services recommendations based on USPSTF guidelines.

Although providing the appropriate preventive services is vital for optimal medical care, it is equally important to recognize which screening tests should not be performed. **Table 8** provides a summary of screening interventions not routinely recommended by the USPSTF, many of which the USPSTF recommends against.

Specific Screening Tests

Screening for Chronic Diseases

The USPSTF strongly recommends screening all men 35 years of age and older for lipid disorders. Screening is also recommended in men 20 to 34 years of age and older if risk factors for atherosclerotic cardiovascular disease (ASCVD) are present (diabetes mellitus, personal history of coronary heart disease or noncoronary atherosclerosis, family history of cardiovascular disease before age 50 years in male relatives or age 60 years in female relatives, tobacco use, hypertension, obesity [BMI ≥30]). The USPSTF makes no recommendation for or against routine screening for lipid disorders in men aged 20 to 34 years or in women aged 20 years and older who do not have risk factors for ASCVD. However, lipid screening is recommended in women aged 20 years and older if any of the aforementioned risk factors are present. Although the optimal screening interval is undetermined, the USPSTF states that it is reasonable to rescreen every 5 years, or at a shorter interval if the patient's lipid levels are approaching those that would indicate therapy. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cardiovascular risk guideline recommends assessment of cardiovascular risk in all adults 20 to 79 years of age every 4 to 6 years, evaluating for the ASCVD risk factors noted previously, with measurement of total cholesterol and HDL cholesterol levels. As part of this assessment in patients aged 40 to 79 years, calculation of the 10-year risk for ASCVD using the Pooled Cohort Equations is also recommended. (An online ASCVD risk calculator is available at http://tools.cardiosource.org/ASCVD-Risk-Estimator).

All adults should be screened for hypertension. The USPSTF cites the recommendation of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure to screen every 2 years for those with blood pressure below 120/80 mm Hg and yearly for those with systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg. The report of the committee members of the Eighth Joint National Committee addressed management but not detection of hypertension.

In 2008, the USPSTF recommended screening for type 2 diabetes only in asymptomatic adults with sustained blood pressure higher than 135/80 mm Hg. An updated draft guideline, issued in October 2014, recommends screening for abnormal blood glucose and type 2 diabetes in adults with risk factors, including age 45 years or older, obesity or overweight, first-degree relative with diabetes, history of gestational diabetes or polycystic ovary syndrome, and certain high-risk ethnic backgrounds (African Americans, American Indians/Alaska Natives, Asian Americans, Hispanics/Latinos, and Native Hawaiians/Pacific Islanders). Recommended screening tests include fasting plasma glucose level, hemoglobin A_{1c}, or 2-hour oral glucose tolerance test. The American Diabetes Association recommends screening every 3 years if test results are normal.

According to the USPSTF, all adults should be screened for obesity using BMI. A 2013 joint guideline from the AHA, ACC, and The Obesity Society recommends screening for obesity at least annually. Adults with BMI of 30 or higher should be referred for intensive behavioral interventions.

The USPSTF recommends one-time screening for abdominal aortic aneurysm (AAA) with abdominal ultrasonography in all men aged 65 to 75 years who have smoked

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TABLE 7. Summary of USPSTF Screening Recommendations[a]

Condition	Screening Recommendation
Chronic Diseases	
Abdominal aortic aneurysm	One-time abdominal ultrasonography in all men ages 65-75 y who have ever smoked[b]; selective screening in all men ages 65-75 y who have never smoked
Depression	All adults, when staff-assisted depression care support is available
Diabetes mellitus	All adults with sustained blood pressure >135/80 mm Hg according to 2008 recommendation; all adults at increased risk according to 2014 draft recommendation
Hypertension	All adults
Lipid disorders	All men age ≥35 y; all women age ≥45 y at increased risk; start at age 20 y for adults at increased cardiovascular risk
Obesity	All adults
Osteoporosis	Women age ≥65 y; women <65 y of age when 10-year fracture risk is ≥9.3%
Thyroid disease	Insufficient evidence to recommend for or against screening for thyroid disease (grade I)
Infectious Diseases	
Chlamydia	All sexually active women age ≤24 y; all sexually active women at increased risk of infection[c]
Gonorrhea	All sexually active women at increased risk of infection[c]
Hepatitis B virus	All adults at high risk[d]
Hepatitis C virus	One-time screening for adults born between 1945 and 1965; all adults at high risk[e]
HIV infection	One-time screening for all adults ages 15-65 y; repeated screening for adults at high risk[f]
Syphilis	All adults at increased risk of infection[g]
Tuberculosis	USPSTF defers to CDC guidelines, which recommend screening for high-risk individuals[h]
Substance Abuse	
Alcohol misuse	All adults
Tobacco use	All adults
Cancer	
Breast cancer	Biennial screening mammography for women ages 50-74 y; initiation of screening before age 50 y should be individualized (grade C).
Cervical cancer	Women ages 21-65 y with cytology (Pap smear) every 3 y; in women ages 30-65 y who want to lengthen screening, screen with cytology and HPV testing every 5 y.
Colorectal cancer	All adults ages 50-75 y using annual high-sensitivity FOBT, flexible sigmoidoscopy every 5 y, combined high-sensitivity FOBT (every 3 y) plus flexible sigmoidoscopy (every 5 y), or colonoscopy every 10 y
Lung cancer	Not recommended for the average-risk patient; annual low-dose CT in high-risk patients (adults ages 55-80 y with a 30-pack-year smoking history, including former smokers who have quit in the last 15 years) (see MKSAP 17 Pulmonary and Critical Care Medicine)
Skin cancer	Insufficient evidence for skin cancer screening examinations (grade I)

CDC = Centers for Disease Control and Prevention; FOBT = fecal occult blood testing; HPV = human papillomavirus; USPSTF = U.S. Preventive Services Task Force.

[a]Unless otherwise specified, all recommendations listed are grade A or B, for which the USPSTF suggests providing this service in practice. Grade C recommendations are offered for selected patients depending on individual circumstances. Grade D services should be discouraged. Grade I indicates that there is insufficient evidence to assess the balance of benefits and harms for a service.

[b]In the USPSTF recommendation, an "ever-smoker" is a person who has smoked at least 100 cigarettes in his or her lifetime.

[c]Women who are at increased risk of infection include those with a history of sexually transmitted infection (STI), those with new or multiple sexual partners, those who use condoms inconsistently, and commercial sex workers.

[d]Persons at high risk of hepatitis B virus (HBV) infection include those born in countries with at least a 2% prevalence of HBV infection, persons receiving dialysis or cytotoxic or immunosuppressive treatments, HIV-positive persons, injection drug users, men who have sex with men (MSM), and household contacts or sexual partners of persons with HBV infection.

[e]Persons at high risk of hepatitis C virus infection include injection and intranasal drug users, persons who received a blood transfusion before 1992, persons on long-term hemodialysis, prisoners, and persons who received unregulated tattoos.

[f]Persons at high risk of HIV infection include MSM, active injection drug users, persons with behavioral risk factors (those who have unprotected vaginal or anal intercourse; have sexual partners who are HIV-infected, bisexual, or injection drug users; or exchange sex for drugs or money), persons who have acquired other STIs, and persons who live and receive care in a high-prevalence setting (HIV seroprevalence of ≥1%).

[g]Persons at increased risk for syphilis infection include prisoners, MSM, and persons who exchange sex for money or drugs.

[h]Persons at high risk for tuberculosis infection include injection drug users, HIV-positive persons, those who have close contact with persons with known or suspected tuberculosis, those who live or work in high-risk settings, and recent immigrants from countries with a high prevalence of tuberculosis.

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TABLE 8. Screening Interventions Not Routinely Recommended by the USPSTF for Asymptomatic, Average-Risk Adults[a]

Routine urine tests (grade D)[b]
Resting or exercise electrocardiography for CHD screening in asymptomatic adults at low risk for CHD events (grade D)[b,c]
Nontraditional risk factors (including CT coronary artery calcium score[b], high-sensitivity C-reactive protein, ankle-brachial index, carotid intima-media thickness, lipoprotein(a), and homocysteine) in screening asymptomatic adults with no history of CHD to prevent CHD events (grade I)
Screening for asymptomatic carotid stenosis (grade D)[b]
Screening for AAA in women who have never smoked (grade D)
PSA screening for prostate cancer (grade D)[b]
CA-125 measurement or pelvic ultrasonography for ovarian cancer screening (grade D)[b]
Abdominal palpation, serologic markers, or ultrasonography for pancreatic cancer screening (grade D)
Screening for testicular cancer (grade D)
Spirometry in asymptomatic individuals (including asymptomatic smokers) for COPD screening (grade D)[c]
Genetic screening tests for hereditary hemochromatosis (grade D)
Screening for chronic hepatitis B virus infection (grade D)[c]

AAA = abdominal aortic aneurysm; CHD = coronary heart disease; PSA = prostate-specific antigen; USPSTF = U.S. Preventive Services Task Force.

[a]Grade D services should be discouraged. Grade I indicates that there is insufficient evidence to assess the balance of benefits and harms for a service.

[b]Also recommended against in the American Board of Internal Medicine Foundation's Choosing Wisely initiative.

[c]Also recommended against in the American College of Physicians' High Value Care initiative.

at least 100 cigarettes in their lifetime and selective screening in men in this age group who have never smoked. There is insufficient evidence to recommend for or against screening for AAA in women aged 65 to 75 years who have ever smoked. Women who have never smoked should not be screened for AAA.

The USPSTF recommends screening for osteoporosis by measurement of bone mineral density in women aged 65 years and older and in younger women who have a fracture risk equal to or higher than a 65-year-old white woman (9.3%). The physician can use the Fracture Risk Assessment Tool (FRAX) (www.shef.ac.uk/FRAX/) to determine if the 10-year fracture risk for younger women is greater than or equal to 9.3%. The USPSTF concludes that the current evidence is insufficient to recommend routine screening for osteoporosis in men. The ACP recommends periodic individualized assessment of risk factors for osteoporosis in older men. By age 65 years, at least 6% of men have dual-energy x-ray absorptiometry (DEXA)–determined osteoporosis, so risk factor assessment before this age is reasonable. Risk assessment and screening guidelines are further discussed in MKSAP 17 Endocrinology and Metabolism.

The USPSTF concludes that there is insufficient evidence to recommend for or against screening for thyroid disease. The ACP recommends screening women over age 50 years who have at least one symptom that can be attributed to thyroid disease. The American Thyroid Association and the American Association of Clinical Endocrinologists recommend measuring thyroid-stimulating hormone (TSH) in individuals with risk factors for hypothyroidism (for example, personal history of autoimmune disease, neck radiation, or thyroid surgery) and consideration of TSH testing in adults age 60 years and older.

According to the USPSTF, all adults should be screened for depression if adequate resources are available to provide support and treatment. A useful clinical tool for screening is the two-item Patient Health Questionnaire (PHQ-2), which has an 83% sensitivity and 90% specificity for depression, which is comparable to longer, more complex screening instruments. Using this tool, the clinician asks, "During the past 2 weeks, how often have you been bothered by any of the following problems: (1) little interest or pleasure in doing things, or (2) feeling down, depressed, or hopeless?" If the patient responds positively to either question, further evaluation is indicated.

Screening for Infectious Diseases

The USPSTF recommends screening for chlamydia in all sexually active women age 24 years and younger and in women older than 24 years who are at increased risk of infection. Women who are at increased risk include those with a history of sexually transmitted infection (STI), those with new or multiple sexual partners, those who use condoms inconsistently, and commercial sex workers. The USPSTF concludes that there is insufficient evidence to recommend for or against chlamydia screening in men. Nucleic acid amplification tests can be performed on first-voided urine or vaginal or endocervical swabs. The Centers for Disease Control and Prevention (CDC) recommends that any patient who has a positive test result be retested 3 months after treatment.

Screening for gonorrhea is recommended by the USPSTF for all pregnant and nonpregnant sexually active women who are at increased risk of infection (same risk factors as with chlamydia). The USPSTF has not determined that there is sufficient evidence to recommend for or against screening for gonorrhea in men at high risk, and the task force recommends against screening for men and women who are at low risk. Nucleic acid amplification tests can be performed on first-voided urine or urethral swabs from men and vaginal or endocervical swabs from women. The CDC recommends that any patient who has a positive test result be retested 3 months after treatment.

The USPSTF recommends one-time HIV screening for all adults aged 15 to 65 years. Individuals with risk factors for HIV should be screened regardless of age, and repeated screening is recommended in this population. Based on prevalence data, men who have sex with men (MSM) and active injection drug users have a very high risk for HIV infection. Other individuals

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at risk for HIV include those with behavioral risk factors (those who have unprotected vaginal or anal intercourse; have sexual partners who are HIV-infected, bisexual, or injection drug users; or exchange sex for drugs or money), those who have acquired other STIs, and those who live and receive care in a high-prevalence setting (HIV seroprevalence of ≥1%). The USPSTF also recommends screening all pregnant women for HIV. Combined HIV antibody immunoassay/p24 antigen testing is the preferred screening test for HIV infection. Diagnosis of HIV is discussed in MKSAP 17 Infectious Disease.

The USPSTF also recommends screening for hepatitis B virus (HBV) in all adults at high risk, which includes persons born in countries with at least a 2% prevalence of HBV infection, persons receiving dialysis or cytotoxic or immunosuppressive treatments, HIV-positive persons, injection drug users, MSM, and household contacts or sexual partners of persons with HBV infection. Screening is performed with hepatitis B surface antigen (HBsAg) serologic studies; antibodies to hepatitis B antigens (anti-HBs and anti-HBc) are also obtained to differentiate between immunity and infection. All pregnant women should also be screened for HBV.

According to the USPSTF, all adults born between 1945 and 1965 should receive one-time screening for hepatitis C virus (HCV) with anti-HCV antibody testing. Additionally, all adults at high risk (injection and intranasal drug users, persons who received a blood transfusion before 1992, persons on long-term hemodialysis, prisoners, and persons who received unregulated tattoos) should receive HCV screening. The CDC recommends that HIV-positive patients undergo annual HCV screening. Screening is performed with anti-HCV antibody followed by polymerase chain reaction (PCR) viral load testing if positive (see MKSAP 17 Gastroenterology and Hepatology).

The USPSTF recommends syphilis screening for all pregnant women and all adults at increased risk for infection. Populations at risk are prisoners, MSM, and persons who exchange sex for money or drugs. Initial screening tests include the VDRL test and rapid plasma reagin (RPR) test.

The CDC has issued guidelines for tuberculosis (TB) screening that recommend screening in high-risk individuals, including injection drug users, persons who are positive for HIV, those who have close contact with persons with known or suspected TB, those who live or work in high-risk settings, and recent immigrants from countries with a high prevalence of TB. Appropriate screening tests include tuberculin skin testing or the interferon-γ release assay.

Screening for Substance Use Disorders

According to the USPSTF, all adults should be screened for alcohol misuse. The Alcohol Use Disorders Identification Test (AUDIT) is the most validated screening test for identifying hazardous and harmful drinking in primary care patients (available at http://pubs.niaaa.nih.gov/publications/Audit.pdf). Shorter tests that are comparable to AUDIT include the AUDIT-C test (three items from AUDIT) and single-item screening ("How many times in the past year have you had five [four for women] or more drinks in one day?"). The physician also should provide persons engaged in risky or hazardous drinking with brief behavioral counseling.

The USPSTF recommends that all adults be screened for tobacco use. To engage patients, physicians should consider using the 5 A's (Ask, Advise, Assess, Assist, and Arrange) (see Behavioral Counseling).

Although the USPSTF has concluded that there is not enough evidence to recommend for or against illicit drug screening, there are several questionnaires that are valid and reliable in screening for drug use. The Drug Abuse Screening Test (DAST-10) (available at https://www.drugabuse.gov/sites/default/files/files/DAST-10.pdf) is a 10-item survey similar to the AUDIT tool used for alcohol screening. A single-item screening question ("How many times in the past year have you used an illegal drug or used prescription medications for nonmedical reasons?") has been shown to be highly sensitive and may be used for screening.

Screening for Cancer

Cancer screening guidelines have evolved significantly in recent years based on accumulating evidence of the potential benefits and harms associated with screening, diagnosis, and treatment. As a result, guidelines issued by organizations may differ significantly, and some recommendations may be controversial. This highlights the need to understand the evidence underlying the different guidelines and to engage in shared decision-making when deciding on an appropriate cancer screening strategy for an individual patient.

There is also sparse evidence on when to stop screening for cancer. In general, it is recommended that individuals with fewer than 10 years of quality life expectancy not receive most cancer screening.

Breast Cancer

Breast cancer screening discussed in this section applies to asymptomatic average-risk women. Women with significant risk factors for breast cancer, including family history of breast or ovarian cancer or personal history of atypia or lobular carcinoma in situ, should undergo a formal breast cancer risk assessment. Screening for breast cancer in women with increased risk is discussed in MKSAP 17 Hematology and Oncology.

In 2009, the USPSTF updated its recommendations for breast cancer screening to endorse biennial screening mammography for all women aged 50 to 74 years. Additionally, routine mammographic screening for women younger than 50 years is no longer recommended; rather, the USPSTF recommends individualized screening decisions for women younger than 50 years based on patient context and values regarding specific benefits and harms. The USPSTF reasons that while the benefit of screening may be similar in women ages 40 to 49 years (1 breast cancer death avoided per 1900 invited to screen, 15% relative risk reduction) compared with women ages 50 to 59 years (1 breast cancer death avoided per

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1300 invited to screen, 14% relative risk reduction), there is a lower incidence of breast cancer and higher risk of harms in the younger age group. Harms can include false-positive screening results, which may lead to unnecessary emotional stress, biopsies, and unnecessary treatment. The ACP, AAFP, and Kaiser Permanente Care Management Institute concur with these guidelines; however, specialty organizations including the American Cancer Society (ACS), National Comprehensive Cancer Network, American Congress of Obstetricians and Gynecologists (ACOG), American College of Surgeons, American College of Radiology, and Society of Breast Imaging continue to recommend annual screening mammography starting at age 40 years. The ACP advises against screening average-risk women younger than 40 years for breast cancer.

For women age 75 years and older, the USPSTF found insufficient evidence to recommend for or against screening mammography, and other organizations recommend shared decision-making for this age group to develop an individualized approach. The ACP advises against screening for breast cancer in average-risk women age 75 years and older. As with other cancer screening tests, studies have suggested that women should have a life expectancy of at least 10 years to benefit from screening mammography.

The USPSTF does not recommend for or against clinical breast examination (CBE) and cites potential harms of CBE, including false-positive test results that lead to anxiety and additional imaging and biopsies. The ACS and ACOG recommend CBE every 3 years for women ages 20 to 39 years and yearly for women older than 40 years. The USPSTF recommends against breast self-examination (BSE), citing two trials showing increased imaging and biopsies for women who performed BSE. The ACS and ACOG have shifted towards recommending breast self-awareness, encouraging women to know how their breasts normally look and feel, with BSE as an option.

Breast density is an increasingly recognized risk factor for breast cancer. In addition to increasing breast cancer risk, high breast density is common (present in up to 50% of women) and also decreases the sensitivity of mammography. Evidence has shown that digital mammography may be better than film mammography in women with high breast density; however, currently, high breast density alone does not necessitate additional breast imaging other than routine screening mammography.

Prostate Cancer

In 2012, the USPSTF issued updated guidelines recommending against prostate-specific antigen (PSA) screening for prostate cancer. The USPSTF outlined harms associated with PSA screening, including those resulting directly from screening and diagnostic procedures (anxiety, additional testing including biopsies, overdiagnosis), and harms related to treatment of screen-detected cancer (surgical complications, urinary incontinence, erectile dysfunction, radiotherapy-induced bowel dysfunction). The benefit of PSA screening and associated early treatment is prevention of between 0 and 1 prostate cancer deaths per 1000 men screened. Therefore, the USPSTF concluded that the benefits of PSA screening do not outweigh the harms. Most other organizations recommend a shared decision-making approach for men in the age group most likely to benefit (50-69 years of age according to the ACP, 50 years of age to 10 years of life expectancy according to the ACS, and 55-69 years of age according to the American Urological Association [AUA]). As a high value care intervention, the ACP recommends that clinicians have a one-time discussion (more if the patient requests) with average-risk men aged 50 to 69 years who inquire about PSA-based prostate cancer screening to inform them about the limited potential benefits and substantial harms of screening for prostate cancer using the PSA test. The ACP and AUA do not recommend PSA screening for men older than 69 years or those with less than a 10- to 15-year life expectancy.

Many organizations, including the ACP, ACS, and the American College of Preventive Medicine, recommend earlier thresholds for discussing prostate cancer screening in men at increased risk. In general, PSA discussions are recommended to start at age 45 years for black men or men who have a first-degree relative younger than 65 years with prostate cancer, and at age 40 years for men with several family members younger than 65 years with prostate cancer or men who have known or suspected *BRCA1* or *BRCA2* mutations. Although the USPSTF acknowledges that certain groups are at increased risk for prostate cancer, the task force concluded that there was not enough evidence to make separate recommendations. The current USPSTF recommendations do not apply to men with known *BRCA1* or *BRCA2* mutations.

The digital rectal examination (DRE) in combination with PSA screening has been shown to increase prostate cancer detection; however, no studies have suggested benefit of DRE for patient-important outcomes. Therefore, both the USPSTF and AUA do not make a recommendation for or against the use of DRE for screening purposes.

Additional Cancer Screening Tests

According to the USPSTF, women ages 21 to 65 years should be screened for cervical cancer every 3 years with cytology (Pap smear). In women ages 30 to 65 years who want to lengthen the screening interval, a combination of cytology and human papillomavirus (HPV) testing can be performed every 5 years. Screening for cervical cancer is not recommended in women younger than 21 years, women age 65 years and older who are not at high risk and have had adequate prior Pap smears (three consecutive negative cytology results or two consecutive negative cytology results and HPV testing within the past 10 years, with the most recent test performed within 5 years), and women who have had a hysterectomy with removal of the cervix with no history of a precancerous lesion.

The USPSTF recommends screening all adults ages 50 to 75 years for colorectal cancer using high-sensitivity fecal occult blood testing (FOBT) every year, flexible sigmoidoscopy

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every 5 years, combined high-sensitivity FOBT (every 3 years) plus flexible sigmoidoscopy (every 5 years), or colonoscopy every 10 years. According to a guidance statement issued by the ACP in 2012, patient preference, availability, and benefit and harms should guide the choice of test. The ACS, U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Gastroenterology (ACG) prefer the use of cancer prevention tests (colonoscopy, flexible sigmoidoscopy, double contrast barium enema, or CT colonography) to cancer detection tests (guaiac FOBT or fecal immunochemical testing). Given higher mortality rates, the ACP recommends that screening start at age 40 years for black persons, whereas the ACG recommends that screening begin at age 45 years in this population. Most guidelines recommend stopping screening if life expectancy is less than 10 years, and the USPSTF recommends against screening after age 85 years. For a discussion on screening recommendations for patients at high risk, see MKSAP 17 Gastroenterology and Hepatology.

The USPSTF concludes that there is insufficient evidence to recommend for or against whole-body skin examinations for the early detection of skin cancer; however, the USPSTF did not examine outcomes in patients at high risk for skin cancer. The ACS recommends monthly skin self-examinations as well as skin examination as part of a periodic health examination for adults age 20 years and older. Behavioral counseling on minimizing exposure to ultraviolet radiation is recommended by the USPSTF for persons younger than 24 years who have fair skin.

Lung cancer screening is not recommended for the average-risk patient. Annual low-dose CT is recommended for high-risk patients, defined as adults ages 55 to 80 years with a 30-pack-year smoking history, including former smokers who have quit in the last 15 years. Refer to MKSAP 17 Pulmonary and Critical Care Medicine for a more detailed discussion on screening in high-risk patients.

KEY POINTS

IIVC
- Screening based on clinical guidelines needs to be individualized to account for patient circumstances; shared decision-making discussions should be documented and include the rationale for not providing screening that might otherwise be recommended.

IIVC
- Although providing the appropriate preventive services is vital for optimal medical care, it is equally important to recognize what screening tests should not be performed.

IIVC
- The U.S. Preventive Services Task Force recommends that all adults be screened for obesity, hypertension, tobacco use, alcohol misuse, and depression (if adequate resources are available to provide support and treatment for depression).
- The U.S. Preventive Services Task Force and the American College of Physicians recommend biennial screening mammography for all women aged 50 to 74 years to screen for breast cancer.

(Continued)

KEY POINTS *(continued)*

HVC
- The U.S. Preventive Services Task Force recommends against using prostate-specific antigen level to screen for prostate cancer.
- According to the U.S. Preventive Services Task Force, women ages 21 to 65 years should be screened for cervical cancer every 3 years with a Pap smear.
- The U.S. Preventive Services Task Force recommends screening all adults ages 50 to 75 years for colorectal cancer using high-sensitivity fecal occult blood testing (FOBT) every year, flexible sigmoidoscopy every 5 years, combined high-sensitivity FOBT (every 3 years) plus flexible sigmoidoscopy (every 5 years), or colonoscopy every 10 years.

Genetics and Genetic Testing

Clinical genetics has traditionally focused on identification of specific disease-causing mutations that follow a mendelian pattern of inheritance; however, an increasing number of identifiable genetic variants or groups of specific genetic polymorphisms that do not follow a mendelian pattern of inheritance have been associated with the development of complex diseases. The understanding of the role of these genetic factors in predisposing an individual to certain diseases is rapidly evolving, although the predictive accuracy and appropriate use of this form of genetic testing remain to be established. Additionally, genetic information is increasingly used to individualize treatment for specific patients, such as those with blood disorders and tumors, and to predict individual response to specific medications. The increasing availability and lowering cost of direct-to-consumer genetic testing require clinicians to understand the basics of detecting, diagnosing, and managing genetic diseases.

Taking a Family History

Historical clues, including characteristics of the family history, can suggest the presence of an inherited condition and can be used by clinicians to help guide the appropriateness of obtaining genetic testing (**Table 9**). Despite this recognition, there is no standardized definition as to what constitutes an appropriate family history, and there is also no consensus on how to properly obtain and collect family history information for use in assessing risk for genetic diseases.

A reasonable approach is to obtain a three-generation family history, including information on grandparents, parents, aunts, uncles, siblings, cousins, children, nieces, and nephews. The sex, age, relationship to patient, and presence of any birth defects or medical conditions, including age of onset, should be elicited for each family member. Evidence suggests that persons are better at reporting absence rather than presence of disease in relatives, and accuracy may be increased by asking the patient to confer with other family members. Drawing a pedigree or family tree is often helpful in recognizing patterns of inheritance.

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TABLE 9. "Red Flags" Suggesting an Increased Genetic Risk in an Individual or Family

"Red Flag"	Description	Example
Family history of multiple affected family members with the same or related disorders	Such a pattern indicates increased risk, whether through genetic or environmental risk factors or a combination of genes and environment.	Three family members in two generations with cardiovascular disease
Earlier age at onset of disease than expected	Disorders that arise at a younger age than expected may occur because of a genetic predisposition that makes an individual more susceptible to environmental exposures.	Cardiovascular disease occurring in the fourth decade of life
Condition in the less-often-affected sex	A disorder that occurs in the less common sex may occur because of a genetic predisposition that overrides other hormonal, developmental, and environmental factors that contribute to its occurrence.	Breast cancer in a male
Disease in the absence of known risk factors	Genetic predisposition may lead to the occurrence of a disorder in the absence of obvious environmental factors.	Hyperlipidemia in an individual with an ideal diet and exercise regimen
Ethnic predisposition to certain genetic disorders	Some genetic disorders are more common in certain ethnic groups. Awareness of a patient's ethnicity or ancestral background can aid in recommending genetic testing and evaluation of genetic conditions.	Lactose intolerance in an individual of African ancestry
Close biologic relationship between parents	Consanguinity is a relationship by blood or a common ancestor. Because relatives are more likely to share the same genes, children from a consanguineous couple related as first cousins or closer have an increased risk of having an autosomal recessive condition.	Cystic fibrosis

Based on National Coalition for Health Professional Education in Genetics. Core principles in family history: Interpretation. www.nchpeg.org/index.php?option=com_content&view=article&id=199:principles-for-interpretation&catid=64:core-principles-in-family-history&Itemid=126. Accessed May 29, 2015.

Patients who have no genetic family history available (for example, due to adoption) should not undergo genetic testing without other reason.

Genetic Tests and Testing Strategies

Cytogenetic tests are used to detect structural chromosomal abnormalities. Giemsa staining of chromosomes produces a banding pattern that allows karyotyping and aids in detecting structural abnormalities, and fluorescence in situ hybridization and microarray analysis can both be used to detect more subtle chromosomal abnormalities. Direct DNA tests are designed to detect specific genetic mutations. Examples of direct DNA tests include enzyme-linked immunosorbent assay, polymerase chain reaction, and Southern blot analysis. Linkage analysis is an indirect DNA test used when the responsible gene location is known but the precise gene or genetic mutation is not. Biochemical testing relies on measuring the levels of metabolites involved in biochemical pathways to assess enzymatic activity. When an enzymatic defect is present, metabolite levels may be either increased or decreased.

There are several strategies that clinicians may use in genetic testing. Predictive genetic testing uses a genetic test to determine whether or not an individual will develop a condition at some point in his or her lifetime. Diagnostic genetic testing is the use of a genetic test to diagnose or to rule out a condition that is suspected based on results of clinical findings. Pharmacogenetic testing is used to predict a patient's response to a medication. Although pharmacogenetic testing is available for many drug-metabolizing enzymes, its use has been clinically limited and is not routinely recommended. **Table 10** compares the different genetic testing strategies.

Direct-to-consumer genetic testing allows patients to obtain testing without the assistance of a health care provider. Direct-to-consumer testing is based on identifying genetic differences between individuals with a condition and those without the condition. In a case-control–based approach, single-nucleotide polymorphisms (SNPs) that are disproportionately found in affected individuals are identified, and odds ratios are determined for each SNP. Unfortunately, most SNPs have very low odds ratios and contribute only a small proportion to total disease burden. Direct-to-consumer testing has many potential drawbacks, including the validity of the tests themselves. Because of a lack of pretest counseling, patients often misinterpret test results, leading to unnecessary angst. Patients also frequently bring the test results to their physicians, many of whom are not properly prepared to interpret the results. Results can also lead to additional testing, which may be unnecessary.

Genetic testing raises many ethical questions, as the results affect not only the patient but also other members of the family. Testing can also lead to possible discrimination. The Genetic Information Nondiscrimination Act of 2008 protects against genetic discrimination in regard to both health insurance and employment but does not provide any protection against discrimination involving disability, life, or long-term care insurance.

Referral for Genetic Counseling

Genetic counseling should always occur before any genetic test is performed. The essential components of counseling include informing the patient of the test purpose, implications of diagnosis, alternative testing options (including foregoing testing), and

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TABLE 10. Types of Genetic Testing and Indications

Genetic Testing Type	Indication
Diagnostic testing	Used to confirm or support a diagnosis in a patient with clinical disease (for example, cystic fibrosis, sickle cell disease)
Predictive testing	Used to identify individuals at risk for heritable disease: *Presymptomatic tests* evaluate for conditions caused by single genes with a high degree of penetrance that will likely eventually cause disease (for example, Huntington disease). *Predisposition tests* evaluate for genetic alterations known to significantly increase the risk of disease (for example, *BRCA* mutation). *Susceptibility tests* evaluate for different genetic markers associated with complex diseases (for example, coronary artery disease).
Pharmacogenetic testing	Tests for genetic factors influencing drug metabolism (for example, TPMT assay for azathioprine)
Tumor (somatic cell) testing	Involves testing tissue (usually cancer) for nonheritable mutations (for example, *HER2, KRAS*) for diagnostic purposes or to assist in selecting a specific treatment
Carrier testing	Used to identify a specific genetic mutation in an asymptomatic family member, frequently for reproductive decision making; typically for the heterozygous state of a disease that presents with disease when homozygous (for example, cystic fibrosis, sickle cell disease)
Prenatal (antenatal) testing	Testing during pregnancy (by amniocentesis or chorionic villus sampling) to identify congenital conditions (for example, Down syndrome, Turner syndrome)
Newborn (neonatal) screening	Testing after birth for presence of disease for which preventive measures or treatment exist (for example, phenylketonuria); often legally mandated and varies by state

BRCA = breast cancer susceptibility genes 1 and 2; *HER2* = human epidermal growth factor receptor 2; *KRAS* = Kirsten rat sarcoma viral oncogene; TPMT = thiopurine methyltransferase.

any possible risks and benefits. Approximately 1 hour of counseling is considered standard for each genetic test performed. Ultimately, the decision of whether or not to be tested rests with the patient. Although genetic counseling can be provided by internists, most do not feel adequately equipped or trained to do so; therefore, referral to a genetic counselor in most situations in which genetic testing is being considered is appropriate. The National Society of Genetic Counselors website (http://nsgc.org) can be used by providers to locate a genetic counselor in their area.

KEY POINTS

HVC
- Patients who have no genetic family history available (for example, due to adoption) should not undergo genetic testing without other reason.
- Predictive genetic testing is used to determine whether a person has genetic mutations that are associated with higher risk of certain disorders.
- Diagnostic genetic testing is used to diagnose or to rule out a condition that is suspected based on results of clinical findings.

HVC
- Although pharmacogenetic testing is available for many drug-metabolizing enzymes, its use has been clinically limited and is not routinely recommended.

Immunization

Even though vaccines are one of the most cost-effective preventive health measures available, immunization rates remain unacceptably low. Vaccination recommendations for adults are published on a yearly basis by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) at www.cdc.gov/vaccines/acip/index.html (**Table 11**). The American College of Physicians offers a free downloadable Immunization Advisor mobile application (available at http://immunization.acponline.org/app/) that provides the latest ACIP immunization recommendations, searchable by patient age and underlying medical condition.

Vaccinations with multiple doses should not be given at shorter-than-recommended intervals; conversely, administering doses at longer-than-recommended intervals does not typically reduce final immunologic response at series completion. If a vaccination series is interrupted, the schedule should be resumed at the point of interruption. Multiple vaccinations can usually be given simultaneously to improve vaccination rates.

Vaccine administration should be deferred when there is a history of anaphylaxis to vaccine components or if the patient is experiencing a moderate to severe illness; however, vaccines can be administered with several minor conditions, including diarrhea, minor upper respiratory tract infections (with or without fever), otitis media, current antimicrobial therapy, convalescent phase of acute illness, and mild to moderate local reactions to a previous vaccine dose. Contraindications to live vaccines are listed in **Table 12**.

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TABLE 11. Summary of Vaccination Recommendations for Adults

Disease	Vaccine Type	ACIP Recommendation
Influenza	Inactivated, live attenuated, recombinant	One dose annually for all persons ≥6 months of age; indications vary by vaccine type (see text)
Tetanus, diphtheria, and pertussis	Inactivated	Primary series for unvaccinated adults; Td booster every 10 y for all adults; one-time pertussis booster with Tdap in adults; all pregnant women between 27 and 36 weeks' gestation during each pregnancy
Varicella	Live attenuated	Two doses given at interval of ≥4 weeks for all persons lacking evidence of VZV immunity[a]
Herpes zoster	Live attenuated	All nonimmunocompromised persons age ≥60 y
Pneumococcal	Inactivated	All adults age ≥65 y; adults ages 19-64 y with risk factors (see Figure 3 and Table 13)
Human papillomavirus	Inactivated	Females at age 11-12 y, or age 13-26 y for unvaccinated females; males at age 11-12 y, or age 13-21 y for unvaccinated males (permitted age 21-26 y); immunocompromised persons (including those infected with HIV) and MSM through age 26 y
Measles, mumps, and rubella	Live attenuated	Adults born in 1957 or later without documented evidence of vaccination or immunity. One dose usually sufficient; second dose recommended for college students, international travelers, and HCWs
Meningococcal	Inactivated	One dose indicated for first-year college students residing in dormitories (unless vaccinated at age ≥16 y), travelers to endemic areas, microbiologists exposed to *Neisseria meningitidis*, military recruits, and exposed persons; two doses indicated for persons with asplenia or complement deficiencies. Revaccination recommended every 5 y for those with persistent risk
Hepatitis A	Inactivated	Any adult requesting immunization and those at high risk (see text)
Hepatitis B	Inactivated	Any adult requesting immunization and those at high risk (see text)

ACIP = Advisory Committee on Immunization Practices; HCW = health care worker; MSM = men who have sex with men; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; VZV = varicella zoster virus.

[a]Evidence of immunity includes either 1) documentation of receiving two doses of varicella vaccine ≥4 weeks apart, 2) U.S.-born before 1980 except health care providers and pregnant women, 3) varicella or herpes zoster diagnosed by health care provider, or 4) laboratory evidence of immunity.

TABLE 12. Contraindications to Live Vaccines

Pregnancy
HIV or AIDS with a CD4 cell count ≤200/μL or ≤15% of total lymphocytes
Immunosuppressant therapy, including high-dose glucocorticoids (≥20 mg/d of prednisone or equivalent)
Leukemia, lymphoma, or other bone marrow and lymphatic system malignancies
Cellular immunodeficiency
Solid-organ transplant recipient
Current hematopoietic stem cell transplantation

Vaccinations Recommended for All Adults

Influenza

Due to ongoing genetic mutations (antigenic drift), influenza vaccination is necessary each year. Adults who are considered to be at high risk for contracting severe disease and complications include those persons aged 50 years and older, women who may potentially become pregnant during the influenza season, residents of chronic care facilities, immunocompromised individuals, and those who have diabetes mellitus or pulmonary, cardiac (excluding hypertension), liver, or kidney conditions.

Influenza vaccination is recommended for all persons aged 6 months and older unless specifically contraindicated. Vaccination should be offered as soon as the vaccine becomes available and should continue until influenza season has ended.

There are currently three different types of influenza vaccine available in the United States: inactivated influenza vaccine (IIV), live attenuated influenza vaccine (LAIV), and recombinant trivalent influenza vaccine (RIV). IIV is approved for use in all adults, including immunosuppressed persons and pregnant women. Four types of IIV are currently available: standard-dose, egg-based trivalent; standard-dose, egg-based quadrivalent; standard-dose, cell culture–based trivalent; and high-dose trivalent. The quadrivalent vaccine contains two influenza A virus antigens and two influenza B virus antigens, whereas the trivalent vaccines contain two influenza A virus antigens and one influenza B virus antigen. The ACIP has no stated preference for administering the quadrivalent formulation over the trivalent counterparts. The standard-dose, egg-based trivalent and quadrivalent IIVs are approved for all adults of any age, whereas the standard-dose, cell culture–based trivalent IIV is approved for use in adults 18 years of age and older. The intradermally administered standard-dose trivalent IIV may be administered to persons aged 18 to 64 years. The high-dose trivalent vaccine is only approved for use in adults age 65 years and older; it has been shown to be

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modestly more effective than the standard-dose IIVs in this patient population. All types of IIV can be administered to immunocompromised individuals.

Intranasal LAIV is approved for use in healthy, nonpregnant individuals aged 2 to 49 years. LAIV should be avoided in immunosuppressed individuals and in those with any egg allergies. RIV is also available and is approved for persons aged 18 years and older. RIV does not contain any egg components and can be safely used in individuals with egg allergies. All vaccine formulations should be avoided in persons who previously developed Guillain-Barré syndrome within 6 weeks of receiving the influenza vaccine.

Clinicians frequently encounter patients with a reported history of egg allergy. The ACIP has developed an algorithm for the administration of the influenza vaccine for this group of patients (**Figure 2**).

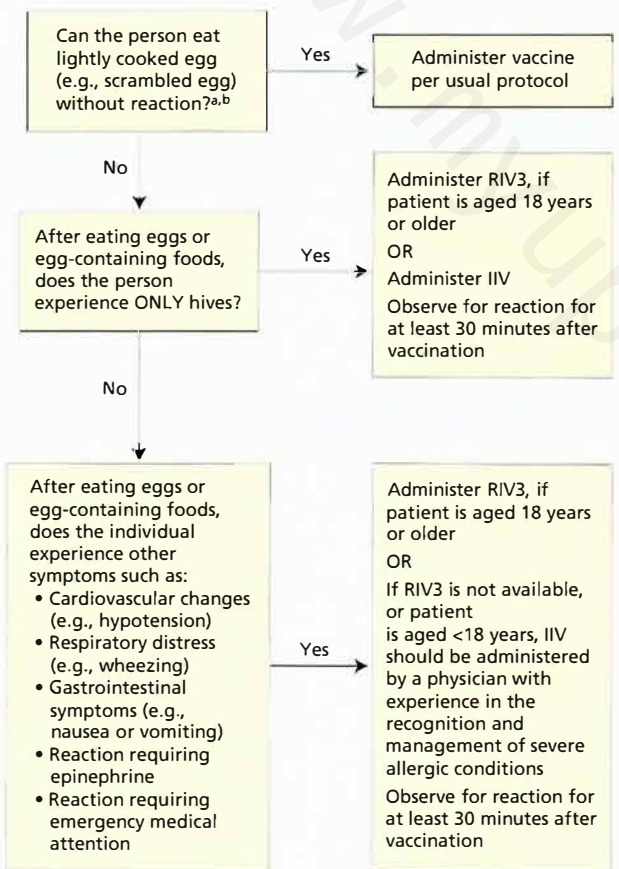

FIGURE 2. Recommendations regarding influenza vaccination of persons who report allergy to eggs.

IIV = inactivated influenza vaccine; RIV3 = recombinant influenza vaccine, trivalent.

[a]Persons with egg allergy might tolerate egg in baked products (for example, bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy.

[b]For persons who have no known history of exposure to egg, but who are suspected of being egg-allergic on the basis of previously performed allergy testing, consultation with a physician with expertise in the management of allergic conditions should be obtained before vaccination. Alternatively, RIV3 may be administered if the recipient is aged 18 years or older.

Adapted from Grohskopf LA, Olsen SJ, Sokolow LZ, et al; Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) - United States, 2014-15 influenza season. MMWR Morb Mortal Wkly Rep. 2014 Aug 15;63(32):691-7. [PMID: 25121712]

Tetanus, Diphtheria, and Pertussis

Although tetanus and diphtheria infections are extremely uncommon, the incidence of pertussis has recently increased, presumably due to waning immunity with age. Primary vaccination against tetanus, diphtheria, and pertussis is recommended during childhood and consists of five doses of the diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine administered at 2 months, 4 months, 6 months, 15 through 18 months, and 4 to 6 years of age. A single booster dose of the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine is also recommended for children between the ages of 11 and 12 years. Adults who did not receive primary vaccination or who did not complete the primary series, defined as receiving fewer than 3 doses, should begin or complete the primary vaccination series with three doses of tetanus and diphtheria-containing vaccines, one of which should be a Tdap dose. The ACIP makes no recommendations regarding testing of serum antibody levels to confirm immunity. All persons aged 11 years and older who completed the primary series should receive a single booster dose of Tdap, followed by a tetanus and diphtheria toxoids (Td) booster every 10 years thereafter. Tdap can be administered regardless of the interval since the most recent tetanus or diphtheria toxoid-containing vaccine. For pregnant women, one dose of the Tdap vaccine should be administered during each pregnancy between 27 weeks' and 36 weeks' gestation, regardless of when the last dose of Td or Tdap was given.

Vaccinations Recommended for Some Adults

Varicella and Herpes Zoster

Primary infection with varicella zoster virus (VZV) causes varicella (chickenpox). Birth in the United States before 1980 is considered to serve as evidence of immunity against varicella, except in health care professionals, pregnant women, and immunocompromised individuals, all of whom require serologic confirmation. For persons born after 1980, evidence of immunity to varicella includes written documentation of age-appropriate vaccination, serologic confirmation of immunity, or verification of either varicella or herpes zoster diagnosis made by a physician. All individuals who lack evidence of VZV immunity by serologic testing should receive two doses of varicella vaccine, given at least 4 to 8 weeks apart. Women should be assessed for varicella immunity during pregnancy, and if not immune, they should be vaccinated following pregnancy. Vaccination is contraindicated during pregnancy. Revaccination is not currently recommended in patients who received the two-dose vaccination series for primary prevention either as a child, adolescent, or adult.

The herpes zoster vaccine is similar to the varicella vaccine but is significantly more potent. It is recommended for individuals aged 60 years and older regardless of whether they have had a previous zoster episode, but vaccination should be avoided in immunocompromised patients. Vaccination is effective for reducing the occurrence of both herpes zoster and postherpetic neuralgia.

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Pneumococcal Disease

Pneumococcal vaccination is indicated for all adults aged 65 years and older and for high-risk persons younger than 65 years (**Table 13**). Two vaccines are currently available: pneumococcal polysaccharide vaccine (PPSV23) is composed of polysaccharide capsular material from 23 pneumococcal subtypes, whereas pneumococcal conjugate vaccine (PCV13) contains capsular material from 13 subtypes conjugated to a nontoxic protein, which increases its immunogenicity. PCV13 is more than 90% effective in preventing invasive pneumococcal disease and is also effective in reducing pneumonia and acute otitis media to a lesser extent, whereas PPSV23 is only 60% to 70% effective in preventing invasive pneumococcal disease and does not reduce the risk of pneumococcal pneumonia.

For pneumococcal vaccine–naïve adults between the ages of 19 and 65 years with certain immunocompromising conditions or who are otherwise at high risk (see Table 13), a single dose of PCV13 should be given, followed by a dose of PPSV23 at least 8 weeks later. For adults between the ages of 19 and 65 years who previously received the PPSV23 vaccine, a single dose of PCV13 should be given at least 1 year after receiving

TABLE 13. Pneumococcal Vaccination Recommendations for Adults Aged 19 Years and Older with Underlying Medical Conditions

		PCV13	PPSV23	
Risk Group	**Underlying Medical Condition**	**Recommended**	**Recommended**	**Revaccination at 5 Years After First Dose**
Immunocompetent persons	Chronic heart disease[a]		X	
	Chronic lung disease[b]		X	
	Diabetes mellitus		X	
	CSF leaks	X	X	
	Cochlear implants	X	X	
	Alcoholism		X	
	Chronic liver disease		X	
	Cigarette smoking		X	
Persons with functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathies	X	X	X
	Congenital or acquired asplenia	X	X	X
Immunocompromised persons	Congenital or acquired immunodeficiencies[c]	X	X	X
	HIV infection	X	X	X
	Chronic kidney failure	X	X	X
	The nephrotic syndrome	X	X	X
	Leukemia	X	X	X
	Lymphoma	X	X	X
	Hodgkin lymphoma	X	X	X
	Generalized malignancy	X	X	X
	Iatrogenic immunosuppression[d]	X	X	X
	Solid-organ transplant	X	X	X
	Multiple myeloma	X	X	X

CSF = cerebrospinal fluid; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

[a]Including heart failure and cardiomyopathies.

[b]Including COPD, emphysema, and asthma.

[c]Including B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).

[d]Diseases requiring treatment with immunosuppressive drugs, including long-term systemic glucocorticoids and radiation therapy.

Adapted from Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2012 Oct 12;61(40):816-9. [PMID: 23051612]

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PPSV23. Giving the PCV13 vaccine sooner than 1 year after administration of PPSV23 appears to reduce the immunogenicity of PCV13. In contrast, PPSV23 can be given as soon as 8 weeks after the administration of PCV13 without concern for reduced immunogenicity.

The ACIP recommends administering PPSV23 alone to selected immunocompetent patients between the ages of 19 and 64 years (see Table 13).

For immunocompetent persons aged 65 years and older who have not received any pneumococcal vaccine, the ACIP recommends administering a single dose of PCV13, followed by a single dose of PPSV23 at least 1 year later. For immunocompetent adults aged 65 years and older who previously received one or more doses of PPSV23, a single dose of PCV13 should be given at least 1 year after the most recent PPSV23 dose (**Figure 3**).

Human Papillomavirus

Human papillomavirus (HPV) is the most common STI in the United States. Genotypes 16 and 18 are responsible for causing most cases of cervical cancer and a large number of cases of vulvar, vaginal, anal, penile, and oropharyngeal cancers. HPV genotypes 6 and 11 cause most cases of genital warts.

Three inactivated vaccines are available: a bivalent vaccine (HPV2), a quadrivalent vaccine (HPV4), and a new nine-valent vaccine (HPV9). All vaccines target genotypes 16 and 18, and the quadrivalent vaccine also targets genotypes 6 and 11. The nine-valent vaccine protects against five additional genotypes that cause cervical cancer, resulting in the potential prevention of 90% of cervical, vulvar, vaginal, and anal cancers.

All vaccines are approved for use in females as a three-dose series at ages 11 to 12 years and between the ages of 13 and 26 years for previously unvaccinated persons. HPV4 and HPV9 are approved for use in males as a three-dose series at ages 11 to 12 years and between the ages of 13 and 21 years for previously unvaccinated males, although males aged 22 to 26 years can be vaccinated. For immunocompromised persons (including those infected with HIV) and MSM, vaccination is recommended through age 26 years. Vaccination is not recommended during pregnancy.

Measles, Mumps, and Rubella

Adults born before 1957, excluding health care workers, are considered to be immune to measles, mumps, and rubella and do not require vaccination. Adults born in 1957 or later who lack documentation of receiving the measles, mumps, and rubella (MMR) vaccine or who lack serologic evidence of immunity should receive at least one MMR dose. A second dose should be administered to students in postsecondary education, health care workers, and international travelers. The MMR vaccine should be avoided in pregnant women and immunocompromised individuals.

Meningococcal Disease

Individuals with asplenia or persistent complement deficiencies should be given two doses of the meningococcal vaccine, separated by at least 2 months. First-year college students living in a dormitory should be vaccinated, unless they were vaccinated at age 16 years or older. A single dose should be administered to individuals traveling to endemic areas, microbiologists exposed to *Neisseria meningitidis*, military recruits, and at-risk individuals who are exposed to a serogroup contained in the vaccine. Revaccination is recommended every 5 years for individuals who remain at increased risk.

Hepatitis A

Hepatitis A virus (HAV) vaccination is recommended for any adult seeking protection against HAV and for those at risk for infection, including MSM, travelers to endemic regions, users of illicit drugs, those with occupational risk such as health care

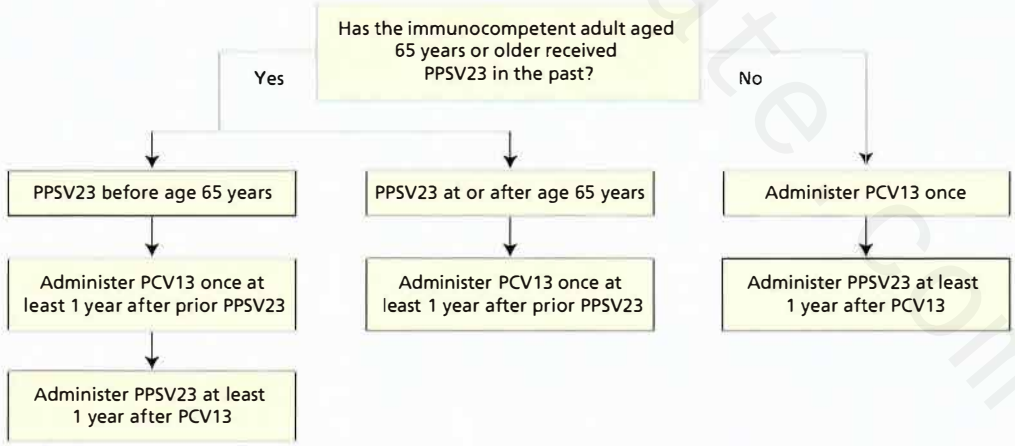

FIGURE 3. Pneumococcal vaccine recommendations for immunocompetent adults aged 65 years and older.

PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

NOTE: For adults aged 65 years or older with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants, the recommended interval between sequential administration of PCV13 and PPSV23 is at least 8 weeks. For those who previously received PPSV23 before age 65 years and for whom an additional dose of PPSV23 is indicated when aged 65 years or older, this subsequent PPSV23 dose should be given at least 1 year after PCV13 and at least 5 years after the most recent dose of PPSV23.

Recommendations from Kobayashi M, Bennett NM, Gierke R, et al. Intervals between PCV13 and PPSV23 vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2015 Sep 4;64(34):944-7. [PMID: 26334788]

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workers, and persons with chronic liver disease or clotting disorders. HAV vaccination of patients infected with either hepatitis B or C is only necessary with evidence of chronic liver disease. The vaccine is typically given as a two-dose regimen.

Hepatitis B

Hepatitis B virus (HBV) vaccination is recommended for any adult seeking protection against HBV and for those at risk due to sexual exposures (MSM, individuals with STIs, individuals not in monogamous relationships, partners of HBsAg-positive individuals) or blood exposures (injection drug users, household contacts of HBsAg-positive persons, health care workers, patients on dialysis). Persons with end-stage kidney disease, HIV-positive persons, persons with chronic liver disease, travelers to endemic areas, persons with diabetes who are younger than age 60 years, and high-risk persons with diabetes who are older than 60 years should also be vaccinated. The vaccine is given as a three-dose regimen.

KEY POINTS

HVC • Even though vaccines are one of the most cost-effective preventive health measures available, immunization rates remain unacceptably low; providing age- and risk-appropriate immunization to patients is essential to the practice of high value care.

HVC • Influenza vaccination is recommended for all persons aged 6 months and older unless specifically contraindicated.

HVC • Pneumococcal vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13) is indicated for all adults aged 65 years and older and for certain high-risk persons younger than 65 years.

HVC • Bivalent, quadrivalent, and nine-valent vaccines for human papillomavirus are approved for use in females and quadrivalent and nine-valent vaccines for males between the ages of 11 and 26 years.

HVC • Vaccination with herpes zoster vaccine is recommended for individuals aged 60 years and older, including patients with a previous episode of zoster.

Immunization Recommendations for Specific Populations

Health care workers are at increased risk for both contracting and transmitting influenza, pertussis, varicella, measles, mumps, rubella, and HBV. Annual vaccination against influenza and one-time vaccination against pertussis with Tdap is recommended for all personnel. Written documentation of vaccination or serologic evidence of immunity against varicella, measles, mumps, rubella, and HBV should be obtained for all health care workers. Annual screening to assess exposure to tuberculosis in health care workers is also indicated.

Persons with functional or anatomic asplenia are susceptible to infections with encapsulated organisms and therefore should be vaccinated against pneumococcus, *Haemophilus influenzae* type b, and meningococcus.

Smokers should receive a pneumococcal vaccination and annual influenza vaccination.

International travelers should be appropriately counseled and vaccinated to reduce risk of injury and illness (see MKSAP 17 Infectious Disease, Travel Medicine).

KEY POINTS

HVC • Annual vaccination against influenza and one-time vaccination against pertussis with the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine is recommended for all health care workers.

HVC • Smokers should receive pneumococcal vaccination and annual influenza vaccination.

Healthy Lifestyle Counseling

For adults, the five most common causes of death are heart disease, cancer, chronic lower respiratory diseases, stroke, and accidents. Healthy lifestyle counseling is aimed at preventing these most common causes of death.

Healthy lifestyle counseling for the prevention of cardiovascular and cerebrovascular diseases includes behavioral counseling to encourage healthful diet and exercise, stress reduction and management, and tobacco cessation. The risk of cancers that are associated with tobacco use (such as bladder, lung, and upper airway) can be reduced by encouraging patients to avoid tobacco, quit smoking, or avoid secondhand smoke. Smoking cessation is one of the most important interventions health care providers can encourage to help patients achieve improved short- and long-term health. Cancer prevention counseling may also include guidance on avoiding ultraviolet radiation exposure, appropriate sunscreen use, avoiding alcohol excess, choosing foods wisely, and achieving and maintaining an ideal body weight.

Healthy lifestyle counseling for the prevention of accidents includes counseling on routine seatbelt use, helmet use (for bicycles, motorcycles, and all-terrain vehicles), smoke detectors, weapon safety, and setting water heaters to lower than 49° C (120° F). Best practices to mitigate the risk of firearms in the home include storing firearms and ammunition separately in secure and locked safes, using trigger locks, and encouraging firearm owners to obtain expert training on their use and safety. In households with children, adolescents, persons with mental illness, and others at greater risk for firearm-related accidents, violence, or suicide, the physician may recommend that the patient consider not keeping firearms in the home.

Physicians should provide appropriate brief behavioral counseling to reduce alcohol misuse, including education on avoiding driving, swimming, operating machinery, or boating while using alcohol. Screening for domestic violence, especially in women of childbearing age, and home safety is also recommended. For the aging population, screening for polypharmacy, visual and hearing loss, and elder abuse may also be

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of value. For persons at risk for falls, exercise or physical therapy and vitamin D supplementation is recommended.

Behavioral Counseling

Behavioral counseling in the health care setting has long been recognized as an integral part of optimizing healthful lifestyle choices and habits. Although moderate- (31-360 minutes) and high-intensity interventions (>360 minutes) have shown better results than brief interventions (1-30 minutes), even 1- to 5-minute interventions have proved effective in curbing tobacco and alcohol misuse. The USPSTF recommends using the 5 A's for clinical counseling regarding tobacco use. With this behavioral framework, the physician Asks about tobacco use; Advises the patient to quit through clear, personalized messages; Assesses willingness to quit; Assists the patient to quit; and Arranges for follow-up and support.

Healthful dietary choices and regular physical activity have been strongly linked with decreased incidence of cardiovascular disease. However, the effect of behavioral counseling in promoting healthful diet and physical activity in adults without known cardiovascular disease, hypertension, hyperlipidemia, or diabetes is small. Moderate-intensity behavioral counseling has shown beneficial effects on intermediate outcomes (blood pressure and laboratory values) but not in patient-important outcomes (cardiovascular events or mortality).

Given small potential effect, time limitations, and opportunity costs, the USPSTF recommends offering dietary and exercise behavioral counseling based only on individual patient circumstances (grade C). Physicians may choose to selectively counsel patients, which may depend on the patients' level of readiness for change, how far they deviate from ideal health habits, and their risk for cardiovascular disease. Tools such as the ASCVD calculator (http://tools.cardiosource.org/ASCVD-Risk-Estimator/) can be used to stratify risk. For those who have hyperlipidemia or other known risk factors for cardiovascular disease, the USPSTF recommends intensive behavioral dietary counseling (grade B recommendation), which can be delivered by internists or by referral to specialists. Additionally, the 2013 joint guideline from the AHA, ACC, and The Obesity Society recommends advising overweight and obese individuals of the increased risk of cardiovascular disease, type 2 diabetes, and mortality with increasing BMI. Overweight and obese adults with cardiovascular disease risk factors should also be counseled that even 3% to 5% weight loss could yield clinically meaningful benefits.

Diet and Physical Activity

Most adults, particularly those with a BMI over 25, can benefit from improving dietary habits and increasing physical activity. The U.S. Department of Health and Human Services (USDHHS) and the AHA have similar recommendations on diet and physical activity. Both organizations recommend limiting the intake of red meat, sugary foods and beverages, saturated fats, sodium, and alcohol (no more than one drink per day for women and two drinks per day for men), while encouraging the intake of fruits, vegetables, whole grains, fiber, low-fat dairy products, poultry, fish, and nuts. The USDHHS and AHA also emphasize that the patient should know his or her daily caloric needs and should not eat more calories than can be expended on a daily basis. The AHA provides a calculator for daily calorie needs at www.myfatstranslator.com/. It is recommended that physical activity be performed for at least 150 minutes per week, usually 30 minutes a day; however, shorter intervals are also encouraged. Muscle-strengthening exercises should be performed at least twice per week.

KEY POINTS

- Moderate- (31-360 minutes) and high-intensity behavioral counseling (>360 minutes) have shown better results than brief behavioral counseling (1-30 minutes); however, even 1- to 5-minute counseling interventions have proved effective in reducing tobacco and alcohol misuse.
- Given small potential effect, time limitations, and opportunity costs, the U.S. Preventive Services Task Force recommends offering dietary and exercise behavioral counseling based only on individual patient circumstances (grade C). HVC
- The U.S. Preventive Services Task Force recommends intensive behavioral dietary counseling for persons who have hyperlipidemia or other known risk factors for cardiovascular disease.

Supplements and Herbal Therapies

The Dietary Supplement Health and Education Act of 1994 defines a dietary supplement as any product (other than tobacco) intended to supplement the diet. This broad definition includes products that contain amino acids, botanicals (including herbals), metabolites, vitamins, and minerals. All products marketed as dietary supplements must be clearly labeled as dietary supplements. Although manufacturers are not allowed to make specific medical claims, they can describe the product's effect on body structure or function. There is no requirement to demonstrate a supplement's efficacy or safety prior to market introduction. Additionally, in order for a supplement to be removed from the market, the FDA must demonstrate that it is unsafe. In contrast, over-the-counter and prescription medications must be proved safe by the manufacturer prior to being introduced on the market. Furthermore, there is not necessarily standardization between supplement preparations in purity, formulation, or dosage.

Recent estimates suggest that nearly half of all adults use dietary supplements for alleviation of chronic disease symptoms and health promotion. Despite widespread usage, patients frequently fail to report supplement use to their health care providers. Because the use of supplements can be associated with adverse effects and can also have interactions with other medications, it is essential that all providers attempt to elicit dietary supplement use in a nonjudgmental manner.

Vitamin supplementation (**Table 14**) is used to treat known deficiencies and to address dietary deficiencies such

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TABLE 14. Common Vitamin Supplements

Vitamin	Function	Sources	Deficiency	Toxicity
Water-Soluble Vitamins				
Vitamin B_1 (thiamine)	Cofactor for amino acid and carbohydrate metabolism	Cereals, rice, legumes, pork, yeast	Dry beriberi (peripheral neuropathy), wet beriberi (peripheral neuropathy and cardiomyopathy), Wernicke-Korsakoff syndrome	None
Vitamin B_2 (riboflavin)	Cofactor for multiple pathways, including energy production	Meats, fish, eggs, milk, green vegetables, yeast	Cheilitis, stomatitis, glossitis, pharyngitis	None
Vitamin B_3 (niacin)	Involved in synthesis of carbohydrates, fats, and proteins	Cereals, meats, legumes, seeds, yeast	Pellagra (hyperpigmented rash on sun-exposed skin, confusion, insomnia, vomiting, diarrhea)	Flushing, elevation of serum uric acid levels, nausea, vomiting, pruritus
Vitamin B_5 (pantothenic acid)	Active form is coenzyme A; involved in synthesis of vitamins A and D, cholesterol, steroids, fatty acids, amino acids, proteins, heme A	Broccoli, egg yolk, liver, milk	Anemia, paresthesias, intestinal distress	None
Vitamin B_6 (pyridoxine)	Amino acid metabolism, gluconeogenesis, immune function	Meats, whole grains, nuts, vegetables	Stomatitis, glossitis, cheilitis	Neuropathy, photosensitivity, dermatoses
Vitamin B_9 (folate)	Synthesizes, repairs, and methylates DNA; cofactor	Dark green leafy vegetables	Macrocytic anemia	None
Vitamin B_{12}	Involved in DNA synthesis and regulation; fatty acid and amino acid metabolism	Eggs, meat, milk	Peripheral neuropathy, macrocytic anemia	None
Vitamin C (ascorbic acid)	Antioxidant, cofactor	Citrus fruits, tomatoes, potatoes, broccoli, spinach	Scurvy (bleeding gums, petechiae, hyperkeratosis, arthralgia)	Abdominal bloating and diarrhea with large doses; large doses have not been shown to prevent illness
Biotin	Involved in carbohydrate and lipid metabolism	Egg yolk, liver, soybeans, yeast	Dermatitis, alopecia	None
Fat-Soluble Vitamins				
Vitamin A (retinoic acids)	β-carotene is precursor; vision	Liver, kidney, egg yolk, butter, green leafy vegetables, carrots, sweet potatoes	Xerophthalmia, night blindness (early), complete blindness	Teratogenic; acute toxicity (nausea, vomiting, vertigo, blurred vision); chronic toxicity (hepatotoxicity, visual impairment, ataxia)
Vitamin D	Bone and calcium/phosphorus metabolism	Fortified milk, fish, cod liver oil, eggs, fortified cereals	Hypocalcemia, hypophosphatemia, osteomalacia	Hypercalcemia
Vitamin E	Free radical scavenger	Eggs, meat, leafy vegetables, oil	Neuromuscular disorders, hemolysis	Increased all-cause mortality with ≥400 U/d, hemorrhagic strokes
Vitamin K	Coagulation	Green leafy vegetables	Easy bruising, mucosal bleeding, other bleeding	None

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as may occur in patients who follow a restricted diet (vegetarians or vegans). Supplementation in the absence of deficiency is employed by some individuals to prevent disease. Although many patients take multivitamins, evidence is lacking on the benefits of this practice. Additionally, in the Iowa Women's Health Study, use of multivitamins was associated with an increased risk of overall mortality compared with nonuse. The USPSTF recently concluded that there is insufficient evidence to recommend either for or against the use of vitamin A, vitamin C, folic acid, and antioxidant combinations in the prevention of cardiovascular disease and cancer, and the USPSTF recommends against the use of vitamin E and β-carotene for these purposes. The USPSTF also determined that there is insufficient evidence for calcium and vitamin D supplementation to prevent fractures, though the Institute of Medicine recommends intake of 1000 to 1200 mg of calcium daily and 600 to 800 U of vitamin D daily for adult men and women. The USPSTF does recommend that all women who are either planning to become pregnant or capable of becoming pregnant take 400 to 800 μg of folic acid on a daily basis. For patients with age-related macular degeneration, a multivitamin containing copper, zinc, β-carotene (or vitamin A), and vitamins C and E has been shown to slow progression. For smokers with age-related macular degeneration, health care providers should use an alternative formulation that does not contain β-carotene or vitamin A, as high doses have been shown to increase the risk of lung cancer in smokers.

Herbal (botanical) supplements refer to dietary supplements that are plant derived. Despite their long history of use, the efficacy of these substances has only recently been studied. Definitive evidence on the effectiveness of herbal supplements is still either lacking or conflicting. Additionally, many herbals can interact with both prescription and over-the-counter medications, leading to adverse effects and reduced medication efficacy. Some natural products can exert deleterious effects independent of interactions with medications. It is the responsibility of health care providers to be aware of the reasons for use and also of the potential harms (**Table 15**). The National Institute of Health's MedlinePlus directory of herbs and supplements (www.nlm.nih.gov/medlineplus/druginfo/herb_All.html) is a useful resource.

TABLE 15. Common Herbal Supplements

Name	Function	Adverse Effects	Drug Interactions	Effectiveness
Black cohosh	Treatment of menopausal hot flashes	Headaches, stomach discomfort	None	Does not appear to be more effective than placebo
Cranberry	Prevention of urinary tract infections	Heartburn (rare), increased glucose intake	None	Does not appear to be effective
Echinacea	Treatment and prevention of upper respiratory tract infections	Dyspepsia, diarrhea, unpleasant taste	None	Does not appear to be effective in prevention or treatment
Garlic	Reduction in serum cholesterol levels	Bad breath, heartburn, increased risk of bleeding	Isoniazid, saquinavir, nonnucleoside reverse transcriptase inhibitors, warfarin	Does not significantly lower cholesterol levels
Ginkgo biloba	Treatment and prevention of cognitive dysfunction, treatment of peripheral arterial disease	Allergic skin reactions, increased risk of bleeding and bruising	Alprazolam, buspirone, efavirenz, fluoxetine, warfarin	Data appear conflicting, of questionable benefit
Ginseng	Immune system enhancement, stress reduction, general health	Diarrhea, pruritus, insomnia, elevated blood pressure	Warfarin, monoamine oxidase inhibitors	May lower postmeal serum glucose levels and prevent viral upper respiratory tract infections
Milk thistle	Reduction in liver inflammation	Nausea, indigestion, diarrhea	May interact with medications metabolized by CYP2C9 and CYP3A4 enzymes	Does not appear to be effective
Red yeast rice	Treatment of hyperlipidemia	Myalgia, abnormal liver chemistry tests	May interact with medications metabolized by CYP3A4 enzymes	Appears to lower LDL and total cholesterol levels
Saw palmetto	Treatment of benign prostatic hyperplasia-related symptoms	Headache, nausea, dizziness	Oral contraceptives, hormone therapy	Does not appear to be more effective than placebo
St. John's wort	Treatment of depression	Insomnia, vivid dreams, anxiety, restlessness	Many interactions; do not use with antidepressants	Appears effective for mild to moderate depression

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Patient Safety and Quality Improvement

Introduction

Patient safety is defined conceptually as prevention of harm to patients, and patient safety practices are those that reduce the risk of adverse events related to exposure to medical care. The Institute of Medicine (IOM) considers patient safety to be indistinguishable from the delivery of high quality health care. However, the process by which patient safety is integrated into daily medical practice and systems of patient care is complex. Not only are individual clinicians required to engage in safe patient practices, but systems of care should ideally be built on a culture of safety, be structured to prevent errors, and be open to change based on errors that do occur.

Quality improvement (QI) consists of systematic and continuous actions that lead to measurable improvement in the quality and safety of patient care. Internists are increasingly becoming involved in QI efforts individually and as a part of interprofessional teams; therefore, it is important to understand QI methods and models of implementation. QI at the health care systems level involves efforts by an organization to understand its own care delivery mechanisms and make changes that lead to improvement in patient safety and the quality of services provided.

Although patient safety and quality are dependent both on the individuals providing care and the systems in which that care takes place, it is often helpful to consider potential issues arising at the direct patient care level and those at the health care systems level.

Direct Patient Care-Related Safety and Quality Issues

Diagnostic Errors

A diagnostic error (a missed, delayed, or incorrect diagnosis) may or may not result in harm to the patient. Despite the fact that diagnostic errors are less common than medication errors, there are twice as many tort claims for diagnostic errors.

Several types of diagnostic errors are common. Cognitive errors involve biases or failed heuristics (shortcuts in reasoning) during medical decision-making. Common examples of cognitive errors include premature closure, anchoring, triage cueing, confirmation bias, and gender bias. Premature closure is concluding the decision-making process before a diagnosis is fully confirmed (for example, when a patient with shortness of breath is diagnosed with a heart failure exacerbation without fully considering other causes such as asthma or pulmonary embolism). Anchoring involves locking into features of a patient's initial presentation despite new information. Triage cueing occurs when a patient's specialist selection or specialty team admission affects the workup and diagnosis (for example, when a patient with chest pain is admitted to a cardiology service and receives an extensive myocardial infarction workup rather than an evaluation for esophageal reflux). Confirmation bias is the tendency to look for evidence to confirm a suspected diagnosis rather than considering evidence to refute it. Gender bias is the incorrect belief that gender is a factor in the probability of a patient having a certain disease. Suggestions to help avoid diagnostic errors and other examples of heuristics are provided in **Table 16**.

Medication Errors

Between 500,000 and 1.5 million preventable adverse events from medication errors occur each year in the United States, with an estimated 1 medication error daily for each hospitalized patient. The IOM reports that medication errors cause 1 of 131 outpatient deaths and 1 of 854 inpatient deaths. A medication error has been defined as a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient. A medication error can result from prescribing faults of the physician (irrational, inappropriate, or ineffective prescribing; underprescribing; and overprescribing) or from prescription errors (incorrect recipient, drug, formulation, dose, route, timing, frequency, and duration of administration). Medication errors differ from adverse drug effects, which are defined as unintended or harmful reactions to a medication and can occur due to a medication being given appropriately or as a result of a medication error.

Medications with similar names or a low therapeutic index may be more likely to be associated with errors. Polypharmacy, advanced patient age, and kidney or hepatic impairment may also make medication errors more likely. The use of abbreviations and illegible handwriting are easily modifiable factors that can lead to medication errors. Other methods to prevent medication errors include improved drug labeling for sound-alike medications, computerized physician order entry (CPOE), medication reconciliation, and bar-code-assisted medication administration.

The Institute for Healthcare Improvement (IHI) has published several tools and how-to guides to decrease harms related to medications. The how-to guides describe key evidence-based care components to prevent adverse drug events and harms from high-alert medications and how to implement these interventions and gauge improvement (available at www.ihi.org). Additionally, the Institute for Safe Medication Practices has published a best practices statement on medication safety issues that cause fatal and harmful errors in patients (available at www.ismp.org/Tools/BestPractices/default.aspX).

Transitions of Care

Transitions between care settings (inpatient and outpatient) provide challenges to patient safety. At discharge, 28% of patients can state all of their medications, and 42% of patients can state their diagnoses, affecting their adherence to discharge instructions. Forty percent of discharged patients have pending laboratory or radiology results of which the ambulatory care physician is unaware, even though roughly 10% of the results are potentially actionable. One in five patients

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TABLE 16. Twelve Tips for Avoiding Diagnostic Errors

Technique	Comments
(1) Understand heuristics[a]	*Availability heuristic:* Diagnosing based upon what is most easily available in the physician's memory (e.g., because of a patient recently seen) rather than what is most probable
	Anchoring heuristic: Settling on a diagnosis early in the diagnostic process despite data that refute the diagnosis or support another diagnosis (premature closure)
	Representativeness heuristic: Application of pattern recognition (a patient's presentation fits a "typical" case; therefore, it must be that case)
(2) Utilize "diagnostic timeouts"	Taking time to periodically review a case based on data but without assuming that the diagnosis is that which was previously reached
(3) Practice "worst-case scenario medicine"	Consider the most life-threatening diagnoses first:
	• Lessens chance of missing these diagnoses
	• Does not mandate testing for them, however
(4) Use systematic approach to common problems	For example, anatomic approach to abdominal pain beginning from exterior to interior
(5) Ask why	For example, when a patient presents with diabetic ketoacidosis or a COPD exacerbation, ask what prompted this acute exacerbation of a chronic condition
(6) Utilize the clinical examination	Decreases reliance on a single test and decreases chance of premature closure
(7) Use Bayes theorem	Utilize pre- and posttest probabilities
	• Helps avert premature closure based on a single test result
(8) Acknowledge the effect of the patient	How does the patient make the physician feel?
	• Physicians may avoid making unfavorable diagnoses in patients with whom they identify
	• Physicians may discount important data in patients with whom they have difficult encounters
(9) Look for clinical findings that do not fit the diagnosis	Encourages a comprehensive approach and incorporates healthy skepticism
(10) Consider "zebras"	Resist temptation to lock onto common diagnoses at risk of missing the uncommon
(11) Slow down and reflect	Difficult to do in most health care systems, which stress the economy of "getting it right the first time"
(12) Admit mistakes	Awareness of one's own fallibility may lead to fewer diagnostic errors later

[a]Heuristics are shortcuts in reasoning used in discovery, learning, or problem solving.

Based on Trowbridge RL. Twelve tips for teaching avoidance of diagnostic errors. Med Teach. 2008 Jun;30(5):496-500. [PMID: 18576188]

CONT.

discharged from the hospital will experience an adverse event within 3 weeks of discharge.

To improve patient safety at transitions of care, hospital-to-primary provider communication at discharge, predischarge patient education, medication reconciliation, and timely post-hospitalization follow-up are all necessary. Discharge summaries are an important tool for the hospital provider to communicate with the primary provider. Components of a standardized discharge summary are provided in **Table 17**. Timely follow-up with a primary care physician after discharge is also important to prevent rehospitalization.

Medication reconciliation is the process of developing an accurate and comprehensive list of a patient's prescribed and nonprescribed medications and comparing the list to medication orders to rectify any discrepancies. Medication reconciliation is a dynamic process that needs to be completed frequently and at all transitions of care to prevent medication errors, including omissions, duplications, dosing errors, or drug interactions. Despite the recent focus on medication reconciliation, systematic reviews show mixed results on its ability to improve morbidity and mortality.

The IHI has published a how-to guide that summarizes strategies for transitioning patients from the hospital to the next setting of care, with the goal of reducing avoidable readmissions (available at www.ihi.org/resources/Pages/Tools/HowtoGuideImprovingTransitionstoReduceAvoidableRehospitalizations.aspx). H

KEY POINT

- Hospital-to-primary provider communication at discharge, predischarge patient education, medication reconciliation, and timely post-hospitalization follow-up are all necessary to improve patient safety during transitions of care. HVC

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TABLE 17. Suggested Content of a Standardized Discharge Summary

Dates of admission and discharge
Reason for hospitalization
Discharge diagnosis
Significant findings from admission workup:
• History and physical examination
• Laboratory studies
• Imaging studies
• Other tests
Procedures performed
Results of procedures and significant testing
Condition at discharge
Discharge medications and reasons for any changes from admission medications
Follow-up issues
Pending studies and laboratory tests
Counseling provided to patient and family
Follow-up appointments/plans

Systems Patient Care-Related Safety and Quality Issues

Quality Improvement Models

A number of quality improvement models are in use by health care systems; some of these models were developed by the manufacturing industry but are applicable to health care delivery systems. These models apply rigorous processes to identify, measure, and correct areas in need of improvement. The Model for Improvement, Lean, and Six Sigma quality improvement models are compared in **Table 18**.

Model for Improvement

The Model for Improvement involves defining the goal of the project (aim), measuring the baseline to see if interventions lead to improvement (measures), determining what changes can be made to improve quality (ideas), and implementing and testing the change in a process called a Plan-Do-Study-Act (PDSA) cycle (**Figure 4**). For example, the aim of a quality improvement project may be to improve the accuracy of medication lists in patients discharged from the hospital. After study, a quality improvement team may decide to implement

TABLE 18. Models for Quality Improvement

Approach	Goal	Methods	Sample Use
Model for Improvement	Achieve a measurable change in care delivery for a specific patient population	Aim statement, project charter, iterative experiments, PDSA cycle	Improve medication list accuracy at hospital discharge
Lean	Improve efficiency and eliminate waste in a process	Value stream mapping	Reduce patient waiting times
Six Sigma	Decrease variability and defects in a process	DMAIC, PDSA cycle	Decrease line-associated infections in an ICU

DMAIC = Define, Measure, Analyze, Improve, Control; PDSA = Plan, Do, Study, Act.

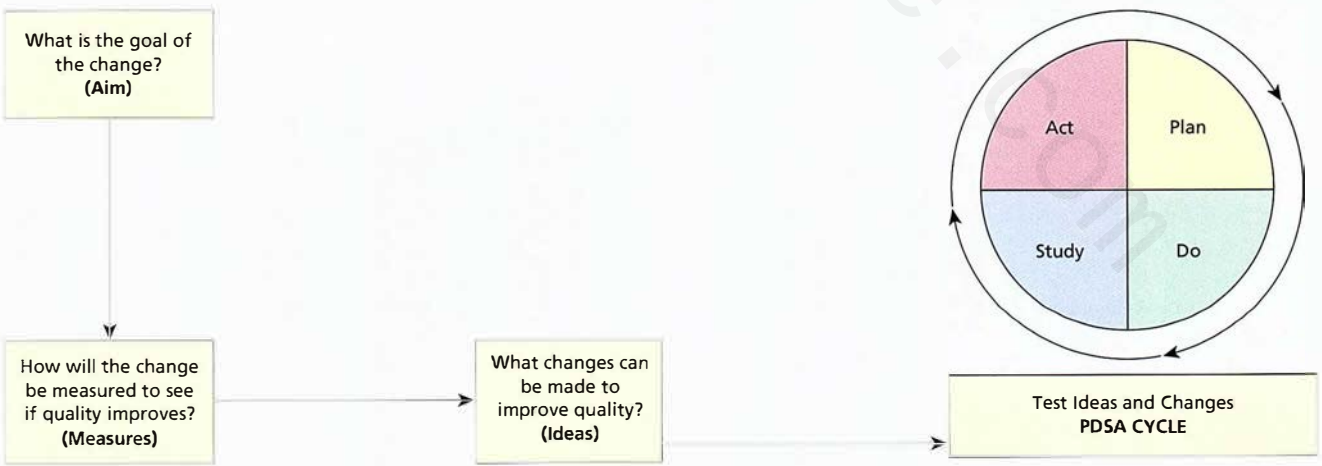

FIGURE 4. Plan-Do-Study-Act (PDSA) Model for Improvement.

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an intervention whereby a pharmacist will review the list of medications with the patient prior to discharge. A PDSA cycle could be done for a short period to test if the intervention was successful. If problems were encountered, changes in the intervention could be made and additional PDSA cycles completed until the desired improvements were reached. PDSA cycles are rapid tests of change.

Lean

The Lean model, developed by the Toyota Corporation, focuses on closely examining a system's processes and eliminating non-value-added activities, or waste, within that system. Using a tool called value stream mapping that graphically displays the steps of a process (and the time required for each step) from beginning to end, inefficient areas (waste) in a process can be identified and addressed. Lean also uses a 5S strategy (Sort, Shine, Straighten, Systemize, and Sustain). Lean relies on establishing a culture of continuous improvement, in which processes are constantly being refined. Although cost effectiveness is not the focus of the Lean model, cost savings are realized when all process steps add value and waste is eliminated. In the context of health care, the most common type of waste for patients is waiting time; Lean methods could be useful is reducing patient waiting times for various services.

Six Sigma

Six Sigma is a quality improvement model developed by the Motorola Corporation. The name Six Sigma is derived from measures used in industrial manufacturing to indicate the percentage of defect-free products that are created; a Six Sigma measure indicates almost perfect production quality. There are several Six Sigma methodologies, with a stepwise process called DMAIC used primarily to attempt to improve existing processes. DMAIC represents five separate steps: Define, Measure, Analyze, Improve, and Control. The define phase involves developing the aims of the project. In the measure phase, baseline data on the number and types of defects within the system are collected. The analyze step uses the data collected to determine the magnitude of the defects. In the fourth step, solutions are implemented to improve the process. Finally, the control phase works to sustain the gains and disseminate the improvements to other areas. Overall, the goal of Six Sigma is to reduce cost, variation, or defects within a process to make the process more effective. An example of a problem in health care where Six Sigma methods could be employed is a project focusing on decreasing line-associated infections in an ICU. In this case, the defect is the infection, and the goal would be to implement changes so that no future infections were encountered.

Additional Quality Improvement Tools

Several additional methods exist that are helpful in analyzing health care systems for quality improvement. Root cause analysis is a method used to discover the factors that contributed to an error and involves talking to all stakeholders involved in the error. A technique used in root cause analysis is the Five Whys, which involves asking the question "Why?" successively to drill down to the real root of a problem. To organize the root causes, a cause-and-effect diagram (also known as a fishbone diagram or Ishikawa diagram) can be used. The problem, or error, forms the backbone of the diagram and root causes are branched off like ribs. As an example, a quality team may complete a root cause analysis to determine why routine immunizations are not being given in the outpatient setting. After interviewing the physicians, nurses, desk staff, and patients, potential root causes identified might include physician failure to recognize immunization needs or failure to offer immunizations, patient refusal due to lack of insurance coverage or lack of appropriate informed consent, lack of immediate nursing availability, or lack of available immunization supplies.

Another commonly used quality improvement tool is the control chart. Control charts are used to graphically display variation in a process over time and can help determine if variation is from a predictable or unpredictable cause. Additionally, control charts can be used to determine if an intervention has had a positive change. For example, the rate of medication errors could be tracked before and after the initiation of a CPOE system to determine if it has had an impact on reducing errors. H

KEY POINTS

- The Model for Improvement involves defining the goal of the project (aim), measuring the baseline to see if interventions lead to improvement (measures), determining what changes can be made to improve quality (ideas), and implementing and testing the change in a process called a Plan-Do-Study-Act cycle. HVC
- The Lean model focuses on closely examining a system's processes and eliminating non-value-added activities, or waste, within that system. HVC
- The Six Sigma model has an emphasis on reducing cost, variation, or defects within a process to make the process more effective. HVC

Measurement of Quality Improvement H

The measurement of quality improvement is a focus of the Joint Commission, and since 2004, the Joint Commission has required collection of data on core measure sets, such as myocardial infarction, heart failure, pneumonia, and pregnancy. Additionally, the Centers for Medicare and Medicaid have implemented a policy of "meaningful use." Meaningful use is the use of electronic health record (EHR) technology to improve quality, safety, and efficiency, and reduce health disparities; engage patients and family members; improve care coordination; and maintain privacy and security of patient

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health information. The intended outcomes for meaningful use compliance are better clinical and population health outcomes, increased efficiency, empowered patients, and more robust research data on health outcomes. The meaningful use program is to be implemented in three stages from 2011 to 2016. Eligible professionals and hospitals must achieve specific objectives to qualify for reimbursement and incentive programs; financial penalties took effect in 2015 for providers who did not transition to EHR technology.

Patient-Centered Medical Home

The patient-centered medical home (PCMH) is a health care model in which a patient's comprehensive care is coordinated by a primary provider in a team-based medical practice (**Table 19**). The goal of the PCMH is to improve quality of care, access to services, cost effectiveness, and patient understanding. Studies are ongoing to measure the effectiveness of the PCMH, and the quality core measures have been recommended to ensure standardized and effective care. Programs are also being developed that offer financial incentives to health care providers if they implement the PCMH and meet specific quality measures.

Health Information Technology and Patient Safety

Health information technology has been used as a tool to mitigate medical errors. Three such forms of technology are CPOE, the EHR, and clinical decision support.

CPOE is a system in which the health care provider directly enters patient orders, such as orders for medications or laboratory tests, into a computer interface. The goals of CPOE are to reduce errors due to illegible handwriting, to eliminate confusing abbreviations, and improve order timeliness. Additionally, CPOE systems can use protocols or order sets to standardize care, create one place for medication lists, and employ drug-drug interaction software to reduce medication errors.

An EHR is a collection of all clinical data on a patient in an electronic format. An advantage of an EHR is that it serves as a central repository for patient information for multiple users, including the primary physician, specialists, and nurses. EHRs can also allow for systematic review of indicators, such as preventive service compliance, for a population of patients.

Clinical decision support (CDS) systems use technology to supplement a provider's clinical reasoning, allowing the provider to make an informed decision quickly. The systems are designed to provide relevant and filtered information specific to the patient at an appropriate time. A CDS system may display clinical guidelines and references, provide diagnostic support, house documentation templates, and issue medication interaction warnings. CDS technology can be integrated with CPOE and EHR systems to enhance care delivery.

Health information technology is not without limitations. Systems can be expensive to implement and maintain, and the potential for error is not eliminated with their use. For example, using a CPOE system, a physician may still enter prescriptions for the wrong patient.

National Patient Safety Goals

Since 2002, the Joint Commission has established annual National Patient Safety Goals (NPSGs) to address emerging patient safety issues (www.jointcommission.org/standards_information/npsgs.aspx). The NPSGs apply to multiple patient care settings, including hospitals, ambulatory clinics, behavioral health care centers, nursing care centers, and office-based surgery clinics. Objectives and metrics provided for each NPSG guide the implementation of the goal. For example, a new hospital NPSG introduced in 2014 focuses on clinical alarm systems, which can compromise patient safety if not managed

TABLE 19. Five Functions and Attributes of the Patient-Centered Medical Home

Comprehensive care	Meets the majority of each patient's physical and mental health care needs, including prevention and wellness, acute care, and chronic care, with a team that may include physicians, advanced practice nurses, physician assistants, nurses, pharmacists, nutritionists, social workers, educators, and care coordinators
Patient-centered	Provides primary health care that is relationship-based with an orientation toward the whole person; ensures that patients are fully informed partners in establishing care plans
Coordinated care	Coordinates care across all elements of the broader health care system, including specialty care, hospitals, home health care, and community services; builds clear and open communication among patients and families, the medical home, and members of the broader care team
Accessible services	Delivers accessible services with shorter waiting times for urgent needs, enhanced in-person hours, around-the-clock telephone or electronic access to a member of the care team, and alternative methods of communication such as e-mail and telephone care
Quality and safety	Demonstrates a commitment to quality and quality improvement by ongoing engagement in activities, such as using evidence-based medicine and clinical decision-support tools to guide shared decision-making with patients and families, engaging in performance measurement and improvement, measuring and responding to patient experiences and patient satisfaction, and practicing population health management

Adapted from U.S. Department of Health and Human Services. Defining the PCMH. Agency for Healthcare Research and Quality Web site. http://pcmh.ahrq.gov/page/defining-pcmh. Accessed May 20, 2015.

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properly. With a multi-phase implementation in 2014 and 2016, this NPSG has an initial performance metric of identifying the critical alarm systems to manage based on staff input, risk to patient if alarm is unanswered, alarm necessity, and published guidelines. These safety goals can provide a framework for interprofessional collaboration to achieve quality and safety in health care.

Professionalism and Ethics

Professionalism

A profession is a calling that requires mastery and continuous maintenance of a specialized body of knowledge and skills, commitment to a code of ethics, and self-regulation of its responsibilities to society. Adherence to the principles, responsibilities, and behaviors that characterize a profession constitute professionalism. In exchange for the authority to maintain its unique autonomous role in society, the medical profession must ensure that its members maintain clinical competence and adhere to professional responsibilities and the principles of medical ethics.

The Physician Charter on Medical Professionalism developed by the American Board of Internal Medicine Foundation, the American College of Physicians Foundation, and the European Federation of Internal Medicine focuses on three fundamental principles and ten professional commitments that characterize medical professionalism (**Table 20**). The three fundamental principles in the Charter include primacy of patient welfare, patient autonomy, and social justice. These

TABLE 20. Principles and Commitments of Professionalism

Principle or Commitment	Comment
Fundamental Principle	
Primacy of patient welfare	Altruism is a central trust factor in the physician-patient relationship. Market forces, societal pressures, and administrative exigencies must not compromise this principle.
Patient autonomy	Patients' decisions about their care must be paramount, as long as those decisions are in keeping with ethical practice and do not lead to demands for inappropriate care.
Social justice	Physicians should work actively to eliminate discrimination in health care, whether based on race, gender, socioeconomic status, ethnicity, religion, or any other social category.
Professional Commitment	
Competence	Physicians must be committed to lifelong learning and to maintaining the medical knowledge and clinical and team skills necessary for the provision of quality care.
Honesty with patients	Obtain informed consent for treatment or research. Report and analyze medical errors in order to maintain trust, improve care, and provide appropriate compensation to injured parties.
Patient confidentiality	Privacy of information is essential to patient trust and even more pressing with electronic health records.
Appropriate patient relations	Given the inherent vulnerability and dependency of patients, physicians should never exploit patients for any sexual advantage, personal financial gain, or other private purpose.
Improve quality of care	Work collaboratively with other professionals to reduce medical errors, increase patient safety, minimize overuse of health care resources, and optimize the outcomes of care.
Improve access to care	Work to eliminate barriers to access based on education, laws, finances, geography, and social discrimination. Equity requires the promotion of public health and preventive medicine, as well as public advocacy, without concern for the self-interest of the physician or the profession.
Just distribution of resources	Work with other physicians, hospitals, and payers to develop guidelines for cost-effective care. Providing unnecessary services not only exposes one's patients to avoidable harm and expense but also diminishes the resources available for others.
Scientific knowledge	Uphold scientific standards, promote research, create new knowledge, and ensure its appropriate use.
Manage conflicts of interest	Medical professionals and their organizations have many opportunities to compromise their professional responsibilities by pursuing private gain or personal advantage. Such compromises are especially threatening with for-profit industries, including medical equipment manufacturers, insurance companies, and pharmaceutical firms. Physicians have an obligation to recognize, disclose to the general public, and deal with conflicts of interest that arise.
Professional responsibilities	Undergo self-assessment and external scrutiny of all aspects of one's performance. Participate in the processes of self-regulation, including remediation and discipline of members who have failed to meet professional standards.

Adapted with permission from ABIM Foundation. American Board of Internal Medicine; ACP-ASIM Foundation. American College of Physicians-American Society of Internal Medicine; European Federation of Internal Medicine. Medical professionalism in the new millennium: a physician charter. Ann Intern Med. 2002 Feb 5;136(3):243-6. [PMID: 11827500] Copyrigt 2002, American College of Physicians.

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principles embody four basic concepts of medical ethics: beneficence (duty to promote patients' welfare and the health of society), nonmaleficence (duty to avoid harming patients), patient autonomy (duty to respect patients' values, goals, and preferences), and justice (duty to treat patients fairly).

In addition to guiding the patient-physician relationship, professionalism encompasses a wide range of additional responsibilities, including self-assessment and maintaining the highest possible degree of clinical competency, the use of the best available evidence in making diagnostic and treatment decisions, maintaining collaborative relationships with trainees and other health care workers, and participation in activities that seek to advance the public good.

In clinical practice, the principles expressed in the Charter may sometimes be at odds with each other, such as when a physician's desire to promote a patient's welfare conflicts with the patient's health care values, goals, and preferences. Clinical ethics is the identification, analysis, and manner of resolution of these conflicts as they occur.

Primacy of Patient Welfare

Maximizing patient welfare is the primary aim of medicine. There is an expectation that the physician will act on behalf of a patient's best interests (beneficence) while attempting to prevent or minimize harms (nonmaleficence). Patients inherently are vulnerable and dependent due to illness or lack of medical knowledge; they may also have poor health literacy, strained social circumstances, and lack financial and other supportive resources. Therefore, patients must trust that physicians are acting in their best interests and protecting them from harm; in many instances, the physician may effectively be a patient's sole advocate. The ten professional commitments in the Charter are the means by which physicians maximize patient welfare.

Appropriate Physician-Patient Relationships

Patient welfare should be promoted regardless of patient characteristics (age, sex, religion, decision-making capacity, insurance status) or health care setting. Once a physician-patient relationship has been established, the physician has made a commitment to care for the patient regardless of these factors.

Accordingly, the imbalance of power between the physician and the patient should not be exploited to serve the interests of the physician or anyone else (for example, researchers). It is unethical for physicians to become sexually involved with current patients or former patients because vulnerability and transference issues may persist after the professional relationship has ended.

Physicians should maintain appropriate boundaries during the medical history, physical examination, and other health care activities. To avoid patient misperceptions, physicians should describe what they are doing during examinations (for example, "I am going to lift your left breast in order to examine your heart."). At times, a chaperone should be offered (for example, during gynecologic examinations).

Under most circumstances, physicians should avoid caring for family members and close friends. In these situations, the physician's objectivity may be compromised, and patients may receive inferior care, undergo inadequate or inappropriate assessment, or not receive counseling on sensitive issues. Medical records also may not be updated properly.

Online communication and social media can bring substantial benefits to patients and physicians (for example, education and community building); however, they also pose ethical challenges. The American College of Physicians and the Federation of State Medical Boards recently released a policy statement regarding online professionalism. First, online communication with patients should be held to the same standards as in-person contact. Second, online media can blur professional and social boundaries between physicians and patients. Physicians should keep their social and professional online presences separate and conduct themselves professionally in both spheres. Physicians should never post content that might impair relationships with patients or erode public trust in the profession. Online postings are often permanent. Finally, electronic communication should be used only for established physician-patient relationships and with patients' consent. Such communications should be secure and documented in the patients' records.

Challenging Physician-Patient Relationships

Relationships with patients can be challenging or "difficult" for physicians at times. For instance, a patient may reject a physician's recommendations. Under these circumstances, the physician should seek to understand the patient's reasons for the rejection (for example, cultural or religious reasons) and to formulate a mutually agreeable plan. If the patient agrees to, but is nonadherent with, the physician's recommendations, the physician should discern the reasons for the patient's behavior (for example, low health literacy, chaotic home environment, poor transportation, lack of insurance) and address the reasons, if possible, with the assistance of a public health nurse or case worker, social worker, or other professional colleague.

The physician is not obliged to carry out a patient's request for an intervention or treatment that violates the physician's personal values and conscience, standards of medical care and ethical practice, or the law. Again, the physician should attempt to understand the patient's request and seek a mutually agreeable plan. If the matter cannot be resolved, the physician and patient should discuss the option of transferring care of the patient to another physician.

Similarly, circumstances may develop in which there is a lack of trust between the patient and physician, the relationship has become nontherapeutic, and the physician no longer believes he or she can continue to care for the patient. Under these circumstances, physicians may pursue termination of the physician-patient relationship as long as the patient's health is not jeopardized and care can be provided by an

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alternative provider. The alternative provider must agree to the transfer of care, and the physician should notify the patient in writing of the termination and transfer of care. Physicians should not abandon patients; abandonment is unethical and can be cause for legal action.

Conflicts of Interest

Conflicts of interest, either real or perceived, have the potential to disrupt the trust relationship between the patient, public, and physician. The possibility that medical decisions may be influenced or based on factors other than the patient's best interests may be damaging to the process of providing medical care. Activities that may be viewed as potential conflicts of interest, such as accepting drug samples or gifts or participating in consulting agreements, should be avoided. The Institute of Medicine provides recommendations for controlling conflicts of interest (**Table 21**). In the United States, the Physician Payments Sunshine Act requires pharmaceutical and device companies that participate in federal health care programs to report payments and gifts to physicians and teaching hospitals. H

KEY POINT

- Physicians may pursue termination of the physician-patient relationship as long as the patient's health is not jeopardized and care can be provided by an alternative provider; however, abandonment is unethical and can be cause for legal action.

Respecting Patient Autonomy

Confidentiality

The principle of patient autonomy requires that physicians maintain patient confidentiality. For a patient to be autonomous, the patient must have control of his or her personal information. Also, maintaining confidentiality is necessary for the proper assessment and treatment of the patient; the patient must trust that his or her personal and medical information will be kept confidential. Release of such information should be done only with the explicit permission of the patient.

Circumstances exist, however, when physicians may be obliged to breach patient confidentiality. Depending on the jurisdiction, physicians may be required to report suspected child abuse, infectious diseases, patients who are a threat to themselves or others, and patients who are hazardous drivers (for example, those with dementia). In these cases, the physician's duty to protect the public's health overrides the duty to maintain patient confidentiality.

Online communication and social media pose substantial challenges to patient confidentiality. Physicians should ensure that electronic communications with patients have adequate security precautions. Physicians should not disseminate patient information using social media.

Another unique challenge to patient confidentiality is genetic testing. If genetic testing is performed, the patient should be informed of the implications of a "positive" test result—not only for the patient, but also for the patient's family. The physician and patient should agree on a plan for disclosing genetic test results to potentially affected family members. Inappropriate disclosure of genetic test results can negatively affect patients and their family members (for example, in regard to insurability and employment). For more information on genetic testing, refer to Routine Care of the Healthy Patient.

TABLE 21. A Selection of Institute of Medicine Recommendations for Individual Physicians to Control Conflicts of Interest

Forego all gifts or items of material value from pharmaceutical, medical device, and biotechnology companies, accepting only payment at fair market value for a legitimate service in specified situations.
Do not make educational presentations or publish scientific articles that are controlled by industry or contain substantial portions written by someone who is not identified as an author or who is not properly acknowledged.
Do not meet with pharmaceutical and medical device sales representatives except by documented appointment and at the physician's express invitation.
Do not accept drug samples except in certain situations for patients who lack financial access to medications.
Until institutions change their policies, physicians and trainees should voluntarily adopt these recommendations as standards for their own conduct.

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Informed Consent

Informed consent includes a discussion of the information that a reasonable patient would want to know about his or her illness (proposed diagnostic and treatment plans, the risks and benefits of the proposed plans, and any alternatives), an assessment of patient understanding, and the acceptance or refusal of the treatment. The patient must have decision-making capacity and make each decision of his or her own free will for consent to be considered valid. Importantly, obtaining a signed consent form is not equivalent to obtaining informed consent; physicians should engage patients in meaningful conversations about their diagnoses and treatment options and document these conversations.

Decision-Making Capacity

Competence is a determination made by the legal system, whereas physicians determine decision-making capacity in the clinical setting. The essential elements of decision-making capacity are an understanding of the risks and benefits of the proposed intervention and the ability to communicate a decision. A diagnosis of dementia or mental illness does not signify that the patient is incapable of making decisions; the physician should ensure such decisions are consistent with the patient's health care values, goals, and preferences. A patient's

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decision-making capacity should be questioned if the patient does not understand the situation; the patient does not understand the risks, benefits, and alternatives to the decision to be made; or the patient's decision is inconsistent with his or her previously expressed values, goals, and preferences.

A patient with decision-making capacity has the right to refuse a proposed diagnostic or therapeutic intervention, including those that prolong life. Although the physician may regard a given refusal as the wrong decision, the physician must recognize that the refusal is not necessarily irrational. In these instances, the physician should not abandon the patient and should determine the patient's rationale for the refusal (and whether it is informed) and correct misinformation if necessary. If the patient's refusal remains steadfast, the physician should respect the patient's decision and work with the patient to formulate an alternative diagnostic or therapeutic plan.

Advance Care Planning

Advance care planning is a process in which the patient articulates and documents his or her values, goals, and preferences for future health care. Advance care planning includes completion of an advance directive, which contains written instructions for health care that are used in the event that the patient loses decision-making capacity.

Advance directives include the living will and the durable health care power of attorney (or health care proxy). In a living will, the patient outlines preferences regarding specific treatments (for example, mechanical ventilation, hemodialysis, and artificial hydration and nutrition) and management preferences to direct care when he or she is no longer able to make medical decisions. The durable health care power of attorney designates a surrogate who will serve as the legal decision maker in the event the patient is no longer able to make health care decisions.

Ethically and legally, physicians and surrogates are required to adhere to the preferences expressed by patients in their advance directives (assuming that doing so is reasonable and legal). However, in the United States, laws governing advance directives vary by state; an advance directive executed in one state may not fulfill the legal requirements of another state. Physicians should be familiar with these requirements in their jurisdictions.

Unfortunately, only about 20% of U.S. adults have advance directives. Patients, especially those with chronic illnesses and limited longevity, should be encouraged to engage in advance care planning.

Surrogate Decision-Making

For the patient who lacks decision-making capacity, a surrogate must make decisions. If the patient has an advance directive, the person named in that advance directive is the most appropriate (and legal) surrogate. This choice is protected by U.S. federal law and must be respected. If the patient's advance directive does not name a surrogate, or the patient does not have an advance directive, the best surrogate is the person who best knows the patient's health care preferences. This person may not be the next of kin or a family member. Many U.S. states stipulate a hierarchy of surrogate decision-makers in the absence of an advance directive (for example, spouse, followed by adult child). In states that do not stipulate a hierarchy, the surrogate is identified by the patient's loved ones and care team.

Respect for patient autonomy requires that the surrogate adhere to instructions in the patient's advance directive. If the patient does not have an advance directive, the surrogate should make decisions based on substituted judgment (decisions the patient would make if capable). The physician can facilitate the surrogate's substituted judgment with the following question, "If [your loved one] could wake up for 15 minutes and understand his or her condition fully, and then had to return to it, what would he or she tell you to do?" If the surrogate is unable to answer this question or does not know the patient's values, the surrogate should make decisions in the best interest of the patient.

Withholding or Withdrawing Treatment

Patients have the right to refuse or request the withdrawal of any treatment, even those that are life prolonging. In these circumstances, the physician's duty is to understand the reasons for the request and to ensure that the request is informed. If a physician begins or continues a treatment that a patient has refused, the physician, regardless of his or her intent, is committing battery. Notably, patients who lack decision-making capacity also have the right to refuse or request the withdrawal of treatments through advance care planning and surrogate decision makers.

Carrying out a request to withhold or withdraw a life-prolonging treatment is not equivalent to physician-assisted death. The intent of carrying out a request to withhold or withdraw a life-prolonging treatment is to allow for a natural death and to free the patient from the burdens of treatment that he or she perceives as outweighing the benefits. After carrying out such a request, the cause of death is the underlying disease.

Depending on the circumstances, a physician may conscientiously object to a patient's request to withhold or withdraw life-prolonging treatments. In this situation, the physician should arrange for transferring the patient's care to another physician if carrying out the request would violate the physician's conscience.

Physician-Assisted Death

In contrast to carrying out a request to withhold or withdraw a life-prolonging treatment, the intent of physician-assisted death is termination of the patient's life. In physician-assisted suicide, death occurs when the physician provides a means for the patient to terminate his or her life (lethal prescription). In euthanasia, the physician directly terminates the patient's life (for example, by lethal injection). In both

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physician-assisted suicide and euthanasia, a new pathology is introduced, which is the cause of death. In the United States, physician-assisted death, in the form of lethal prescriptions but not euthanasia, is legal in only a few states. The American College of Physicians does not support the legalization of physician-assisted death, as it may damage the trust established between physician and patient and divert attention from end-of-life care reform.

In caring for patients at the end of life, there may be circumstances in which an intervention may hasten death (for example, intravenous narcotic analgesics). Using such interventions is ethical if doing so satisfies the doctrine of *double effect*: (1) the action itself is good or indifferent (for example, pain control); (2) the good effect (pain control), not the bad effect (death), is intended; (3) the good effect is not achieved by means of the bad effect; and (4) there is a proportionally serious reason (refractory pain due to widely metastatic cancer) for risking the bad effect.

Requests for Interventions

Physicians often encounter patients or surrogates who request specific tests and treatments. However, physicians are not obliged to grant requests for ineffective tests and treatments (for example, antibiotics for viral infection). Physicians should advise patients that using an ineffective intervention does not promote patient well-being, may cause harm, and violates the profession's commitment to stewardship of health care resources.

Patients may also request tests and treatments of questionable efficacy (certain complementary medicine practices) that support uncontroversial ends (improved health and well-being). In these situations, the physician should discern the patient's reasons for the request; inform the patient of the risks, benefits, and alternatives to the requested intervention; and formulate a mutually agreeable care plan. There are instances in which patients and surrogates request tests and treatments that are effective but support controversial ends, which may be best illustrated by requests to sustain the critically ill patient with technologically advanced treatments (mechanical ventilation, hemodialysis, mechanical circulatory support). Such requests reflect a gap between a patient's (or a surrogate's) values and the physician's values regarding goals of care. For example, a physician may regard life-sustaining interventions in the patient in a persistent vegetative state as futile, as the interventions will not restore the patient to health. However, the interventions may be fulfilling what the family desires—keeping the patient alive. For situations in which the physician and patient (or surrogate) cannot agree on how to move forward, a multidisciplinary care conference, consultation with an experienced colleague, and ethics consultation can be helpful. Sometimes, transferring the care of the patient to a colleague who is willing to work with and accommodate the patient's (or surrogate's) preferences resolves the matter. Rarely, resorting to court intervention is necessary. H

KEY POINTS

- Physicians may be required to breach patient confidentiality to report suspected child abuse, infectious diseases, patients who are a threat to themselves or others, and patients who are hazardous drivers.
- Informed consent includes a discussion of the information that a reasonable patient would want to know about his or her illness, an assessment of patient understanding, and the voluntary acceptance or refusal of the intervention.
- Patients have the right to refuse or request the withdrawal of any treatment, even those that prolong life.
- Physicians are not ethically obliged to grant patient requests for ineffective tests and treatments; they should advise patients that using an ineffective intervention does not promote patient well-being, may cause harm, and violates the profession's commitment to stewardship of health care resources. HVC

Justice

H

Justice requires that physicians treat patients fairly and that all health care decisions be based on medical need. Unfortunately, evidence suggests that there are disparities in the allocation of health care resources related to sex, race, and socioeconomic status. Physicians should work to eliminate these allocation inequalities and to reduce barriers to care.

Medical Error Disclosure

Medical errors are unintended acts or omissions that harm or have the potential to harm the patient. Research has shown that patients want to be apprised of all medical errors regardless of whether there was an adverse outcome, and the ethics principles of beneficence, patient autonomy, and justice obligate physicians to disclose these errors. A medical error does not necessarily constitute negligent behavior; however, failure to disclose an error may.

Error disclosure has a number of potential benefits. For patients, disclosing errors optimizes informed decision-making and promotes trust. For physicians, disclosing errors may reduce stress and risk for litigation. Although physicians may feel uneasy in disclosing errors to patients, the following approach can mitigate this burden. First, disclosure should be done in private with the patient's loved ones and essential health care team members present. Interruptions should be minimized. Before disclosing the error, the physician should determine the patient's knowledge of the problem and then correct any misinformation. When disclosing the error, the physician should speak clearly (without jargon) and check for comprehension. After disclosing the error, the physician should apologize and advise the patient how the physician and institution will act to prevent similar errors; the physician should not blame others for the error. The physician should

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CONT. also empathetically acknowledge the patient's emotional responses to the disclosure. Finally, the physician should formulate a patient-centered follow-up plan and document the discussion.

KEY POINT

- Patients want to be apprised of all medical errors regardless of whether there was an adverse outcome; doing so optimizes informed decision-making, promotes trust, and may reduce stress and risk for litigation.

Colleague Responsibility

Physicians have a shared responsibility with other health care professionals in maintaining competence, reducing medical errors, increasing patient safety, minimizing overuse of health care resources, and optimizing outcomes. Physicians should "speak up" about impaired and disruptive colleagues; such colleagues should be confronted directly or reported to appropriate authorities. Physicians should strive to promote a culture of speaking up, and institutions should encourage speaking up and provide relevant training if necessary. In addition to providing direct feedback (confronting an impaired colleague), other means should be available for speaking up (division or department chair, anonymous hotline, quality committee). Institutions should have nonretaliation policies in place for those who make a report. Physicians should also report practices and systems issues that result in suboptimal outcomes and compromise patient safety and quality of care.

Approaching Ethical Dilemmas

When faced with a clinical ethical dilemma, the physician should approach the situation with a review of (1) the medical indications (the patient's medical problems, treatments, and treatment goals), (2) patient preferences (and identifying a surrogate if the patient lacks capacity to make decisions), (3) patient quality of life (including the prospects of restoring the patient—with or without treatment—to normal life, the deficits the patient will experience if treatment is successful, and the patient's and physician's definitions of quality of life), and (4) contextual features (financial, family, legal, religious, and other issues that might affect decision-making). This approach allows for discernment and analysis of the ethically relevant information and usually defines the ethical dilemma. In so doing, it also often suggests a solution to the dilemma.

Nevertheless, physicians may encounter ethical dilemmas that are difficult to resolve. In these situations, ethics consultation should be obtained. The Joint Commission requires that health care institutions have established processes for addressing ethical concerns that arise in clinical practice.

Palliative Care

Introduction

Palliative medicine maximizes quality of life for patients with serious, life-limiting illness. Palliative medicine accomplishes this through meticulous symptom management—whether those symptoms are physical, emotional, spiritual, or social—and by aligning comprehensive care to meet the patients' goals as much as possible. All physicians practice some degree of palliative care; that is, all physicians provide basic symptom management, prognostication, and advance care planning. Although subspecialty palliative care consultation may be appropriate for patients with complex symptoms or fractious communication scenarios, all internists should possess selected palliative medicine skills. It is important to note that subspecialty palliative care consultation neither precludes nor replaces existing care providers; rather, subspecialty palliative care consultation provides an added layer of support, supplementing the care of existing providers rather than supplanting it.

Historically, palliative care was equated only with end-of-life care or hospice; however, palliative care may be accessed at any time during a patient's illness, from diagnosis to death. Palliative care may be provided concurrently with life-prolonging therapies or with therapies with curative intent. Hospice, on the other hand, is a specialized type of palliative care that is reserved for patients in the terminal phase of their disease, arbitrarily defined as the last 6 months of life (Table 22). Ideally, palliative care is initiated early and integrated throughout the disease trajectory. Evidence suggests that patients with metastatic non-small cell lung cancer who have palliative care consultation at the time of diagnosis have decreased depression and prolonged life by 2.7 months.

Any patient with a limited life expectancy who has significant symptom burden, who needs assistance determining goals of care or with medical decision-making, or who requires help with advance care planning is appropriate for palliative care. This includes not only those with advanced cancer but also critically ill patients in the ICU and patients with noncancer diagnoses.

TABLE 22. Comparison of Palliative Care and Hospice

Palliative Care	Hospice
Maximize quality of life through meticulous symptom management, clarification of goals of care, and advance care planning	
Can access at any point during life-limiting illness, from diagnosis to death	Can access during terminal phase of disease (life expectancy of less than 6 months)
Can occur concurrently with life-prolonging or curative treatments	Must forego life-prolonging treatments
No limitation on treatment or hospitalization	Goal of avoiding further hospitalization, unless there is no alternative to adequately manage symptoms

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KEY POINTS

HVC
- Palliative medicine maximizes quality of life for patients with serious illness through meticulous symptom management and by aligning comprehensive care to meet the patients' goals as much as possible.

HVC
- Palliative care may be provided concurrently with life-prolonging therapies or with therapies with curative intent; hospice is palliative care that is reserved for patients in the terminal phase of their disease.

Communication

Outstanding communication skills are necessary for all physicians, especially when negotiating the rocky course of advanced illness. Breaking bad news is particularly difficult for both the patient and provider. Most patients want to be told the truth, but many physicians fear that bad news will diminish patient hope or leave the patient emotionally inconsolable. In fact, physicians can convey bad news and still maintain patient hope. When bad news is communicated in a skillful and empathic manner, patient satisfaction increases, and depression and anxiety decrease.

One strategy for breaking bad news involves communication steps summarized by the SPIKES mnemonic (Setting, Perception, Invitation, Knowledge, Empathy, Strategize) (**Table 23**). Physicians can balance the medical facts and hope by being sensitive to what patients are ready to hear and how the information is affecting them (S, P, I, K, and E in SPIKES), and emphasizing what can be done (the last S in SPIKES). The key to maintaining hope is to compassionately support the patient through his or her grief and then to reorient the patient's goals toward those that are more achievable. Identifying what is most important to or most feared by the patient within this new medical reality helps to define what the patient hopes to achieve and what the patient hopes to avoid. New goals are set, and with new goals comes the hope to achieve them.

An important aspect of communication with patients is advance care planning, the process of elucidating the patient's future goals of care as disease progresses and identifying a surrogate decision maker. The outcomes of these discussions are recorded in an advance directive. See Professionalism and Ethics for a discussion of advance care planning and advance directives. H

KEY POINT

HVC
- When bad news is communicated in a skillful and empathic manner, patient satisfaction is increased, and depression and anxiety are decreased.

Symptom Management

H

Meticulous symptom control is one of the cornerstones of palliative medicine. The most common symptoms encountered in patients receiving palliative care include pain, dyspnea, nausea, depression, anorexia, and delirium.

Pain

Pain is common in patients with serious illness. Pain adversely affects functional status and quality of life, and unfortunately, it is often inadequately treated. Patients with serious illness should be routinely assessed for the presence of pain using a pain rating scale. Providers should remain vigilant in addressing emotional, social, and existential distress, which increase suffering related to pain.

TABLE 23. SPIKES Protocol for Breaking Bad News

	Step	Actions	Comments
S	Setting	Plan ahead and have the appropriate personnel and family members present. Anticipate and plan for possible patient reactions.	
P	Perception	Ask the patient what he or she has been told about the disease and/or the purpose of the meeting. Correct any misconceptions.	Gauge the patient's understanding of the situation. During this step, avoid the temptation to discuss the medical reality with the patient. Rather, let the patient tell you what he or she has heard.
I	Invitation	Find out how much the patient wants to know and how he or she would prefer to hear information.	If the patient does not want information, ask to whom you should speak on the patient's behalf.
K	Knowledge	Give the patient the news. Use short declarative sentences without jargon. Pause after giving the news to address any emotion.	Provide a "warning shot" that bad news is coming. Do not "sugarcoat" the truth. You cannot change bad news into good news. More words just create confusion.
E	Empathy	Use empathic statements to address emotion. Resist the temptation to rush in and "fix" the situation.	This is a critical step. Empathic statements demonstrate an understanding and continued commitment to the patient despite the bad news, letting the patient know that you are "in this together."
S	Strategize	Emphasize what can be done. Shift hope to achievable goals.	

Based on Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer. Oncologist. 2000;5(4):302-11. [PMID: 10964998]

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Pharmacologic management of pain progresses in a stepwise manner. The World Health Organization pain ladder has proved efficacious in managing pain (**Figure 5**). Mild pain is treated with nonopioid analgesics such as acetaminophen, NSAIDs, salicylates, or topical agents (lidocaine patches, topical NSAIDs). For moderate pain, a weak opioid such as hydrocodone is added. For severe pain, strong opioids such as morphine, oxycodone, hydromorphone, or fentanyl are used. Additionally, if indicated, adjuvants such as antidepressants or anticonvulsants can be added to the analgesic agents at any step. Dosing of various opioids is delineated in **Table 24**.

Certain opioids should be used with caution or avoided altogether. Fentanyl should only be used in opioid-tolerant patients. Transdermal fentanyl requires adequate subcutaneous fat stores for reliable absorption, and absorption rates are increased by temperature elevations, such as with fever or external heat sources, which can cause overdose. The use of buccal formulations of fentanyl can be especially complicated, as the different buccal formulations are not interchangeable; dosing regimen, escalation, and frequency of use differ between brands. Buccal formulations of fentanyl should only be initiated by experts. Codeine has relatively poor analgesic effect and significant side effects, and as a result, it is not routinely recommended. Meperidine is not recommended for pain due to the accumulation of metabolites with repeated doses, which increases the risk of seizure. Morphine, codeine, and meperidine are all contraindicated in patients with kidney failure (glomerular filtration rate <30 mL/min/1.73 m^2). Opioid partial agonists or agonist-antagonist medications, such as buprenorphine, nalbuphine, and butorphanol, have less incremental analgesic effect when used alone and are therefore used only under limited circumstances. Tramadol and tapentadol are complex drugs that have weak opioid activity and other pharmacologic effects, such as inhibition of serotonin or norepinephrine reuptake, that may result in significant drug interactions. Therefore, tramadol and tapentadol should be used with caution in chronically ill patients for long-term control of pain. Methadone is an excellent and inexpensive pain medication, but complex pharmacokinetics increase the risk for inadvertent overdose. Methadone should only be initiated and titrated by experts.

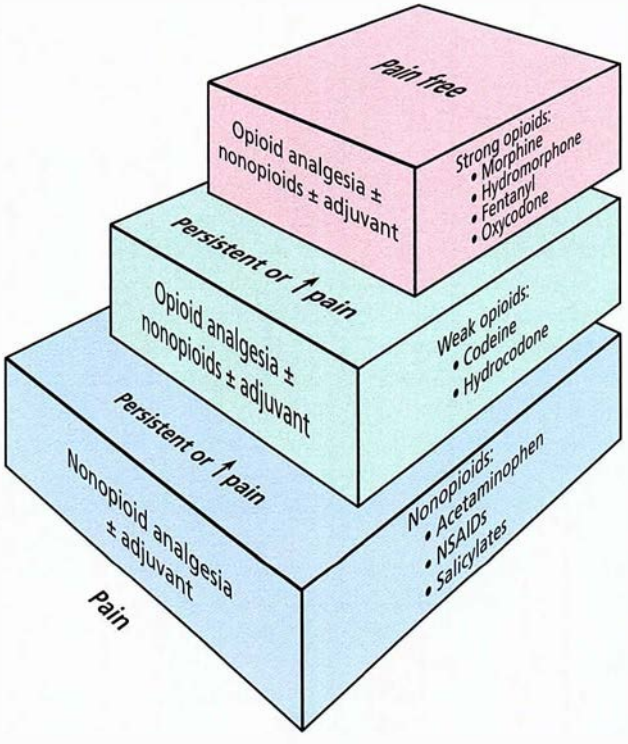

FIGURE 5. World Health Organization analgesic ladder.

In the administration of opioids, oral routes are preferred. Use of long-acting formulations is based on patient preference, as there is no evidence of improved pain control with long-acting formulations when compared with short-acting formulations. Intramuscular administration is discouraged because of the associated pain at the injection site. Subcutaneous administration is well tolerated and effective for patients unable to use an oral route. Continuous subcutaneous infusion may be used to achieve a steady state of analgesia in selected patients.

Opioid medications are accompanied by predictable side effects. Constipation is nearly universal, and tolerance to constipation does not develop over time. All patients on scheduled opioids should be on a scheduled stimulant laxative, such as senna or bisacodyl, in combination with docusate. These laxatives should be titrated to effect. If the maximal dose is still ineffective, osmotic laxatives, such as polyethylene glycol powder, sorbitol, or lactulose, can be added. When maximal laxative therapy has failed, methylnaltrexone can be considered. Methylnaltrexone, an injectable peripheral opioid antagonist that does not cross the blood-brain barrier, is very effective in treating opioid-induced constipation without adversely affecting analgesia. Bowel obstruction is an absolute contraindication to methylnaltrexone. Stool softeners are inadequate to manage opioid-induced constipation when given alone.

Nausea related to opioids is not uncommon. No one opioid is known to be less emetogenic than another. Opioid-induced nausea is usually transient, and tolerance generally develops over 2 to 7 days; therefore, opioids should not be switched too quickly in patients with opioid-induced nausea. Antidopaminergic agents, such as metoclopramide or prochlorperazine, are the preferred agents to treat opioid-induced nausea.

Adjunctive medications can be effective for specific pain syndromes. Neuropathic pain is characterized by burning, tingling, or lancinating pain. Tricyclic antidepressants (amitriptyline, nortriptyline), serotonin–norepinephrine reuptake inhibitors (venlafaxine, duloxetine), and antiepileptic medications (gabapentin, pregabalin, carbamazepine) have been shown to be beneficial in neuropathic pain syndromes. Visceral pain is caused by injury to internal organs, most typically malignancy. Visceral pain is often vague, dull, and difficult to localize. In opioid-refractory visceral pain,

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TABLE 24. Dosing and Conversion Chart for Opioid Analgesics

	Usual Starting Dose[a,b]		Equianalgesic Dosing[c]	
Medication	**Oral**	**Parenteral**	**Oral**	**Parenteral**
Hydrocodone	5 mg every 3-4 h	Not available	30 mg	Not available
Oxycodone	5-10 mg every 3-4 h (immediate release or oral solution)	Not available	20 mg	Not available
Morphine[d]	5-15 mg every 3-4 h (immediate release or oral solution)	2.5-5 mg SQ/IV every 3-4 h	30 mg	10 mg
Oxymorphone[e]	10 mg every 4-6 h (immediate release)	1-1.5 mg SQ/IM every 4-6 h	10 mg	1 mg
Hydromorphone	1-2 mg every 3-4 h	0.2-0.6 mg SQ/IV every 2-3 h	7.5 mg	1.5 mg
Fentanyl		25-50 µg IM/IV every 1-3 h	Sublingual tablets, lozenges, films, and buccal formulations available; consultation is advised for dosing of these agents	100 µg (single dose)
				Initial transdermal patch dose based on 24-h oral morphine dose
				30-59 mg — 12 µg/h
				60-134 mg — 25 µg/h
				135-224 mg — 50 µg/h
				225-314 mg — 75 µg/h
				315-404 mg — 100 µg/h

IM = intramuscularly; IV = intravenously; SQ = subcutaneously.

[a]Adult, opioid-naïve patients with body weight greater than 50 kg (110 lb).

[b]Dose should be reduced by half in older patients or those with liver or kidney disease.

[c]Estimated dose offering equivalent analgesia as other medications.

[d]Morphine should be avoided in patients with kidney failure.

[e]Oxymorphone should be avoided in patients with moderate to severe liver disease.

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glucocorticoids can be helpful in decreasing tumor-related swelling and/or peritoneal irritation. Additionally, nerve blocks for the appropriate abdominal plexus can be helpful. Bony metastatic pain is typically complex, involving somatic, neuropathic, and inflammatory components; it is classically worse at night. Anti-inflammatory medications, such as NSAIDs or glucocorticoids, can be particularly helpful. Bisphosphonates can significantly reduce the pain of bony metastases.

Dyspnea

Dyspnea is the subjective sense of breathlessness. Although dyspnea is often related to advanced cardiopulmonary pathology, dyspnea is also common in many chronic progressive diseases near the end of life. In advanced disease, dyspnea may occur with normal oxygen saturations and normal oxyhemoglobin measurements. Reversible causes of dyspnea, such as pleural effusions, infection, and anemia, should be investigated and treated. Any cardiopulmonary pathology, such as heart failure or COPD, should be maximally medically managed. Oxygen supplementation is helpful if the patient is hypoxic but has not been shown to be effective in the absence of hypoxia. There is mixed evidence regarding the benefit of nonpharmacologic interventions in relieving dyspnea. Mindfulness practices, relaxation, acupuncture, chest wall vibration, or electrical stimulation may be reasonable in selected patients. Systemic opioids are the standard of care for refractory dyspnea in advanced disease. Substantial evidence supports a consensus statement issued by the American College of Chest Physicians that suggests that systemic opioids, dosed and titrated appropriately, are effective and safe for dyspnea in the setting of advanced disease. Conversely, meta-analysis has shown no benefit of nebulized opioids over nebulized saline in the treatment of dyspnea. Benzodiazepines may have a role in the treatment of patients with both dyspnea and anxiety.

Nausea

Nausea and vomiting are a major source of distress for patients. Many patients rate unrelieved nausea as more distressing than unrelieved pain. Management of nausea is based on expert

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opinion and small case series studies. Most experts recommend attempting to identify the cause of the nausea first. Knowledge of the purported pathophysiologic mechanism of the nausea allows the provider to therapeutically target specific neurotransmitter pathways (**Table 25**). In severely ill patients, more than one mechanism may be at play. For persistent nausea, adding a second medication that targets a different neurotransmitter is appropriate. Glucocorticoids can be adjuvant to all antiemetic therapy and are particularly useful in patients with increased intracranial pressure.

Depression

Anticipatory grief and demoralization are common at the end of life, whereas pathologic depression is never normal. Diagnosing depression in the terminally ill, however, is challenging. Most screening tools for depression rely heavily on the presence of symptoms associated with functions necessary to maintain life (historically termed "vegetative symptoms") such as changes in appetite, sleep, and energy level, which are frequent and anticipated in advanced illness. Helplessness, hopelessness, worthlessness, guilt, and anhedonia are signs of depression rather than normal grief. Suicidal intent is abnormal and should be addressed promptly and aggressively. **Table 26** compares the signs and symptoms of grief to those of depression.

Depression in terminally ill patients responds well to both pharmacologic and nonpharmacologic treatment. Tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and mirtazapine are all effective agents. Prognosis should be taken into account since these medications take weeks to reach peak effect. If prognosis is less than 6 weeks, a psychostimulant with a faster onset, such as methylphenidate, may be considered.

Anorexia

Anorexia, weight loss, and cachexia reflect a final common pathway during the terminal phase of most disease processes. Assuming potentially reversible conditions (nausea, altered taste, medication side effects, bowel obstruction, dysphagia, psychological comorbidities) have been ruled out, disease-related cachexia is caused by an altered neurohormonal, inflammatory milieu that results in a profoundly deranged metabolism. The deranged metabolism decreases appetite but also decreases the body's ability to use caloric intake in a productive way. As such, cachexia cannot be fully reversed by conventional nutritional support. Artificial nutrition in cachexia of advanced disease does not improve morbidity or mortality. Medications used to stimulate appetite (progestins, dronabinol, glucocorticoids) do not improve morbidity or mortality, are only effective in 20% to 30% of patients, and are associated with side effects. Head-to-head studies have shown that dronabinol is less effective than progestins or glucocorticoids. Educating patients and families on the etiology and pathophysiology of cachexia is the primary intervention and may help them to better accept the expected course of the disease.

Delirium

Delirium is common in terminally ill patients. Potentially reversible causes include medication side effects, inadequately treated pain, urinary obstruction, or bowel impaction. Often, no reversible cause is found. Nonpharmacologic interventions, such as maintaining a calm and quiet environment, reorienting and reassuring the patient, and attempting to normalize sleep-wake cycles, may be helpful in controlling delirium. If these measures fail and the delirium is distressing to the patient or family, pharmacologic therapy may be considered. First-generation antipsychotics, such as haloperidol or chlorpromazine, are usually effective and can be uptitrated as necessary. There is little evidence to support the use of newer-generation antipsychotics over older-generation antipsychotics. Benzodiazepines are less effective than first-generation antipsychotics, are associated with occasional paradoxical reactions, and are only recommended in refractory terminal delirium.

TABLE 25. Treatment of Nausea in the Palliative Care Patient

Cause of Nausea	Mediating Receptor Pathway	Treatment
Gut wall stretching or dilatation (constipation, bowel obstruction, ileus)	Dopamine type 2 (D_2) receptors in the gastrointestinal tract	Antidopaminergic antiemetics (metoclopramide, prochlorperazine, haloperidol)
Gut mucosal injury (radiation, chemotherapy, infection, inflammation, direct tumor invasion)	Serotonin (5-hydroxytryptamine-3 [5-HT_3]) receptors in the gastrointestinal tract	Serotonin antagonists (ondansetron, granisetron)
Drugs, metabolic by-products, bacterial toxins	D_2 receptors, 5-HT_3 receptors, and neurokinin type 1 receptors in the chemoreceptor trigger zone	Antidopaminergic antiemetics and serotonin antagonists
Motion sickness, labyrinthine disorders	Histamine type 1 (H_1) receptors and muscarinic acetylcholine receptors in the vestibular system	Anticholinergic antiemetics (scopolamine, diphenhydramine, promethazine)
Anticipatory nausea	Unknown, presumed cerebral cortex	Benzodiazepines
Increased intracranial pressure	Unknown	Glucocorticoids

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TABLE 26. Grief Compared with Depression in Terminally Ill Patients

Characteristics of Grief	Characteristics of Depression
Patients experience feelings, emotions, and behaviors that result from a particular loss.	Patients experience feelings, emotions, and behaviors that fulfill criteria for a major psychiatric disorder; distress is usually generalized to all facets of life.
Almost all terminally ill patients experience grief, but only a minority of patients develop full-blown affective disorders requiring treatment.	Major depression occurs in 1%-53% of terminally ill patients.
Patients usually cope with distress on their own.	Medical or psychiatric intervention is usually necessary.
Patients experience somatic distress, loss of usual patterns of behavior, agitation, sleep and appetite disturbances, decreased concentration, and social withdrawal.	Patients experience similar symptoms, plus hopelessness, helplessness, worthlessness, guilt, and suicidal ideation.
Grief is associated with disease progression.	Depression has an increased prevalence (up to 77%) in patients with advanced disease; pain is a major risk factor.
Patients retain the capacity for pleasure.	Patients enjoy nothing.
Grief comes in waves.	Depression is constant and unremitting.
Patients express passive wishes for death to come quickly.	Patients express intense and persistent suicidal ideation.
Patients are able to look forward to the future.	Patients have no sense of a positive future.

Reproduced with permission from Block SD. Assessing and managing depression in the terminally ill patient. ACP-ASIM End-of-Life Care Consensus Panel. American College of Physicians - American Society of Internal Medicine. Ann Intern Med. 2000 Feb 1;132(3):209-18. [PMID: 10651602]

KEY POINTS

- Use of long-acting opioids for pain control is based on patient preference, as there is no evidence of improved pain control with long-acting opioids when compared with short-acting opioids.
- All patients on scheduled opioids should be on a scheduled stimulant laxative, such as senna or bisacodyl, in combination with docusate.
- Systemic opioids are the standard of care for refractory dyspnea in advanced disease.
- Terminally ill patients with depression respond well to tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and mirtazapine.

Common Symptoms

Introduction

Internists are tasked with diagnosing and treating a wide range of symptoms in adults. Specific symptom complaints account for nearly half of all outpatient visits, with half of these complaints being related to pain, and one third of all symptom complaints ultimately remaining unexplained. However, nearly 75% of symptoms, regardless of type, resolve in 2 weeks.

In evaluating common complaints, clinicians must determine the significance of these symptoms and the need for any further diagnostic testing. Given the array of available diagnostic tests (many of which have high associated costs), it is imperative that each physician approach these symptoms in a systematic manner that utilizes diagnostic testing rationally and cost effectively. This approach forms the basis for the American College of Physicians' High Value Care initiative.

Despite the many advances that have occurred in the field of medicine over the past century, studies indicate that approximately 85% of diagnoses are correctly made simply by performing a detailed history and physical examination. Each question and examination maneuver can be regarded as an independent diagnostic test to help arrive at the correct diagnosis. Therefore, the diagnostic process involves establishing a pretest probability of disease, with sequential application of diagnostic tests, including the history, physical examination, and selected laboratory and/or imaging studies, until a threshold is reached where the physician can be comfortable in either excluding or treating a disorder.

Diagnostic testing beyond the history and physical examination should not be avoided; rather, testing should be used when indicated by the information obtained during patient interactions. A "shotgun" approach to diagnosis, in which the physician orders a barrage of diagnostic tests, is rarely indicated. Studies have shown that nearly 30% of all health care costs in the United States (a total of more than $750 billion each year) are spent unnecessarily on diagnostic testing. Instead, a logical, intentional, and stepwise approach to testing should be used.

It has also been shown that ordering additional diagnostic testing does not alleviate patient fears and concerns. As such, it is important that physicians develop strong relationships with their patients and that physicians explain the rationale for their diagnostic approach while allowing patients to ask questions. Patients should always be made an active partner in their health care.

Given this information, appropriate evaluation of common symptom complexes becomes paramount in order to avoid unnecessary testing, manage costs, and prevent escalation of health-related anxiety. This chapter presents the recommended approaches to managing many symptoms encountered by the general internist, including chronic pain, medically unexplained symptoms, cough, fatigue, dizziness, insomnia, syncope, and edema.

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Chronic Noncancer Pain

Chronic pain not caused by cancer is discussed here; see Palliative Care for a discussion of cancer pain. In this context, chronic pain can be defined as pain, with or without a clear precipitant, that has persisted beyond 3 months. Chronic pain results in varying degrees of debility in patients.

The approach to the patient with chronic pain is guided by the type of pain the patient experiences. Pain may be classified by biologic mechanism as neuropathic, nociceptive, or central; however, the physician should keep in mind that once pain becomes chronic, considerable overlap develops. Medication choice is generally based on this classification.

Neuropathic pain is caused by injury or dysfunction of the nervous system. Neuropathic pain is usually described as burning, stinging, tingling, or shooting pain. It typically follows the distribution of the nerve (or nerve root) that is damaged, but it can be bilateral and more diffuse, as in peripheral neuropathies. Pain may be localized, such as in postherpetic neuralgia, or more widespread, such as in diabetic peripheral neuropathy. Physical findings typically reveal pain, numbness, or allodynia (sensitivity to non-noxious stimuli) in the nerve distribution.

Nociceptive pain is pain that is detected by specialized sensory nerves called nociceptors. These nerves are located throughout the soft tissues, such as in muscles and skin, as well as the internal organs. Two types of nociceptive pain exist: somatic pain (pain from the joints, bones, muscles, and other soft tissues) and visceral pain (pain from the internal organs). Nociceptors located in somatic structures provide a wide range of sensory experience, including touch, tickle, pressure, or pain. Somatic pain is usually characterized by more localized, dull, aching, throbbing, or squeezing pain. In contrast, nociceptors in the viscera either transmit no sensation or a poorly localized sensation of fullness, pressure, or pain. Nociceptive pain may have an inflammatory component in some disease states.

Central pain is caused by damage to or dysfunction of the central nervous system, which includes the brain, brainstem, and spinal cord. Central pain syndrome typically occurs shortly after the causative injury or damage, but it may be delayed by months or even years, especially if it is related to stroke. In addition to stroke, this syndrome can be caused by multiple sclerosis, tumors, epilepsy, brain or spinal cord trauma, or Parkinson disease. The character of the pain varies widely and may affect a specific area of the body or occur more diffusely. The pain is usually constant, with bursts of more severe pain, often exacerbated by cough, temperature changes, movement, or emotions. Central pain is often associated with allodynia and/or hyperalgesia (oversensitivity to noxious stimuli). Patients usually describe one or more types of pain sensation, the most prominent being burning. In addition to burning, sensations of numbness, pressure, lacerating pain, aching pain, "pins and needles," and episodic brief bursts of sharp pain have been described. Central pain syndromes can also evolve out of unrelenting chronic pain when persistent stimulation of peripheral pain receptors results in the upregulation of central pain modulators. When such upregulation occurs, the pain generator shifts, becoming more central than peripheral over time. Fibromyalgia is thought to be one example of this type of central pain process.

Assessment

Patients who present with reports of chronic pain should undergo a thorough history and physical examination in an attempt to determine the cause. Specific diagnoses or syndromes should be evaluated and managed accordingly. "Red flag" symptoms, such as nocturnal worsening of pain (often seen in cancer), fever, or weight loss, should spur further investigation. In the absence of red flag symptoms or abnormalities on physical examination, there is little evidence to support additional extensive testing.

The physician should also conduct a thorough assessment to determine all aspects of the patient's life that pain is affecting. A psychosocial history should assess impact of pain on sleep, work function, and family relationships. Functional impairment secondary to pain should be elicited in a detailed and specific way. Psychological screening for depression, anxiety, and somatization is also important. Depression, in particular, very commonly coexists with chronic pain.

Management

When pain becomes chronic, it inevitably affects many aspects of the patient's life. Interventions to improve chronic pain should be multifaceted and individualized. Medications may be part of the treatment plan, but care should be taken to avoid situations in which medications are overemphasized or become the sole management strategy. Patients should be educated early regarding the pathophysiologic mechanisms of chronic pain, the rationale behind a multimodal treatment approach, and reasonable expectations for improvement with the emphasis on functional improvement.

Nonpharmacologic Therapy

Nearly all pain management guidelines recommend introducing an exercise program in patients with chronic pain as a way to both improve pain and function. There is high-quality evidence that shows low-magnitude but significant improvements in both pain and function in certain pain populations. A recent Cochrane review showed an absolute improvement of 8% in pain and 7% in function for adults with osteoarthritis of the hip who exercised. A similar review that focused on patients with nonspecific chronic low back pain showed absolute improvements of 13% and 7% for pain and function, respectively. The type of exercise program will vary from patient to patient, depending on patient needs, preferences, and resources in the community. There is no evidence that one form of exercise is better than another. Options might include formal physical therapy, muscle

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strengthening, muscle stretching, low-impact aerobic exercise, water-based exercise, or tai chi.

Other nonpharmacologic modalities often employed as part of a multimodal approach to pain management include ice and heat therapy, transcutaneous electric nerve stimulation (TENS), massage, acupuncture, and chiropractic manipulation. Only massage and acupuncture are supported by low-quality evidence, with modest improvements compared with conventional therapy. Optimal duration of treatment for these interventions is unknown.

Chronic pain is often associated with psychological issues. The presence of psychological difficulties should in no way invalidate the patient's report of pain. Identified psychological issues should be specifically addressed as part of the treatment plan. Patients who meet the criteria for diagnosis of a psychological comorbidity, such as depression or anxiety, should be treated accordingly (see Mental and Behavioral Health). Cognitive-behavioral therapy (CBT) is consistently recommended in pain management guidelines to treat chronic pain, and there are data supporting its use but little information to guide pairing a specific technique to a specific type of patient. As such, the supporting data are difficult to interpret. CBT helps replace maladaptive coping skills with more valuable ones. CBT techniques, which may include cognitive restructuring, problem solving, relaxation techniques, and mindfulness-based stress reduction, help mitigate maladaptive behavior patterns, such as catastrophizing, fear avoidance, and overgeneralizing. How individual physicians incorporate CBT techniques into the multimodal management of their patients with chronic pain will depend on local resource availability.

Pharmacologic Therapy

Medications have a role in the management of chronic pain but are more valuable as part of a multimodal approach than as the sole treatment solution.

For neuropathic pain, localized symptoms can be treated with topical agents, such as capsaicin cream or a lidocaine patch or cream. Both topical capsaicin and lidocaine have been shown to be effective for diabetic neuropathy and postherpetic neuralgia. The anticonvulsant drugs gabapentin and pregabalin are considered first-line agents for systemic therapy, are well tolerated, and have the fewest side effects and drug interactions. Carbamazepine has demonstrated efficacy for trigeminal neuralgia, but evidence for effectiveness in other neuropathic syndromes is lacking. Newer anticonvulsants, such as topiramate and lamotrigine, are under investigation for this use. Tricyclic antidepressants, such as amitriptyline and nortriptyline, are effective for neuropathic pain independent of their effect on depression, but they have increased drug interactions, poor side effect profile, and potential cardiac toxicities, especially in the elderly. The serotonin-norepinephrine reuptake inhibitors duloxetine and venlafaxine have demonstrated efficacy in treating diabetic neuropathy. Tramadol and opioids also have demonstrated efficacy in treating neuropathic pain. However, because of the complex risk-benefit ratio associated with these medications, their use should be limited to selected low-risk patients who have failed to respond to more traditional neuromodulators.

For nociceptive pain, acetaminophen is usually the first-line agent owing to its safety and tolerability. NSAIDs can be considered if there is an inflammatory component to the pain and the patient does not have contraindications to oral NSAID use. Ideally, NSAIDs would be used for periodic flares and not on a continuous basis. Topical NSAIDs have improved tolerability, fewer side effects, and demonstrated efficacy in osteoarthritis of the knees.

Central pain syndromes, in particular, benefit from the multimodal approach to pain management. From a pharmacologic standpoint, neuromodulators seem to be the most efficacious medications. Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentin, and pregabalin are all reasonable options.

Opioid Therapy

Opioid use has increased dramatically in the United States over the past decade. The sales of opioid analgesics quadrupled between 1999 and 2010, and the estimated number of opioid prescriptions filled in the United States exceeded 256 million in 2010. Prescription opioid-related deaths increased from 4000 in 1999 to 14,000 in 2006. Half of fatal overdoses involved concomitant use of sedative-hypnotic medications. In 2012, 60% of prescription opioid overdoses occurred in patients taking opioids as prescribed and within accepted guidelines of prescribing; most of these patients were on high doses of opioids exceeding the equivalent of 100 mg of oral morphine per day.

There is no evidence to support the efficacy of long-term opioids in managing chronic pain. In one study, patients on long-term opioids for chronic pain had more pain, poorer quality of life, and poorer function than a population of patients with chronic pain who were not taking opioids. Any decision to use opioids for the management of chronic noncancer pain should be entered into carefully and with thorough assessment of risk relative to any potential benefit.

Although the evidence that shows improved outcomes with various risk mitigation strategies is low, the numerous guidelines currently available are in general agreement in their recommendations. Once medical need for opioid analgesia has been established, risk assessment is the next step. The physician should assess the patient for risk of opioid misuse (diversion or addiction) but also for risk of unintended and potentially lethal adverse events. This should include a review of chemical dependency and mental health history. Most guidelines strongly recommend employing a risk assessment tool, such as a DIRE (Diagnosis, Intractability, Risk, and Efficacy) score (**Table 27**). Despite the lack of evidence, written treatment agreements and adherence monitoring, including baseline and periodic urine drug screens and surveillance using prescription monitoring programs, are recommended by most guidelines. Additionally, most guidelines recommend

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TABLE 27. DIRE Score: Patient Selection for Chronic Opioid Analgesia

Factor[a]	Explanation
*D*iagnosis	1 = Benign chronic condition with minimal objective findings or no definite medical diagnosis. Examples: fibromyalgia, migraine, nonspecific back pain
	2 = Slowly progressive condition concordant with moderate pain, or fixed condition with moderate objective findings. Examples: failed back surgery syndrome, back pain with moderate degenerative changes, neuropathic pain
	3 = Advanced condition concordant with severe pain with objective findings. Examples: severe ischemic vascular disease, advanced neuropathy, severe spinal stenosis
*I*ntractability	1 = Few therapies have been tried and the patient takes a passive role in his/her pain management process.
	2 = Most customary treatments have been tried, but the patient is not fully engaged in the pain management process or barriers are present (insurance, transportation, medical illness).
	3 = Patient is fully engaged in a spectrum of appropriate treatments but with inadequate response.
*R*isk	(R = Total of P + C + R + S below)
*P*sychological:	1 = Serious personality dysfunction or mental illness interfering with care. Example: personality disorder, severe affective disorder, significant personality issues
	2 = Personality or mental health interferes moderately. Example: depression or anxiety disorder
	3 = Good communication with clinic. No significant personality dysfunction or mental illness
*C*hemical health:	1 = Active or very recent use of illicit drugs, excessive alcohol, or prescription drug abuse
	2 = Chemical coper (uses medications to cope with stress) or history of chemical dependency in remission
	3 = No chemical dependency history. Not drug-focused or chemically reliant
*R*eliability:	1 = History of numerous problems: medication misuse, missed appointments, rarely follows through
	2 = Occasional difficulties with compliance but generally reliable
	3 = Highly reliable patient with medications, appointments, and treatments
*S*ocial support:	1 = Life in chaos. Little family support and few close relationships. Loss of most normal life roles
	2 = Reduction in some relationships and life roles
	3 = Supportive family/close relationships. Involved in work or school and no social isolation
*E*fficacy	1 = Poor function or minimal pain relief despite moderate to high doses
	2 = Moderate benefit with function improved in a number of ways (or insufficient information [hasn't tried opioid yet or very low doses or too short of a trial])
	3 = Good improvement in pain and function and quality of life with stable doses over time

[a]For each factor, rate the patient's score from 1 to 3 based on the explanations in the right-hand column. Total score = D + I + R + E. Score of 7-13: Not a suitable candidate for long-term opioid analgesia. Score of 14-21: Good candidate for long-term opioid analgesia.[b]

[b]Score cutoffs were not included on the physician rater's score sheet.

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against concurrently prescribing both opioids and sedative-hypnotics and recommend referral for patients requiring doses of opioids greater than 100-mg oral morphine equivalents per day to physicians or clinics where this level of opioid use may be more closely managed. Furthermore, given the lack of evidence to support chronic opioid therapy, the continued use of opioids for chronic pain should be justified at every follow-up visit by documenting the patient's sustained functional improvement due to effective opioid therapy, lack of adverse events such as opioid-induced side effects (cognitive impairment, sedation, constipation, falls), and lack of aberrant behavior (lost prescriptions, early refill requests, multiple concurrent opioid providers or "doctor shopping," consistently missed appointments, or erratic follow-up). Physicians must have the fortitude to avoid prescribing opioids to those at significant risk or those who demonstrate adverse events or consistent aberrant behavior.

KEY POINTS

- Studies indicate that approximately 85% of diagnoses are correctly made simply by performing a detailed history and physical examination. **HVC**
- Diagnostic testing beyond the history and physical examination should be used in an intentional, logical, and stepwise fashion; nearly 30% of all health care costs are spent on unnecessary tests and treatments. **HVC**

(Continued)

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KEY POINTS *(continued)*

H/C • Reasonable quality evidence refutes the commonly held belief that ordering additional, unnecessary diagnostic testing alleviates patient fears and concerns.

H/C • Nonpharmacologic modalities that can be effective when part of a multimodal approach to pain management include exercise, ice and heat therapy, transcutaneous electric nerve stimulation, massage, acupuncture, and chiropractic manipulation.

• Pharmacologic management of chronic pain may include topical agents, anticonvulsant drugs, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, acetaminophen, NSAIDs, and opioids.

H/C • There is no evidence to support the efficacy of long-term opioids in managing chronic pain.

Medically Unexplained Symptoms

Many primary care and subspecialty physicians frequently encounter patients with medically unexplained symptoms (MUS), symptoms that cannot be attributed to a known medical cause after examination and testing. In the literature, patients with MUS frequently are described as "challenging," "time consuming," "frustrating," "discouraging," and "puzzling." These symptoms have a higher prevalence in women and in those with lower formal education and lower self-reported quality of life. Patients with MUS also have higher rates of unemployment. Care of patients with MUS and the uncertainty of definitive diagnosis may lead to increased utilization of health care resources, excessive diagnostic testing, and a strained physician-patient relationship. Additionally, family dynamics may be adversely affected.

Some patients with MUS may meet diagnostic criteria for somatic symptom disorder or illness anxiety disorder (replacing the previous diagnostic terms hypochondriasis, conversion disorder, or functional disorder) (**Table 28**). However, most patients with MUS do not have a clear psychiatric illness. Although psychological factors often play a role in the development of unexplained physical symptoms, there is little evidence to support the premise that psychological distress alone is the cause of the symptoms. Therefore, MUS is the preferred terminology, as this does not imply any sense of psychological causation. Additionally, the presence of symptoms without a medical explanation almost always affects the patient's thoughts, feelings, and actions, and assessing the impact and significance of the symptoms in an individual patient is an essential component of management of MUS.

TABLE 28. Diagnostic Criteria for Somatic Symptom Disorder and Illness Anxiety Disorder

Somatic Symptom Disorder	Illness Anxiety Disorder
At least 1 somatic symptom causing distress or interference with daily life	Preoccupation with having or acquiring an illness
Excessive thoughts, behaviors, and feelings related to the somatic symptom(s):	Somatic symptoms are not present or, if present, are only mild in intensity
Disproportionate or persistent concern about seriousness of symptoms	
Persistent high level of anxiety about health	
Excessive focus of time and energy on health concerns	
Persistent somatic symptoms for at least 6 months (the same somatic symptom does not have to persist for 6 months)	

Clinical Presentation and Evaluation

The most common symptoms in patients presenting with MUS are chest pain, fatigue, dizziness, headache, swelling, back pain, shortness of breath, insomnia, abdominal pain, and numbness. Frequently, patients have seen many primary care and subspecialty physicians over the course of many years; have undergone extensive laboratory testing, imaging studies, and procedures; and have availed themselves of medical literature in an attempt at self-diagnosis. Because patients with MUS present on a continuum of physical and mental health, a comprehensive, holistic approach is essential. Each presenting symptom merits the relevant history and physical examination. In most cases, a review of prior records should occur before repeating or extending the evaluation unless there is a significant change in the patient's condition. Physicians must possess excellent patient-centered communication skills and listen carefully to the patient, validating concerns and responding to emotions. Additionally, the initial assessment should include specific questions to elicit the patient's concerns, underlying psychological status, and degree of distress and disability attributable to the symptoms (**Table 29**).

When the history, physical examination, and diagnostic evaluation fail to delineate a precise anatomic or physiologic cause of continued symptoms, patients may request or even demand additional testing. Physicians may comply with these requests, as they feel that a negative result will reassure the patient and themselves. Physicians may also find it challenging to limit further testing, prescribing, or referral because they fear missing an elusive diagnosis. The evidence that more testing helps reassure patients with MUS or improves outcomes is limited. Negative test results may, in fact, increase patient anxiety over a potentially missed diagnosis. In a randomized controlled trial of 150 patients with chronic daily headaches, those randomized to receive MRI had a similar level of symptoms at 1 year compared with those who did not undergo testing; however, physicians made fewer referrals to specialists in the tested patients.

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TABLE 29. Elements of a Thorough Assessment of the Patient with Medically Unexplained Symptoms

Why now and what's the agenda? (Questions for the patient)
What is your main concern about this symptom?
What made you come today?
Is there something particular that you hoped I could do for you or your symptoms?
Assess the presentation.
What are the symptoms?
Take a full history of the onset of all symptoms, exacerbating factors, and relieving factors.
How much impairment do the symptoms cause? Do they cause disability? What is a typical day like?
Are there any signs of disease on physical examination?
Encourage discussion of psychosocial difficulties.
Is there associated pathology?
Gather old notes and investigations. Review these first before ordering more investigations.
Balance the iatrogenic risks of further investigation or treatment against the probability of finding associated pathology.
Does the patient have an anxiety or depressive disorder?
Does the patient have any mood symptoms or anxiety symptoms?
Consider using a screening questionnaire, depression scale, the general health questionnaire, or the patient health questionnaire.
Is this some other emotional distress presenting as physical distress?
What is the patient's model of illness?
Who are the patient's supporters?

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Management

Long-term management of the patient with MUS is challenging. A therapeutic alliance and a mutually respectful physician-patient relationship are key features in the successful management of the patient with MUS. In keeping with a patient-centered approach, the patient should be engaged fully in the plan, focusing on physical, psychological, and social aspects of health. The physician and patient should work together to create and maintain an atmosphere of mutual trust.

In addition to physical symptoms, the patient with MUS may manifest primary or secondary signs and symptoms of significant underlying psychological distress, including depression or anxiety. These underlying mental health problems can be overlooked by physicians during the unsuccessful quest for a unifying or previously undiagnosed organic illness. Rather than pursuing further costly, low-value, and potentially risky diagnostic workups and therapies, it may be more beneficial and value driven to assess and treat any potential underlying psychological symptoms and to educate patients with MUS on successful coping skills based on the personal impact of their symptoms. The point of aborting further diagnostic testing and unsuccessful therapy and shifting primary attention toward mental health care requires clinical judgment on an individualized basis and patient engagement in the conversation. Discussions that address the patient's concerns without invalidating their experiences are most likely to be of help to patients who have these difficult and complex problems.

Participation in well-paced exercise programs with gradual increase in activity level, especially in patients with back pain, fatigue, and fibromyalgia, may be more helpful than rest. Patients with MUS have also demonstrated improvement in symptoms with antidepressant therapy. A recent randomized controlled trial documented a clinically significant improvement in the Mental Component Summary of the Short Form (36) Health Survey among patients who participated in a multidimensional protocol, which consisted of 12 monthly visits with trained nurse practitioners and CBT, pharmacologic therapy (antidepressants), and other programs. Patients with lower mental health scores at baseline, severe body pain, nonsevere physical dysfunction, and at least 16 years of education were more likely to show improvement. A follow-up randomized controlled trial of 206 patients found no significant difference in total costs for the group that received the 12-month intervention (emphasizing provider-patient relationship, CBT, and pharmacologic management) than for the control group. However, the intervention group used less medical care outside of the main treatment site and missed 1 less work day per month.

Regularly scheduled follow-up visits and continuity of care are important when treating patients with MUS. Studies suggest that regularly scheduled appointments with targeted physical examination increase physical functioning. In a single-site study, substituting telephone contact for selected face-to-face visits reduced unscheduled clinic visits, medication use, and hospital days and improved function. The overall approach to the patient with MUS on each follow-up visit is outlined in **Table 30** and **Table 31**. Although CBT is generally performed by trained therapists, the internist can reinforce the basic principles at each follow-up visit. The four components of CBT include (1) educating the patient so that he or she understands the plan of care and its purpose, (2) obtaining and reinforcing a commitment from the patient for the chosen plan of care, (3) setting and reviewing mutually chosen patient goals, and (4) negotiating new plans and therapy as needed.

There are minimal data on the long-term prognosis of patients with MUS. In one primary care study, more than 25% of patients had persistent symptoms after 12 months. In a study of patients with MUS who were seen by neurologists, 58% of patients had persistent symptoms at 12 years. The

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TABLE 30. Follow-up Evaluation of the Patient with Medically Unexplained Symptoms

Category	Issue	How?	How Often?	Notes
History	Adherence and response to negotiated treatment plan	Ask about level of old symptoms and progress with stated goals	Every week initially until patient is stable, then progressively lengthen interval of visits to 4-12 weeks as tolerated by patient	Help the patient to develop new short-term goals to achieve long-term goals as he or she achieves current goals
	New comorbid organic disease	Monitor for any change in patient's symptoms	Each visit	
	Exploration of nonsomatic symptoms	Show preferential interest in the psychosocial aspects of the patient's story	Each visit	Most will change from a physical symptom focus to a psychosocial focus after 3-4 months
Physical examination	Physical status	Perform a brief physical examination focused on patient's old symptoms	Each visit	
	New comorbid organic disease	Perform a brief physical examination to assess for organic disease pertinent to any change in patient's history, focusing on new signs rather than new symptoms	Each visit	
Laboratory tests	New comorbid organic disease	Order laboratory tests only as needed for new signs	As needed	Recognize that most symptoms will not require laboratory investigations

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patient should be counseled that treatment may likely improve function and reduce symptoms but is unlikely to produce a cure.

KEY POINTS

HVC • Evidence that further diagnostic testing helps reassure patients with medically unexplained symptoms or improves outcomes is limited; negative test results may, in fact, increase patient anxiety over a potentially missed diagnosis.

HVC • In patients with medically unexplained symptoms, the point of aborting diagnostic testing and unsuccessful therapy and shifting primary attention toward symptom management (and if indicated, mental health care) requires clinical judgment on an individualized basis and patient engagement in the conversation.

Cough

Cough accounts for approximately 30 million physician visits annually, and billions of dollars are spent on prescription and over-the-counter medications as well as homeopathic remedies to relieve this symptom.

An initial approach to the patient is based on duration of cough. Acute cough is present for less than 3 weeks, subacute cough for 3 to 8 weeks, and chronic cough for greater than 8 weeks.

Acute Cough

Acute cough is most commonly caused by viral upper respiratory tract infections (URIs) (rhinosinusitis, pharyngitis) and acute bronchitis. Other causes include pneumonia, COPD, asthma, allergic rhinitis, left ventricular failure, medications, or aspiration.

Rhinosinusitis and acute bronchitis are most commonly caused by influenza types A and B, parainfluenza, coronavirus, rhinovirus, and respiratory syncytial virus. Nonviral causes include *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and, more recently, *Bordetella pertussis* (whooping cough). Purulent sputum does not reliably differentiate between viral or bacterial causes. In acute bronchitis, cough may persist for up to 8 weeks due to bronchial hyperreactivity.

Cough that is accompanied by fever, constitutional symptoms, and abnormalities on physical examination is generally indicative of lower respiratory tract infection. A chest radiograph should be obtained in patients who present with these

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TABLE 31. Follow-up Management of the Patient with Medically Unexplained Symptoms

Category	Issue	How?	How Often?	Notes
Nonpharmacologic therapy	Maintaining an effective relationship with the patient	Elicit and address the patient's emotional concerns; use a negotiated rather than a prescriptive approach; tailor care to patient's personality; address your own negative reactions to the patient.	Each visit	Monitor the provider-patient relationship regularly as you would, for example, monitor blood pressure in a patient with hypertension. Ask, "So how is all this going; how are you and I working together?" Examples of indicators of an effective relationship are adherence to the treatment plan, friendliness, improved eye contact, positive statements about the provider and the treatment.
	Dissociating treatment regimen from symptoms	Schedule regular, consistent, time-contingent visits rather than ad-hoc (as-needed) visits; give all medications on a scheduled rather than on an as-needed basis.	Each visit	Titrate number of scheduled visits and dosages of different aspects of treatment to patient's needs and progress.
Pharmacologic therapy	MUS symptoms	Consider lowest effective dose of antidepressant and nonnarcotic drugs.	Each visit	Minimize or avoid use of narcotics and tranquilizers.
	Comorbid depression and anxiety	Use full doses of SSRIs or other related antidepressants. If depression has not fully remitted after 6-8 weeks, add a second antidepressant from a different class and titrate to full dose (consider drug interactions). If this is not effective, mental health consultation should be obtained.	As needed	
Patient education	Overall management	Review patient's diary and facilitate understanding of how his or her thoughts, emotions, and behaviors are related to symptoms.	Ongoing	
	Education and treatment plan	Educate the patient so that the patient understands the plan of care and its purpose.	Each visit	
	Reinforcing patient commitment to treatment	Give appropriate praise for commitment behavior such as completing homework; address noncommittal behavior, such as not keeping appointments or visiting an acute care facility without prior discussion.	Each visit	
	Reviewing and revising patient goals	Reinforce previous short-term goals or negotiate new ones to operationalize patient's long-term goals.	Each visit	Help patient to identify solutions to roadblocks.
	Negotiating new plans	Negotiate plans to adjust physical activity; recommend relaxation techniques; refer for physical therapy.	Each visit	Continuously encourage the patient to add new healthy behaviors and to progress in what he or she is already doing.

MUS = medically unexplained symptoms; SSRI = selective serotonin reuptake inhibitor.

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findings. Influenza should be considered in any patient who presents with cough, fever, myalgia, and headache during the appropriate season (fall to early spring).

Approximately 15% of patients on an ACE inhibitor develop a nonproductive cough. The cough usually begins within 1 week of starting therapy, although it may appear later. If cough is overly troublesome, the medication should be discontinued. It may take up to 4 weeks to subside. Rechallenge with a different ACE inhibitor is not recommended, as there is a high rate of recurrent cough. Angiotensin receptor blockers generally do not cause cough and can be substituted for ACE inhibitors in this instance.

Treatment of acute cough is based on the primary diagnosis and is largely symptomatic. Routine antibiotic treatment of uncomplicated URIs and acute bronchitis in the nonelderly immunocompetent patient is not indicated, a recommendation supported by the Centers for Disease Control and Prevention (CDC) and the Choosing Wisely initiative. Despite efforts to curb inappropriate prescribing of antibiotics, recent evidence has shown that the overall rate of antibiotic prescribing has increased to 71% for patients presenting with symptoms of acute bronchitis. Antibiotic use is costly and potentially harmful, and it should be emphasized that patient satisfaction depends primarily on physician-patient communication rather than on antibiotic prescription.

For patients with the common cold, inhaled ipratropium, cromolyn sodium, first-generation antihistamine-decongestant preparations, and naproxen are helpful in decreasing sneezing and rhinorrhea. First-generation antihistamines and decongestants, however, should be used with caution in older adults. For treatment of cough accompanying the common cold, the American College of Chest Physicians recommends first-generation antihistamine-decongestant preparations (brompheniramine, sustained-release pseudoephedrine). Newer-generation nonsedating antihistamines are ineffective. A review of 17 trials concluded that centrally acting (codeine, dextromethorphan) or peripherally acting (moguisteine) antitussive therapy results in little improvement in cough. β_2-agonists should not be used unless cough is accompanied by wheezing.

Subacute and Chronic Cough

Subacute cough most commonly develops after an infection, including *B. pertussis* infection. In endemic or sporadic cases of pertussis, patients present with a cough lasting at least 2 weeks plus at least one other clinical finding: paroxysms of coughing, inspiratory "whoop," or post-tussive emesis with no other apparent cause. If infection is unlikely, consideration of the common causes of chronic cough should ensue. Inhaled ipratropium may be beneficial in treating subacute cough if there is no airway hyperreactivity.

Chronic cough has four common causes: upper airway cough syndrome (UACS), asthma, nonasthmatic eosinophilic bronchitis (NAEB), and gastroesophageal reflux disease (GERD). UACS, asthma, and GERD account for approximately 90% of chronic cough cases, excluding cases resulting from smoking or use of ACE inhibitors. Less frequently, chronic cough may be caused by chronic bronchitis, bronchiectasis, lung cancer, aspiration, irritation of the external auditory canal, and psychogenic causes.

Patients with chronic cough, especially smokers, should undergo chest radiography. If the chest radiograph does not reveal a potential cause of cough, the physician should consider UACS, asthma, NAEB, and GERD and begin a stepwise approach for evaluation and treatment. The definitive diagnosis may be suggested by history and physical examination and confirmed by successful empiric treatment.

An algorithmic approach can be used in the immunocompetent patient with chronic cough (excluding the patient who is taking an ACE inhibitor or smoking), leading to successful outcomes in more than 90% of patients (**Figure 6**). In general, if the chest radiograph is unrevealing for a cause of cough, empiric therapy for UACS is begun for 2 to 3 weeks. If the patient does not respond to empiric therapy, appropriate evaluation and treatment for asthma, NAEB, and GERD should follow. All patients with chronic cough who smoke should be offered cessation counseling.

The patient should receive optimized therapy for each diagnosis. For UACS due to allergic rhinitis, intranasal glucocorticoids are effective. For UACS due to nonallergic rhinitis, first-generation antihistamines (for example, chlorpheniramine, brompheniramine, diphenhydramine) and decongestants (pseudoephedrine) remain the therapy of choice. A 2-week trial should be used. Patients with cough-variant asthma may demonstrate reversible airflow obstruction or airway hyperreactivity with bronchoprovocation testing. However, since false-positive results may occur, the diagnosis of asthma should only be given if symptoms abate after 2 to 4 weeks of treatment with an inhaled bronchodilator and inhaled glucocorticoids. In patients in whom UACS and GERD are unlikely by clinical history or who have failed to respond to empiric therapy and in whom pulmonary function tests are normal, sputum testing for eosinophils is a reasonable next evaluation, especially if there is a history of atopy. In patients without airway hyperreactivity but with sputum eosinophilia, NAEB can be diagnosed and subsequently treated with inhaled glucocorticoids. The diagnosis of GERD can be made in patients with typical reflux symptoms (present in 60% of patients) or in those who fit a typical profile and in whom near-complete or complete resolution of symptoms with antireflux treatment occurs. Although 24-hour esophageal pH monitoring may be helpful in the evaluation of suspected GERD, empiric treatment (lifestyle modification and proton pump inhibitor therapy for 1 to 3 months) can be initiated before testing.

In addition to disease-based therapy, symptomatic treatment may be helpful. Broad categories of medications used to treat chronic cough include antitussives (opioids, anesthetics) and protussives (expectorants, mucolytics). Unlike in the treatment of acute cough, studies suggest that opioids may be effective in the treatment of chronic cough. In a recent systematic

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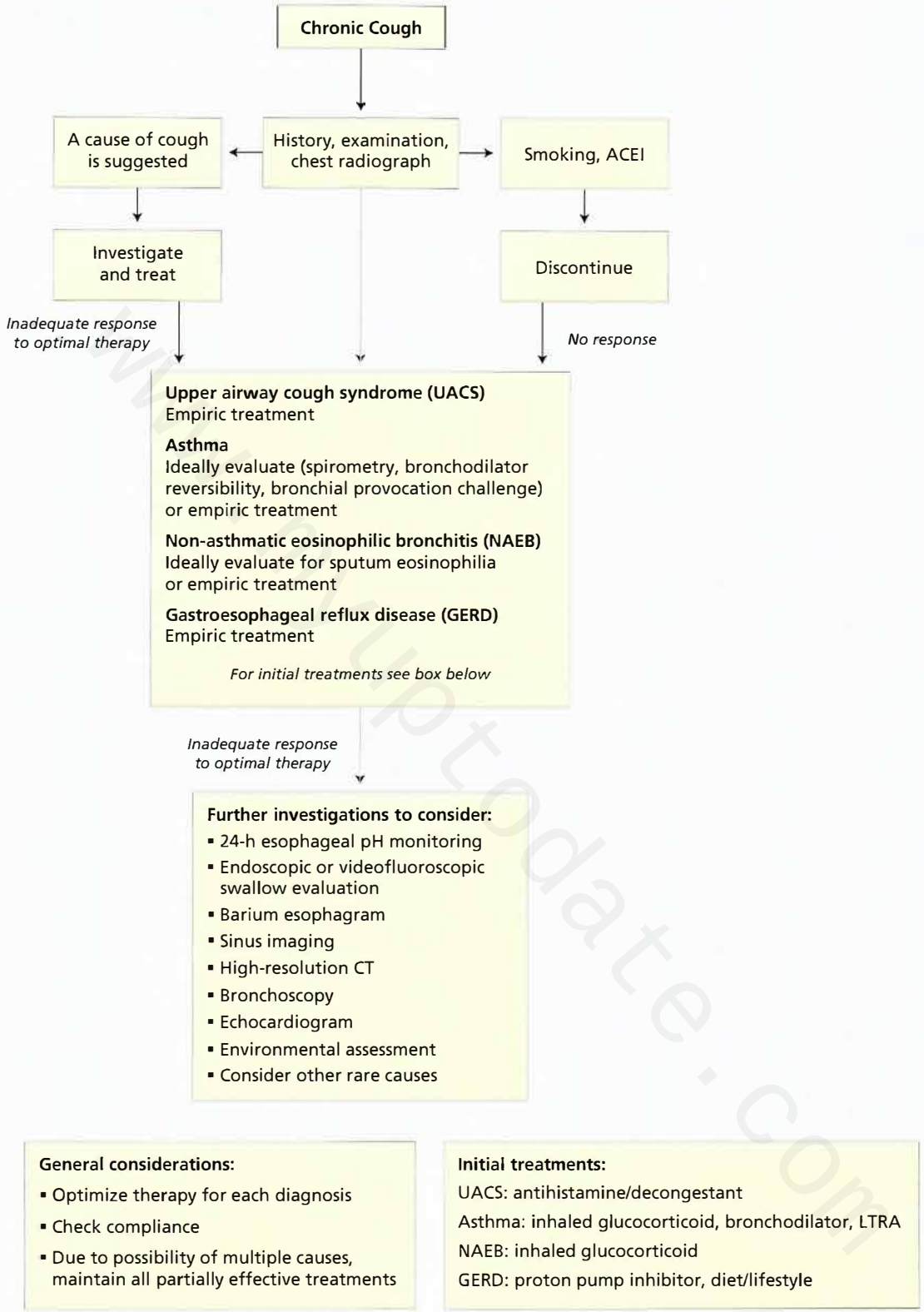

FIGURE 6. Evaluation of chronic cough.

ACEI = ACE inhibitor; LTRA = leukotriene receptor antagonist.

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review, opioids were more effective than placebo in decreasing cough frequency and severity and improving quality of life. No one opioid consistently outperformed another in efficacy. There was neither superiority nor inferiority in performance when comparing opioids to peripherally acting anesthetic antitussives (benzonatate). Dextromethorphan was effective in reducing cough severity and/or frequency, but conflicting results were reported in the comparison of dextromethorphan and opioids. Protussives, such as guaifenesin, improve mucus clearance in patients with copious sputum production and decrease irritation of cough reflexes. Protussives may also reduce cough intensity. In patients with refractory chronic cough, gabapentin may be considered. In a randomized, double-blind, placebo-controlled trial, gabapentin significantly improved cough-specific quality of life (number needed to treat = 3.58). The onset of action of gabapentin was within 4 weeks.

Cough in the Immunocompromised Patient

Special consideration must be given to infectious causes of cough in the immunocompromised patient, who is at risk for the common community-acquired infections but also for tuberculosis, *Pneumocystis jirovecii*, *Aspergillus* species, *Cryptococcus* species, cytomegalovirus, varicella, herpes simplex, and, less commonly, parasitic infections. The severity and duration of the immunosuppression, and whether the primary impairment is in humoral or cell-mediated immunity, can help focus the differential diagnosis. The patient should be started on empiric therapy for suspected infectious causes while diagnostic testing is performed.

Hemoptysis

Hemoptysis, the coughing up of blood from the lower respiratory tract, must be distinguished from nasopharyngeal bleeding or hematemesis, which involves vomiting of blood from the gastrointestinal tract. Sources of hemoptysis include the tracheobronchial tree (bronchitis, bronchiectasis, tumor), pulmonary parenchyma (abscess, pneumonia, tuberculosis, Goodpasture syndrome, granulomatosis with polyangiitis [formerly known as Wegener granulomatosis]), and pulmonary vasculature (arteriovenous malformations, pulmonary embolism, mitral stenosis, left-sided heart failure). Hemoptysis most commonly results from infection or malignancy. All patients with hemoptysis should receive chest radiography and, if indicated, chest CT and/or bronchoscopy.

KEY POINTS

- A chest radiograph should be obtained in patients who present with cough that is accompanied by fever, constitutional symptoms, and abnormalities on physical examination.
- HVC Routine antibiotic treatment of uncomplicated upper respiratory infections and acute bronchitis in the nonelderly immunocompetent patient is not indicated.

(Continued)

KEY POINTS *(continued)*

- Upper airway cough syndrome, asthma, and gastroesophageal reflux disease account for approximately 90% of chronic cough cases, excluding cases resulting from smoking or use of ACE inhibitors, and an algorithmic approach can be used, leading to successful outcomes in more than 90% of patients.

Fatigue and Systemic Exertion Intolerance Disease

Fatigue is an exceedingly common symptom, affecting up to one third of patients in primary care. Fatigue can be caused by a medical condition, psychiatric disorder, or lifestyle factors. The patient's history and physical examination should be used to differentiate fatigue from excessive somnolence, dyspnea, and true muscle weakness. The differential diagnosis is large; more common causes are listed in **Table 32**. The history and physical examination should guide diagnostic testing. If the history (including depression screen, medication reconciliation, and assessment of sleep habits and drug use) and physical examination do not

TABLE 32. Common Causes of Fatigue

Lifestyle
Sleep deprivation; poor sleep habits
Alcohol
Extremes of activity
Drug dependency (overuse and withdrawal)
Medical
Chronic liver and kidney disease
Cancer
Anemia
Chronic lung disease; hypoxemia
Hyperglycemia; uncontrolled diabetes mellitus
Thyroid disorder (hyper- and hypothyroidism)
Medication side effects
β-blockers
Antihistamines
Antidepressants
Benzodiazepines
Antipsychotics
Obesity
Heart failure
HIV/AIDS
Psychological
Depression
Anxiety
Stress

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suggest a particular etiology, reasonable initial laboratory tests for evaluating fatigue include a complete blood count, thyroid-stimulating hormone level, electrolyte panel, fasting glucose, serum creatinine, and liver chemistry tests. Further diagnostic testing is likely to be unrevealing.

Systemic exertion intolerance disease (SEID), formerly known as chronic fatigue syndrome, is a complex and disabling condition without known causation or curative treatment. SEID affects between 800,000 and 2.5 million people in the United States and is more prevalent in women than in men. In February 2015, the Institute of Medicine defined the diagnostic criteria for SEID, which include (1) reduction or impairment in the ability to carry out normal daily activities, accompanied by profound fatigue that is not relieved by rest; (2) post-exertional malaise (worsening of symptoms after physical, cognitive, or emotional effort); and (3) unrefreshing sleep. In addition to the three major criteria, the patient must also demonstrate either cognitive impairment or orthostatic intolerance (symptoms that worsen when a person stands upright and improve when the person lies back down). Symptoms should be present for more than 6 months; however, they may persist for years, and many patients never regain their previous level of health or function. Other associated symptoms include pain, failure to recover from a prior infection, sore throat, painful or tender axillary or cervical lymph nodes, sensitivity to external stimuli (food, chemicals, drugs), and abnormal immune function; fibromyalgia and irritable bowel syndrome are common comorbidities.

Evaluation

The initial approach to the patient presenting with SEID includes obtaining a detailed history and performing a thorough physical examination. The assessment should incorporate a complete review of over-the-counter medications and appropriate screening for depression, sleep disorders, and alcohol or other substance abuse.

There is no specific objective laboratory test to diagnose SEID, and since the presenting symptoms are nonspecific, it remains a diagnosis of exclusion. Recommended value-based screening tests include complete blood count, glucose levels, and thyroid function tests. If indicated by the history and physical examination, electrolytes, calcium, serum creatinine, liver enzyme levels, albumin, INR, total bilirubin, and antinuclear antibodies may be obtained. Viral titers are not recommended. Gender and age-appropriate evidence-based screening should be up to date.

Management

There is no curative treatment for SEID, and no specific medications are approved by the FDA for the treatment of SEID. Management strategies are limited and should be tailored to address the most bothersome symptoms and those that disrupt the patient's daily activities. A team approach to care, utilizing the internist, psychologists trained in CBT, psychiatrists, physical therapists, exercise physiologists, physiatrists, and support groups, may be beneficial.

In the most recent systematic review with meta-analysis evaluating treatment modalities in patients with SEID, two studies reported that severely debilitated patients receiving rintatolimod, an immune modulator and antiviral agent, demonstrated a slight improvement in performance compared with placebo. This drug is not currently available in the United States. Other prescription drugs (galantamine, hydrocortisone, IgG, and fluoxetine) or complementary and alternative approaches, including diets, supplements, and phototherapy, provided no benefit. Although there were inconsistencies among studies included in the review, some found that counseling and CBT improved fatigue, physical function, quality of life, and work impairment. Graded exercise training was also found to improve function, fatigue, and work impairment. Graded exercise training gradually and consistently increases baseline activity level, avoiding extremes in exercise or periods of inactivity and deconditioning.

One 4-week randomized placebo-controlled trial with methylphenidate demonstrated clinically significant (>33% increase) improvement in fatigue and concentration in approximately 20% of patients. Opioids are not indicated for long-term management of pain.

Adequate restorative sleep is essential, and sleep hygiene techniques should be reviewed with the patient. Although strong evidence is lacking for relaxation and stress-reduction programs (biofeedback, massage, meditation, yoga, tai chi), some patients may experience improvement in symptoms with these modalities. Coexisting medical conditions should be appropriately treated.

Approximately 70% of patients with SEID meet criteria for the diagnosis of depression, anxiety, or dysthymia. These diagnoses should be recognized, and the patients should be treated appropriately.

The long-term prognosis for the patient with SEID is variable, which may frustrate both the patient and the physician. In one of the largest follow-up cohorts, functional impairment persisted at 2 to 4 years in 33% of patients. Identified factors for symptom persistence at 2.5 years are more than eight medically unexplained symptoms not included in the SEID case definition, lifetime history of dysthymia, duration of SEID greater than 1.5 years, less than 16 years of formal education, and age greater than 38 years.

To ensure ongoing monitoring and stability of symptoms, and to support the patient with SEID, regular follow-up is recommended. Polypharmacy, excessive testing, and multiple referrals should be avoided.

KEY POINTS

- Treatment strategies that have been shown to have meaningful benefit for patients with systemic exertion intolerance disease are cognitive-behavioral therapy and graded exercise training.
- No pharmacologic agent is FDA approved for the treatment of systemic exertion intolerance disease.

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Dizziness

Approach to the Patient with Dizziness

Dizziness is a common nonspecific symptom that is especially prevalent in the elderly. Although dizziness is sometimes challenging to classify, the physician should attempt to place the symptom into one of four categories based on history and physical examination: (1) vertigo, (2) presyncope, (3) disequilibrium, or (4) nonspecific dizziness. Studies conducted in primary care settings, emergency departments, or dizziness clinics report that approximately 50% of patients with dizziness have vertigo, 4% to 14% of patients have presyncope, and 1% to 16% of patients have disequilibrium. The remaining patients have a psychiatric disorder, hyperventilation, multiple causes, or an unknown cause. In patients presenting to the emergency department, dizziness is the most common symptom linked to a missed diagnosis of stroke.

Acute vestibular syndrome (AVS) is defined as rapid-onset dizziness that is continuous for more than 24 hours and is associated with nystagmus, unsteadiness of gait, nausea, vomiting, and intolerance to head movement. Hemiparesis, hemisensory loss, gaze palsy, and other focal neurologic events are not present. Several common, benign conditions may cause AVS, including vestibular neuronitis and labyrinthitis. However, AVS may also result from brainstem or cerebellar infarction or hemorrhage. Therefore, it is important to consider these diagnoses when evaluating patients with AVS. The continuous and prolonged nature of symptoms in AVS tends to exclude transient and intermittent conditions, such as benign paroxysmal positional vertigo, vestibular migraine, Meniere disease, and transient ischemic attack.

Vertigo

Vertigo is the illusion of either personal or environmental movement. It is frequently associated with nausea and made worse with head movement. Although classically described as a spinning sensation, patients may report swaying, tilting, or other less abrupt movement. Once vertigo is suspected, the next important step is to distinguish central from peripheral causes. The Dix-Hallpike maneuver (**Figure 7**) can help with this task. The latency (time of onset of nystagmus after positioning the patient), direction, and duration of nystagmus should be observed, and habituation (less severe or shorter duration vertigo with repeated assumption of the triggering position), fatigability (decrease in the intensity and duration of nystagmus with repeated maneuvers), and severity of symptoms should be determined. **Table 33** outlines how to interpret the different findings in the Dix-Hallpike maneuver.

Peripheral Vertigo

The most common cause of vertigo is benign paroxysmal positional vertigo (BPPV), which is attributed to debris (canalithiasis), usually in the posterior semicircular canal, perturbing labyrinthine sensory receptors and resulting in the erroneous perception of angular head acceleration. The vertiginous sensation in patients with BPPV is brief (10-30 seconds) and is precipitated by abrupt head movement. Nausea is a common accompaniment. Recurrence rates are high.

Vestibular neuronitis (or labyrinthitis, if hearing is affected), another cause of peripheral vertigo, may follow a viral syndrome that has affected the vestibular portion of cranial nerve VIII. Symptoms are generally more severe and of longer duration than in BPPV and may take longer to resolve. The physical examination findings for both BPPV and labyrinthitis are similar: mixed upbeat-torsional nystagmus may occur, but no focal neurologic findings are present.

Less common causes of peripheral vertigo are Meniere disease (classic triad of vertigo, hearing loss, tinnitus), perilymphatic fistula (vertigo and hearing loss with history of straining or trauma), vestibular schwannoma (acoustic neuroma), aminoglycoside toxicity, herpes zoster, and migraine.

For patients with BPPV, the Epley maneuver (**Figure 8**), also known as the canalith repositioning procedure, is an effective and safe treatment. The American Academy of Neurology and American Academy of Otolaryngology recommend using the Epley maneuver for BPPV involving the posterior canal. Pharmacologic therapy for BPPV generally is ineffective for cure but, as with other causes of peripheral vertigo, may be used for symptom relief. These medications include centrally acting antihistamines (meclizine), vestibular suppressants (benzodiazepines), and antiemetic drugs (**Table 34**, on page 55). It is recommended that these medications be used only for short periods of time, as more prolonged use may suppress vestibular feedback and central compensation mechanisms. Data supporting the use of glucocorticoids, calcium channel blockers, betahistine, and other complementary approaches are weak. Vestibular rehabilitation therapy, delivered by trained physical or occupational therapists, is effective for patients with peripheral vertigo, especially if referred early. Treatment modalities center on desensitization exercises and improving balance.

Central Vertigo

Approximately 20% of cerebrovascular accidents are located in the posterior fossa, and the predominant symptom is dizziness in up to 70% of these strokes. Although disorders of the peripheral vestibular system may cause debilitating symptoms, diseases associated with central vertigo, resulting in ischemia, infarction, or hemorrhage of the cerebellum or brainstem, may be life threatening. Patients at high risk include those with hypertension, diabetes, hyperlipidemia, or advanced age. These patients may have recurrent episodes over the preceding weeks or months, so it is important to elicit a history of similar events. Vertebrobasilar stroke is usually, but not always, accompanied by dysarthria, dysphagia, diplopia, weakness, or numbness. In a systematic review, focal neurologic signs were present in 80% of patients with stroke who presented with dizziness. Cerebellar infarct may present with gait or truncal ataxia or with vertigo alone. In one study, gait unsteadiness was reported in 55% of patients with central vertigo.

Demyelinating conditions, such as multiple sclerosis, can present with vertigo, although a history of other relapsing and

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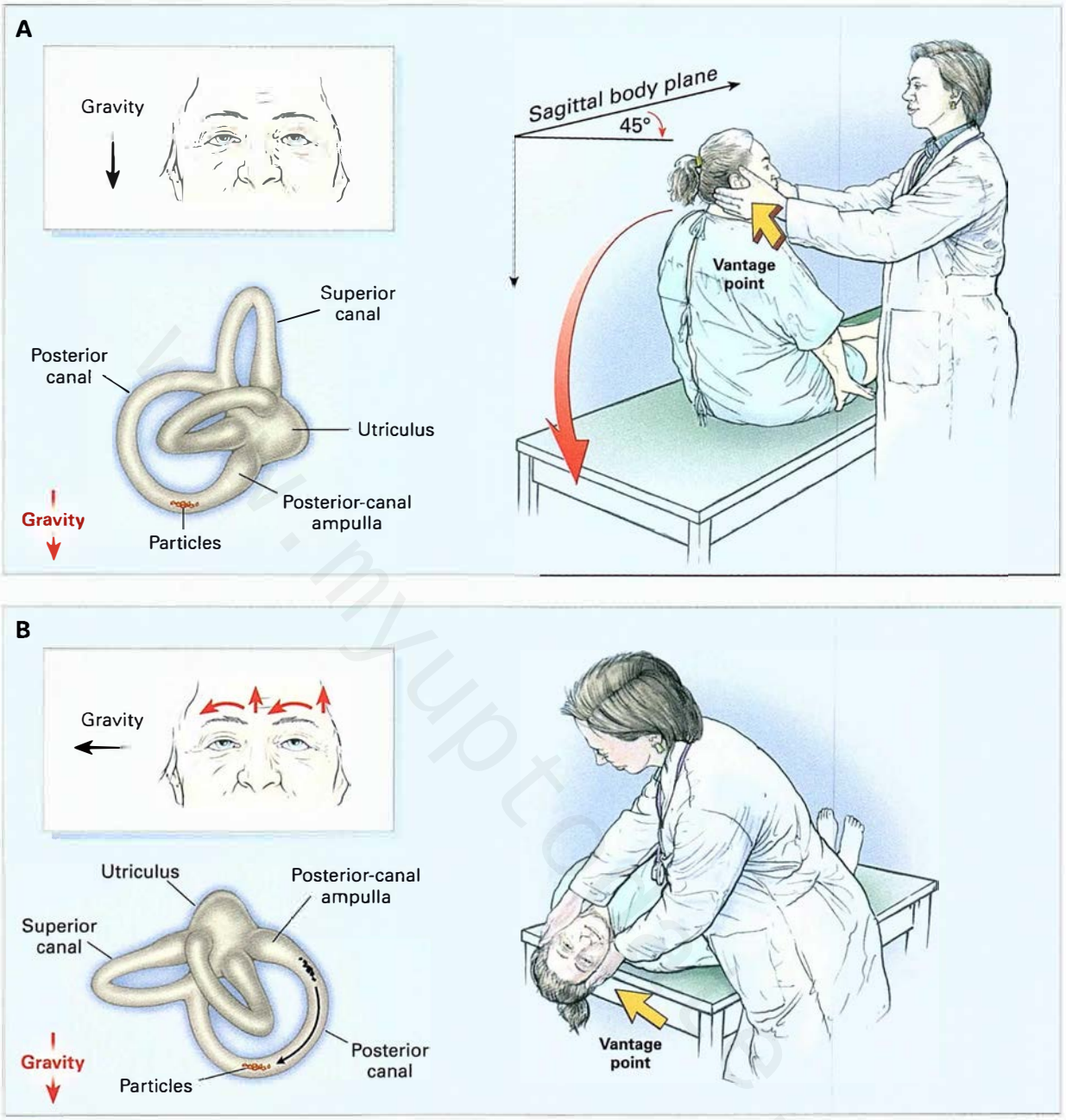

FIGURE 7. The Dix-Hallpike test of a patient with benign paroxysmal positional vertigo (BPPV) affecting the right ear. In *A*, the examiner stands at the patient's right side and rotates the patient's head 45 degrees to the right to align the right posterior semicircular canal with the sagittal plane of the body. In *B*, the examiner moves the patient, whose eyes are open, from the seated to the supine right-ear-down position and then extends the patient's neck slightly so that the chin is pointed slightly upward. The latency, duration, and direction of nystagmus, if present, and the latency and duration of vertigo, if present, should be noted. The red arrows in the inset depict the direction of nystagmus in patients with typical BPPV. The presumed location in the labyrinth of the free-floating debris thought to cause the disorder is also shown.

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remitting neurologic abnormalities, including optic neuritis, is usually present. Other rarer causes of central vertigo include Wernicke syndrome, brainstem encephalitis, and migraine.

In the patient presenting with a suspected central cause of vertigo, MRI is more sensitive than CT for detecting ischemia and is the preferred diagnostic study for nonhemorrhagic stroke. Noncontrast CT can detect hemorrhagic stroke with high sensitivity; however, hemorrhage accounts for only about 4% of cases of central vertigo.

Presyncope

Presyncope is near loss of consciousness without loss of postural tone. Classic vertigo is absent, but patients may have difficulty distinguishing "lightheadedness" from true vertigo.

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TABLE 33. Interpretation of Dix-Hallpike Maneuver Findings in Evaluation of Vertigo

Characteristic	Peripheral Disease	Central Disease
Latency of nystagmus[a]	2-40 s	No latency
Duration of nystagmus	<1 min	>1 min
Severity of symptoms	Severe	Less severe
Fatigability[b]	Yes	No
Direction of nystagmus	Unidirectional, mixed upbeat and torsional with a small horizontal component[c]	Direction of nystagmus may depend on direction of gaze; may be purely vertical or horizontal without a torsional component

[a]Time to onset of nystagmus after positioning the patient.

[b]Decrease in the intensity and duration of nystagmus with repeated maneuvers.

[c]In benign paroxysmal positional vertigo, this pattern of nystagmus is provoked with the affected ear positioned downward when the posterior semicircular canal is involved (most common); when the anterior semicircular canal is involved, nystagmus is mixed downbeat and torsional with the affected ear positioned upward.

The absence of loss of consciousness distinguishes presyncope from true syncope, although the pathophysiology may be similar. Presyncope is the result of a decrease in global cerebral perfusion, tachyarrhythmias, bradyarrhythmias, valvular heart disease, hypotension, or vasovagal reaction (see Syncope). In addition to dizziness, patients with presyncope may also experience nausea, warmth, or tunnel vision.

Disequilibrium

Disequilibrium is an unsteadiness, or sense of imbalance, with standing or walking. The elderly are primarily at risk for

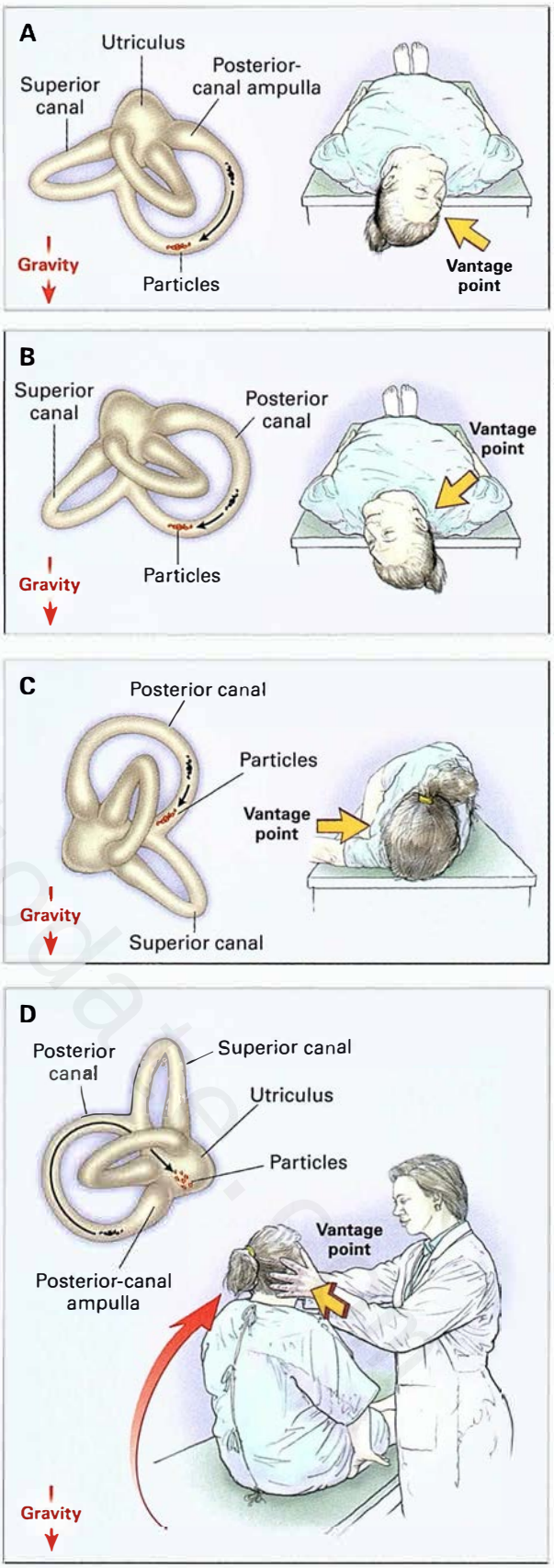

FIGURE 8. The Epley maneuver (canalith or particle repositioning maneuver) for the treatment of a patient with benign paroxysmal positional vertigo (BPPV) affecting the right ear. The presumed position of the debris within the labyrinth during the maneuver is shown in each panel. The maneuver is a three-step procedure. First, a Dix-Hallpike test is done with the patient's head rotated 45 degrees toward the right ear and the neck slightly extended with the chin pointed slightly upward. This position results in the patient's head hanging to the right (*A*). Once the vertigo and nystagmus provoked by the Dix-Hallpike test cease, the patient's head is rotated about the rostral-caudal body axis until the left ear is down (*B*). Then the head and body are further rotated until the head is face down (*C*). The vertex of the head is kept tilted downward throughout the rotation. The maneuver usually provokes brief vertigo. The patient should be kept in the final, facedown position for about 10 to 15 seconds. With the head kept turned toward the left shoulder, the patient is brought into the seated position (*D*). Once the patient is upright, the head is tilted so that the chin is pointed slightly downward.

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TABLE 34. Symptomatic Drug Therapy for Benign Paroxysmal Positional Vertigo

Drug	Drug Class	Dosage	Side Effects	Precautions	Clinical Use
Clonazepam	Benzodiazepine	0.25 mg PO BID	Drowsiness, confusion, respiratory depression, tolerance, dependence, anterograde amnesia, hepatotoxicity, myasthenia	Avoid with pregnancy, closed-angle glaucoma, severe liver disease. Caution with depression, psychosis. Use low dose with mild to moderate liver disease, elderly, CKD. Metabolized by CYP3A4.	Anxiety associated with dizziness
Diazepam	Benzodiazepine	1 mg PO BID	Same as with clonazepam	Same as with clonazepam. Metabolized by CYP2C19 and CYP3A4.	Anxiety associated with dizziness
Meclizine	Centrally acting antihistamine	25 mg PO four times daily	Drowsiness, fatigue, confusion, headache, xerostomia	Avoid with closed-angle glaucoma, MAOI therapy. Caution with elderly, pulmonary disease, diabetes mellitus, seizure disorder, cardiovascular disease, liver disease.	Mild dizziness and nausea
Prochlorperazine	Antiemetic	5-10 mg PO three or four times daily	Agitation, lethargy, dystonia, extrapyramidal symptoms, anticholinergic effects, cardiac conduction disturbances	Avoid with elderly, dementia, liver or kidney impairment, Parkinson disease, seizure disorder. Multiple drug interactions.	Dizziness and nausea

BID = twice daily; CKD = chronic kidney disease; CYP = cytochrome P450 isoenzyme; MAOI = monoamine oxidase inhibitor; PO = orally.

disequilibrium. Causes include impaired visual or auditory acuity, impaired proprioception, motor weakness, joint pain, psychiatric disease, orthostasis, or neuropathic and cerebellar diseases affecting balance and gait. Patients may also experience disequilibrium as a side effect of medication use. Frequently, more than one cause can be identified. Although patients with disequilibrium have difficulty standing or walking, they do not experience true vertigo; sitting or lying down relieves the sensation. Physical therapy, visual and auditory screening followed by correction of impairment, and mobility aids that stabilize ambulation can be beneficial in reducing severity of symptoms and fall risk.

Nonspecific Dizziness and Chronic Subjective Dizziness

Some patients may complain of other dizzy sensations, such as lightheadedness, floating, swimming, heavy-headedness, and feeling "spaced out," that do not fit into a specific diagnostic category. Although nonspecific dizziness may be associated with a wide variety of other medical and psychological conditions, it may also occur in otherwise healthy individuals. Appropriate evaluation includes a patient-specific assessment for possible associated conditions by history and physical examination and selected diagnostic testing as indicated.

In patients with dizziness or disequilibrium that is present for most days over a period of at least 3 months that cannot be explained by an identifiable underlying cause, chronic subjective dizziness (CSD) should be considered. Symptom severity may fluctuate, but symptoms are usually more severe when walking or standing and less severe when lying down. Symptoms are often worsened with motion, highly stimulating or moving visual environments, and settings with indistinct visual orientation clues (for example, a dimly lit room). CSD can be precipitated by an acute disorder affecting the vestibular system and is often accompanied by the presence of medical and/or psychiatric problems, such as depression, anxiety, or obsessive-compulsive traits. Physical examination findings are normal, as are vestibular testing results. Treatment is multimodal: pharmacologic therapy, vestibular and balance rehabilitation therapy (VBRT), and CBT. Selective serotonin

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reuptake inhibitors are effective in treating CSD, even in patients without psychiatric comorbidity; they are usually effective in the low therapeutic range. Vestibular suppressants (for example, meclizine) are not effective in treating CSD. VBRT is a program of habituation/desensitization exercises that can be integrated with medication and psychotherapy. All patients with CSD should undergo VBRT. Additionally, CBT may be beneficial if there is a coexisting psychiatric disorder in patients with CSD, although it appears to be less effective for improving the physical symptoms of dizziness.

KEY POINTS

- Dizziness is the most common symptom linked to a missed diagnosis of stroke in patients presenting to the emergency department.
- HVC The Dix-Hallpike maneuver can be used to distinguish central from peripheral causes of vertigo; for peripheral causes, the Epley maneuver is an effective and safe treatment; neuroimaging is not necessary in patients with peripheral vertigo.
- In the patient presenting with a suspected central cause of vertigo, MRI is more sensitive than CT for detecting ischemia and is the preferred diagnostic study for non-hemorrhagic stroke.
- Vertebrobasilar stroke as a cause of vertigo is usually accompanied by dysarthria, dysphagia, diplopia, weakness, or numbness.

Insomnia

Insomnia is defined as the inability to initiate or maintain adequate sleep and is a common disorder. Its prevalence is higher in women; older adults (in whom it is estimated to occur in up to 34%); patients with depression, stress, or altered sleep cycles; and patients who engage in long-distance traveling. Insomnia can lead to daytime somnolence, work absenteeism, motor vehicle accidents, poor general health, functional impairment, and impaired quality of life.

Evaluation

The initial comprehensive assessment of the patient with insomnia should include a history and physical examination, along with a psychological and psychiatric assessment. The history should elicit past and current symptoms of sleep apnea, restless legs syndrome, hypothyroidism, arthritis, cardiopulmonary disease, neurologic disease, and depression. Obtaining a history of medication and other substance use, including caffeine and other stimulants, alcohol, and over-the-counter medications, and a detailed description of sleep behavior and sleep environment is essential. A 2-week diary, documenting all activities from bedtime to final arising time, can be helpful. The patient should be encouraged to include all activities related to the use of electronic devices at night as well. Studies suggest that mobile device usage while in bed before going to sleep is positively associated with insomnia. A targeted physical examination, with appropriate laboratory testing, to uncover medical conditions associated with sleep disturbance is indicated in most patients.

Additional selected diagnostic testing is useful for patients in whom the history is consistent with sleep-disordered breathing (sleep apnea), periodic limb movement disorders, or narcolepsy, or who fail to respond to initial therapeutic measures for insomnia. These specialized testing modalities, such as polysomnography and multiple sleep latency tests, require referral to sleep specialists and sleep laboratories.

Management

Nonpharmacologic Therapy

The initial treatment of insomnia focuses on implementing good sleep hygiene, which refers to the optimization of the environmental and behavioral factors associated with sleep. Key instructional information to discuss with the patient is outlined in **Table 35**.

CBT for insomnia is brief, multicomponent therapy that includes both cognitive components (to provide sleep education and address maladaptive beliefs and expectations about sleep) and behavioral components (including sleep restriction therapy, stimulus-control therapy, and relaxation techniques). Sleep restriction may be helpful in the motivated patient if the techniques of sleep hygiene are inadequate. Sleep restriction limits and then gradually increases the time in bed for sleep, and utilizes the concept of sleep efficiency (total sleep time divided by total time in bed). The patient is instructed to keep

TABLE 35. Techniques for Good Sleep Hygiene

During the Day
Ensure adequate exposure to natural light
Avoid napping
Avoid the following close to bedtime:
Substances that may fragment sleep (caffeine, nicotine, alcohol, pseudoephedrine)
Vigorous exercise
Large meals
Emotionally upsetting activities or conversations
At Bedtime
Establish a regular relaxing bedtime routine (30 minutes)
Associate the bed and the bedroom with sleep
Keep the bedroom quiet and dark
Keep stable bedtime and arising time
Spend no more than 20 minutes awake in bed
Spend no more than 8 hours in bed
Avoid use of television, radio, computer, or phone (texting) in bed

Based on Masters PA. In the clinic. Insomnia. Ann Intern Med. 2014 Oct 7;161(7): ITC1-15; quiz ITC16. [PMID: 25285559]

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a sleep diary for 2 weeks and to calculate the average total sleep time per day. The patient then spends that amount of time in bed, keeping the arising time constant. The time in bed gradually increases by 15 minutes as long as the sleep efficiency is greater than 85%. Stimulus-control therapy reinforces the connection between the bedroom and sleep by setting bedtimes and awaking times, removing stimuli that may keep the patient awake (electronic devices), and restricting the use of the bedroom to sleep. Relaxation techniques such as diaphragmatic breathing, visualization, and progressive muscle relaxation, sometimes coupled with biofeedback, are also effective behavioral treatments for insomnia.

CBT for insomnia is highly effective and is generally recommended as initial treatment. Unfortunately, not all clinicians are skilled at providing all of the elements of CBT, and referral for specific components to trained therapists may be needed.

Pharmacologic Therapy

The role of over-the-counter and prescription sleep aids is limited in chronic insomnia due to the potential for adverse effects and dependency. Pharmacologic therapy should generally be considered only after behavioral therapy has been insufficient in controlling insomnia symptoms.

Over-the-Counter Medications

Sedating antihistamines, such as diphenhydramine, are commonly used to treat insomnia. Although they may induce sedation, the resultant anticholinergic side effects, daytime somnolence, and cognitive impairment limit their overall safety and benefit, especially in the elderly, and they are generally not recommended. Antihistamines are also contraindicated in patients with glaucoma and men with benign prostatic hyperplasia. Melatonin may be effective for short-term insomnia due to travel or shift work. The efficacy and safety for melatonin's long-term use, as well as for other marketed natural remedies, are unknown. Alcohol, though sedating, is not recommended as it disrupts continuous sleep.

Prescription Medications

Approximately 9 million Americans take prescription medication for poor sleep, and 59 million sleeping pills were prescribed in the United States in 2012. The prevalence of use is higher in women and increases with age and level of education. Although targeted use can be effective in improving sleep, prescription sleep agents are approved only for short-term (1-month) continuous use; however, there are less data regarding using these medications on an as-needed basis. The two most commonly prescribed categories of medication are benzodiazepines, which are nonselective γ-aminobutyric acid (GABA)-receptor agonists, and nonbenzodiazepines, which are chemically unrelated to benzodiazepines and are more selective GABA-receptor agonists. Prescription drugs that are FDA approved for the treatment of insomnia are compared in **Table 36**. The American Geriatrics Society recommends that benzodiazepines of any type be avoided for the treatment of insomnia in the elderly, as an increased sensitivity to these medications coupled with decreased metabolism raise the risk of delirium, falls, fractures, cognitive impairment, and motor vehicle accidents in this population.

Although effective for short-term therapy, the use of benzodiazepines (flurazepam, triazolam, temazepam) is limited by tolerance; the side effects of daytime somnolence, falls, cognitive impairment, anterograde amnesia; and the potential for dependence. Rebound insomnia may occur upon discontinuation, especially if discontinuation is abrupt. The selective nature and shorter half-life of nonbenzodiazepines (zolpidem, zaleplon, eszopiclone) leads to fewer side effects (including rebound insomnia), making these drugs better initial choices if pharmacotherapy is warranted. However, sedation, disorientation, and agitation may occur as well as, rarely, sleep driving, sleep walking, and sleep eating.

Some antidepressants are sedating and may improve sleep. Doxepin, in low doses, is the only antidepressant approved for the treatment of insomnia. Most expert opinion recommends against using antidepressants for treating insomnia in patients without depression; however, doxepin, trazodone, and mirtazapine can be useful if a sedating antidepressant is indicated.

In patients with restless legs syndrome, dopaminergic agonists have been effective in reducing involuntary leg movement and, hence, improving sleep. Pramipexole or ropinirole are the drugs of choice.

Referral

Referral to a sleep specialist and/or psychiatrist is indicated if the diagnosis remains uncertain or if the initial treatments are ineffective. Additionally, referral to the appropriate specialist may be indicated to assist in the management of the underlying cause of the insomnia.

KEY POINTS

- The initial treatment of insomnia is nonpharmacologic and focuses on implementing good sleep hygiene via patient education or brief cognitive-behavioral therapy. **HVC**
- Although effective for short-term treatment of insomnia, the use of benzodiazepines is limited by dependence, tolerance, and the side effects of daytime somnolence, falls, cognitive impairment, and anterograde amnesia. **HVC**

Syncope

Syncope is nontraumatic, complete transient loss of consciousness and loss of postural tone. Onset is abrupt and recovery is spontaneous, rapid, and complete. Syncope accounts for 6% of hospital admissions each year, and syncope-related hospital admissions cost $2.4 billion annually in the United States.

Syncope is caused by global cerebral hypoperfusion secondary to a decrease in cardiac output and/or a decrease in

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TABLE 36. FDA-Approved Prescription Drug Treatment for Insomnia

Agent[a]	Usual Dosage	Onset of Action[b]	Duration of Action[c]	Notes
Benzodiazepines (oral)				
Estazolam	1-2 mg	Slow	Intermediate	
Flurazepam	15-30 mg	Rapid	Long	
Quazepam	7.5-15 mg	Slow	Long	
Temazepam	7.5-30 mg	Slow	Intermediate	
Triazolam	0.125-0.5 mg	Rapid	Short	Short-acting benzodiazepines have been associated with an increased risk of anterograde amnesia
Nonbenzodiazepines				
Zolpidem				
Oral tablet	5-10 mg	Rapid	Short	
Extended-release oral tablet	6.25-12.5 mg	Rapid	Intermediate	
Sublingual				
Intermezzo (Transcept Pharmaceuticals)	1.75-3.5 mg	Rapid	Short	Indicated for as-needed use for treatment of middle-of-the-night insomnia with ≥4 h of sleep time remaining
Edluar (Meda Pharmaceuticals)	10 mg	Rapid	Short	
Oral spray	10 mg	Rapid	Short	
Eszopiclone	1-3 mg	Rapid	Intermediate	The recommended initial dose was reduced to 1 mg because of prolonged impaired driving skills, memory, and coordination at the previously recommended 3-mg dose
Zaleplon	10-20 mg	Rapid	Short	
Orexin-Receptor Antagonist				
Suvorexant	5-20 mg	Slow	Long	The recommended initial dose is 10 mg; the daily dose should not exceed 20 mg
Antidepressant				
Doxepin	3-6 mg	Rapid	Intermediate	
Melatonin Agonist				
Ramelteon	8 mg	Rapid	Short	

[a]All agents classified as schedule C-IV by the Drug Enforcement Agency (DEA) except doxepin and ramelteon, which are not scheduled.

[b]Onset of action: rapid = 15 to 30 minutes; slow = 30 to 60 minutes.

[c]Based on elimination half-life and preparation: short = 1 to 5 hours; intermediate = 5 to 12 hours; long = greater than 12 hours.

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CONT.

systemic resistance. Specific etiology is based on underlying pathophysiologic mechanisms (**Table 37**). Neurally mediated syncope, the most common cause of syncope, generally occurs with standing and is associated with a prodrome of nausea, lightheadedness, and warmth. It may follow cough, urination, defecation, pain, or laughing. Orthostatic syncope is associated with a decline of 20 mm Hg or more in systolic blood pressure (SBP) (or ≥10 mm Hg drop in diastolic blood pressure) within 3 minutes of standing. Orthostatic syncope occurs as a result of primary autonomic failure, secondary autonomic failure (diabetes, amyloidosis, spinal cord injuries, Parkinson disease), hypovolemia, medications (vasodilators, diuretics), or age-associated changes in blood pressure regulation. Cardiac syncope, most commonly caused by an arrhythmia, is typically abrupt and without prodrome. A history of coronary artery or valvular heart disease may not be present. Patients may report palpitations, which may occur in the seated or recumbent position, immediately before syncope. Cerebrovascular disease is a rare cause of syncope. With cerebrovascular disease of the anterior circulation, global cerebral hypoperfusion is rare;

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TABLE 37. Classification of Syncope
Neurally Mediated Syncope (Reflex Syncope)
Vasovagal
Situational
Carotid sinus syndrome
Orthostatic Syncope
Primary
Secondary
Drug-induced
Volume depletion
Cardiac Syncope
Tachyarrhythmia or bradyarrhythmia
Atrioventricular block
Structural heart disease
Valvular heart disease (aortic stenosis)
Cardiomyopathy
Hypertrophic cardiomyopathy
Atrial myxoma
Ischemia
Other (saddle pulmonary embolism, aortic dissection, pulmonary hypertension)
Cerebrovascular Syncope
Vertebrobasilar transient ischemic attack
Subclavian steal
Psychiatric Disease (Pseudosyncope)
Unknown

CONT.

dizziness and vertigo are the hallmark symptoms of posterior circulation disease. With either severe anterior or posterior cerebrovascular disease, other neurologic symptoms would be expected to precede or accompany syncope.

Diagnosis and Evaluation

The purpose of the initial evaluation of the patient with syncope is to substantiate true syncope, identify patients at risk for subsequent life-threatening events or sudden death, and identify specific etiology. The first step in the approach is to distinguish true syncope from nonsyncope. Although dizziness, vertigo, and seizures may be confused with syncope, a careful history can usually distinguish between these conditions. Dizziness and vertigo do not lead to loss of consciousness, and seizures generally are accompanied by aura, rhythmic involuntary movements, postictal confusion, and, occasionally, urinary and fecal incontinence; a history of tongue biting is helpful for ruling in, but not ruling out, a seizure diagnosis.

The physical examination should include orthostatic blood pressure measurements and a careful cardiovascular examination, including auscultation for valvular heart disease (aortic stenosis) and the murmur of hypertrophic cardiomyopathy, especially with syncope related to exertion. In the appropriate patient, carotid sinus massage can detect carotid sinus hypersensitivity (ventricular pause >3 seconds and/or decrease in SBP >50 mm Hg). This response may predict subsequent spontaneous asystole. Carotid massage, however, should not be performed in patients with a transient ischemic attack or stroke within the past 3 months or in those with known carotid stenosis.

In addition to a history and physical examination with orthostatic blood pressure measurements, the European Society of Cardiology and National Institute for Health and Care Excellence recommend 12-lead electrocardiography (ECG). If structural heart disease is suspected, echocardiography is recommended. The cause of syncope can be identified in up to 50% of patients by utilizing this approach.

The subsequent evaluation should include only tests that are most likely to inform the diagnosis, management, and prognosis. In a study of 1920 hospitalized patients, the most commonly ordered tests, in addition to ECGs, were telemetry (95%), cardiac enzymes (95%), and CT of the head (63%). These tests, along with echocardiography, carotid ultrasonography, and electroencephalography, aided diagnosis in less than 2% of patients and altered management decisions in less than 5% of patients. The most valuable diagnostic and management test was postural blood pressure. The American College of Physicians does not recommend brain imaging, either with CT or MRI, in the evaluation of a patient with simple syncope and with a normal neurologic examination.

The diagnostic yield of 24- to 48-hour electrocardiographic monitoring is low (1%–2%), unless there are frequent episodes over a short period of time. More prolonged rhythm monitoring with external loop event recorders (ELRs) improves yield if the patient has clinical or ECG features of arrhythmia-related syncope and an intersymptom interval of less than 4 weeks. Implantable loop recorders (ILRs) may be beneficial in patients with unexplained recurrent syncope when the intersymptom interval is more than 4 weeks. In pooled data, the average yield of ILRs in diagnosing syncope was 32% over 18 months and 50% at 2 years. In two randomized controlled trials of recurrent unexplained syncope, ILRs were twice as effective as ELRs, tilt-table testing, and electrophysiologic studies. Electrophysiologic studies are useful in unexplained syncope in patients suspected to have arrhythmias and structural or ischemic heart disease. Diagnostic testing for cardiac arrhythmias is further discussed in MKSAP 17 Cardiovascular Medicine.

Tilt-table testing may be helpful in patients with reflex syncope triggered by standing, patients in high-risk settings (for example, construction workers, surgeons) with a single unexplained episode of syncope, patients with recurrent episodes in the absence of organic heart disease, or patients with recurrent episodes in the presence of heart disease when cardiac causes of syncope are excluded. The low sensitivity, specificity, and reproducibility of tilt-table testing limit its diagnostic potential.

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CONT.

Recently, specialized syncope centers have been established. Although studies report increased diagnostic yield and reduction in hospital admissions and testing, long-term outcomes are unknown.

Risk Stratification and Decision for Hospital Admission

Forty percent of patients who present to emergency departments with syncope are admitted to the hospital. Many of these admissions are unnecessary, as only 5% to 6% of these patients have severe physical injuries that require hospital care. The goal of the physician is to identify patients who are at high short-term risk for adverse cardiovascular outcomes (**Table 38**). When the criteria for high risk are absent, a life-threatening event is rare.

The recently validated ROSE (Risk stratification Of Syncope in the Emergency department) rule identifies independent clinical predictors for short-term (1-month) risk of acute myocardial infarction, life-threatening arrhythmia, pacemaker implantation, pulmonary embolism, stroke, intracranial or subarachnoid hemorrhage, need for blood transfusion, or acute surgical procedure. These predictors are elevated B-type natriuretic peptide concentration (≥300 pg/mL), bradycardia (≤50 beats/minute), fecal occult blood in patients with suspected gastrointestinal bleeding, anemia (hemoglobin ≤9 g/dL [90 g/L]), chest pain with syncope, ECG with Q waves (not in lead III), and oxygen saturation less than or equal to 94% on ambient air. If any of these indicators are present in the patient with syncope, the patient should be considered high risk and should be admitted for evaluation and monitoring.

Management

Therapy is guided by the underlying etiology. The treatment for neurally mediated syncope is reassurance, education, and avoidance of hypotensive agents. Orthostatic syncope resulting from hypovolemia may be treated with volume expansion and correction of any other potential contributing factors, such as medications that may cause hypovolemia or hypotension. In patients with persistent orthostatic changes following optimization of volume and other possible contributing factors, other medications are often used, although data on these agents for treating orthostatic syncope are limited. Fludrocortisone, β-blockers, and selective serotonin reuptake inhibitors have not been shown to be uniformly beneficial. Midodrine, an α-agonist, may be effective; however, its use is limited by the side effects of hypertension and urinary retention. Pacemakers are only recommended for patients with symptomatic bradycardia or asystolic pauses. Most patients with cardiac syncope are referred to cardiologists.

TABLE 38. High-Risk Criteria for the Patient with Syncope

Features suggesting arrhythmic syncope
Clinical: syncope during exertion, palpitations at time of syncope, family history of sudden death
Electrocardiography: nonsustained ventricular tachycardia, bifascicular block, sinus bradycardia (<50 beats/min or sinoatrial block), prolonged QT interval
Severe structural or coronary artery disease
Heart failure
Low ejection fraction
Previous myocardial infarction
Comorbidities
Severe anemia
Electrolyte disturbances

Prognosis

Prognosis, like treatment, depends upon the cause of the syncope. Patients with neurally mediated syncope have the same mortality rate as that of comparably aged healthy individuals. Cardiac syncope is associated with 1-year mortality rate of 18% to 33%, and the mortality rate with syncope due to cerebrovascular disease is less than 10%. In addition to clinical predictors of adverse outcomes in the ROSE rule, age greater than 65 years, abnormal ECG, history of heart failure, ischemic heart disease, ventricular arrhythmias, and lack of warning signs or symptoms have been shown to adversely affect outcomes. Gender, tilt-test response, and severity of presentation have low predictive value for adverse outcomes. Quality of life is adversely affected in patients with recurrent syncope, especially the elderly. Driving restrictions may also be imposed on patients with recurrent syncope, and physicians should be familiar with the state laws that govern these restrictions. H

KEY POINTS

- The physical examination of the patient with syncope should include orthostatic blood pressure measurements and a careful cardiovascular examination, including auscultation for valvular heart disease (aortic stenosis) and the murmur of hypertrophic cardiomyopathy, especially with syncope related to exertion.
- The most valuable diagnostic and management test in patients with syncope is postural blood pressure measurement; extensive additional testing, including telemetry, cardiac enzyme testing, CT of the head, echocardiography, carotid ultrasonography, and electroencephalography, aided diagnosis in less than 2% of patients and altered management decisions in less than 5% of patients. HVC
- The American College of Physicians does not recommend brain imaging, either with CT or MRI, in the evaluation of a patient with simple syncope and a normal neurologic examination. HVC

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KEY POINTS *(continued)*

HVC

- The majority of patients with syncope can be safely managed as outpatients; indications for hospital admission for patients with syncope include presence of severe traumatic injuries or a high short-term risk for adverse cardiovascular outcomes.
- High short-term risks for adverse cardiovascular outcomes for patients with syncope include history suggestive of arrhythmic syncope (syncope during exertion, palpitations at the time of syncope, family history of sudden death, abnormal electrocardiographic findings), severe structural or coronary heart disease (heart failure, low ejection fraction, previous myocardial infarction), and comorbidities (severe anemia, electrolyte disturbances).

Lower Extremity Edema

Lower extremity edema results from increased movement of fluid from the intravascular to the interstitial space or decreased movement of fluid from the interstitium into the capillaries or lymphatic vessels. The mechanism involves one or more of the following: increased capillary hydrostatic pressure, decreased plasma oncotic pressure, increased capillary permeability, or obstruction of the lymphatic system.

Lower extremity edema can usually be subdivided into systemic and more localized causes. Systemic causes such as heart failure, cirrhosis, the nephrotic syndrome, chronic kidney disease, and obstructive sleep apnea typically cause bilateral fluid accumulation in gravity-dependent areas. Bilateral leg edema may also be caused by certain medications (**Table 39**). Unilateral leg edema is most commonly due to venous thromboembolism or cellulitis, but it can also be caused by lymph obstruction from significant joint swelling or prior surgery or other processes that disturb lymphatic drainage in the leg or pelvis.

TABLE 39. Drugs Commonly Associated with Edema

Androgens
Aromatase inhibitors
Calcium channel blockers
Clonidine
Estrogens
Gabapentin and pregabalin
Glucocorticoids
Hydralazine
Insulin
Minoxidil
NSAIDs
Progestins
Tamoxifen
Thiazolidinediones

Although the differential diagnosis for the cause of lower extremity edema is broad, a careful history and physical examination are central to establishing a correct diagnosis and to guiding diagnostic testing. In patients with generalized edema, obtaining a complete blood count, electrolytes, blood urea nitrogen level, serum creatinine level, liver chemistry tests, serum albumin level, and urinalysis is a reasonable initial step. For patients with acute unilateral leg pain and swelling, venous ultrasonography to evaluate for thromboembolism should be considered. Subsequent testing should be based on the likelihood of the potential causes of edema that may be present in a specific patient; treatment is based on managing the underlying cause.

Chronic Venous Insufficiency

Leg edema is frequently caused by chronic venous insufficiency, which can result from various conditions that damage the leg veins and their valves. Risk factors associated with the development of chronic venous insufficiency include tobacco use, obesity, increasing age, family history of venous disease, history of venous thromboembolism and/or lower extremity trauma, and pregnancy. Postthrombotic syndrome is the development of chronic venous insufficiency following an acute deep venous thrombosis.

The edema associated with chronic venous insufficiency typically is insidious in onset. It worsens with prolonged standing and is improved with elevating the legs and with walking. Leg discomfort is another common manifestation of chronic venous insufficiency. The pain is often gradual in onset and is described as a tired or heavy sensation in the legs. Pain is also worsened with prolonged standing and improves with walking and leg elevation. Other symptoms can include pruritus, skin discoloration, and ulceration. On examination, there is leg edema, and skin findings can include a shiny, atrophic appearance to the skin in addition to varicose veins and telangiectasias. In severe cases, there may be ulceration overlying the medial malleolus. The ulceration is often surrounded by skin that is erythematous, scaled, and weeping. The pain associated with venous ulcers is variable, ranging from mild to severe. Additional diagnostic testing is not usually necessary to correctly diagnose chronic venous insufficiency; however, venous duplex ultrasonography can help to determine severity and document valvular incompetence.

For patients with chronic venous insufficiency, first-line therapy includes compression, leg elevation, and exercise. Addressing reversible risk factors, such as weight loss in obese patients, is also advisable. Diuretics should generally be avoided in these patients. Ablation therapy (chemical, surgical, and thermal) should be reserved for patients who have failed to respond to conservative therapy for at least 6 months and who have documented retrograde valvular flow on duplex ultrasonography (>0.5 seconds in duration). Compression stockings are frequently used to prevent postthrombotic syndrome following venous thromboembolism, although a recent randomized controlled trial did not find any benefit. Dry skin, itching, and eczematous changes are treated with moisturizers. Venous ulcers are discussed within MKSAP 17 Dermatology.

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Musculoskeletal Pain

Low Back Pain

Diagnosis and Evaluation

Low back pain may be acute (lasting <4 weeks), subacute (lasting 4–12 weeks), or chronic (lasting >12 weeks). Most episodes are self-limited, and 90% of patients recover fully within 6 weeks. Recommendations from the American College of Physicians for diagnosing and treating patients with low back pain are provided in **Table 40**.

History and Physical Examination

Patients with low back pain can be grouped into one of three broad categories: those having nonspecific pain (about 85%); those having pain with radiculopathy or spinal stenosis (about 7%); and those having pain possibly associated with another specific spine disorder, such as cancer (0.7%), compression fracture (4%), infection (0.01%), or ankylosing spondylitis (0.3%). Low back pain my also stem from problems outside of the back (such as pancreatitis, aortic aneurysm, systemic illness, nephrolithiasis), but these conditions are unlikely to present with an isolated symptom of low back pain. Prevalence of various causes of back pain should be considered when assessing a patient, and testing to rule out uncommon causes in patients without risk factors or supportive history should not be performed. The history and physical examination should focus on determining the likelihood of a specific underlying condition causing the back pain and identifying neurologic involvement.

Although most patients with low back pain have nonspecific findings, features of the history associated with specific underlying disorders are presented in **Table 41**. A stepwise approach to the initial evaluation (**Figure 9**) and management

TABLE 40. Recommendations for Managing Low Back Pain

Perform a focused history and physical examination, including assessment of psychosocial risk factors, to classify patients into one of three broad categories:

- Nonspecific low back pain
- Back pain potentially associated with radiculopathy or spinal stenosis
- Back pain potentially associated with another specific spinal cause

Do not routinely obtain imaging or other diagnostic tests in patients with nonspecific low back pain.

Perform diagnostic imaging and testing when severe or progressive neurologic deficits are present or when serious underlying conditions are suspected.

Evaluate patients with persistent low back pain and signs or symptoms of radiculopathy or spinal stenosis with MRI (preferred) or CT only if they are potential candidates for surgery or epidural glucocorticoid injection for suspected radiculopathy.

Provide patients with evidence-based information on low back pain with regard to their expected course, advise patients to remain active, and provide information about effective self-care options.

Consider the use of medications with proven benefits in conjunction with back care information and self-care. For most patients, first-line medication options are acetaminophen or NSAIDs.

For patients who do not improve with self-care options, consider the addition of nonpharmacologic therapy with proven benefits, such as spinal manipulation, exercise therapy, and massage therapy.

Adapted with permission from Chou R, Qaseem A, Snow V, et al; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007 Oct 2;147(7):478-91. Erratum in: Ann Intern Med. 2008 Feb 5;148(3):247-8. [PMID: 17909209]

TABLE 41. History Features and Suggested Diagnoses in Low Back Pain

Suggested Diagnosis	History Feature
Cancer	Unexplained weight loss
	Failure to improve after 1 month
	No relief with bed rest
Infection	Fever
	Injection drug abuse
	Urinary tract infection
	Skin infection
Inflammatory/ rheumatologic condition	Presence of morning stiffness
	Pain not relieved when supine
	Pain persisting for >3 months
	Gradual onset
	Involvement of other joints
Nerve root irritation (radiculopathy)	Sciatica
	Increased pain with cough, sneeze, or Valsalva maneuver
Spinal stenosis	Severe leg pain
	No pain when seated
	Pseudoclaudication[a]
Compression fracture	Trauma
	Glucocorticoid use
	Osteoporosis
Cauda equina syndrome[b]	Bowel or bladder dysfunction
	Saddle sensory loss
	Rapidly progressive neurologic deficits

[a]Lower extremity symptoms caused by lumbar spinal stenosis mimicking vascular ischemia, including worsened pain with walking or standing and relief with sitting; also termed neurogenic claudication.

[b]Compression of the lumbar and sacral nerves below the termination of the spinal cord (conus medullaris). Characterized by back pain; sensory changes in the S3 to S5 dermatomes (saddle anesthesia); bowel, bladder, and sexual dysfunction; and absent Achilles tendon reflexes bilaterally.

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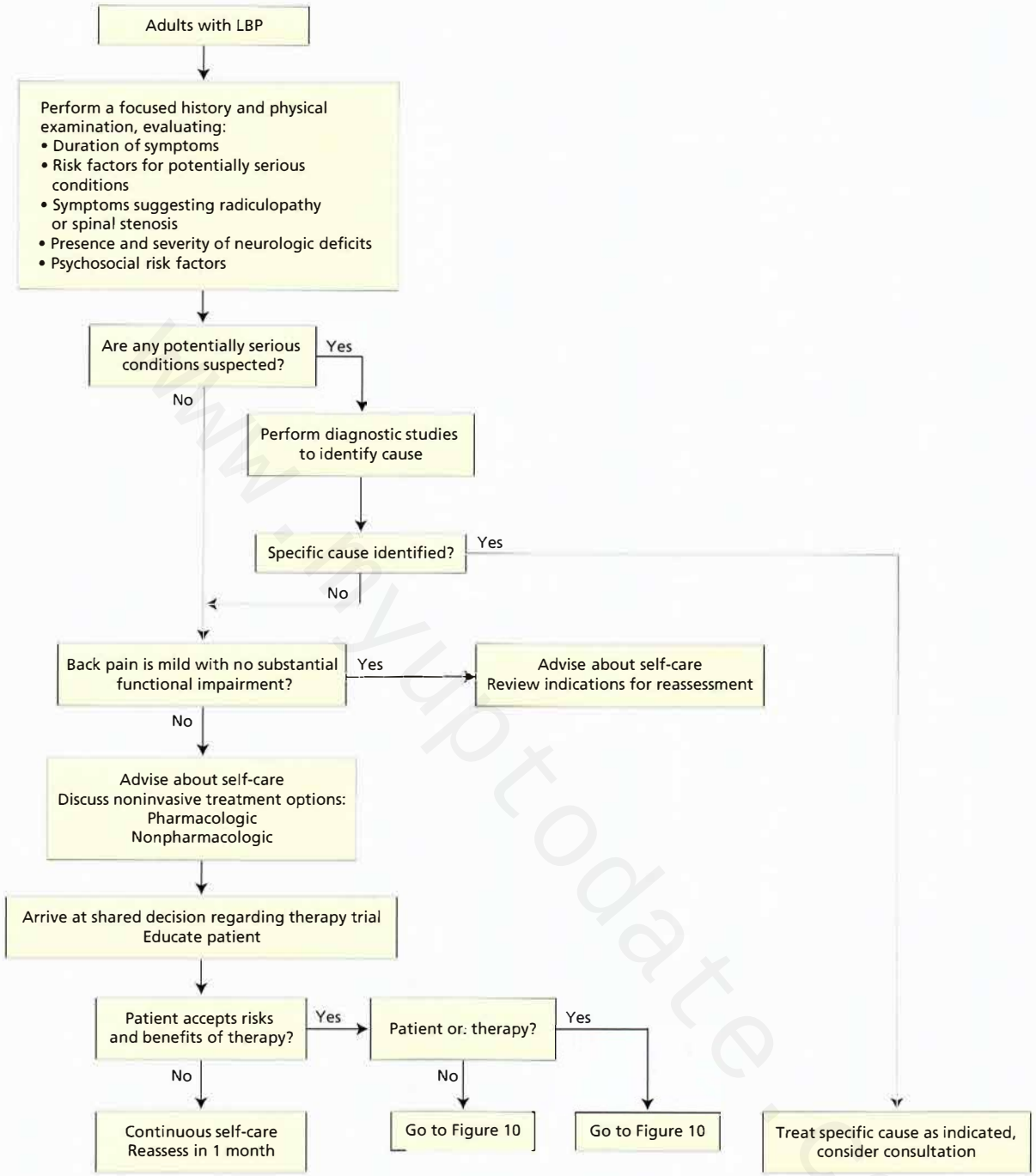

FIGURE 9. Initial evaluation of low back pain. NOTE: Do not use this algorithm for back pain associated with major trauma, nonspinal back pain, or back pain due to systemic illness.

LBP = low back pain.

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(**Figure 10**) of low back pain is provided. Age is a useful predictor to help differentiate causes of low back pain, as the risk for concerning diagnoses, cancer, compression fractures, and spinal stenosis are significantly more likely in patients older than 50 years.

Physical examination findings may help determine whether the patient has nonspecific low back pain, radiculopathy or spinal stenosis, or a specific spinal pathology. Skin findings such as erythema or psoriasis may suggest infection or an inflammatory arthritis. Percussion over the spinal processes

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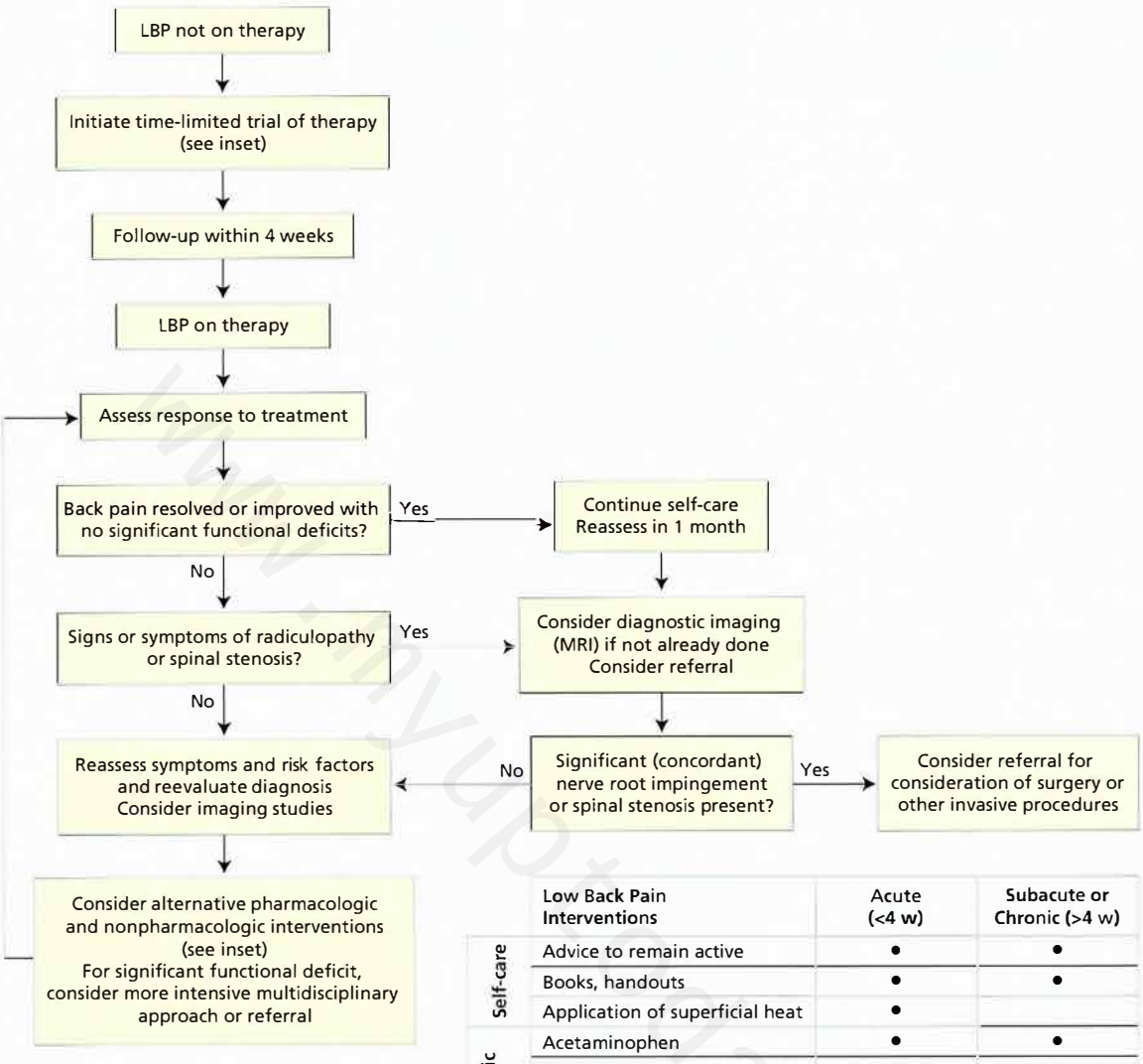

	Low Back Pain Interventions	Acute (<4 w)	Subacute or Chronic (>4 w)
Self-care	Advice to remain active	•	•
	Books, handouts	•	•
	Application of superficial heat	•	
Pharmacologic therapy	Acetaminophen	•	•
	NSAIDs	•	•
	Skeletal muscle relaxants	•	
	Antidepressants (TCAs)		•
	Benzodiazepines	•	•
	Tramadol, opioids	•	•
Nonpharmacologic therapy	Spinal manipulation	•	•
	Exercise therapy		•
	Massage		•
	Acupuncture		•
	Yoga		•
	Cognitive-behavioral therapy		•
	Progressive relaxation		•
	Intensive interdisciplinary rehabilitation		•

• Intervention supported by grade B evidence (at least fair-quality evidence of moderate benefit, or small benefit but no significant harms, costs, or burdens). No intervention was supported by grade A evidence (good-quality evidence of substantial benefit).

FIGURE 10. Management of low back pain.

LBP = low back pain; TCAs = tricyclic antidepressants.

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that induces pain may indicate compression fracture or disk space infection. Reproduction of pain with palpation over the paraspinus muscles or the posterior superior iliac spine is more consistent with nonspecific (musculoskeletal) pain. Reproduction of the pain with back range of motion can also be helpful in determining etiology.

Physical examination findings for patients with possible lumbar disk herniation and nerve root impingement are provided in **Table 42**. The straight-leg raise test has a sensitivity of 91% for diagnosing disk herniation. This maneuver involves raising the patient's leg 30 to 70 degrees off the table with the patient in the supine position. A positive test is defined as development of a shooting or electric shock sensation from the hip to the ankle when the leg is raised.

KEY POINT

- In patients with low back pain, the history and physical examination should focus on determining the likelihood of a specific underlying condition causing the pain and identifying neurologic involvement.

Further Diagnostic Testing

Most patients who present with back pain do not require additional imaging or testing and will recover with supportive measures. Diagnostic studies should not be routinely obtained in patients with nonspecific low back pain; such testing should be reserved for patients with severe or progressive neurologic deficits, patients for whom a serious underlying condition is suspected, or patients who do not have symptom improvement after 4 to 6 weeks of conservative management.

In patients with radiculopathy or spinal stenosis, routine imaging has not been shown to improve outcomes. For those patients in whom a trial of conservative therapy fails, further testing might be considered. The American College of Physicians recommends MRI (preferred) or CT for radiculopathy or spinal stenosis only for those patients who are candidates for epidural glucocorticoid injection or surgery. If cancer or vertebral infection is suspected, a plain radiograph, MRI, or erythrocyte sedimentation rate may be helpful. MRI or electromyography should be considered in patients with suspected spinal stenosis, cauda equina syndrome, or severe and progressive neurologic deficits. A vertebral fracture can usually be diagnosed by plain radiography. If features of ankylosing spondylitis are present, plain radiography of the sacroiliac joints and erythrocyte sedimentation rate may help determine the cause of pain.

When to Refer

Indications for surgical referral include features of cauda equina syndrome (a surgical emergency), presence of severe neurologic deficits, suspected spinal cord compression, neuromotor deficits, or significant pain that persists after 6 weeks of conservative therapy. H

KEY POINTS

- Most patients who present with low back pain do not require additional imaging or testing. HVC
- Diagnostic testing for low back pain should be reserved for patients with severe or progressive neurologic deficits, patients for whom a serious underlying condition is suspected, or patients who do not have symptom improvement after 4 to 6 weeks of conservative management. HVC

Treatment

Most patients with acute low back pain recover quickly no matter what therapeutic intervention is used. Because the overall prognosis for acute musculoskeletal low back pain is excellent, therapeutic interventions should focus on symptom management and maintaining function (see Figure 10). Follow-up should occur within 4 weeks to determine response to therapy and whether additional treatment or evaluation is needed. If there is no response to treatment, additional workup for spinal stenosis or radiculopathy should be considered if suggestive symptoms are present. If no symptoms of spinal stenosis are present, alternative pharmacologic and nonpharmacologic interventions should be considered.

TABLE 42. Physical Examination Findings for Lumbar Disk and Nerve Root Impingement

Disk	Nerve Root	Affected Reflex	Involved Muscles	Location of Altered Sensation
L3-L4	L4	Patellar reflex	Anterior tibialis (dorsiflexion and inversion of foot at ankle)	Medial leg, medial foot, medial aspect of great toe
L4-L5	L5	None	Extensor hallucis longus, anterior tibialis, deep peroneal (extension of great toe and dorsiflexion of foot at ankle); extensor digitorum longus and brevis (dorsiflexion of toes 2, 3, 4); gluteus medius and minimus (hip and pelvic abduction)	Lateral leg; dorsum of foot; toes 2, 3, 4
L5-S1	S1	Achilles tendon reflex	Gastrocnemius and soleus (plantar flexion of foot at ankle); peroneus longus and brevis (foot plantar flexion and eversion); gluteus maximus (hip extension)	Posterior aspect of the leg, lateral aspect of foot, lateral aspect of little toe

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Nonpharmacologic Treatment

An important part of treatment of acute low back pain is educating patients that recovery is generally quick regardless of the intervention used. Whenever possible, maintaining daily activities should be encouraged. Application of heat may also be beneficial for acute back pain. Bed rest for patients with and without sciatica should generally be avoided, as bed rest is associated with decrease in functional recovery and increase in pain. Spinal manipulation is associated with modest benefits in treating acute low back pain, comparable to conventional therapy. Physical therapy is not typically recommended for treatment of acute low back pain.

For subacute and chronic low back pain, interdisciplinary rehabilitation (physician coordination of psychological, physical, and vocational therapy) has been shown to improve pain. A systematic review concluded that massage for low back pain may be beneficial for patients with subacute and chronic pain without neurologic symptoms. Lumbar supports are unlikely to be better than no intervention at all. Acupuncture, yoga, cognitive-behavioral therapy, and intensive rehabilitation should be reserved for patients with chronic low back pain.

Pharmacologic Treatment

Acetaminophen or NSAIDs are first-line pharmacotherapy for low back pain. NSAIDs should be used with caution in patients at increased risk for nephrotoxicity or for gastrointestinal ulcer. All NSAIDs are equally effective for treatment of low back pain. Opioid analgesics may be helpful when acetaminophen or NSAIDs are not adequate. Medications should be given at the lowest possible dose and for the shortest possible time. Muscle relaxants and benzodiazepines may be modestly beneficial for pain relief; however, side effects of dizziness and sedation limit their usefulness. Systemic glucocorticoids have not been shown to be effective in the treatment of low back pain.

Interventional and Surgical Treatment

Epidural glucocorticoid injections may provide short-term relief for patients with radiculopathy caused by disk herniation; however, the FDA issued a warning in 2014 regarding injection of glucocorticoids into the epidural space. The warning states that these injections may result in rare, but serious, adverse events, such as vision loss, stroke, paralysis, and death. Furthermore, the FDA states that the effectiveness and safety have not been established and glucocorticoids are not approved for this use.

Surgery has been shown to have definite benefits only for patients with disk herniation causing persistent radiculopathy, patients with painful spinal stenosis, and those with cauda equina syndrome. For patients with radiculopathy, diskectomy is associated with improved outcomes at 6 to 12 weeks compared with nonsurgical therapy. In patients with spinal stenosis, decompressive laminectomy has been shown to provide moderate benefit compared with nonsurgical therapy for the first 1 to 2 years postoperatively. However, effects diminish over time.

Treatment of cauda equina syndrome typically involves prompt surgical decompression of the affected area of the spinal cord.

KEY POINTS

- Most patients with acute musculoskeletal low back pain have an excellent prognosis no matter what therapeutic intervention is used; therapeutic interventions should focus on symptom management and maintaining function. **HVC**
- Most patients with acute low back pain should try to maintain daily activities and avoid bed rest whenever possible.
- Acetaminophen or NSAIDs is first-line pharmacotherapy for treatment of low back pain.
- Surgery has been shown to have definite benefits only for patients with low back pain due to disk herniation causing persistent radiculopathy, patients with painful spinal stenosis, and those with cauda equina syndrome. **HVC**

Neck Pain

Diagnosis and Evaluation

Neck pain may be broadly grouped into three categories (**Table 43**). Mechanical pain arises from the muscles, soft tissues, and joints. Neurogenic pain originates from cervical nerve roots or the spinal cord. Systemic diseases induce neck pain because of inflammation or mass effect.

Onset, character, and location of neck pain should be determined, along with precipitating and mitigating factors and any associated symptoms. Physical examination should focus on reproducing the pain by palpation, assessing range of motion, and testing strength and reflexes, as well as identifying any upper motoneuron signs.

Mechanical neck pain is usually an aching sensation that is isolated to the neck but can radiate to the posterior head or shoulders. History often reveals an antecedent injury, such as a fall or motor vehicle accident. Mechanical neck pain can also be exacerbated by an unaccustomed activity or overuse. Physical examination findings usually show decreased range of motion, tenderness to palpation, and reproduction of the pain with flexion or extension.

Neurogenic neck pain is usually described as a burning or tingling sensation that may radiate down the arms. Dermatomal numbness or muscle weakness may be present (**Table 44**). On physical examination, maneuvers to compress the spinal nerves may reproduce the pain or cause radiation down the arms. Examples include worsening of symptoms with extension and rotation of the patient's neck toward the symptomatic side when an axial load is placed on the patient's head (Spurling test), and improvement when the symptomatic arm is lifted above the head with resting of the hand on the top

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TABLE 43. Evaluation of Neck Pain

Category	History	Physical Examination Findings
Mechanical neck pain (muscle, ligament, facet, intervertebral disk, soft tissue)	Pain (usually episodic, deep, dull, and aching) and stiffness Pain may be precipitated or aggravated by excessive or unaccustomed activity or sustaining an awkward posture without a specific injury Ligament, muscle, and facet pain are localized and asymmetric Pain from upper cervical segments is referred toward the head; pain from lower segments is referred to the upper limb girdle	Decrease in active and passive range of motion Superficial tenderness indicates soft-tissue pain; deep tenderness indicates muscle or bone pain Pain on extension or ipsilateral lateral flexion usually indicates facet pain; pain on flexion or contralateral lateral flexion usually indicates soft-tissue pain
Neurogenic neck pain (cervical nerve root and/or spinal cord)	Significant root pain; sharp, intense, often described as a burning sensation; may radiate to the trapezial and periscapular regions or down the arm Numbness in a dermatomal distribution and motor weakness in a myotomal distribution Symptoms often more severe with certain movement	Neurologic examination may show motor weakness, usually involving several cervical levels and often asymmetric, affecting one or both arms Look for plantar extensor response, gait disorder, and spasticity in patients with spinal cord involvement Bilateral or multilevel involvement indicates more severe pathology
Neck pain associated with systemic disease	Fever, malaise, or pain in areas in addition to the neck Pain is usually severe, relentless, and progressive Symptoms or signs may be progressive despite treatment	Complete physical examination may show underlying systemic disease, such as inflammatory joint disease, organ infection, or neoplastic process

Adapted with permission from Huang S, Tsang IK. Neck pain. http://smartmedicine.acponline.org/content.aspx?gbosId=88. In ACP Smart Medicine (online database). Philadelphia: American College of Physicians, 2015. Accessed May 5, 2015.

TABLE 44. Physical Examination Findings for Cervical Disk and Nerve Root Impingement

Disk	Nerve Root	Affected Reflex	Involved Muscles	Location of Altered Sensation
C4-C5	C5	Biceps reflex	Deltoid, biceps, and rhomboid (arm abduction and flexion at the shoulder)	Lateral arm
C5-C6	C6	Brachioradialis reflex	Biceps and brachioradialis (wrist extensors and elbow flexors)	Anterior lateral forearm, palm, thumb, and second digit
C6-C7	C7	Triceps reflex	Triceps and finger extensors (elbow and finger extensors)	Middle of the palm and third digit
C7-T1	C8	None	Finger flexors	Anterior and medial hand and forearm, fourth and fifth digits
T1-T2	T1	None	Hand intrinsics (abduction and adduction)	Anterior medial arm (distal aspect of arm to proximal aspect of forearm)

of the head (shoulder abduction relief test). Both of these tests have low to moderate sensitivity but relatively high specificity for cervical nerve root compression. Upper motoneuron findings such as spasticity or hyperreflexia may indicate spinal cord involvement.

Features in the history that indicate a possible systemic origin of neck pain include fever, weight loss, polyarthritis, and changes in vision, as well as a history of immunosuppression, cancer, or injection drug use.

Imaging studies are not needed for most patients with neck pain. When mechanical pain is present, imaging is primarily indicated after trauma to rule out fracture. Plain cervical radiography may be helpful for evaluating older patients with examination findings suggestive of malignancy or degenerative osteoarthritic changes. MRI or CT myelography is indicated for patients with neurologic signs of weakness or spinal cord involvement. Imaging may also be indicated if tumor, abscess, or pathologic fracture is suspected.

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Laboratory testing is also not needed for most patients with neck pain. However, if a systemic illness such as an infectious, malignant, or rheumatologic disorder is suspected, targeted blood tests (such as erythrocyte sedimentation rate, C-reactive protein measurement, and complete blood count) may aid in establishing the diagnosis.

KEY POINT

HVC
- Imaging studies and laboratory testing are not needed for most patients with neck pain; patients with a history of trauma, presence of neurologic signs or symptoms, fever, weight loss, or immunosuppression may require additional testing.

Treatment

The mainstays of treatment for neck pain are mobilization, exercise, and analgesic agents. Most patients with neck pain recover with conservative therapy. Mechanical neck pain is treated with mobilization and physical therapy that focuses on improving range of motion and posture; systematic reviews have shown that these interventions improve neck pain over the short and intermediate terms. Over-the-counter acetaminophen and NSAIDs often provide acute pain relief. Opioid analgesic agents and skeletal muscle relaxants should only be used if over-the-counter agents are ineffective in treating moderate to severe neck pain. Neurogenic neck pain may respond to agents such as gabapentin and tricyclic antidepressants. Therapy for neck pain associated with systemic illness should focus on treating the underlying condition.

Acupuncture has been studied in the treatment of chronic neck pain and may provide short-term improvement in symptoms. Glucocorticoid injections have been used for patients with cervical radiculopathy that does not respond to pharmacotherapy; however, the FDA does not approve glucocorticoids for this use. Systemic glucocorticoids are not indicated for the treatment of neck pain. Surgery may be beneficial for patients with progressive neurologic symptoms that are caused by a defined anatomic abnormality. Surgical management of chronic neck pain is controversial and is usually limited to patients with neurologic symptoms.

KEY POINT

HVC
- Most patients with neck pain recover with conservative therapy, including mobilization, exercise, analgesic agents, and physical therapy.

Upper Extremity Disorders

Thoracic Outlet Syndrome

Thoracic outlet syndrome is caused by compression of the brachial plexus, subclavian artery, and subclavian vein as these structures pass through the thoracic outlet. There are three main clinical subtypes of thoracic outlet syndrome, defined by the primary structure involved.

Neurogenic thoracic outlet syndrome is the most common subtype and is caused by compression of the brachial plexus nerve roots as they exit the triangle formed by the first rib and the scalenus anticus and medius muscles. Symptoms include paresthesias and pain that typically worsen with activities that involve continued use of the arm or hand, especially those that include elevation of the arm. First-line therapy consists of physical therapy, rest, avoiding aggravating activities, and ergonomic modifications. Surgical intervention consists of resection of the first rib and anterior scalenectomy; surgery can be considered in patients who fail to respond to conservative measures.

Venous thoracic outlet syndrome is usually caused by thrombosis of the subclavian and/or axillary veins as they pass through the triangle formed by the clavicle, first rib, and subclavius and scalenus anticus muscles. Common symptoms include pain, swelling, and cyanosis, which occur with repeated activities involving the arms, especially when such activities involve using the arm above the plane of the shoulder. Dilated collateral veins may be seen on the chest wall, neck, and shoulder. First-line therapy consists of timely catheter-directed thrombolysis, followed by surgical decompression shortly thereafter.

Arterial thoracic outlet syndrome refers to compression of the subclavian artery usually by a cervical rib or anomalous bone, with or without distal thromboembolism. It is the least common form of thoracic outlet syndrome but is potentially dangerous as it can result in significant morbidity. This compression leads to ischemic symptoms such as exertional pain, easy fatigability, pallor, and paresthesias in the involved arm. Surgical repair or resection alleviates the compression of the affected structure. For patients with associated thrombosis, treatment consists of catheter-directed thrombolysis for patients with mild symptoms and surgical embolectomy for patients with more severe symptoms.

Shoulder Pain

Diagnosis and Evaluation

The initial diagnostic step is to determine whether the pain is originating in the shoulder or referred from a distant site. Pain with shoulder movement accompanied by stiffness and limited range of motion favors an intrinsic disorder, whereas a normal shoulder examination suggests referred pain. Neck pain and stiffness, decreased neck range of motion, and pain extending below the elbow all support pain being referred from the cervical spine.

Shoulder examination includes inspection, palpation, range-of-motion testing, and specific test maneuvers (**Table 45**). Both shoulders should be fully exposed to detect asymmetry. All important structures should be palpated in a systematic manner. Both active and passive range of motion should be tested. Articular disorders are characterized by limited active and passive movements, whereas extra-articular disorders are associated only with limited active movements.

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TABLE 45. Shoulder Examination Maneuvers

Test	Description
Cross-arm	Patient abducts arm to 90 degrees and then actively adducts arm across body.
	Positive test: Pain in the acromioclavicular joint region (suggests acromioclavicular joint disorder)
Drop-arm	Patient's arm is passively abducted to 90 degrees; patient is then asked to slowly lower arm to waist.
	Positive test: Patient's arm will drop down (indicates supraspinatus tear)
External rotation lag	Patient's arm is abducted to 20 degrees. Examiner passively externally rotates arm.
	Positive test: Patient is unable to maintain a position of full external rotation (suggests possible tear of supraspinatus and infraspinatus muscles)
External rotation resistance	Patient's arm is placed at side with elbow flexed 90 degrees. Examiner stabilizes elbow and applies force proximal to wrist while patient attempts external rotation.
	Positive test: Pain or weakness (suggests infraspinatus tear or tendinopathy)
Hawkins	Patient's shoulder is flexed to 90 degrees, elbow is flexed to 90 degrees, and forearm is placed in neutral rotation. Then, while supporting the arm, the humerus is rotated internally.
	Positive test: Pain (suggests subacromial impingement)
Internal rotation lag	Patient internally rotates arm behind back. Examiner lifts hand off patient's back and patient is asked to maintain position while examiner applies a counteracting force.
	Positive test: Patient is unable to maintain position (suggests subscapularis tear)
Neer	Patient's scapula is stabilized and shoulder is flexed with arm fully pronated.
	Positive test: Pain (suggests subacromial impingement or rotator cuff tendinitis)
Painful arc	Patient actively abducts arm.
	Positive test: Pain between 60 and 120 degrees of abduction (suggests subacromial impingement)
Yergason	Patient's elbow is flexed to 90 degrees with thumb pointing up. Examiner grasps wrist and attempts to resist active supination and elbow flexion by patient.
	Positive test: Pain (suggests bicipital tendinitis)
"Empty can"	Patient's shoulder is passively abducted to 90 degrees in forward flexion and then is maximally internally rotated with thumb pointing down. Examiner applies downward pressure at wrist or elbow while patient resists.
	Positive test: Weakness (suggests supraspinatus tendon tear)

KEY POINT

- When evaluating patients with shoulder pain, pain with shoulder movement accompanied by stiffness and limited range of motion favors an intrinsic disorder, whereas a normal shoulder examination suggests referred pain.

Rotator Cuff Disorders

Rotator cuff disorders include rotator cuff tendinitis, rotator cuff tears, and subacromial bursitis. The subacromial impingement syndrome results from altered mechanics of the shoulder that lead to compression of the soft tissues of the shoulder complex between the humeral head and the undersurface of the acromion, acromioclavicular joint, or the coracoacromial arch, leading to rotator cuff tendinitis and subacromial bursitis. Pain is often described as dull and worsened with overhead activities and at night. The site of pain varies but is frequently located in the deltoid region. Decreased range of motion, weakness, and stiffness may also be reported.

On examination, posterior inspection may reveal supraspinatus and infraspinatus muscle atrophy. Tenderness associated with bicipital tendinitis may be elicited on palpating the insertion of the long head of the biceps tendon. Active range of motion is usually limited, whereas passive range of motion is preserved. Strength is usually preserved in the absence of a full-thickness rotator cuff tear. Specific maneuvers for diagnosis can generally be divided into those that attempt to provoke pain, such as the painful arc test (**Figure 11**), and those that assess strength, such as the drop-arm test (**Figure 12**; see Table 45). Only limited and largely suboptimal quality data exist concerning the usefulness of each of these maneuvers. Imaging of the shoulder is typically not needed but should be considered if a full-thickness rotator cuff tear is suspected or if there is diagnostic uncertainty. MRI is the preferred imaging modality.

Conservative therapy is indicated for patients with suspected rotator cuff tendinitis and subacromial bursitis. Patients should be instructed to avoid repetitive overhead activities and to refrain from lifting heavy objects. Performing exercises that strengthen the rotator cuff muscles and improve flexibility has also been shown to be effective in improving pain, as has the use of NSAIDs. Although data are limited, acetaminophen can be used as a safe alternative to NSAIDs. The effectiveness of

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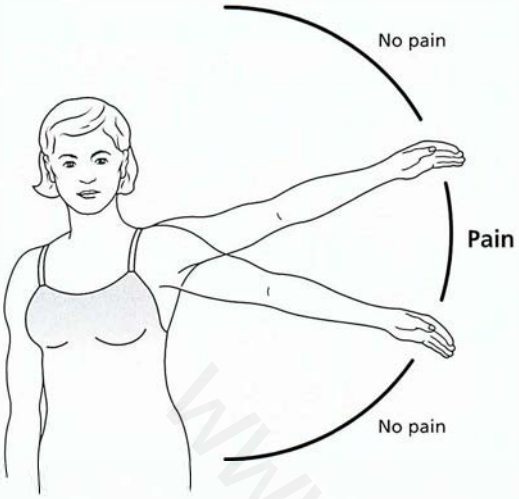

FIGURE 11. The painful arc test. The painful arc test is performed by asking the patient to actively abduct the affected arm and is considered to be positive when pain is present between 60 degrees and 120 degrees of active abduction. A positive test result suggests the presence of subacromial impingement syndrome due to subacromial bursitis or rotator cuff tendinitis.

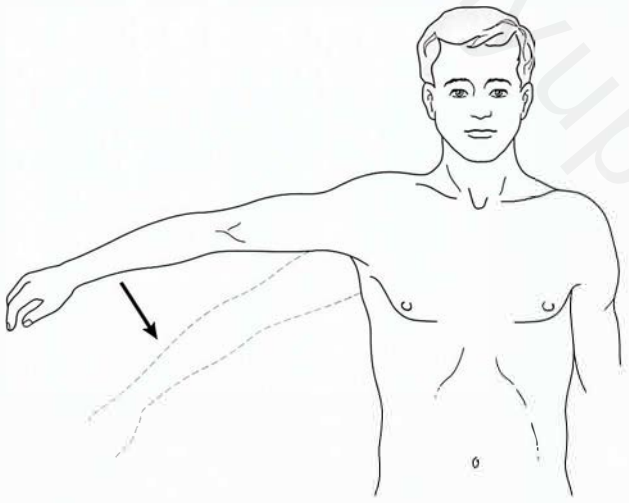

FIGURE 12. Drop-arm test. The patient's arm is passively abducted to 90 degrees. The patient is then asked to lower the arm slowly. The test is positive when the arm quickly drops down to the side.

subacromial glucocorticoid injections appears to be short-lived, although the available evidence is conflicting. Given the conflicting evidence, it is reasonable to offer a single glucocorticoid injection to patients who fail to respond to 4 to 6 weeks of the aforementioned measures or initially in patients whose pain is so severe that they are unable to participate in therapy.

Initial management of partial rotator cuff tears is identical to that for rotator cuff tendinitis and subacromial bursitis. Immediate surgery is indicated for an acute full-thickness tear in younger patients, although full-thickness tears are frequently managed conservatively in older patients. Surgery may also be considered for patients with partial tears who fail to respond to conservative therapy.

KEY POINT

- Although most rotator cuff tears can be managed conservatively, immediate surgery is indicated for younger patients with an acute full-thickness tear, and surgery may be indicated for patients with partial tears who do not respond to conservative therapy. HVC

Adhesive Capsulitis

Adhesive capsulitis ("frozen shoulder") is a poorly understood condition associated with development of glenohumeral joint capsule thickening and fibrosis. It most frequently occurs in patients aged 40 to 70 years and is more common in women than in men. Adhesive capsulitis may be idiopathic but may also occur following shoulder injury or surgery. Other associated conditions include diabetes mellitus, hypothyroidism, Parkinson disease, stroke, and prolonged immobility. Patients report loss of shoulder movement accompanied by pain. Examination discloses tenderness at the deltoid insertion site and significant loss of both active and passive range of motion. Plain radiographs are typically normal.

Injection of glucocorticoids into the glenohumeral joint appears to be beneficial, particularly when it is performed early in the course of the disease. Benefits are likely due to the effect of the glucocorticoid on reducing intra-articular inflammation. A systematic review supports giving up to three intra-articular glucocorticoid injections. Physical therapy appears to be less beneficial than intra-articular glucocorticoid injection, although there may be a role for physical therapy following glucocorticoid injection. NSAIDs and acetaminophen can be used for pain control. Surgery is generally reserved for patients who do not improve with 6 to 12 weeks of conservative measures. Patients should be informed that improvement in range of motion and pain may not occur for several years postoperatively.

KEY POINT

- Glucocorticoid injections into the glenohumeral joint appear to be beneficial in the treatment of adhesive capsulitis.

Acromioclavicular Joint Degeneration

Acromioclavicular joint degeneration typically presents as pain located on the superior aspect of the shoulder, although pain may be poorly localized. The acromioclavicular joint is often tender to palpation. Pain is frequently elicited on physical examination with the arm on the affected side adducted across the body (see cross-arm test in Table 45) and with abduction beyond 120 degrees. Plain radiographs reveal degenerative changes. Treatment includes NSAIDs and activity modification. Glucocorticoid injection may also provide short-term pain relief. Surgery is rarely indicated.

Elbow Pain

Diagnosis and Evaluation

Elbow pain may originate from disease in the elbow joint, its adjacent tissues, or proximate nerves. Neck, shoulder, and

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wrist pathology may also cause pain referred to the elbow. Thorough examination of the neck and affected arm is required.

Epicondylosis

Epicondylosis and epicondylitis are terms used interchangeably to refer to noninflammatory pathology of the major tendons traversing the elbow joint. Lateral and medial epicondylosis are considered to be overload injuries, which occur after minor, often unrecognized, trauma to the proximal insertion of the extensor (tennis elbow) or flexor (golfer's elbow) muscles of the forearm. Lateral epicondylosis is induced by activities requiring repetitive wrist extension, such as prolonged computer use or racquet sports. Pain is located over the lateral elbow but may also radiate to the dorsal forearm. Tenderness over the lateral elbow and pain with resisted wrist extension are characteristic examination findings. Medial epicondylosis is caused by repetitive wrist flexion. Pain and tenderness are located over the medial elbow and ventral forearm and worsen with resisted wrist flexion.

Imaging studies are not indicated for patients with clinical findings consistent with epicondylosis. Initial management includes NSAIDs and avoidance of activities that cause pain. A brace may be useful when exacerbating activities cannot be avoided. Both oral and topical NSAIDs may provide short-term pain relief. Gentle physical therapy (stretching and strengthening exercises) can begin after the acute pain has improved. Glucocorticoid injections may improve symptoms in the short-term, but data are conflicting on long-term benefit. Surgery is indicated only for patients with intractable pain.

KEY POINT

HVC
- Imaging studies are not indicated for patients with clinical findings consistent with epicondylosis.

Olecranon Bursitis

Trauma, gout, rheumatoid arthritis, and infection may cause inflammation of the olecranon bursa. Examination reveals swelling and tenderness over the posterior elbow but normal range of motion (**Figure 13**). Most cases are of benign cause (painless swelling) and are self-limited with conservative management including ice, compression elbow sleeve, and avoiding trauma by protective padding over the elbow. Aspiration with fluid culture, cell count, and crystal analysis should be performed in patients with severe pain, fever, or other suspicion of infection. The cornerstone of therapy is patient education regarding joint protection, such as avoiding impact and pressure on the elbow. Noninfectious olecranon bursitis may be treated with NSAIDs. Glucocorticoid injections have questionable efficacy and considerable side effects (for example, hyperglycemia, infection); therefore, they should be reserved for refractory cases. Infectious or refractory bursitis may require surgery.

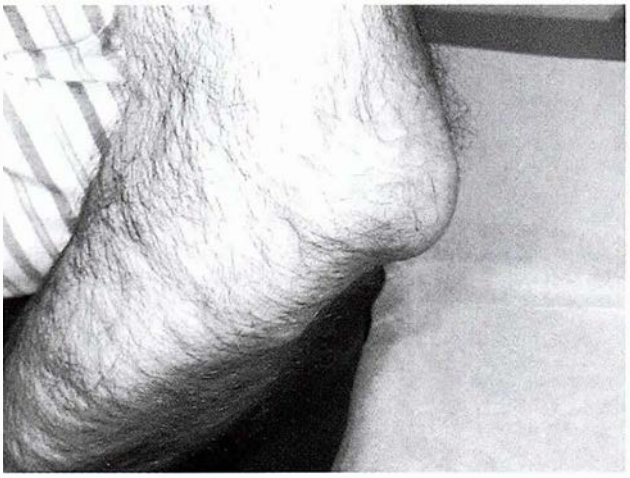

FIGURE 13. Olecranon bursitis with swelling restricted to the posterior elbow.

Ulnar Nerve Entrapment

Ulnar nerve entrapment, sometimes referred to as cubital tunnel syndrome, may occur at the level of the elbow and may be caused by bone spurs, ganglion cysts, ulnar nerve subluxation, or constriction from fibrous tissue. Repetitive elbow flexion and extension can further exacerbate the syndrome. Symptoms and signs range from elbow pain that worsens with flexion of the elbow to paresthesias and numbness of the fourth and fifth fingers and weakness of the interosseous muscles. Diagnosis may be made clinically in patients with characteristic manifestations, although electromyography may be helpful in some patients. Plain radiography is useful to identify potential bony causes, although MRI and ultrasound are usually reserved for unclear cases. Initial treatment consists of activity modification, NSAIDs, splinting the elbow at night to prevent prolonged elbow flexion, and use of an elbow pad during the day to avoid direct trauma. Surgery is reserved for patients who fail to respond to conservative measures.

Wrist and Hand Pain

Carpal Tunnel Syndrome

Carpal tunnel syndrome is caused by median nerve compression within the carpal tunnel. Pain and paresthesias are typically present in a median nerve distribution (**Figure 14**) but may radiate into the arm and involve all five fingers. Pain frequently worsens at night and with repetitive actions. Bilateral symptoms are common (>50% of patients). Known risk factors include obesity, female gender, pregnancy, hypothyroidism, diabetes mellitus, and connective tissue disorders.

Common findings on physical examination include hypalgesia of the median nerve distribution and weakness of thumb abduction. Thenar muscle atrophy suggests severe disease. The presence of Phalen and Tinel signs has minimal diagnostic utility. Hand diagrams are useful diagnostic instruments for identifying symptom patterns associated with carpal tunnel syndrome. When diagnostic uncertainty exists, nerve conduction studies can be obtained.

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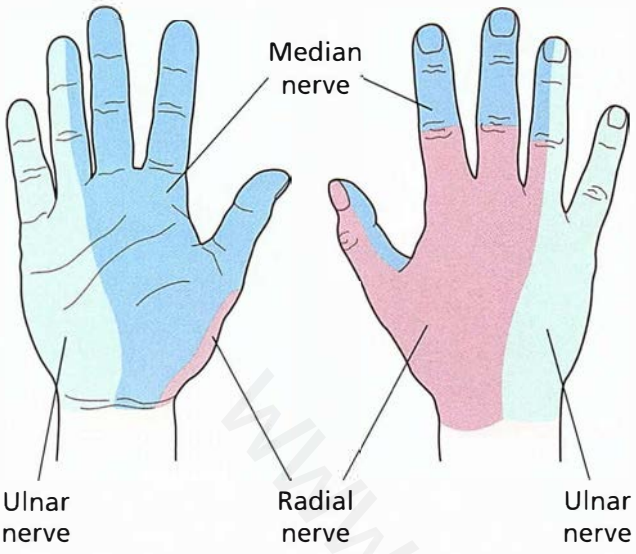

FIGURE 14. Innervation of the hand.

For patients with mild to moderate symptoms, initial therapy consists of avoiding repetitive hand and wrist motions. Neutral-position wrist splinting appears to be more effective when used full time rather than only at night. Local glucocorticoid injection can provide short-term symptomatic improvement (up to 10 weeks), and a 2-week course of an oral glucocorticoid can result in short-term symptom improvement lasting for up to 1 month. Data are lacking for use of NSAIDs and vitamin B_6. Surgery is considered first-line therapy for those who have severe disease on nerve conduction testing and in those who have muscle wasting on examination. Additional indications for surgery include failure to respond to conservative therapy, intolerable pain, and progressive numbness or weakness.

KEY POINT

HVC
- Surgery in carpal tunnel syndrome is reserved for patients who do not respond to conservative measures, have intolerable pain, have severe disease on nerve conduction testing, or have evidence of muscle wasting on examination.

Other Causes of Wrist and Hand Pain

Hamate fractures may be due to trauma or to repetitive forces such as swinging a baseball bat. Initial treatment usually consists of a short-arm cast, although surgical intervention should be considered in patients with displaced fractures.

A history of falling on an outstretched hand accompanied by pain in the anatomic snuffbox should raise suspicion for a scaphoid fracture. If plain radiographs are initially normal but clinical suspicion for a scaphoid fracture remains high, management includes immobilization with a thumb splint and repeating radiographs in 10 to 14 days. MRI is both highly sensitive and specific for diagnosing scaphoid fractures and can be useful when plain radiographs are inconclusive and a high degree of clinical suspicion remains.

Subacute pain at the thumb base that radiates to the distal radius is characteristic of de Quervain tenosynovitis (inflammation of the dorsal thumb tendons). Examination reveals distal radial styloid tenderness and pain with resisted thumb abduction and extension. Pain is also caused when the patient makes a fist over the thumb with ulnar deviation (Finkelstein test). Initial treatment consists of applying ice, using NSAIDs, and splinting. For patients with persistent symptoms who fail to improve after 4 to 6 weeks of initial therapy, local glucocorticoid injection should be offered. Glucocorticoid injection can be repeated 4 to 6 weeks later if there is no significant improvement. Surgery is reserved for patients who fail to respond to two glucocorticoid injections.

Osteoarthritis of the first carpometacarpal and proximal and distal interphalangeal joints is common. Pain is usually insidious in onset, worsens with activity, and improves with rest. Management of osteoarthritis is addressed in MKSAP 17 Rheumatology.

Ganglion cysts are cystic swellings overlying tendon sheaths or joints that are thought to be caused by herniated synovial tissue. Asymptomatic ganglion cysts do not require treatment, as they frequently regress in size. When painful, cysts can be aspirated and injected with either a crystalline glucocorticoid or hyaluronidase. For ganglion cysts that are symptomatic and fail to respond to aspiration and injection, surgical resection is a highly effective treatment option.

Ulnar nerve entrapment at the wrist may cause sensory and motor abnormalities; however, this is seen infrequently compared with carpal tunnel syndrome.

Lower Extremity Disorders

Hip Pain

Diagnosis and Evaluation

Hip pain can arise from the hip joint or from surrounding structures, including the pelvis, abdomen, or retroperitoneum. Therefore, patients reporting hip pain should be asked to identify the specific location of the pain and characterize the associated discomfort. History should focus on what activities make the pain worse or better, trauma, prior surgeries, prior cancer, occupational activities, and a review of the gastrointestinal, gynecologic, and genitourinary systems.

Physical examination should include observation of gait, inspection and palpation of the affected and unaffected hips, examination of the sacroiliac and knee joints, and hip range-of-motion testing. Having the patient isolate the most painful area by pointing with one finger may also be helpful. The FABER test assesses the ability to Flex, ABduct, and Externally Rotate the hip (**Figure 15**). If the sacroiliac joint is painful with the FABER test and there is no pain on passive range of motion, sacroiliac joint disease is likely.

The American College of Rheumatology appropriateness criteria endorse plain radiographs of the hip and pelvis as initial testing in patients with acute or chronic hip pain. Advanced imaging techniques are usually not needed and should be

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FIGURE 15. The FABER test assesses Flexion, ABduction, and External Rotation of the hip. With the leg in a figure-four position, the normal leg should attain a parallel plane with the table. Gentle downward pressure on the knee in this position simultaneously places stress on the ipsilateral sacroiliac joint.

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reserved for patients in whom osteonecrosis, occult fracture, or tumor is suspected, or in those in whom the diagnosis remains unclear or other specific diagnoses are being considered.

Specific Causes of Hip Pain

Degenerative hip disease is common and usually presents with pain radiating to the groin that often becomes worse with weight bearing. On physical examination, internal and external rotation at the hip will be limited or painful. Plain radiographs can confirm the diagnosis; changes include superolateral joint space narrowing with subchondral sclerosis. Cystic changes can also occur, and the femoral head can appear to be irregular. Oral analgesic agents are the initial treatment (see MKSAP 17 Rheumatology).

Patients with trochanteric bursitis describe an aching sensation over the greater trochanteric bursa (lateral hip) that may radiate to the buttock or knee and is often worse when lying on the affected side. It can be differentiated from hip joint pain in that it does not usually radiate to the groin or limit hip range of motion on examination. Diagnosis is made by history and by eliciting pain with palpation over the greater trochanter or reproduction of the pain when the patient takes a step up. Oral analgesic agents and physical therapy to improve gait, strength, and range of motion are first-line treatments. If these therapies are not effective, consideration of glucocorticoid injection is warranted.

Meralgia paresthetica is caused by entrapment of the lateral femoral cutaneous nerve. Patients often present with paresthesias over the anterolateral thighs. Risk factors include obesity, pregnancy, diabetes mellitus, and tight clothing or belts around the waist. Treatment should focus on mechanisms to relieve the entrapment (for example, avoiding tight clothing, weight loss). Oral analgesic agents can also provide symptomatic relief. Additionally, more aggressive management of diabetes may be indicated in appropriate patients.

Piriformis syndrome is caused by compression of the sciatic nerve by the piriformis muscle. Patients describe chronic posterior pain in the buttock. Risk factors include prolonged sitting, such as in truck drivers. Analgesic agents and physical therapy focusing on stretching exercises are the mainstays of therapy.

Osteonecrosis (avascular necrosis) of the femoral head is caused by a loss of blood supply and subsequent death and collapse of the bone. Risk factors include glucocorticoid use, prior fracture or radiation exposure, excessive alcohol use, and sickle cell anemia. Patients may initially report pain with weight bearing, but the pain can progress significantly to occur at rest and can be associated with significant decrease in joint function. Imaging with MRI (early-stage disease) or plain radiographs (later-stage disease) is necessary to establish the diagnosis. Initial treatment includes therapies to control pain (such as NSAIDs), reduced weight bearing, and range of motion exercises. Most patients with osteonecrosis will eventually need surgical intervention with hip replacement.

KEY POINT

- If the FABER (Flex, ABduct, and Externally Rotate) test demonstrates limited range of motion or hip pain, hip pathology is likely.

Knee Pain

Diagnosis and Evaluation

Pain location, circumstances of onset (including antecedent trauma), and duration can help to narrow the differential diagnosis of knee pain. Other signs and symptoms, including joint stiffness, locking, instability, and constitutional symptoms, may provide additional diagnostic clues.

Examination should be performed with both knees fully exposed. Both knees should be inspected for asymmetry, swelling, or erythema and palpated to detect focal tenderness, joint effusion, or warmth. Active and passive range of motion should then be assessed, followed by maneuvers that test the integrity of the knee ligaments and menisci (**Table 46**). Referred pain to the knee should always be considered, especially when the knee examination is normal.

Arthrocentesis is indicated for patients presenting with acute-onset knee pain accompanied by an effusion, overlying erythema, warmth, and marked tenderness. Plain radiographs are generally needed for evaluation of acute pain only if a fracture due to trauma is suspected.

Degenerative disease of the knee is discussed in MKSAP 17 Rheumatology.

KEY POINT

- In patients with acute knee pain, plain radiographs are generally needed only if a traumatic fracture is suspected. HVC

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TABLE 46. Knee Examination Maneuvers

Test	Purpose	Description
Anterior drawer	ACL integrity	Patient is supine with hip flexed to 45 degrees and knee flexed to 90 degrees. Examiner sits on dorsum of foot and places hands on proximal calf and then pulls anteriorly while assessing movement of tibia relative to femur.
		Positive test: Increased laxity with lack of firm end point (suggests ACL tear)
Lachman	ACL integrity	Patient is supine with leg in slight external rotation and knee flexed 20 degrees to 30 degrees at examiner's side. Examiner stabilizes femur with one hand and grasps proximal calf with other. Calf is pulled forward while assessing movement of tibia relative to femur.
		Positive test: Increased laxity with lack of firm end point (suggests ACL tear)
Posterior drawer	PCL integrity	Patient is supine with hip flexed to 45 degrees and knee flexed to 90 degrees. Examiner sits on dorsum of foot and places hands on proximal calf, and then pushes posteriorly while assessing movement of tibia relative to femur.
		Positive test: Increased laxity with lack of firm end point (suggests PCL tear)
Valgus stress	MCL integrity	Patient is supine with knee flexed to 30 degrees and leg slightly abducted. Examiner places one hand on lateral knee and other hand on medial distal tibia and applies valgus force.
		Positive test: Increased laxity and pain (suggests MCL tear)
Varus stress	LCL integrity	Patient is supine with knee flexed to 30 degrees and leg slightly abducted. Examiner places one hand on medial knee and other hand on lateral distal tibia and applies varus force.
		Positive test: Increased laxity and pain (suggests LCL tear)
Thessaly	Meniscal integrity	Examiner holds patient's outstretched hands while patient stands on one leg with knee flexed to 5 degrees and with other knee flexed to 90 degrees with foot off of floor. Patient rotates body internally and externally three times. Repeat with knee flexed 20 degrees. Always perform on uninvolved knee first.
		Positive test: Medial or lateral joint line pain (suggests meniscal tear)
Medial-lateral grind	Meniscal integrity	With patient supine, examiner places calf in one hand and thumb and index finger of opposite hand over joint line and applies varus and valgus stress to tibia during extension and flexion.
		Positive test: Grinding sensation palpable over joint line (suggests meniscal injury)
Noble	Iliotibial band integrity	With patient supine, examiner repeatedly flexes and extends knee with examiner's thumb placed on lateral femoral epicondyle.
		Positive test: Reproduces patient's pain (suggests iliotibial band syndrome)

ACL = anterior cruciate ligament; LCL = lateral collateral ligament; MCL = medial collateral ligament; PCL = posterior cruciate ligament.

Ligament and Meniscal Tears

Anterior cruciate ligament injury usually occurs when a person rapidly decelerates and pivots but may also develop following direct trauma resulting in knee hyperextension. A complete tear should be suspected when a popping sound is reported and the patient reports pain and knee instability. Knee swelling that begins within 2 hours is also common. The characteristic examination finding is a large effusion with increased laxity seen on both the anterior drawer and Lachman tests. Acute posterior cruciate ligament tears result from posteriorly directed forces on the knee, such as in car accidents when the knee is flexed and strikes the dashboard or when an athlete falls on a knee that is flexed. On examination, increased laxity is seen with the posterior drawer test.

A complete medial collateral ligament tear results from a direct valgus (medially directed) force and typically presents as joint instability accompanied by medial knee pain and swelling. Examination discloses medial joint line tenderness and increased laxity and pain with valgus stress. A lateral collateral ligament tear results from a direct varus (laterally directed) force and is associated with lateral knee pain and swelling. On examination, there is lateral joint line tenderness and increased laxity and pain with varus stress.

Acute meniscal tears occur from a twisting of the knee when the foot is planted and the knee is flexed. Patients with acute meniscal tears are typically able to continue participating in the activity that resulted in the injury. Chronic degenerative meniscal tears are becoming increasingly common and occur in older adults in the absence of significant twisting. Locking and catching are common symptoms of meniscal injuries. Patients with meniscal injuries frequently have positive Thessaly and medial-lateral grind tests on examination. Initial therapy for acute meniscal tears includes rest, ice, and physical therapy to strengthen the quadriceps and hamstring muscles. Consideration for surgical intervention for acute meniscal tears is typically limited to patients who have significant mechanical symptoms that persist beyond 4 weeks. MRI is reserved for patients in whom surgery is being considered and in patients with persistent locking and catching despite appropriate initial management. First-line therapy

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for chronic degenerative meniscal tears is physical therapy. Surgery for chronic degenerative meniscal tears is usually limited to patients with persistent mechanical symptoms or effusions.

KEY POINTS

- A complete anterior cruciate ligament tear should be suspected when a popping sound is reported and there is evidence of knee instability.
- A complete medial or lateral collateral ligament tear typically causes joint instability accompanied by joint line tenderness and swelling.
- Patients with acute meniscal injuries frequently have positive Thessaly and medial-lateral grind tests on examination.

Patellofemoral Pain Syndrome

Patellofemoral pain syndrome is characterized by anterior knee pain that is usually gradual in onset and worsens with running, prolonged sitting, and climbing stairs. The exact cause is not clear but appears to be due to multiple factors that affect the load distribution underneath the patella including deconditioning and patellofemoral malalignment. On physical examination, patellar tracking should be assessed by medially and laterally displacing the patella. Applying direct pressure to the patella with the knee extended may reproduce the pain. Imaging studies are usually not needed.

Treatment is challenging because of the varied causes but generally includes addressing the underlying disorder, activity modification, and physical therapy. NSAIDs, acetaminophen, bracing, and patellar taping all have limited efficacy.

Bursitis

Prepatellar bursitis is caused by inflammation of the prepatellar bursa that overlies the patella. Patients present with acute anterior knee pain and swelling. Possible causes include trauma, infection, and gout. Physical examination reveals a palpable fluid collection with preserved active and passive range of motion of the knee. Aspiration is indicated for both diagnostic and therapeutic purposes. After aspiration, a compression dressing should be applied and patients should be advised to avoid kneeling.

Pes anserine bursitis is caused by inflammation of the pes anserine bursa located at the proximal anteromedial tibia. It usually develops as a result of overuse or constant friction and stress on the bursa. Pes anserine bursitis is common in athletes, particularly runners. Persons with osteoarthritis of the knee are also susceptible. Tenderness on the anteromedial aspect of the knee 5 to 8 cm below the joint line is reproduced by palpation or by having the patient take a step up. Treatment consists of anti-inflammatory medications and application of ice as well as avoidance of direct pressure, squatting, and overuse. If conservative measures are ineffective, glucocorticoid injection may be considered.

KEY POINTS

- Patellofemoral pain syndrome is characterized by anterior knee pain that is usually gradual in onset and worsens with running, prolonged sitting, and climbing stairs; this is a clinical diagnosis and imaging studies are not usually needed.
- In patients with prepatellar bursitis, aspiration is indicated for both diagnostic and therapeutic purposes.

HVC

Iliotibial Band Syndrome

Iliotibial band syndrome is caused by inflammation of the distal iliotibial band as it slides over the lateral femoral epicondyle during knee movement. It can occur from overuse or from alterations in anatomic alignment or biomechanical function. It is a common cause of lateral knee pain in runners and can also occur in patients with significant leg length difference, excessively pronated foot, genu varum, or gluteal muscle weakness. Pain initially may be present only at completion of an activity but can progress to occur earlier during the activity and even at rest. Physical examination reveals tenderness to palpation approximately 2 cm proximal to the lateral knee joint line accompanied by weakness of hip abductors, knee flexors and extensors, and a positive Noble test (see Table 46). Initial treatment consists of activity modification, ice application, and NSAIDs to reduce inflammation. Once inflammation subsides, stretching and then strengthening exercises are indicated.

Popliteal Cyst

Popliteal (Baker) cysts in adults are synovial fluid–containing extensions of the knee joint space and generally occur as the result of osteoarthritis or trauma of the knee. The cyst is usually asymptomatic but may become painful as it enlarges. Swelling is seen in the popliteal fossa on physical examination. The knee should be examined for signs of meniscal pathology, effusion, or mechanical signs that indicate an intra-articular irritant causing excessive joint fluid. Treatment is usually directed at the underlying cause of the increased synovial fluid (such as repair of a torn meniscus or knee replacement). The cyst is often not diagnosed until it ruptures, which may result in significant pain and swelling of the calf, mimicking thrombophlebitis.

Ankle and Foot Pain

Ankle Sprains

Most ankle sprains result from inversion injuries that damage the lateral ankle ligaments. Characteristic findings include pain, swelling, and decreased proprioception. Physical examination reveals swelling, ecchymosis, and lateral ankle tenderness. Immediate inability to bear weight may indicate a more serious injury.

High ankle sprains result from excessive dorsiflexion or eversion that causes injury to the tibiofibular syndesmotic ligaments connecting the distal tibia and fibula. Pain can be

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elicited by compressing the leg at midcalf (squeeze test) or by having the patient cross the legs with the midcalf of the injured leg resting on the other knee (crossed-leg test).

The Ottawa ankle and foot rules (**Figure 16**) are useful in excluding ankle fractures, with an extremely high sensitivity (>95%). According to these validated rules, radiographs should be obtained when a patient is unable to walk four steps both immediately after the injury and during evaluation and when focal tenderness is present at the posterior aspect of either malleolus, the navicular bone, or the fifth metatarsal base. If these criteria are not met, obtaining radiographs is not necessary, as the probability of an ankle fracture is exceedingly low.

Initial therapy includes Rest, Ice, Compression, and Elevation (RICE). NSAIDs are useful for pain control. Early mobilization appears to be superior to prolonged rest. Once pain and swelling subside, proprioception training along with range-of-motion and strengthening exercises should be initiated to prevent chronic instability and predisposition to reinjury. Surgery is indicated only for patients with complete tears and those with chronic instability in whom conservative interventions are ineffective.

KEY POINT

HMC
- The Ottawa ankle and foot rules are useful in excluding ankle fractures, with an extremely high sensitivity (>95%); if these rules are not met, obtaining radiographs is not necessary, as the probability of an ankle fracture is exceedingly low.

Hindfoot Pain

Achilles tendinopathy commonly occurs in persons who begin exercising or increase exercise too rapidly. The usual presentation is of posterior heel pain, stiffness, and tenderness approximately 2 to 6 cm proximal to the Achilles tendon insertion. Pain is generally burning, worsens with activity, and improves with rest. Treatment consists of rest, activity modification, and application of ice. NSAIDs can be used for pain control.

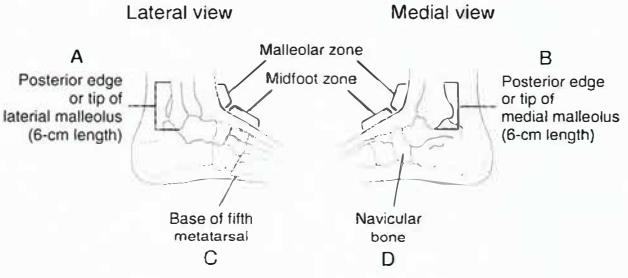

FIGURE 16. Ottawa ankle and foot rules. An ankle radiographic series is indicated if a patient has pain in the malleolar zone and any of the following findings: bone tenderness at *A*, bone tenderness at *B*, or inability to bear weight immediately and in the emergency department (or physician's office). A foot radiographic series is indicated if a patient has pain in the midfoot zone and any of the following findings: bone tenderness at *C*, bone tenderness at *D*, or inability to bear weight immediately and in the emergency department (or physician's office).

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Achilles tendon rupture should be suspected when a person participating in a strenuous activity such as basketball hears a popping sound in the heel. Rarely, fluoroquinolone antibiotics are associated with Achilles tendinopathy or rupture. Sudden posterior heel pain is common but not always present. Plantar flexion may be preserved. Patients usually have a positive Thompson test (sensitivity, 96%; specificity 93%) (**Figure 17**). A palpable tendon defect may be present. Treatment is controversial. Patients treated with either surgery or immobilization of the ankle in plantar flexion accompanied by an early range-of-motion protocol appear to have a similar risk of rerupture, although surgery is associated with a high risk of complications, including infection.

Plantar fasciitis is characterized by pain and tenderness near the medial plantar heel surface. Pain typically occurs upon awakening and after prolonged rest. Risk factors include obesity, improper footwear, overpronation, pes cavus, pes planus, and leg-length discrepancies. Management should be individualized to address specific historical and examination findings and reevaluated at regular intervals. Initial treatment is multimodal and consists of patient education, activity modification, application of ice, correcting improper mechanics (for example, using arch supports for pes planus), and heel stretches. Acetaminophen or NSAIDs can be used to control pain, although neither is thought to alter the underlying pathologic process. For patients who fail to respond to the aforementioned therapies, ultrasound therapy and glucocorticoid injections may be beneficial, although some experts do not recommend glucocorticoid injections because of the risk of fat atrophy in the heel pad. Plantar fascia release is reserved for patients in whom other therapies are ineffective.

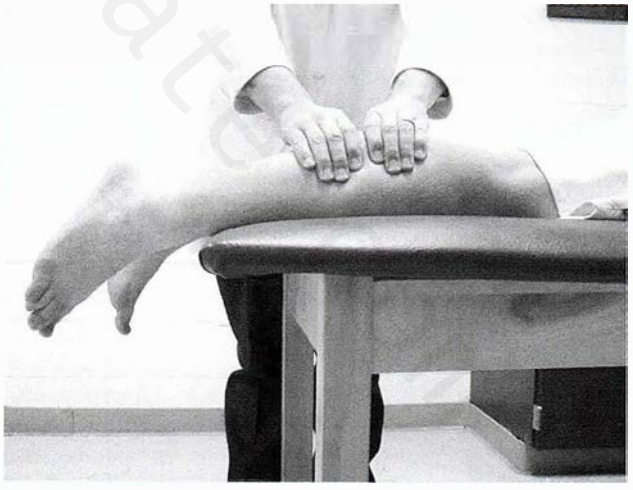

FIGURE 17. Thompson test. The patient is positioned in the prone position. The examiner squeezes mid-calf and observes for plantar flexion of the foot. When the patient has an intact Achilles tendon, plantar flexion will occur. When there is a complete Achilles tendon rupture, no plantar flexion is observed.

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KEY POINTS

- Achilles tendon rupture should be suspected when a person participating in a strenuous activity such as basketball hears a popping sound in the heel.
- Plantar fasciitis is characterized by pain and tenderness near the medial plantar heel surface; the pain typically occurs upon awakening and after prolonged rest.
- HVC Initial treatment of plantar faciitis is multimodal and consists of patient education, activity modification, application of ice, correcting improper mechanics, and heel stretches.

Midfoot Pain

Tarsal tunnel syndrome is usually caused by posterior tibial nerve compression within the tarsal tunnel below the medial malleolus. It most commonly arises in the setting of a calcaneous, medial malleolus, or talus fracture, but it can also be associated with rheumatoid arthritis, diabetes mellitus, thyroid disorders, pregnancy, and wearing tight-fitting shoes. Patients commonly present with pain and paresthesias in the medial ankle extending into the foot that worsen with standing, walking, and running. Pain can be reproduced by tapping on the posterior tibial nerve along its course. Treatment includes activity modification, orthotics, anti-inflammatory agents, and occasionally glucocorticoid injections. Surgical decompression is reserved for patients who do not benefit from conservative measures.

Forefoot Pain

Hallux valgus deformity (bunion) is characterized by lateral great toe deviation with bony deformity on the medial aspect of the first metatarsal phalangeal joint. Osteoarthritis can develop in this joint, and bursitis can occur overlying the bony deformity. Treatment includes NSAIDs, orthotic devices, and possibly surgery.

Morton neuroma refers to common digital nerve entrapment that usually occurs between the third and fourth toes. Patients describe a "walking on a pebble" sensation and burning pain with weight bearing that radiates distally into the toes. Treatment consists of using metatarsal padding, wearing broad-toed footwear, and avoiding high-heeled shoes. For patients who fail to respond to these conservative measures, a single combination lidocaine and glucocorticoid injection often provides significant pain relief. Surgical intervention is reserved for patients who fail to respond to at least 12 months of conservative therapy.

Dyslipidemia

Evaluation of Lipid Levels

Screening for lipid disorders is discussed in Routine Care of the Healthy Patient.

In a marked change from previous guidelines, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol treatment guideline does not focus on LDL cholesterol treatment targets, but rather on a person's overall risk of developing atherosclerotic cardiovascular disease (ASCVD). Furthermore, although non-HDL cholesterol (total cholesterol minus HDL cholesterol) represents the sum of all potentially atherogenic cholesterol, non-HDL cholesterol treatment targets are no longer included in the current ACC/AHA management guidelines. Therefore, the primary utility of measuring specific lipid levels is for ASCVD risk assessment.

LDL Cholesterol

LDL cholesterol is the most atherogenic of the lipoproteins. Elevated LDL cholesterol is strongly associated with increased risk of cardiovascular disease. Although statin therapy lowers LDL cholesterol levels and reduces the risk of cardiovascular events, no randomized trials have demonstrated the value of treating to specific LDL cholesterol goals, which is the basis for the change in guideline recommendations. The utility of LDL cholesterol measurement is therefore limited to determining the need for treatment and monitoring the response to therapy. Patients with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher should be evaluated for familial hypercholesterolemia and secondary causes of hyperlipidemia, including hypothyroidism, diabetes mellitus, and glucocorticoid use.

Triglycerides

Prevailing literature suggests that elevated triglyceride levels more likely represent a marker of metabolic syndrome and cardiovascular disease than a cause. Therefore, they are not measured routinely as part of assessing risk for ASCVD. However, severe fasting hypertriglyceridemia (≥500 mg/dL [5.65 mmol/L]), which is associated with familial combined hyperlipidemia, excessive alcohol use, hypothyroidism, exogenous estrogens, chronic kidney disease, and use of protease inhibitors, can trigger pancreatitis with postprandial triglyceride level increases (to >1000 mg/dL [11.30 mmol/L]). Measurement of triglyceride levels is indicated in these clinical situations as well as before initiation of drug therapy.

HDL Cholesterol

HDL cholesterol levels have a strong inverse correlation with cardiovascular risk. However, the pathophysiologic link between low HDL cholesterol and ASCVD is uncertain, especially as studies have yet to clearly demonstrate a reduction in cardiovascular risk with HDL cholesterol–raising medications. Subsequently, the ACC/AHA cholesterol treatment guideline provides no recommendation for treatment of low HDL cholesterol levels. However, HDL cholesterol level is a factor used in 10-year ASCVD risk estimation.

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Nonstandard Lipid Risk Factors

Currently, there is insufficient evidence to support the routine measurement of lipoprotein(a), apolipoprotein B, and LDL particles in the evaluation or management of dyslipidemia. Several other biomarkers and cardiovascular tests have been shown to correlate with increased cardiovascular risk (**Table 47**). The ACC/AHA guideline does not include them as primary factors to be considered in treatment decisions, although these risk factors may be used to guide the decision to initiate statin therapy in patients who do not clearly meet treatment criteria. Carotid artery intima-media thickness measurement is not recommended for ASCVD risk assessment in primary prevention.

TABLE 47. Additional Risk Factors for Atherosclerotic Cardiovascular Disease

African-American ancestry
Family history of premature cardiovascular disease (onset before age 55 y in first-degree male relative or before age 65 y in first-degree female relative)
Elevated lifetime risk (>50% for men, >40% for women) of cardiovascular disease (as determined from the ASCVD Risk Estimator based on the Pooled Cohort Equations [available at http://tools.cardiosource.org/ASCVD-Risk-Estimator/])
LDL cholesterol ≥160 mg/dL (4.14 mmol/L)
High-sensitivity C-reactive protein ≥2 mg/L
Coronary artery calcium score ≥300 or ≥75th percentile for age
Ankle-brachial index <0.90

ASCVD = atherosclerotic cardiovascular disease.

Data from Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jul 1;63 (25 Pt B):2889-934. Erratum in: J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):3024-3025. [PMID: 24239923]

KEY POINTS

- The 2013 American College of Cardiology/American Heart Association cholesterol treatment guideline does not focus on LDL cholesterol treatment targets, but rather on a person's overall risk of developing atherosclerotic cardiovascular disease.
- Patients with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher should be evaluated for familial hypercholesterolemia and secondary causes of hyperlipidemia, including hypothyroidism, diabetes mellitus, and glucocorticoid use.
- There is insufficient evidence to support the routine measurement of lipoprotein(a), apolipoprotein B, and LDL particles in the evaluation or management of dyslipidemia. HVC

Management of Dyslipidemias

Therapeutic Lifestyle Changes

The AHA and ACC advise counseling all adult patients on healthy lifestyle modifications prior to, and in addition to, pharmacologic therapy for dyslipidemia. Habits that should be encouraged include avoiding tobacco, maintaining a healthy weight, and regularly engaging in physical exercise.

A heart-healthy diet emphasizing the intake of vegetables, fruits, whole grains, and low-fat dairy products, while limiting the intake of red meats and simple carbohydrates, reduces LDL cholesterol levels. The DASH (Dietary Approaches to Stop Hypertension) eating plan (**Table 48**) has been shown to lower

TABLE 48. Dietary Approaches to Stop Hypertension (DASH) Eating Plan

Food	Number of Servings[a]	Serving Examples
Fats and simple carbohydrates	Limited	Sugar (1 tbsp)
Lean meats (including fish and poultry)	2 or fewer	Fish or poultry (3 oz)
Legumes, nuts, seeds	4-5 per week	Nuts (1/3 cup), seeds (2 tbsp), peanut butter (2 tbsp), beans (1/2 cup)
Low-fat or non-fat dairy products	2-3	Skim milk (1 cup), yogurt (1 cup), low-fat cheese (1 oz)
Fruits	4-5	Fresh fruit (size of a baseball), fruit juice (1/2 cup), dried fruit (1/4 cup)
Vegetables	4-5	Raw lettuce or spinach (1 cup), cooked carrots or broccoli (1/2 cup), vegetable juice (1/2 cup)
Grains	7-8 (at least 3 whole-grain foods due to higher fiber and nutrient content)	Bread (1 slice); cooked rice, cereal, or pasta (1/2 cup); dry cereal (1 oz)

oz = ounce; tbsp = tablespoon.

[a]For a daily 2000-calorie diet.

Adapted from National Heart, Lung, and Blood Institute. Following the DASH eating plan. www.nhlbi.nih.gov/health/health-topics/topics/dash/followdash. Updated June 6, 2014. Accessed June 24, 2015.

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LDL cholesterol levels more than 10 mg/dL (0.26 mmol/L) while also lowering HDL cholesterol levels 4 mg/dL (0.10 mmol/L). Adjusting the DASH eating plan to replace 10% of calories from carbohydrates with 10% of calories from protein provides a small additional reduction in LDL cholesterol levels, HDL cholesterol levels, and triglyceride levels (reduction of 16 mg/dL [0.18 mmol/L]); replacing 10% of calories from carbohydrates with 10% of calories from unsaturated fat slightly increases HDL cholesterol levels and lowers LDL cholesterol and triglycerides levels. Reducing the intake of saturated fatty acids to 5% to 6% of calories and reducing the intake of *trans* fatty acids also provides slight improvements in lipid profiles. Limitation of dietary cholesterol has no clear impact on dyslipidemia.

The ACC/AHA guideline on lifestyle management to reduce cardiovascular risk recommends that adults engage in aerobic physical activity (3-4 sessions per week, with an average of 40 minutes per session, and involving moderate- to vigorous-intensity physical activity) to lower LDL cholesterol levels, non-HDL cholesterol levels, and blood pressure. Aerobic exercise reduces LDL cholesterol levels by 3 to 6 mg/dL (0.08-0.16 mmol/L) and non-HDL cholesterol levels by 6 mg/dL (0.16 mmol/L). Data on the impact of exercise on triglyceride or HDL cholesterol levels have been more inconsistent.

Drug Therapy

Strong evidence indicates that statins are effective in both primary and secondary prevention of ASCVD. The ACC/AHA cholesterol treatment guideline identifies four patient groups for which there is evidence that treatment of hyperlipidemia with statin therapy is beneficial: (1) established clinical ASCVD, (2) LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher, (3) diabetes and age 40 to 75 years with an LDL cholesterol level of 70 to 189 mg/dL (1.81-4.90 mmol/L) and no ASCVD, and (4) no ASCVD or diabetes and estimated 10-year ASCVD risk greater than or equal to 7.5% as estimated by the Pooled Cohort Equations. When statin therapy is indicated, either high- or moderate-intensity therapy is utilized based upon the clinical scenario (**Figure 18**).

In patients with clinical ASCVD (coronary artery disease, peripheral arterial disease, cerebrovascular disease), the decision to give high- or moderate- intensity statin dosing is based upon the patient's age and tolerance to the statin dose. High-intensity therapy, defined as statin doses with expected LDL cholesterol reduction of 50% or more, is recommended for all patients aged 75 years and younger who can tolerate it. Atorvastatin and rosuvastatin are the only high-intensity statins recommended by the ACC/AHA cholesterol treatment guideline. Simvastatin, 80 mg/d, has been studied in trials, but this dosage is not recommended by the FDA because of an increased risk of rhabdomyolysis. Moderate-intensity therapy is recommended for patients with risk factors for statin-related adverse effects, including age older than 75 years, impaired kidney or liver function, muscle disorders, and use of drugs affecting statin metabolism (calcium channel blockers, fibrates, protease inhibitors, amiodarone, macrolide antibiotics). Moderate-intensity statin treatment provides an expected reduction in LDL cholesterol of 30% to 49% (**Table 49**).

Patients over the age of 20 years with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher should receive a high-intensity statin unless they have risk factors for statin-associated side effects.

For patients 40 to 75 years of age with diabetes and an LDL cholesterol level of 70 to 189 mg/dL (1.81-4.90 mmol/L), intensity of statin therapy is dictated by the estimated 10-year risk for ASCVD. High-intensity statin therapy should be used in these patients with a 10-year ASCVD risk of 7.5% or higher, whereas moderate-intensity therapy should be used if the risk is below 7.5%.

Patients with no history of ASCVD or diabetes and an LDL cholesterol level of 70 to 189 mg/dL (1.81-4.90 mmol/L) are candidates for either high- or moderate-intensity statin therapy if their 10-year ASCVD risk is greater than or equal to 7.5%. Thorough discussion of the benefits and risks of statin therapy of either potency is necessary before starting treatment. In select patients who do not qualify for one of the indication groups, statin therapy may be considered based on additional factors (see Table 47).

Clinical judgment and patient preference must be taken into account when selecting a statin dose. Furthermore, adjustment of statin therapy after failure to achieve the expected LDL cholesterol reduction requires individualized decision-making. Alteration of a well-tolerated statin regimen that was started before the release of the updated guideline is not necessarily indicated.

Before initiating statin treatment, a fasting lipid panel and alanine aminotransferase (ALT) level should be obtained. Baseline creatine kinase (CK) measurement is not routinely indicated before starting statin therapy. During statin treatment, monitoring of ALT and CK is only required if a patient develops symptoms of liver or muscle disease. To determine medication adherence and response to therapy, repeat lipid panels should be obtained 1 to 3 months after initiation of statin treatment and then every 3 to 12 months as clinically indicated.

Statins may cause myopathy and liver aminotransferase elevations and are associated with an increased risk of diabetes and, possibly, cognitive dysfunction. The incidence of these adverse effects ranges from 1% to 10%, but permanent disability related to statin intolerance is rare. For patients with signs or symptoms of statin intolerance, the benefits and risks of continued statin therapy should be discussed with the patient. Often, switching to a different statin or decreasing the dosage eliminates side effects. In those patients unable or unwilling to take statins, alternative cholesterol-lowering therapy should be considered.

Combination and Nonstatin Drug Therapy

Nonstatin drugs, such as ezetimibe, fibrates, niacin, bile acid sequestrants, and omega-3 fatty acids, favorably affect lipid profiles, and some reduce cardiovascular events compared with placebo. However, there are minimal data supporting the

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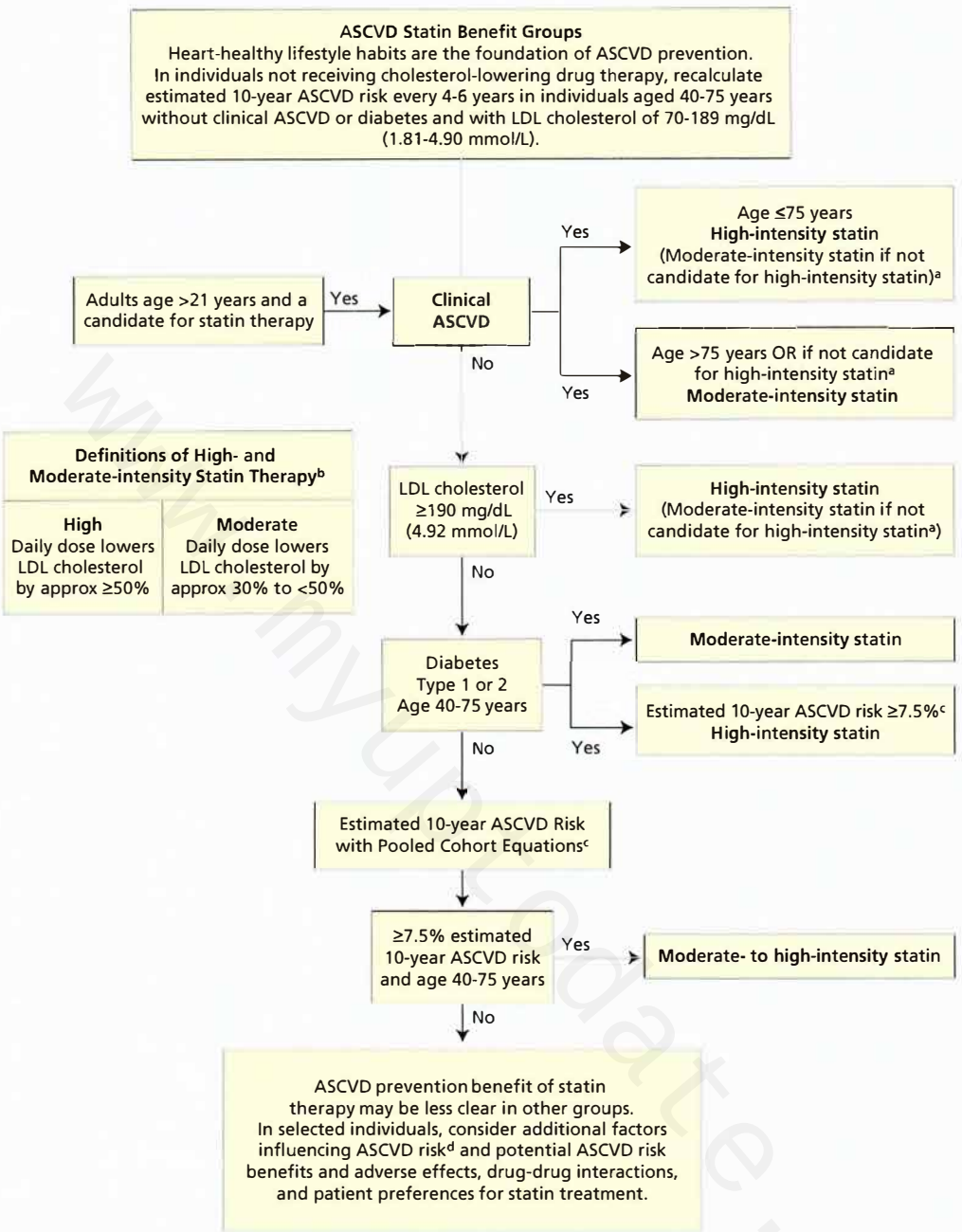

FIGURE 18. Major recommendations for statin therapy for ASCVD prevention. This flow diagram is intended to serve as a reference guide summarizing recommendations for ASCVD risk assessment and treatment. Assessment of the potential for benefit and risk from statin therapy for ASCVD prevention provides the framework for clinical decision-making incorporating patient preferences.

ASCVD = atherosclerotic cardiovascular disease.

[a]Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when high-intensity statin therapy is contraindicated or when characteristics predisposing them to statin-associated adverse effects are present.

Characteristics predisposing individuals to statin adverse effects include, but are not limited to:

- Multiple or serious comorbidities, including impaired kidney or liver function
- History of previous statin intolerance or muscle disorders
- Unexplained alanine aminotransferase elevations >3 times upper limit of normal
- Patient characteristics or concomitant use of drugs affecting statin metabolism
- >75 years of age

Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:

- History of hemorrhagic stroke
- Asian ancestry

[b]Percent reduction in LDL cholesterol can be used as an indication of response and adherence to therapy but is not in itself a treatment goal.

[c]The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-toold.aspx.

[d]Primary LDL cholesterol level ≥160 mg/dL (4.14 mmol/L) or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; high sensitivity C-reactive protein ≥2 mg/L; coronary artery calcium score ≥300 or ≥75th percentile for age, sex, and ethnicity; ankle-brachial index <0.90; or elevated lifetime risk of ASCVD.

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TABLE 49. High- and Moderate-Intensity Statin Therapy

High-Intensity (≥50% LDL Cholesterol Reduction with Daily Dose)	Moderate-Intensity (30% to <50% LDL Cholesterol Reduction with Daily Dose)
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg
Rosuvastatin 20-40 mg	Pravastatin 40-80 mg
	Lovastatin 40 mg
	Fluvastatin 40 mg twice daily

Adapted with permission from Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934. Erratum in: J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):3024-3025. [PMID: 24239923] Copyright 2014, Elsevier.

use of nonstatin drugs combined with statin therapy to further reduce ASCVD events. Nonstatin drugs are also associated with many significant side effects (**Table 50**). Therefore, the ACC/AHA cholesterol treatment guideline recommends consideration of these drugs only in high-risk patients (those with known ASCVD, diabetes, or LDL cholesterol level ≥190 mg/dL [4.92 mmol/L]) who fail to respond as expected to the recommended intensity of a statin or have poor tolerance to statins.

Management of Hypertriglyceridemia

Patients with elevated triglyceride levels should be counseled on weight loss (if appropriate), regular aerobic exercise, abstinence from alcoholic beverages, avoidance of *trans* fatty acids, and limitation of saturated fats and added sugars. Polyunsaturated omega-3 fatty acids should be included in the diet due to their favorable impact on triglyceride levels.

In patients with a fasting triglyceride level of 500 mg/dL (5.65 mmol/L) or higher, triglyceride-lowering drug therapy (alone or in combination with therapy to reduce LDL cholesterol if a concurrent indication for treatment exists) is useful to prevent pancreatitis. Fibrates are the most potent triglyceride-lowering agents, causing an average reduction in triglyceride levels of 30% to 50%. Niacin, statins, and omega-3 fatty acid supplements also provide significant reduction in triglyceride levels (see Table 50).

KEY POINTS

- Strong evidence indicates that statins are effective in both primary and secondary prevention of atherosclerotic cardiovascular disease.
- In patients with clinical atherosclerotic cardiovascular disease, high-intensity therapy (statin doses with expected LDL cholesterol reduction of 50% or more) is recommended for all patients aged 75 years and younger who can tolerate it.
- In patients with clinical atherosclerotic cardiovascular disease who have risk factors for statin-related adverse effects, including age older than 75 years, impaired kidney or liver function, muscle disorders, and use of drugs affecting statin metabolism, moderate-intensity statin treatment should be used.
- Patients over the age of 20 years with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher should receive a high-intensity statin unless they have risk factors for statin-associated adverse effects.
- For patients 40 to 75 years of age with diabetes mellitus and an LDL cholesterol level of 70 to 189 mg/dL (1.81-4.90 mmol/L), intensity of statin therapy is dictated by the estimated 10-year risk for atherosclerotic cardiovascular disease (ASCVD); patients with a 10-year ASCVD risk of 7.5% or higher should receive high-intensity statin therapy, and patients with a 10-year ASCVD risk below 7.5% should receive moderate-intensity therapy.

(Continued)

TABLE 50. Characteristics of Nonstatin Drugs

Medication	Effects on Lipids: LDL Cholesterol	HDL Cholesterol	Triglycerides	Adverse Effects
Ezetimibe	↓↓	—	—	Abdominal pain, fatigue, myositis, elevated liver aminotransferases (especially when combined with statins)
Bile acid sequestrants	↓↓	—	↑[a]	Constipation, nausea, bloating, elevated liver aminotransferases, interference with medication/vitamin absorption
Fibrates	↓	↑	↓↓↓	Nausea, abdominal pain, myositis (particularly when combined with statins)
Niacin	↓	↑↑	↓↓	Flushing, nausea, diarrhea, gout, hyperglycemia, myositis
Omega-3 fatty acids	—	↑	↓↓↓	Bloating, fishy taste

[a]Bile acid sequestrants increase triglyceride levels only if baseline triglycerides are elevated.

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KEY POINTS *(continued)*

- Patients with no history of atherosclerotic cardiovascular disease (ASCVD) or diabetes mellitus and an LDL cholesterol level of 70 to 189 mg/dL (1.81-4.90 mmol/L) are candidates for either high- or moderate-intensity statin therapy if their 10-year ASCVD risk is greater than or equal to 7.5%.
- Baseline creatine kinase measurement is not routinely indicated before starting statin therapy or for monitoring therapy in the absence of symptoms of muscle disease.

Dyslipidemia Management in Unique Populations

Evidence suggests that it is safe to continue statin therapy in a patient older than 75 years if the patient is already taking and tolerating statin drugs. Moderate-intensity statin therapy is effective for the secondary prevention of ASCVD in this population. The use of statins for primary prevention or at high intensity in patients older than 75 years is not well supported.

Due to a paucity of evidence, the ACC/AHA guidelines provide no recommendations for statin therapy in patients who require hemodialysis or patients with New York Heart Association functional class II to IV heart failure.

Metabolic Syndrome

Epidemiology and Pathophysiology

The concurrence of type 2 diabetes and multiple cardiovascular disease risk factors, including abdominal obesity, dyslipidemia, hypertension, and hyperglycemia, is known as the metabolic syndrome. Diagnosis of metabolic syndrome is made by the presence of three of the five diagnostic criteria used by the International Diabetes Federation and the AHA (**Table 51**).

Metabolic syndrome may be present in over 25% of the world population, with even higher rates in Mexican Americans and black women. Metabolic syndrome is associated with a 5- to 10-fold increase in the risk of developing diabetes and a 1.5- to 2-fold increase in ASCVD risk.

There is still much debate on whether the metabolic syndrome is a truly unique entity with its own pathophysiologic basis. The insulin resistance, hyperinsulinemia, and increased adipocyte cytokines seen in this condition induce vascular endothelial changes that promote atherosclerosis. Additionally, metabolic syndrome is associated with several other pathologic changes, including hepatic steatosis, kidney impairment, sleep apnea, and polycystic ovary syndrome.

Management

The AHA recommends weight loss with a goal BMI of less than 25, exercise for at least 30 minutes per day five times weekly, and a heart-healthy diet (as described previously).

TABLE 51. Criteria for Clinical Diagnosis of the Metabolic Syndrome

Measure	Categorical Cut Points
Elevated waist circumference[a]	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)[b]	≥150 mg/dL (1.7 mmol/L)
Reduced HDL cholesterol level (drug treatment for reduced HDL cholesterol is an alternate indicator)[b]	<40 mg/dL (1.0 mmol/L) in men; <50 mg/dL (1.30 mmol/L) in women
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose[c] (drug treatment of elevated glucose level is an alternate indicator)	≥100 mg/dL (5.6 mmol/L)

[a]It is recommended that the International Diabetes Federation (IDF) cut points (waist circumference ≥94 cm [37 in] in men or ≥80 cm [31.5 in] in women) be used for non-Europeans and either the IDF or American Heart Association/National Heart, Lung, and Blood Institute cut points (waist circumference ≥102 cm [40.2 in] in men or ≥88 cm [34.6 in] in women) be used for people of European origin until more data are available.

[b]The most commonly used drugs for elevated triglycerides and reduced HDL cholesterol are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL cholesterol. High-dose omega-3 fatty acids presumes high triglycerides.

[c]Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

Reprinted with permission from Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009 Oct 20; 120(16):1640-5. [PMID: 19805654] Copyright 2013, American Heart Association, Inc.

Patients with hypertension should be treated aggressively to achieve the blood pressure goals outlined in the report from the panel members appointed to the Eighth Joint National Committee (see MKSAP 17 Nephrology). Similarly, dyslipidemia should be treated as detailed previously, and hyperglycemia should be managed per guidelines from the American Diabetes Association. In some studies, metformin has been shown to reduce the risk of developing metabolic syndrome; however, therapeutic lifestyle interventions are as effective or superior to metformin.

The AHA recommends low-dose aspirin for patients with metabolic syndrome and a 10-year cardiovascular risk of 10% or higher.

KEY POINT

- The American Heart Association recommends low-dose aspirin for patients with metabolic syndrome and a 10-year cardiovascular risk of 10% or higher.

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Obesity

Definition and Epidemiology

Obesity is currently defined as a BMI greater than or equal to 30, whereas overweight is defined as a BMI between 25 and 29.9 (**Table 52**). Online BMI calculators are widely available (https://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm).

The prevalence of obesity has increased dramatically in recent decades. Currently, one third of U.S. adults are obese. Obesity is a leading cause of preventable death and is associated with increased risk for dyslipidemia, type 2 diabetes mellitus, hypertension, cardiovascular disease (CVD), stroke, cancer (breast, colon, and endometrial), osteoarthritis, obstructive sleep apnea, and other diseases. These risks increase with rising BMI. Obesity is also associated with reduced quality of life, impaired physical functioning, and increased health care costs.

Screening and Evaluation

Although current guidelines and recommendations urge physicians to identify and counsel overweight or obese patients, obesity is often not diagnosed or addressed as a medical issue in affected adults. Patients who report being told they are obese by physicians are more likely to have realistic self-perceptions of weight, greater desire to lose weight, and to have made attempts to lose weight.

The U.S. Preventive Services Task Force (USPSTF) recommends screening all adults for obesity by calculating BMI but concludes that there is no evidence regarding an appropriate interval for obesity screening. The American Heart Association (AHA), American College of Cardiology (ACC), and The Obesity Society (TOS) recommend screening for overweight and obesity annually (or more frequently depending on the patient) by calculating BMI and measuring waist circumference at the level of the iliac crest. Central adiposity (waist circumference >102 cm [40 in] in men and >88 cm [35 in] in women) is associated with increased cardiovascular risk independent of BMI.

TABLE 52. Classification of Overweight and Obesity by BMI

Category	BMI	Obesity Class
Underweight	<18.5	
Normal	18.5-24.9	
Overweight	25.0-29.9	
Obesity	30.0-34.0	I
	35.0-39.9	II
Extreme obesity	≥40	III

Reprinted from National Heart, Lung, and Blood Institute. Aim for a Healthy Weight. www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis.htm. Accessed June 24, 2015.

In evaluating the obese patient, the chronology of weight gain, prior weight loss attempts, eating and exercise patterns, family history of obesity, and use of medications that promote weight gain (**Table 53**) should be elicited. A history of risk factors for and symptoms of obesity-associated comorbidities, including insulin resistance and type 2 diabetes, dyslipidemia, hypertension, CVD, stroke, sleep apnea, gallstones, hyperuricemia and gout, and osteoarthritis, should also be obtained. During the history, obese patients should be asked about their perceptions of healthy weight and their own weight.

Evaluation should include a thorough physical examination. Additionally, the AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults recommends obtaining a fasting glucose level and fasting lipid profile in obese patients. Further testing should be guided by the history and physical examination.

KEY POINT

- The U.S. Preventive Services Task Force recommends screening all adults for obesity by calculating BMI.

Treatment

Treatment of overweight and obese patients should begin with establishing a weight loss goal and individualized treatment plan. A reasonable goal is weight loss of 0.5 kg to 1.0 kg (1.1-2.2 lb) per week to achieve a total weight loss of 10%. The mainstay of obesity treatment is lifestyle modification that includes diet for weight loss, increased physical activity, and behavioral therapy. A strategy that combines all three elements is likely to be more successful than any one element alone. Involving dieticians, exercise therapists, and behavioral therapists in the process increases the chances of success. Some patients may also be candidates for pharmacologic treatments and bariatric surgery. The overall management of the obese patient is presented in **Figure 19**.

TABLE 53. Medications That Promote Weight Gain

Drug Category	Example Medications
α-Blockers	Clonidine, prazosin, terazosin
Antidiabetic drugs	Insulin, sulfonylureas (especially glyburide and glipizide), thiazolidinediones
Anticonvulsant drugs	Carbamazepine, gabapentin, valproic acid
Antidepressant drugs	Amitriptyline, imipramine, doxepin, paroxetine, mirtazapine
Antihistamines	Cyproheptadine
Atypical antipsychotic drugs	Clozapine, olanzapine, quetiapine, risperidone
β-blockers	Atenolol, metoprolol, propranolol
Glucocorticoids	Prednisone
Hormonal contraceptives	Progestins (especially depot injections)

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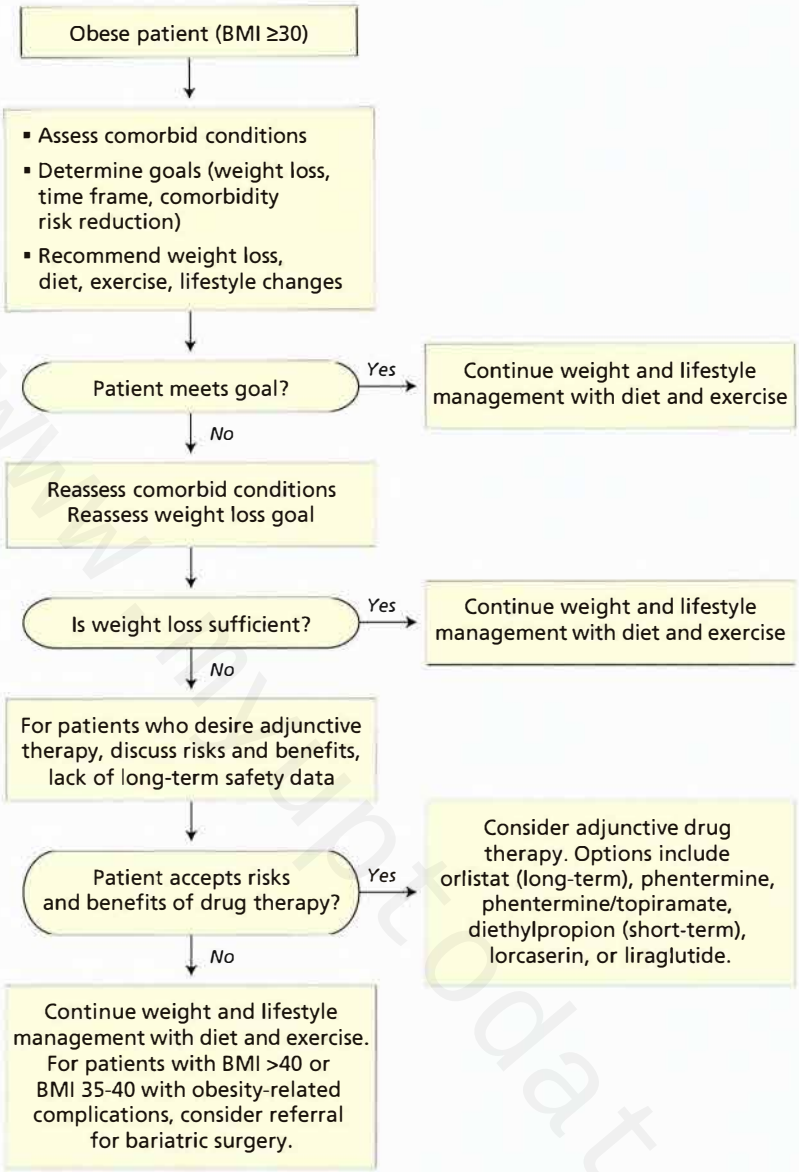

FIGURE 19. Management of the obese patient.

Adapted with permission from Snow V, Barry P, Fitterman N, Qaseem A, Weiss K; Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2005;142(7):526. [PMID: 15809464] Copyright 2005, American College of Physicians.

Lifestyle Modification

According to the USPSTF and the AHA/ACC/TOS obesity guideline, all obese patients should be offered a comprehensive lifestyle intervention (comprised of diet, physical activity, and behavioral treatments) for weight loss. Additionally, the USPSTF recommends offering overweight or obese adults who have cardiovascular risk factors intensive behavioral counseling interventions to promote a healthful diet and physical activity for CVD prevention. In overweight and obese adults with cardiovascular risk factors such as hypertension, hyperglycemia, and hyperlipidemia, lifestyle changes that result in modest and sustained weight loss (3% to 5%) produce clinically meaningful health benefits (reduced triglycerides, blood glucose, hemoglobin A_{1c}, and risk for type 2 diabetes). Greater weight loss results in greater benefits (reduced blood pressure and improved LDL and HDL cholesterol levels).

Reduced Dietary Energy Intake

Maintaining a continuous negative energy balance (that is, energy intake less than expenditure) of 500 kcal/d results in a weight loss of about 0.5 kg (1.1 lb) per week. Calorie restriction can be further guided by estimating a patient's basal energy requirement using the Harris-Benedict equation; calculators are available online (http://www-users.med.cornell.edu/~spon/picu/calc/beecalc.htm). Based on the result, a specific daily calorie limit should be prescribed (typically, 1500-1800 kcal/d for men and 1200-1500 kcal/d for women).

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All diets, when effective, maintain negative energy balance. There are numerous diet options available, including very-low-fat diets, high-protein and low-carbohydrate diets, pattern diets (for example, the Mediterranean diet), and meal replacement diets. After diet implementation, the average total weight loss in obese adults is maximal at 6 months (typical range, 4-12 kg [8.8-26.5 lb]); thereafter, weight regain usually occurs (typical range of total weight loss at 1 year, 4-10 kg [8.8-22 lb]; at 2 years, 3-4 kg [6.6-8.8 lb]).

In a recent meta-analysis, investigators compared weight loss outcomes for various popular diets. All diets were superior to no diet at 6 months (median difference in weight loss, 8.7 kg [19.2 lb]); however, weight loss differences between individual diets were nonexistent or minimal. These results suggest that clinicians should prescribe a diet with which the patient will adhere (that is, a diet that is palatable and affordable) and that maintains negative energy balance in order to achieve weight loss. Inadequate exercise and sleep compromise the success of dietary interventions.

Exercise

Most studies have shown little or no weight loss with exercise programs alone; however, regular exercise improves fitness and maintains weight after weight loss. Overweight and obese patients should be advised to engage in physical activities, such as brisk walking, for 30 minutes or longer per day, at least 5 days per week.

Overweight and obese patients should also be encouraged to engage in activities that increase nonexercise activity thermogenesis (NEAT), which is defined as all of the energy expended except during sleeping, eating, and exercising. NEAT has dramatically declined during the past 100 years due to the sedentary aspects of modern life (reliance on automobiles and appliances). People who engage in activities that increase NEAT (for example, parking farther from workplaces, climbing stairs instead of using elevators, doing desk work while standing) are less likely to gain weight.

Behavioral Therapy

Overweight and obese patients should be provided with strategies to facilitate a shift from personal maladaptive eating patterns toward healthful eating and exercise. Although best conducted by a trained therapist, behavioral therapy can be initiated by internists. Specifically, internists can emphasize the behavioral therapy components of self-monitoring, stimulus control, goal setting, and social support.

Self-monitoring of energy intake and expenditure has been shown to facilitate weight loss and is a key component of behavioral therapy. It frequently involves the use of food and activity diaries and self-weighing.

Stimulus control entails modifying the physical environment by purchasing low-energy-density foods (high-fiber foods) for consumption, keeping unhealthy foods unavailable, and avoiding sugar-sweetened drinks and fast foods. Patients should also be advised to modify their cognitive environment through avoidance (placing food out of sight), distraction (going for a walk rather than eating), and reframing (shifting focus from the pleasure of eating to the adverse consequences of obesity). Planning for high-risk situations (for example, "If I am tempted by food at the ball game, I will chew gum.") is also essential.

Goal setting involves establishing explicit, reasonable, and proximate weight loss and exercise goals. When a goal is achieved, a new one should be set. If a goal is not achieved, the patient should determine the reason why and then set a new goal.

Patients should be advised to enlist social support to adhere with diet and exercise plans. Including family members and spouses may also lead to increased weight loss.

A recent meta-analysis assessed the effects of behavioral interventions in obese patients. Participants who received behavioral interventions experienced more weight loss (3.0 kg [6.6 lb]) and were less likely to develop diabetes and hypertension than participants in the control group.

If weight plateauing occurs despite these lifestyle interventions, the physician should review the patient's diet and physical activities, recalculate the patient's daily calorie limit, and make new recommendations. These recommendations may include referral to dieticians, nutritionists, and behavioral therapists, whose assistance may facilitate the patient's weight loss.

KEY POINTS

- The mainstay of obesity treatment is lifestyle modification that includes diet for weight loss, increased physical activity, and behavioral therapy; a strategy that combines all three elements is likely to be more successful than any one element alone.
- Patients who maintain a continuous negative energy balance of 500 kcal/d lose about 0.5 kg (1.1 lb) per week.
- Obese patients should be advised to engage in physical activities, such as brisk walking, for 30 minutes or longer per day, at least 5 days per week.

Pharmacologic Therapy

Pharmacologic therapy may be used as an adjunct to diet, physical activity, and behavioral treatments in patients with a BMI of 30 or higher or in patients with a BMI of 27 or higher with overweight- or obesity-associated comorbidities. Drugs used in the treatment of obesity generally produce weight loss by reducing absorption of dietary fat or suppressing appetite.

Orlistat is an inhibitor of gastric and pancreatic lipases that results in malabsorption of approximately 30% of ingested fat. A meta-analysis showed that 12 months of orlistat treatment (120 mg three times daily), compared with placebo, resulted in greater reductions in weight (mean difference, 2.9 kg [6.4 lb]), BMI, waist circumference, blood pressure, blood cholesterol levels, and risk for type 2 diabetes. Diarrhea and oily

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stools are common side effects but subside over time. Given its mechanism of action, patients taking orlistat should also take a daily multivitamin containing vitamins A, D, and E, although the multivitamin should be taken 2 hours before or 2 hours after orlistat. A reduced-strength form (60 mg) of orlistat is available over the counter; this dose is also effective for weight loss.

Combination low-dose phentermine (a sympathomimetic drug) and low-dose topiramate (an antiepileptic drug) has demonstrated efficacy in reducing weight, possibly by suppressing appetite, altering taste, and increasing metabolism. In a 56-week trial, patients taking placebo achieved weight loss of 1.4 kg (3.1 lb), whereas patients taking 7.5 mg phentermine/46 mg topiramate had weight loss of 8.1 kg (17.9 lb). Patients taking 15 mg phentermine/92 mg topiramate lost 10.6 kg (23.4 lb). Both treatment groups that received phentermine-topiramate experienced improved blood pressure, fasting glucose levels, and lipid levels. Contraindications to phentermine-topiramate include pregnancy, glaucoma, hyperthyroidism, and recent use of monoamine oxidase inhibitors; its long-term safety and efficacy are unknown.

Lorcaserin, a brain serotonin 2C receptor agonist, acts as an appetite suppressant. In a 1-year trial, treatment with lorcaserin was superior to placebo and resulted in an additional weight loss of 3.6 kg (7.9 lb). Lorcaserin also led to significant reductions in BMI, waist circumference, and systolic blood pressure. Lorcaserin should be used with caution in patients taking medications that increase serotonin levels. There are limited data on the long-term safety and efficacy of lorcaserin.

The FDA recently approved combination sustained-release bupropion (a norepinephrine-dopamine reuptake inhibitor) and sustained-release naltrexone (an opioid receptor antagonist) for weight loss. In a 56-week trial, patients who received placebo achieved weight loss of 1.9 kg (4.2 lb), whereas patients taking sustained-release naltrexone (16 mg/d) plus sustained-release bupropion (360 mg/d) had weight loss of 6.5 kg (14.3 lb). Those taking combination sustained-release naltrexone (32 mg/d) and sustained-release bupropion (360 mg/d) lost 8.0 kg (17.6 lb). Combination bupropion-naltrexone is contraindicated in patients with epilepsy or uncontrolled hypertension and in patients taking opioids or opioid agonists.

The FDA also recently approved liraglutide, an injectable long-acting glucagon-like peptide-1 agonist used to improve glycemic control in patients with type 2 diabetes, for use as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of 30 or greater or 27 or greater in the presence of at least one weight-related comorbid condition. The average weight loss with liraglutide is about 5%. If, after 16 weeks of treatment, a patient has not lost at least 4% of baseline weight, the drug should be stopped. Liraglutide is contraindicated in patients with multiple endocrine neoplasia syndrome type 2 and patients with a family or personal history of medullary thyroid carcinoma.

Several sympathomimetic drugs (phentermine, phendimetrazine, diethylpropion, and benzphetamine) are available specifically for short-term use (12 weeks or less) in the treatment of obesity. Hypertension may be experienced as a side effect of these drugs.

KEY POINT

- Pharmacologic therapy may be used as an adjunct to diet, physical activity, and behavioral treatments in patients with a BMI of 30 or higher or in patients with a BMI of 27 or higher with overweight- or obesity-associated comorbidities.

Bariatric Surgery

Bariatric surgery should be considered in all patients with a BMI of 40 or higher and in patients with a BMI of 35 or higher with obesity-related comorbid conditions. Since the bariatric surgery requirement of a BMI of 35 or higher was established, emerging evidence has supported the clinical and cost effectiveness of surgical intervention in patients with a BMI of 30 to 35 who do not achieve substantial weight and comorbidity improvement with nonsurgical methods. However, most guidelines (and third-party payers) still support withholding surgical intervention until the BMI is 35 or higher. Candidates should be evaluated by a multidisciplinary team with medical, surgical, nutritional, and psychiatric expertise. Additional criteria for bariatric surgery are presented in **Table 54**.

TABLE 54. Patient Criteria for Bariatric Surgery

BMI ≥40 or BMI 35-39.9 and obesity-related comorbidities (e.g., type 2 diabetes mellitus, coronary heart disease, obstructive sleep apnea, osteoarthritis)
Unlikeliness to lose weight or maintain weight loss with nonsurgical interventions
Acceptable operative risk
Knowledge of the benefits, risks, and alternatives of the proposed procedure
Commitment to ongoing diet, physical activity, and behavioral treatments after the procedure
Awareness of how life may change as a result of the procedure (e.g., need to chew food thoroughly, inability to eat large meals)
No psychological contraindications to surgery
Commitment to lifelong medical follow-up including monitoring for nutritional deficiencies
Evaluation by a multidisciplinary team with medical, surgical, nutritional, and psychiatric expertise

Adapted from National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. Bariatric Surgery for Severe Obesity. Bethesda, Md: National Institutes of Health; March 2009, Updated June 2011. NIH Publication No. 08-4006. Available at www.niddk.nih.gov/health-information/health-topics/weight-control/bariatric-surgery-severe-obesity/Pages/bariatric-surgery-for-severe-obesity.aspx. Accessed June 24, 2015; Thompson WG, Cook DA, Clark MM, Bardia A, Levine JA. Treatment of obesity. Mayo Clin Proc. 2007 Jan;82(1):93-101. [PMID: 17285790]; and Vest AR, Heneghan HM, Schauer PR, Young JB. Surgical management of obesity and the relationship to cardiovascular disease. Circulation. 2013 Feb 26;127(8):945-59. [PMID: 23439447]

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Bariatric surgical procedures result in reduced stomach capacity (restriction), malabsorption of ingested nutrients, hormone changes that suppress appetite, or a combination of these mechanisms. Mortality risk associated with bariatric surgery is low. Weight loss equal to or greater than 50% of excess body weight (current weight minus ideal body weight) is considered a success.

Commonly performed bariatric procedures include laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass, and sleeve gastrectomy (**Figure 20**). Laparoscopic adjustable gastric banding, a restrictive procedure, involves placement of a soft silicone band below the gastroesophageal junction, which results in a small (approximately 30 mL) gastric pouch. The band is adjusted (via a port) to achieve early satiety without dysphagia. Three to 6 years after gastric banding, excess weight loss is 45% to 72%.

Roux-en-Y gastric bypass, a combination restrictive and malabsorptive procedure, involves creation of a small (30 mL) proximal gastric pouch, which is separated from the distal stomach and connected to a Roux limb of small bowel. Digestion and absorption of nutrients occur in the mid-small intestine. With Roux-en-Y gastric bypass, stomach capacity is reduced, as is absorption of calories. Additionally, delivery of nutrients to the mid-small intestine triggers hormone changes that suppress appetite. Three to 6 years after Roux-en-Y gastric bypass, excess weight loss is 62%.

Sleeve gastrectomy, a restrictive procedure, involves resection of the greater curvature of the stomach; this procedure reduces stomach capacity and suppresses appetite by removing tissue that produces ghrelin, a hunger-stimulating hormone. Excess weight loss 3 to 6 years after sleeve gastrectomy is 53% to 77%.

In a meta-analysis that compared bariatric surgery with nonsurgical treatment (diet, exercise, behavioral modification, and medications), participants randomized to bariatric surgery lost more weight (26.0 kg [57.3 lb]) and were more likely to experience remission of type 2 diabetes and metabolic syndrome, improved quality of life, and reduced medication use. Evidence suggests that bariatric surgery is also associated with reduced mortality and improvement of obstructive sleep apnea, osteoarthritis, and other conditions.

Patients who undergo bariatric surgery should continue dietary, physical activity, and behavioral measures and should receive nutrient replacement therapy (**Table 55**). Complications of bariatric surgery are discussed in MKSAP 17 Gastroenterology and Hepatology.

TABLE 55. Nutrient Deficiencies and Replacement after Bariatric Surgery

Nutrient Deficiency	Replacement Therapy
Iron	MVI with iron, or elemental iron 80-100 mg/d orally
Vitamin B_{12}	Vitamin B_{12} 500-1000 µg/d orally, or 1000 µg IM monthly
Folic acid	MVI with folate; for women of childbearing age, folate 1 mg/d orally
Calcium	Calcium citrate 1500 mg/d orally
Vitamin D	Vitamin D 400-800 U/d orally
Thiamine	25-50 mg/d orally
Vitamin A	MVI daily; if deficient, 2500 U/d orally with ongoing monitoring
Vitamin E	MVI daily; if deficient, 10 mg/d orally

IM = intramuscularly; MVI = multivitamin.

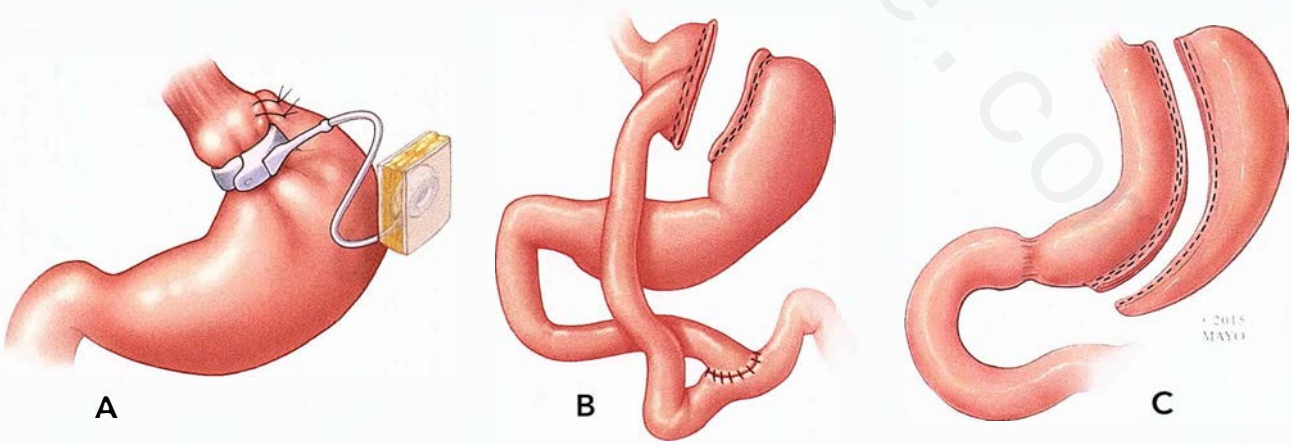

FIGURE 20. Commonly performed surgical procedures for obesity. *A*, gastric banding; *B*, Roux-en-Y gastric bypass; *C*, sleeve gastrectomy.

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KEY POINTS

- Bariatric surgery should be considered in all patients with a BMI of 40 or higher and in patients with a BMI of 35 or higher with obesity-related comorbid conditions.
- Patients who undergo bariatric surgery lose more weight and are more likely to experience remission of type 2 diabetes mellitus and metabolic syndrome, improved quality of life, and reduced medication use than patients who receive nonsurgical treatment alone.

Men's Health

Male Sexual Dysfunction

Erectile Dysfunction

Erectile dysfunction (ED) is the inability to maintain an erection that is adequate for sexual performance. Incidence increases with age; approximately two thirds of men report some degree of ED by the age of 70 years. The most important risk factor is cardiovascular disease (diabetes mellitus, hyperlipidemia, hypertension, smoking, family history). Other risk factors include aging, obesity, sedentary lifestyle, prior genitourinary surgery, substance abuse, and trauma. Neurologic (dementia, multiple sclerosis, stroke, quadriplegia), hormonal (hypogonadism, hypothyroidism, hyperprolactinemia), and psychiatric (depression) conditions are also risk factors for ED. Medications, especially psychiatric and antihypertensive agents, are common causes of ED (**Table 56**).

The history for ED should include an accurate description to verify that patients are not experiencing decreased libido, premature ejaculation, anorgasmia, or an anatomic problem such as penile curvature or pain from Peyronie disease. Determining sudden onset of symptoms and persistence of firm nocturnal or morning erections are important indicators of an inorganic (psychological) etiology of ED. Assessment of coinciding medical or psychiatric conditions, relationships (including the partner's condition), and history of surgery or trauma is appropriate.

TABLE 56. Drugs Commonly Associated with Erectile Dysfunction

Antidepressants: monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants
Benzodiazepines
Opioids, nicotine, alcohol, amphetamines, barbiturates, cocaine, marijuana, methadone
Anticonvulsants: phenytoin, phenobarbital
Antihypertensives and diuretics: α-blockers, β-blockers, calcium channel blockers, clonidine, spironolactone, thiazide diuretics, loop diuretics, ACE inhibitors
5α-Reductase inhibitors: dutasteride, finasteride
Antihistamines and histamine H_2-receptor antagonists: dimenhydrinate, diphenhydramine, hydroxyzine, meclizine, promethazine, cimetidine, nizatidine, ranitidine
NSAIDs: naproxen, indomethacin
Parkinson disease medications: levodopa, bromocriptine, biperiden, trihexyphenidyl, benztropine, procyclidine

Physical examination includes vital signs, genital examination, digital rectal examination, lower extremity pulses, secondary sexual characteristics, and a neurologic assessment. The choice of laboratory studies is directed by findings on the history and examination. Based on typical causes of ED, testing may include glucose, lipids, and thyroid-stimulating hormone. The role of routine hormonal testing is less clear, with inconclusive evidence regarding its value in diagnosis and guiding therapy. If pursued, a fasting morning total testosterone level is the most appropriate study.

Treatment should be based on the underlying etiology. First-line therapy includes lifestyle modification (smoking cessation and weight loss), psychotherapy, and/or phosphodiesterase type 5 (PDE-5) inhibitor therapy. Obese patients may experience substantial improvements in erectile function solely from weight loss (BMI <30).

PDE-5 inhibitors increase cyclic guanosine monophosphate (cGMP) levels in the corpus cavernosum of the penis, which leads to vascular smooth muscle relaxation, increased penile blood flow, and erection. Available formulations include sildenafil, vardenafil, and tadalafil, all of which are believed to be equally efficacious. Avanafil is a newer PDE-5 inhibitor medication that was recently approved by the FDA. Because ED shares many risk factors with atherosclerotic disease, it is important to assess cardiovascular risk and safety for sexual activity before initiating a PDE-5 inhibitor (**Table 57**). For all PDE-5 inhibitors, starting with a low dose and increasing the dose based on response and side effects is indicated. Sildenafil should be taken on an empty stomach at least 1 hour before sex; counselling patients on the proper use of PDE-5 inhibitors leads to success in a high proportion of repeat users. PDE-5 inhibitors are generally well tolerated and safe. The most common side effect is headache (10%). Other side effects include dizziness, dyspepsia, flushing, rhinitis, syncope, and blue visual disturbances from inhibition of PDE-6 in the retina. PDE-5 inhibitors are contraindicated in patients taking nitrates and should be used with caution in patients taking α-blockers (such as tamsulosin) due to the risk of profound hypotension. PDE-5 inhibitors also inhibit cytochrome P-450 3A4 and may alter the metabolism of medications metabolized through this pathway (for example, protease inhibitors, erythromycin, ketoconazole).

Second-line treatment for ED includes intraurethral or injected prostaglandin E_1 (alprostadil), which is more efficacious than PDE-5 inhibitors at producing erections but is more inconvenient and less tolerated. Penile pump therapy may also be considered.

The evidence of effectiveness of testosterone replacement therapy for ED in men with low serum levels is conflicting but should not be considered except in men with clinical hypogonadism.

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TABLE 57. Third Princeton Consensus Conference Guidelines for Treatment of Erectile Dysfunction in Patients with Cardiovascular Disease or Cardiac Risk Factors

Risk Level	Treatment Recommendation
Low Risk	
Patients who are able to do moderate-intensity exercise without symptoms Successfully revascularized patients (e.g., coronary artery bypass grafting, coronary stenting, or angioplasty) Asymptomatic controlled hypertension Mild valvular disease Mild left ventricular dysfunction (NYHA functional class I and II) who can achieve 5 METS without ischemia as determined by recent exercise testing	Can initiate or resume sexual activity or treat for ED with PDE-5 inhibitor (if not using nitrates)
Intermediate/Indeterminate Risk	
Mild to moderate stable angina Recent MI (2-8 weeks) without intervention awaiting exercise ECG Heart failure (NYHA functional class III) Noncardiac atherosclerotic disease (clinically evident PAD, history of stroke/TIA)	Further cardiac evaluation and restratification before resumption of sexual activity or treatment for ED If the patient can complete 4 minutes of the standard Bruce treadmill protocol without symptoms, arrhythmias, or a decrease in blood pressure, treatment for ED can be safely initiated
High Risk	
Unstable or refractory angina Uncontrolled hypertension Moderate to severe heart failure (NYHA functional class IV) Recent MI (<2 weeks) without intervention High-risk arrhythmia (exercise-induced ventricular tachycardia, ICD with frequent shocks, poorly controlled atrial fibrillation) Obstructive hypertrophic cardiomyopathy with severe symptoms Moderate to severe valvular disease (particularly aortic stenosis)	Defer sexual activity or ED treatment until cardiac condition is stabilized and reassessed

ECG = electrocardiography; ED = erectile dysfunction; ICD = implantable cardioverter-defibrillator; METS = metabolic equivalents; MI = myocardial infarction; NYHA = New York Heart Association; PAD = peripheral arterial disease; PDE = phosphodiesterase; TIA = transient ischemic attack.

Recommendations from Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012 Aug;87(8):766-78. [PMID: 22862865]

Premature Ejaculation

Premature ejaculation is defined as ejaculation that occurs sooner than desired. Treatments are counseling and pharmacologic therapy. Topical medications (lidocaine, prilocaine), which work by reducing tactile stimulation, may be used with or without a condom. Oral medications (fluoxetine, paroxetine, sertraline) work based on their tendency to cause delayed ejaculation as a side effect.

Decreased Libido

Decreased libido is defined as diminished desire for sexual activity. Hypoactive sexual desire disorder is diagnosed when impaired libido causes marked distress and harms interpersonal relationships. Common causes are aging, hypogonadism, hyperprolactinemia, medications, and psychiatric conditions (mainly depression). Treatment is directed at the underlying cause. Many so-called natural supplements have been touted as effective for treating decreased libido and sexual dysfunction; however, none of these supplements has strong evidence to support their efficacy. Furthermore, the FDA has warned that many of the ingredients in these products are potentially harmful.

KEY POINTS

- First-line therapy for erectile dysfunction includes lifestyle modification, psychotherapy, and/or phosphodiesterase type 5 inhibitor therapy.
- Because erectile dysfunction shares many risk factors with atherosclerotic disease (smoking, diabetes, hypertension, hyperlipidemia, and family history of cardiovascular disease), it is important to assess cardiovascular risk and safety for sexual activity before initiating a phosphodiesterase type 5 inhibitor.
- Phosphodiesterase type 5 inhibitors are contraindicated in patients taking nitrates and should be used with caution in patients taking α-blockers due to the risk of profound hypotension.

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Androgen Deficiency

The diagnosis of androgen deficiency is based on typical symptoms and documented hypogonadism (**Table 58**). Testing should be performed judiciously because symptoms of hypogonadism overlap with many common conditions. The Endocrine Society guidelines recommend against screening of asymptomatic men in the general population, regardless of age.

History should address conditions that alter testosterone production or metabolism, including systemic illnesses and medications (for example, high-dose systemic glucocorticoids, opioids, marijuana), or conditions that lower testosterone transiently, such as eating disorders and excessive exercise. Diagnosis of hypogonadism can be made by obtaining a fasting morning total testosterone level and confirming abnormal results with at least one repeat test. Before initiating treatment, identifying the cause of hypogonadism is indicated, including whether it is primary or secondary in origin. Treatment goals include inducing and maintaining secondary sex characteristics as well as improving well-being, sexual function, muscle mass/strength, and bone mineral density. Due to potential adverse effects, testosterone therapy is contraindicated in patients with prostate or breast cancer, prostate nodules or induration, a prostate-specific antigen (PSA) level greater than 4 ng/mL (4 µg/L) or greater than 3 ng/mL (3 µg/L) if at high risk for prostate cancer, a hematocrit greater than 50%, severe obstructive sleep apnea, severe lower urinary tract symptoms, or poorly controlled heart failure.

See MKSAP 17 Endocrinology and Metabolism for details on the evaluation of hypogonadism and testosterone treatment.

TABLE 58. Symptoms and Signs Suggestive of Androgen Deficiency in Men

More Specific Symptoms and Signs
Incomplete or delayed sexual development, eunuchoidism
Reduced sexual desire (libido) and activity
Decreased spontaneous erections
Breast discomfort, gynecomastia
Loss of body (axillary and pubic) hair, reduced shaving
Very small (especially <5 mL) or shrinking testes
Inability to father children, low or zero sperm count
Height loss, low-trauma fracture, low bone mineral density
Hot flushes, sweats
Less Specific Symptoms and Signs
Decreased energy, motivation, initiative, and self-confidence
Feeling sad or blue, depressed mood, dysthymia
Poor concentration and memory
Sleep disturbance, increased sleepiness
Mild anemia (normochromic, normocytic, in the female range)
Reduced muscle bulk and strength
Increased body fat, BMI
Diminished physical or work performance

Adapted with permission from Bhasin S, Cunningham GR, Hayes FJ, et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010 Jun;95(6):2537. [PMID: 20525905] Copyright 2010, The Endocrine Society.

KEY POINTS HVC

- Current guidelines recommend against screening for androgen deficiency in asymptomatic men, regardless of age.
- Diagnosis of hypogonadism can be made by obtaining a fasting morning total testosterone level and confirming abnormal results with at least one repeat test.

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is a common cause of lower urinary tract symptoms (LUTS) in men. The prostate is about the size of a walnut in men aged 30 years and gradually increases in size. Most men older than 60 years have LUTS. BPH begins in the central transition zone of the prostate and causes obstruction to urine flow, which may ultimately lead to detrusor muscle dysfunction and uninhibited bladder contractions. LUTS may be categorized by the type of symptoms. Obstructive symptoms include decreased stream, urinary retention, incomplete emptying, and incontinence. Irritative symptoms, which are caused by detrusor hyperactivity and may occur later in the course of BPH, include nocturia, frequency, and urgency.

Diagnosing BPH can be challenging because of the many causes of LUTS; furthermore, there is poor correlation between prostate size on examination and urinary symptoms. Nonetheless, a careful history and examination can usually render the diagnosis. Men older than 50 years are likely to have BPH as a cause for LUTS, whereas men younger than 40 years are likely to have other causes for LUTS. Some medications may cause LUTS, including diuretics (urinary frequency), sympathomimetics, and anticholinergics (increased urethral sphincter tone and decreased detrusor muscle contractions); over-the-counter medications (especially sympathomimetic decongestants and anticholinergic antihistamines) may also cause LUTS. Other causes of LUTS are malignancy (prostate, bladder), infection (prostatitis, sexually transmitted infections), neurologic (spinal cord injury, stroke, Parkinson disease), medical conditions (poorly controlled diabetes mellitus, hypercalcemia), and behavior (alcohol or caffeine intake, excessive water consumption).

The American Urological Association (AUA) guidelines recommend obtaining a baseline AUA Symptom Index (AUA-SI) score to determine the severity of and to monitor LUTS. This questionnaire (available at www.hiv.va.gov/provider/manual-primary-care/urology-tool1.asp) assesses urinary frequency, nocturia, weak stream, hesitancy, intermittency, incomplete emptying, and urgency and generates a score reflecting mild,

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moderate, or severe symptoms. Prostate examination can reveal the characteristic findings of BPH, including symmetric enlargement and a firm consistency (like the tip of nose). Findings of prostate adenocarcinoma include asymmetry, induration, and nodularity. The penile meatus should be inspected to exclude evidence of stricture. The abdomen should be palpated to exclude masses or bladder distention. The examination should also exclude neurologic defects such as decreased anal sphincter tone, absent cremasteric reflex, saddle anesthesia, and lower extremity neurologic abnormalities. The AUA recommends urinalysis to exclude infection and malignancy (hematuria). Because PSA may be elevated in BPH, and increased levels of PSA associated with BPH do not reliably correlate with lower urinary tract symptoms, PSA testing is not required for the diagnosis of BPH and is not routinely followed in patients with BPH. Although not required for diagnosis, uroflow studies are a noninvasive means for evaluating LUTS and may be helpful in some patients in whom the cause is unclear. Accurate interpretation requires a minimum urine volume of 150 mL. Peak flow rates of less than 15 mL/s are often found in BPH, although this finding may also be associated with detrusor muscle dysfunction.

The main goals of treatment of BPH are to reduce symptoms from LUTS and improve quality of life. The AUA suggests a treatment approach based on AUA-SI score severity. Mild LUTS (AUA-SI score <8) can be addressed by conservative measures and observation. The approach to moderate to severe LUTS (AUA-SI score ≥8) may range from conservative measures and observation to medical treatment or invasive interventional therapy such as transurethral resection of the prostate (TURP) or transurethral needle ablation (TUNA). Conservative measures to treat LUTS in men with BPH include reduced fluid intake, timed voiding (every 3 hours while awake), limiting caffeine/alcohol, modifying medications, improving mobility, and avoiding bladder irritants.

First-line pharmacotherapy for LUTS due to BPH that does not respond to conservative measures consists of α-blockers, which act on the dynamic component of bladder outlet obstruction by relaxing smooth muscles in the urethral and bladder neck. Common side effects are headache, dizziness, nasal congestion, hypotension, edema, palpitations, fatigue, and ED. α-Blockers currently FDA approved for treatment of LUTS are alfuzosin, doxazosin, tamsulosin, terazosin, and silodosin. All α-blockers are equally effective but differ with regard to their cardiovascular safety and tolerability. Generally, α-blockers that are efficacious in treating hypertension (doxazosin, terazosin, alfuzosin) are more likely to cause more hypotensive side effects than tamsulosin and silodosin, which have little effect on blood pressure. The PDE-5 inhibitor tadalafil is also available for treatment of BPH, which may be a reasonable option for men with BPH and erectile dysfunction. Combinations of α-blockers and PDE-5 inhibitors can cause significant hypotension and should be initiated with caution.

Pharmacologic agents that inhibit the action of testosterone have also been shown to be efficacious in treating BPH. 5α-reductase inhibitors (5-ARIs) act on the anatomic component of bladder outlet obstruction by reducing the conversion of testosterone to dihydrotestosterone in the prostate, thus reducing prostate size and growth. 5-ARIs are most effective in men with large prostates (>40 mL), moderate to severe symptoms, and elevated PSA. Because 5-ARIs are associated with major reductions in PSA, it is recommended that physicians multiply the value of the PSA by 2 in patients taking 5-ARIs who require PSA testing. 5-ARIs reduce prostate size gradually, so the therapeutic effect may require several months. These medications are well tolerated; side effects include ejaculatory dysfunction and decreased libido. The combination of α-blockers and 5-ARIs is recommended in men with large prostates and elevated PSA levels.

Numerous herbal medications have been used for BPH, including saw palmetto, African star grass, African plum tree bark, rye grass pollen, stinging nettle, and cactus flower; however, recent studies have demonstrated no clear benefit.

Indications for referral to a urologist and possible invasive treatment for BPH include severe symptoms refractory to medical therapy, acute urinary retention, bladder stones, persistent gross hematuria, recurrent urinary tract infections, and obstructive nephropathy.

KEY POINTS

- First-line pharmacotherapy for benign prostatic hyperplasia consists of α-blockers.
- 5α-Reductase inhibitors are most effective in men with benign prostatic hyperplasia who have large prostates, moderate to severe symptoms, and elevated prostate-specific antigen levels.

Acute Testicular and Scrotal Pain

Common causes of acute testicular pain are testicular torsion, epididymitis, orchitis (viral, such as the mumps), and extension of infection from the epididymis or the urinary tract. Other causes are referred pain from abdominal aortic aneurysm, inguinal hernia with strangulation of the bowel/omentum, nephrolithiasis, lumbosacral nerve impingement, and retroperitoneal inflammation.

The causes of testicular and scrotal pain are usually diagnosed by history and examination. Discussion should include onset (sudden or gradual), pain quality and severity, LUTS, trauma, and association of pain with sexual activity. Examination includes scrotal inspection, palpation, transillumination, and the cremasteric reflex (stroking the inner thigh and observing rise in ipsilateral testicle). Testing includes urinalysis with microscopy to exclude infection as well as testicular ultrasonography.

Testicular Torsion

Testicular torsion occurs when the testes twist on the spermatic cord, leading to ischemia; it is considered a surgical emergency. It is most common in boys and men younger than

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30 years. Symptoms are sudden and severe, including scrotal pain along with nausea and vomiting. Examination reveals a testis that is high riding, oriented transversely, and edematous. Testicular pain worsens with manual elevation, and the cremasteric reflex may be absent. Assessing blood flow using Doppler ultrasonography is sensitive (82%) and specific (100%) in making the diagnosis. Treatment is surgical decompression to restore blood flow.

Epididymitis

Epididymitis causes pain superolateral to the testicle and results from inflammation of the epididymis. Although symptoms are usually subacute, the pain ranges from acute to chronic and may be accompanied by dysuria, frequency, and urgency. Examination is remarkable for pain that is relieved by testicular elevation.

Epididymitis is most commonly infectious in etiology. Infectious epididymitis is characterized by acute onset, fever, leukocytosis, and possibly concomitant prostatitis. Infectious epididymitis has a bimodal distribution: men younger than 35 years and older than 55 years. In younger patients, sexually transmitted infections (chlamydia and gonorrhea) are most likely. In older patients and those who practice anal intercourse, *Escherichia coli*, Enterobacteriaceae, and *Pseudomonas* species should be considered. In older men and persons who practice anal intercourse, infectious epididymitis should be treated with ceftriaxone and a fluoroquinolone. All other men are treated with ceftriaxone (250-mg intramuscular injection in one dose) plus doxycycline (100 mg by mouth twice daily for 10 days).

Epididymitis can also be due to noninfectious causes (for example, trauma, autoimmune disease, or vasculitis). Treatment includes scrotal support, ice, and NSAIDs.

KEY POINTS

- Testicular torsion occurs when the testes twist on the spermatic cord, leading to ischemia; it is a surgical emergency treated with surgical decompression.
- Infectious epididymitis in older men and persons who practice anal intercourse is treated with ceftriaxone and a fluoroquinolone; all other men are treated with ceftriaxone plus doxycycline.

Hydroceles, Varicoceles, and Epididymal Cysts

Hydroceles

Hydroceles are fluid collections between layers of the tunica vaginalis and occur in approximately 1% of adult men. Communicating hydroceles involve fluid that flows from the peritoneal space into the scrotum through a patent processus vaginalis, whereas simple hydroceles do not have this communication. Most hydroceles are asymptomatic, but larger ones may be painful. Examination typically reveals a tense, smooth, and transilluminating scrotal mass; this is in contrast to varicoceles, hernias, and solid masses, which do not transilluminate. Ultrasonography is used for confirmation. Treatment is reserved for large, painful hydroceles and communicating hydroceles, which may require surgery or aspiration with sclerotherapy.

Varicoceles

Varicoceles are caused by dilation of the testicular vein and pampiniform plexus. They are common, occurring in 15% of adult men. Varicoceles are believed to be a leading cause of infertility, as 40% of men who are infertile have varicoceles. Examination reveals a left-sided (90%) scrotal mass with a "bag of worms" consistency that increases with standing and decreases while supine. Ultrasonography is used for confirmation. Management is usually conservative. Surgery may be indicated in men with infertility and abnormal sperm counts; however, surgical repair may increase sperm counts without improving fertility.

Epididymal Cysts

Epididymal cysts are fluid-filled structures that contain spermatozoa and occur near the head of the epididymis. When greater than 2 cm in diameter, they are termed spermatoceles. Epididymal cysts and spermatoceles are usually asymptomatic, nontender to palpation, and confirmed by ultrasonography. Surgery is required only in rare cases of chronic pain.

Acute and Chronic Prostatitis and Pelvic Pain

Prostatitis and pelvic pain account for approximately 2 million physician visits annually. Presenting symptoms typically include pain originating from the perineum, testes, penis, or suprapubic region or as LUTS such as dysuria, frequency, and incomplete emptying.

Causes of symptomatic prostatitis may be acute bacterial infection (discussed in further detail in MKSAP 17 Infectious Disease), chronic bacterial infection, or chronic abacterial prostatitis/chronic pelvic pain syndrome. In patients with chronic symptoms, the National Institutes of Health Chronic Prostatitis Symptom Index can be used to aid in the diagnosis and symptom monitoring of prostatitis (www.prostate.net/wp-content/uploads/pdf/chronic-prostatitis-symptom-test.pdf).

Evaluation of symptoms of prostatitis and pelvic pain include the exclusion of identifiable sources of symptoms originating from the urethra, testicles, rectum, or bladder. In acute prostatitis, the prostate is typically very tender and edematous, whereas the degree of prostate tenderness is much more variable with chronic bacterial prostatitis or chronic abacterial prostatitis/chronic pelvic pain syndrome. Laboratory evaluation of suspected prostatitis includes urinalysis with microscopy and gram stain and culture; vigorous prostate

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massage is not indicated in acute prostatitis due to lack of diagnostic or therapeutic benefit. Imaging is not required for uncomplicated cases of acute prostatitis. **Table 59** provides details on the classification and management of prostatitis.

KEY POINT

- Causes of symptomatic prostatitis may be acute bacterial infection, chronic bacterial infection, or chronic abacterial prostatitis/chronic pelvic pain syndrome.

Hernias

Hernias are organs that bulge through an area of muscle or weak connective tissue, which may be congenital or acquired. Most hernias occur in the groin; they may also occur in the abdomen (ventral, umbilical) or at incision sites. Hernias are exacerbated by increased intra-abdominal pressure from straining or coughing. Hernias are more common in men.

Inguinal hernias can be direct or indirect. Direct hernias involve the herniation of intra-abdominal contents through a weak region of the fascia between the rectus abdominis and inguinal ligament. Indirect hernias, which comprise the vast majority, involve the protrusion of contents through the internal inguinal ring. Femoral hernias, which are less common, are due to protrusion of contents through the femoral canal.

Symptoms of inguinal hernias include an asymptomatic bulge, pressure in the groin or abdomen, and severe pain from movement of abdominal contents into the inguinal ring or scrotum. Direct hernias present with a low abdomen bulge, are less painful, and less frequently incarcerate. Diagnosis is made by physical examination, which reveals a visible, palpable bulge in the lower abdomen or within the inguinal canal

TABLE 59. Classification and Management of Prostatitis

Class	Definition	Symptoms	Management
I. Acute bacterial prostatitis (see MKSAP 17 Infectious Disease)	Acute infection of the prostate	Fever, LUTS, prostate tenderness on examination	Empiric antibiotic coverage for gram-negative organisms, usually with a fluoroquinolone or trimethoprim-sulfamethoxazole; narrow antibiotic spectrum based on Gram stain and culture results, if available
II. Chronic bacterial prostatitis	Recurrent infection of the prostate	Pain, LUTS	First-line treatment is an antibiotic with good penetration into prostatic tissue, often with an extended, 1-month course of a fluoroquinolone
III. Chronic abacterial prostatitis/chronic pelvic pain syndrome (CPPS)	No demonstrable infection	Pain, LUTS	Often refractory to treatment; usually treated with a 1-month course of empiric therapy (not supported by evidence and not repeated if ineffective); other treatments are NSAIDs, α-blockers for LUTS, muscle relaxants, finasteride, gabapentin for neuropathic pain and if other drugs are ineffective; efficacy of complementary treatments (e.g., pollen extract, saw palmetto) not determined; in the absence of structural causes for pain, surgery should be avoided
IIIA. Inflammatory CPPS	Leukocytes in semen, expressed prostatic secretions, or post-prostatic massage urine		
IIIB. Noninflammatory CPPS	No leukocytes in semen, expressed prostatic secretions, or post-prostatic massage urine		
IV. Asymptomatic inflammatory prostatitis	Detected either by prostate biopsy, or the presence of leukocytes in semen samples during evaluation for other disorders	No symptoms	

LUTS = lower urinary tract symptoms.

Class and Definition columns reprinted from Litwin MS, McNaughton-Collins M, Fowler FJ Jr., et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol. 1999 Aug;162(2)369-375. [PMID: 10411041] with permission from American Urological Association. Copyright 1999, American Urological Association.

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or scrotum that increases with standing and the Valsalva maneuver.

Asymptomatic hernias may be monitored, but patients should be educated on symptoms and potential complications such as strangulation and incarceration. Symptomatic hernias require surgical consultation for consideration of repair. The benefit of laparoscopic versus open repair remains controversial. Hernia repair with polypropylene mesh may have lower complication rates. Possible complications of surgery include infection, seroma, hematoma, chronic pain, and recurrence.

KEY POINT

- Asymptomatic hernias may be monitored; symptomatic hernias require surgical consultation for consideration of repair.

Women's Health

Abnormal Uterine Bleeding

Clinical Presentation

Abnormal uterine bleeding can generally be categorized into ovulatory and anovulatory patterns. Ovulatory abnormal uterine bleeding (menorrhagia) occurs at normal, regular intervals but is excessive in volume or duration. Women with ovulatory bleeding have estrogen-mediated endometrial proliferation, produce progesterone, slough the endometrium regularly following progesterone withdrawal, and have a minimal risk of developing uterine cancer. Menorrhagia may be caused by coagulation disorders, anatomic abnormalities such as polyps or fibroids, medications that interfere with hemostasis, and thyroid dysfunction. Approximately 50% of women with menorrhagia have no identifiable cause.

Anovulatory cycles are characterized by unpredictable bleeding of variable flow and duration caused by absence of normal cyclic hormonal flux. Without cyclic progesterone, the estrogen-mediated endometrium proliferates excessively, resulting in endometrial instability, erratic bleeding, and increased risk of uterine cancer. Terms commonly associated with anovulatory bleeding include amenorrhea (absent menses for more than three cycles), oligomenorrhea (abnormally infrequent menses occurring at intervals of more than 35 days), and metrorrhagia (menses at irregular intervals with excessive bleeding or lasting more than 7 days). These terms apply only to women of reproductive age who are menstruating. Approximately 6% to 10% of women with anovulation have polycystic ovary syndrome. Other causes include diabetes mellitus, thyroid disorders, hyperprolactinemia, and medications such as antiseizure and psychotropic agents.

Anovulation increases in perimenopause and can cause abnormal uterine bleeding, including menorrhagia, metrorrhagia, and menometrorrhagia. The perimenopausal transition begins with changes in the interval between menstrual periods and ends 1 year after the last period; it is highly variable, lasting between 4 to 8 years.

Any uterine bleeding is always abnormal in postmenopausal women (absent menses for 1 year) and requires further evaluation.

KEY POINT

- Any uterine bleeding is always abnormal in postmenopausal women and requires further evaluation.

Evaluation

Initial evaluation of abnormal uterine bleeding in premenopausal women includes a detailed history, noting estimated changes in menstrual pattern and severity of bleeding, such as needing increased numbers of pads or tampons, leaking through pads or tampons, and the presence of clots. The history may provide clues to an underlying endocrine or bleeding disorder, liver or kidney disease, or sexually transmitted infection (STI). Physical examination requires a complete pelvic examination. Screening studies for cervical malignancy should be current. Because pregnancy commonly causes changes in the normal bleeding pattern, pregnancy testing must be performed in all women. Other laboratory tests should be based on clinical evaluation.

Abnormal ovulatory bleeding warrants consideration of a possible bleeding disorder or other causes of excessive bleeding, such as a structural uterine abnormality (polyps, fibroids). In women with anovulatory bleeding, exposure to unopposed estrogen increases the risk for endometrial cancer. Additional risk factors for endometrial cancer in premenopausal women include obesity, nulliparity, age 35 years or older, diabetes mellitus, family history of colon cancer, infertility, and treatment with tamoxifen. In women younger than 35 years of age with anovulatory bleeding and no other risk factors for endometrial cancer, no additional evaluation prior to treatment is usually indicated. However, in women younger than 35 years of age with risk factors, or any patient with anovulatory bleeding 35 years of age or older, endometrial biopsy should be performed to exclude significant endometrial pathology. Transvaginal ultrasonography is not helpful in evaluating premenopausal bleeding unless a structural uterine abnormality is suspected as a cause of bleeding.

Perimenopause is frequently characterized by abnormal bleeding patterns and should be approached on an individualized basis. Pelvic examination and transvaginal ultrasound are useful for ruling out common causes of bleeding, such as endometrial hyperplasia, polyps, and STIs, and endometrial sampling is definitive in cases of diagnostic uncertainty or increased risk for endometrial cancer. Unless bleeding is excessive, laboratory studies, including hormone levels, are generally not indicated.

In postmenopausal women, any vaginal bleeding requires assessment to exclude malignancy. Initial evaluation may be with either transvaginal ultrasonography or endometrial biopsy; both studies are not required. When transvaginal ultrasonography is performed as an initial study and an endometrial thickness of less than or equal to 4 mm is found, endometrial sampling is not required. Endometrial thickness of

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greater than 4 mm should be further evaluated by endometrial sampling.

KEY POINTS

HVC
- Because pregnancy commonly causes changes in the normal bleeding pattern, pregnancy testing must be performed in all women with abnormal uterine bleeding before more extensive testing is ordered.
- Exposure to unopposed estrogen increases the risk for endometrial cancer in women with prolonged anovulation.

Management

Management of abnormal ovulatory bleeding is focused on addressing any underlying causes and reducing flow volume, which may be done with hormonal therapy or other treatments such as NSAIDs. Treatment of anovulatory bleeding is directed toward restoring hormonal balance and stabilizing the endometrium. A progestin such as medroxyprogesterone acetate may be used to promote withdrawal bleeding for women who wish to become pregnant. Hormonal contraceptives may be used to regulate cycles for women not desiring pregnancy. NSAIDs can decrease uterine bleeding by up to 40%, owing to the high concentrations of prostaglandins in the endometrium. Tranexamic acid, an antifibrinolytic agent that stabilizes clot formation, is FDA-approved for treatment of menorrhagia but is expensive. Patients with severe bleeding may require short courses of gonadotropin-releasing hormone (GnRH) agonists or intravenous high-dose estrogens. Endometrial ablation or hysterectomy may be considered for patients who do not respond to medical treatment or in whom anatomic causes are identified.

Breast Mass

Clinical Presentation

A breast mass is characterized by a lesion that persists throughout the menstrual cycle and differs from the surrounding breast tissue and the corresponding area in the contralateral breast. The differential diagnosis of a palpable breast mass includes cyst, abscess, fibroadenoma, fat necrosis, and neoplasm. Distinguishing between benign and malignant breast masses is critical. Although up to 90% of breast masses are benign cysts or fibroadenomas, neither the history nor the physical examination findings can definitively rule out underlying malignancy.

KEY POINT

- Although up to 90% of breast masses are benign cysts or fibroadenomas, neither the history nor the physical examination findings can definitively rule out underlying malignancy.

Evaluation

Evaluation of a palpable breast mass varies, based on the patient's age and risk factors and the degree of clinical suspicion. Mammography and ultrasonography are the initial imaging modalities. Ultrasonography is often preferred in women younger than age 35 years because the increased density of breast tissue in younger women limits the usefulness of mammography. Ultrasonography may also be a better choice for pregnant patients in order to avoid radiation exposure. The main utility of ultrasonography is its ability to differentiate cystic from solid lesions. A simple cyst is likely to be benign if it has symmetric, round borders with no internal echoes; aspiration reveals nonbloody fluid and complete resolution of the cyst. Any bloody fluid obtained from cyst aspiration requires cytologic examination. A solid lesion with uniform borders and uniformly sized internal echoes is consistent with a benign fibroadenoma, but it must be evaluated completely with fine needle aspiration or biopsy.

A suspicious mass is solitary, discrete, hard, and sometimes adherent to adjacent tissue. If such a mass is present, mammography is performed before a pathologic diagnosis is attempted. The radiologist should be informed of the area of clinical concern to ensure that any noted mammographic abnormalities correspond to the clinical findings. Which breast is to be imaged, clock face location of the mass, dimension, and distance from the areola must be indicated. On mammography, an irregular mass with microcalcifications or spiculations is suspicious for malignant disease, and biopsy is mandatory.

Mammography results are reported in a standardized format called BI-RADS (Breast Imaging Reporting and Data System) that uses a 0 to 6 scale (**Table 60**). Approximately 10%

TABLE 60. Breast Imaging Reporting and Data System (BI-RADS) Assessment Categories

Category 0	Mammography: Incomplete—Need additional imaging evaluation and/or prior mammograms for comparison
	Ultrasound and MRI: Incomplete—Need additional imaging evaluation
Category 1	Negative
Category 2	Benign
Category 3	Probably benign
Category 4	Suspicious
	Mammography and ultrasound:
	Category 4A: Low suspicion for malignancy
	Category 4B: Moderate suspicion for malignancy
	Category 4C: High suspicion for malignancy
Category 5	Highly suggestive of malignancy
Category 6	Known biopsy-proven malignancy

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to 20% of palpable breast cancers are not detected by ultrasonography or mammography. If a mass is present, a nondiagnostic mammogram or ultrasound should not be considered proof of the absence of malignancy, and tissue diagnosis is indicated.

Definitive diagnosis is obtained by tissue sampling using fine needle aspiration, core needle biopsy with or without stereotactic or ultrasound guidance, or excisional biopsy. Fine needle aspiration, generally reserved for ultrasound-confirmed cystic lesions, requires an experienced cytopathologist for interpretation. Core needle biopsy is the test of choice for most solid lesions, as it provides more tissue for histology and tissue markers. Excisional biopsy is used when core needle biopsy findings are nondiagnostic or when biopsy and imaging studies do not concur. Further management of abnormal pathologic findings requires consultation with a breast surgeon and oncologist.

KEY POINTS

- The initial imaging modalities for evaluating a palpable breast mass are mammography and ultrasonography; ultrasonography is often preferred in women younger than age 35 years and pregnant women.
- Any solid mass on imaging must be evaluated completely with fine needle aspiration, core needle biopsy, or excisional biopsy.

Breast Pain

Clinical Presentation

Breast pain (mastalgia) is common and may be cyclic, noncyclic, or extramammary. Generalized mastalgia may be caused by hormonal changes related to pregnancy, hormonal contraception, and medications. Many younger women experience cyclic breast discomfort with the onset of menses. The discomfort is typically bilateral, lasts for several days, and varies in intensity. Noncyclic breast pain is more likely to be unilateral and may be caused by trauma, cysts, duct ectasia, mastitis, ligamentous stretching secondary to large breasts, or a breast mass. Extramammary pain (breast pain referred from other areas) may be caused by musculoskeletal, cardiac, gastrointestinal, or spinal disorders. Chest wall pain, which is a common cause of extramammary pain, typically presents with unilateral, localized, reproducible discomfort.

Evaluation

A thorough history with attention to type of pain, location, and relationship to menses and a careful physical examination are essential to rule out palpable masses or anatomic causes. Women with a palpable breast mass should be referred for diagnostic imaging. Chest wall pain is typically reproduced by palpation or by examination maneuvers that place stress on the painful musculoskeletal structures. All women who are evaluated for mastalgia should be up to date on routine mammographic screening, according to age and personal risk factors for breast cancer.

KEY POINT

- In women with mastalgia, the evaluation focuses on excluding palpable masses or anatomic causes.

Treatment

Because most symptoms of cyclic mastalgia are self-limited, management usually requires only education, reassurance, and appropriate breast support. Studies have not shown that caffeine restriction or vitamin E administration is beneficial. Medical treatment may be considered for women with severe and persistent pain that interferes with quality of life. Danazol is the only therapy that is FDA approved for the treatment of cyclic mastalgia, but side effects limit its use.

KEY POINT

- Because most symptoms of cyclic mastalgia are self-limited, management usually requires only education, reassurance, and appropriate breast support.

HVC

Chronic Pelvic Pain

Chronic pelvic pain (CPP) in women is a syndrome of intermittent or constant noncyclic pain of at least 6 months' duration that localizes to the lower abdomen or pelvis and is sufficiently severe to cause functional disability. Prevalence estimates vary, but in one representative study of female patients aged 15 to 73 years, a point prevalence of 3.8% was comparable with that of asthma (3.7%) and chronic back pain (4.1%).

CPP often presents a diagnostic and therapeutic challenge. It is frequently associated with endometriosis, pelvic adhesions, myofascial pain disorders, interstitial cystitis, irritable bowel syndrome, sleep disorders, and depression. Many women have more than one associated disorder. Risk factors for CPP include physical, sexual, and emotional abuse; pelvic inflammatory disease; obstetric or gynecologic disorders; psychological disorders; abdominopelvic surgery; and chronic pain syndromes, such as fibromyalgia.

Evaluation includes screening for gynecologic, gastrointestinal, urologic, and psychological disorders, and a detailed physical examination is warranted. Laboratory studies are based upon clinical indication. Transvaginal ultrasonography is helpful for identifying anatomic pathology, and a normal study aids in providing reassurance. Laparoscopy may be indicated for evaluation of severe symptoms of unclear etiology.

Treatment should be directed toward the specific cause, if identified. In patients without a clearly defined pathophysiologic or anatomic cause, therapy is usually targeted toward general pain management. NSAIDs may be used as first-line short-term therapy for most women with moderate CPP. Other therapeutic interventions include antidepressant agents, biofeedback, cognitive-behavioral therapy, physical

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therapy, hypnosis, acupuncture, meditation, and stress-reduction techniques.

KEY POINT

- NSAIDs may be used as first-line short-term therapy for most women with moderate chronic pelvic pain in patients without a clearly defined pathophysiologic or anatomic cause.

Contraception

Nearly 50% of all pregnancies in the United States are unintended, with higher prevalence among younger women, racial and ethnic minorities, and women at lower socioeconomic levels. Unintended pregnancy is associated with poor maternal and infant outcomes. Strategies to reduce unintended pregnancy require assessing pregnancy risk, counseling patients regarding contraceptive options, and ensuring correct and consistent use of contraceptives. Most women can start most contraceptive methods at any time, and appropriate methods are available for women with serious medical conditions, in whom the risk of pregnancy-related adverse events is high. The U.S. Selected Practice Recommendations for Contraceptive Use are a useful guide to contraceptive use and detail medical eligibility criteria (www.cdc.gov/reproductivehealth/UnintendedPregnancy/USSPR.htm).

Available contraceptive methods include hormonal contraception; long-acting reversible preparations, including intrauterine devices (IUDs); barrier contraceptives; and sterilization (**Table 61**).

KEY POINT

- Strategies to reduce unintended pregnancy require assessing for pregnancy risk, counseling patients regarding contraceptive options, and ensuring correct and consistent use of contraceptives.

Hormonal Contraception

Other than a thorough history, blood pressure, and BMI measurements, few examinations or tests, if any, are needed before starting a contraceptive method. A negative pregnancy test should be obtained if more than 7 days have elapsed since the start of normal menses. In healthy women of reproductive age, a pelvic examination is not needed before beginning hormonal contraception. Various types of hormonal contraception include oral contraceptive pills, transdermal patch, vaginal ring, and long-acting reversible contraceptives.

KEY POINT

HVC
- Healthy women of reproductive age generally do not require a pelvic examination or other studies before beginning hormonal contraception.

Oral Contraceptive Pills

Oral contraceptive pills are the most common form of contraception. These include combination estrogen-progestin and progestin-only pills. Combination preparations differ based on the strength of estrogen and the type of progestin component. All preparations are therapeutically equivalent in preventing pregnancy. The mechanisms of action include inhibition of ovulation, alteration of the cervical mucus to an environment less conducive to sperm migration, and inhibition of endometrial proliferation. Benefits of combined hormonal contraception are summarized in Table 61. Contraindications to combination products include uncontrolled hypertension, breast cancer, venous thromboembolism, liver disease, and migraine with aura. Estrogen-containing preparations are contraindicated in women older than 35 years who smoke more than 15 cigarettes a day. Progestin-only pills, also called the "mini-pill," may be used by women with contraindications to estrogen.

In addition to oral contraceptive pills, other methods of hormonal contraceptive delivery include transdermal patches and vaginal rings.

Medications that induce the cytochrome P-450 3A4 (CYP3A4) class of liver enzymes may reduce the effectiveness of hormonal contraceptives. These may include, but are not limited to, rifampin, griseofulvin, antiseizure agents (see MKSAP 17 Neurology), St. John's wort, and antiretroviral drugs.

KEY POINTS

- Contraindications to oral combination estrogen-progestin contraceptives include uncontrolled hypertension, breast cancer, venous thromboembolism, liver disease, and migraine with aura.
- Estrogen-containing contraceptive pills are contraindicated in women older than 35 years who smoke more than 15 cigarettes daily.

Long-Acting Reversible Contraceptives

Long-acting reversible contraceptives contain progestin and include depot medroxyprogesterone acetate injections, subcutaneous implants, and progestin-containing IUDs. These preparations are less reliant on user adherence than oral contraceptive pills and are highly effective. Return of fertility may be delayed with these methods, with the median time to conception of 10 months after cessation of use. As with other progestin-only methods, irregular bleeding and amenorrhea are prevalent, and weight gain is a common side effect.

Depot medroxyprogesterone acetate is given by intramuscular or subcutaneous injection every 3 months following a negative pregnancy test. The etonogestrel implant is a single matchstick-sized rod inserted subdermally in the upper inner arm and is effective for 3 years.

IUDs are a long-acting reversible contraceptive method in which a small T-shaped device is placed inside the uterus. The levonorgestrel IUD is available in two dosage formulations, one that releases 14 μg and is effective for 3 years and one that releases 20 μg and is effective for 5 years. The levonorgestrel-containing IUD releases a low dose of progestin, which causes endometrial atrophy and generally leads to

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TABLE 61. Comparison of Contraceptive Options

Agent	Percent (%) of Women Experiencing Unintended Pregnancy Within the First Year of Use: Typical Use	Perfect Use[a]	Advantages	Disadvantages
Combination estrogen-progestin preparations			Decreased incidence of endometrial and ovarian cancers	Increased risk of myocardial infarction, ischemic stroke, VTE, hypertension
			Decreased dysmenorrhea, menorrhagia, symptomatic ovarian cysts	Increased risk of cancers of the cervix, liver, and breast
				Breakthrough bleeding
			Less iron-deficiency anemia	
Oral	9	0.3	Easy to use	May exacerbate migraine
			Rapidly reversible	
Patch	9	0.3	Easier adherence	Local skin reaction
				Increased estrogen dose, thus higher VTE risk
Vaginal ring	9	0.3	Easier adherence	Requires self-insertion
			Lowest level of systemic estrogen	
Progestin-only preparations			Use when estrogen is contraindicated	Irregular bleeding, breakthrough bleeding
"Mini-pill"				Must maintain precise daily dosing schedule
Long-acting reversible preparations				Irregular bleeding, amenorrhea, decreased bone mineral density (especially in adolescents)
Depot medroxyprogesterone acetate (IM or SQ)	6	0.2	Administered every 3 months	Delayed return to ovulation (10 months)
			Decreased risk of endometrial cancer, PID	
			Improves endometriosis	
			Decreased menstrual frequency	
Progestin implants	0.05	0.05	Effective up to 3 years	Delayed return to ovulation (6 months)
Intrauterine devices			Least dependence on user	Bleeding, pain, expulsion (rare); no protection from STIs
Copper	0.8	0.6	Nonhormonal	
			Effective up to 10 years	
Levonorgestrel	6	0.2	Decreased blood loss, decreased anemia	
			Effective up to 5 years	
Barrier methods			Only use when needed	Most user-dependent
Cervical cap	16-32	9-26		Requires spermicide
Diaphragm	12	6		Requires spermicide
Male condom	18	2	Protection from STIs	
Female condom	21	5	Protection from STIs	
Vaginal sponge	12-24	9-20		
Sterilization				
Female (tubal ligation)	0.5	0.5	May reduce ovarian cancer risk	Surgical complications
				Regret
				Increased risk of ectopy if pregnancy occurs
Male (vasectomy)	0.15	0.10	Lower costs, fewer complications, and more effective than tubal ligation	Surgical complications

IM = intramuscular; PID = pelvic inflammatory disease; SQ = subcutaneous; STI = sexually transmitted infection; VTE = venous thromboembolism.

[a]Perfect use implies correct and consistent use exactly as directed/intended. Typical use reflects rates in actual practice with patients.

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decrease or absence of menstrual flow. A nonhormonal copper IUD is also available. IUDs are extremely effective and provide long-term protection of 3 to 10 years, depending on the type. They may be placed at any time except during pregnancy in an office setting, without need for anesthesia, in both nulliparous and multiparous women. Expulsion of the device occurs in 2% to 10% of women within the first year. IUDs do not increase risk of ectopic pregnancy, pelvic inflammatory disease, or infertility.

KEY POINT

- Long-acting reversible contraceptives contain progestin and include depot medroxyprogesterone acetate injections, subcutaneous implants, and progestin-containing intrauterine devices; they are less reliant on user adherence than oral contraceptive pills and are highly effective.

Barrier Contraceptive Methods

Barrier methods (see Table 61) provide as-needed contraception but are substantially less reliable than hormonal methods. All barrier methods are more effective when used with spermicides; spermicides alone are not a reliable method of contraception. Condoms reduce risk of STIs. Evidence is strongest for prevention of HIV infection when male condoms are used. Combining a barrier method with a hormonal method is always recommended to prevent STIs, as well as to prevent unintended pregnancy.

KEY POINT

- Combining a barrier method with a hormonal method is always recommended to prevent sexually transmitted infections, as well to prevent unintended pregnancy.

Sterilization

Female surgical sterilization is highly successful and safe and has a low risk for complications. The fallopian tubes can be occluded by ligation, occlusive clips or rings, or with cauterization. Tubal occlusion should be considered a permanent end to fertility and should not be performed in women who may desire future pregnancy. The incidence of regret is significantly higher in women under age 30 years and in those who are postabortion or postpartum at the time of the procedure.

Emergency Contraception

Emergency contraception is postcoital hormonal contraception used to prevent pregnancy after inadequately protected coitus. Two methods are FDA approved: over-the-counter levonorgestrel (1.5 mg) and prescription ulipristal (30 mg). Both are taken as a single dose. The primary documented mechanism of action for both levonorgestrel and ulipristal is interference with the process of ovulation. Ulipristal has been shown to prevent ovulation both before and after the luteinizing hormone surge has started, delaying follicular rupture for at least 5 days. Both agents have no effect on an established pregnancy and do not increase rates of miscarriage.

Ulipristal has slightly greater efficacy than levonorgestrel, and efficacy for both products increases the earlier they are used. Both levonorgestrel and ulipristal may be taken up to 5 days (120 hours) after intercourse. Both agents are less effective in obese women.

KEY POINT

- Two methods of emergency contraception are over-the-counter levonorgestrel and prescription ulipristal; both are taken as a single dose and are effective for up to 5 days (120 hours) after intercourse.

Dysmenorrhea

Dysmenorrhea (painful menstruation) occurs in up to 50% of adolescents and young adults and is classified as primary or secondary. Primary dysmenorrhea, which occurs in 90% of patients, is associated with normal ovulatory cycles and no pelvic pathology. The prevalence of primary dysmenorrhea decreases with increasing age and is highest in the 20- to 24-year-old age group. A secondary cause, such as endometriosis, fibroids, or uterine pathology, is found in 10% of patients. Symptoms of dysmenorrhea include severe abdominal cramps, backache, headache, nausea, vomiting, and diarrhea. Symptoms coincide with the onset of menses and last 2 to 3 days.

Dysmenorrhea is sometimes associated with other cyclic symptom complexes such as premenstrual syndrome and premenstrual dysphoric disorder. These disorders include a wide range of physical and psychological symptoms that begin approximately 1 week before menses and typically cease with menstruation (see Mental and Behavioral Health).

Initial evaluation includes a thorough history, with attention to risks for infection and possible physical, sexual, or emotional abuse. It is important to distinguish between pain associated with menstruation and pain that occurs at other times. If pelvic pathology (previous irradiation, trauma, infection, foreign body) is not suspected and a diagnosis of primary dysmenorrhea is made, symptomatic treatment may begin without further testing. Both NSAIDs and cyclooxygenase-2 inhibitors are effective. For patients with incomplete relief of symptoms, use of combined hormonal contraceptive therapy is effective. Extended-cycle combined oral contraceptive pills may be particularly useful for this indication.

KEY POINTS

- In a patient with dysmenorrhea, if pelvic pathology is not suspected and a diagnosis of primary dysmenorrhea is made, symptomatic treatment may begin without additional evaluation. HVC
- Both NSAIDs and cyclooxygenase-2 inhibitors are effective initial therapy for primary dysmenorrhea; combined hormonal contraceptive therapy is effective for patients whose symptoms do not resolve completely after initial therapy.

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Female Sexual Dysfunction

Female sexual dysfunction describes sexual difficulties that are persistent and personally distressing to the patient. Up to 35% of sexually active women are affected, with a peak occurrence in middle age. Asking an open-ended question about sexual concerns, including pain with intercourse, is appropriate. When indicated, a complete sexual history should be obtained, including a review of medications, medical history, psychiatric disorders, and reproductive surgeries that can contribute to sexual dysfunction. Identifying problems with relationships, desire, arousal, orgasm, or pain may help in determining the cause and potential treatment strategies. Screening for concurrent depression is indicated, as sexual dysfunction and depression often coexist. A pelvic examination is helpful in identifying specific areas of pain or tenderness, menopausal genitourinary symptoms, decreased lubrication, or tissue friability. Laboratory testing is recommended only if an underlying disorder is suspected. If further evaluation is needed, validated self-report questionnaires, such as the Female Sexual Function Index, can supplement the clinical assessment.

KEY POINT

- Women with possible sexual dysfunction should be screened for depression, as both disorders may coexist.

Classification of Female Sexual Disorders

According to the DSM-5, abnormalities in female sexual response fall into three categories: sexual interest/arousal disorder, orgasmic disorder, and genitopelvic pain/penetration disorder. Sexual interest/arousal disorder includes female hypoactive desire dysfunction and female arousal dysfunction; it is diagnosed if a woman reports at least three of the following symptoms: lack of sexual interest, lack of sexual thoughts or fantasies, decreased initiation of sexual activity or decreased responsiveness to partner's initiation attempts, reduced excitement or pleasure during sexual activity, decreased response to sexual cues, or decreased sensations during sexual activity. Female orgasmic disorder is the persistent or recurrent absence, delay, or diminished intensity of orgasm following a normal excitement phase. Genitopelvic pain/penetration disorder is diagnosed when there is difficulty in vaginal penetration, marked vulvovaginal or pelvic pain during penetration, fear of pain or anxiety about pain in anticipation of or during penetration, or tightening or tensing of pelvic floor muscles during attempted penetration. The diagnosis of a sexual disorder requires both significant distress more than 75% of the time and a minimum duration of 6 months.

Treatment

Therapy is aimed at identifying and treating underlying contributing causes, which may include vulvodynia (an idiopathic chronic pain syndrome affecting the vulvovaginal area), vaginitis, interstitial cystitis, pelvic adhesions, infections, or endometriosis. Coexisting genitourinary syndrome of menopause or inadequate lubrication may worsen genitopelvic pain/penetration disorder and generally can be diagnosed on physical examination. Vaginal or systemic hormone therapy frequently improves atrophy and lubrication and helps alleviate dyspareunia.

Successful treatment strategies must address the complex psychological and behavioral changes that accompany these disorders. Cognitive-behavioral therapy is most effective in helping to minimize negative attitudes and decrease anxiety. Individual and couples psychotherapy or sex therapy may be beneficial. Sex therapy is a form of talk therapy comprised of a combination of counseling, cognitive-behavioral interventions, and treatment of concomitant psychiatric conditions such as depression and anxiety disorders. With genitopelvic pain/penetration disorder, sex therapy with systematic desensitization teaches deep muscle relaxation and uses objects of increasing diameter, such as dilators, to achieve gradual vaginal tolerance.

There are currently no FDA-approved pharmacologic agents for treatment of sexual dysfunction in women. Although study results are inconsistent, systemic hormone therapy may improve sexual function. Treatment with low-dose testosterone in women has been shown to increase sexual function scores and the number of satisfying sexual episodes; however, it may be associated with adverse effects and therefore has not been FDA approved for female sexual dysfunction. Phosphodiesterase inhibitors are generally ineffective in women.

Menopause

Menopause describes the cessation of menses and fertility and is definitive once a woman has experienced amenorrhea for 12 months. Menopause may be natural, surgical (induced by bilateral oophorectomy), or medical (induced by chemotherapy or medical treatment). The average age of experiencing natural menopause is 51 years, and 95% of women will experience menopause between ages 40 and 59 years. Menopause occurring before age 40 years is known as premature menopause.

The transitional phase of perimenopause varies in length and may begin as early as 8 years before the final menstrual period. Irregular menstrual cycles, sometimes associated with vasomotor symptoms, are characteristic findings. The length of the menstrual cycles may increase or decrease as episodes of anovulation become more frequent. Follicle-stimulating hormone (FSH) levels begin to rise during perimenopause. However, FSH levels fluctuate depending on the frequency of anovulation. Hormone measurements during perimenopause are imprecise, cannot predict onset of menopause, and are therefore not recommended. Salivary testing of reproductive hormones is inaccurate and never indicated, and measurement of FSH is not routinely needed. The North American Menopause Society suggests measurement of FSH only to evaluate premature menopause. After 1 year of amenorrhea, a

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woman is considered to be postmenopausal, and elevated serum FSH levels stabilize (>35 mU/mL [35 units/L]).

The hallmark symptoms of menopause vary greatly in severity, duration, and frequency but may include vasomotor symptoms (hot flushes, night sweats) and urogenital symptoms (vaginal dryness, dyspareunia). Symptoms generally resolve spontaneously within a few years, and treatment should be based on symptom severity.

The differential diagnosis of menopausal symptoms associated with amenorrhea includes thyroid disease, elevated serum prolactin levels, and pregnancy, and testing for these conditions may be considered in selected patients.

Contraceptive needs must continue to be addressed during perimenopause. For perimenopausal women without contraindications, the use of combined hormonal oral contraceptive pills is helpful in providing both vasomotor symptom relief and contraception.

KEY POINTS

HVC
- Hormone measurements during perimenopause are imprecise, cannot predict onset of menopause, and are therefore not recommended.
- Contraceptive needs should continue to be addressed during perimenopause.

Management of Vasomotor Symptoms

The most effective treatment of moderate to severe vasomotor symptoms is systemic hormone therapy. Multiple formulations and routes of administration are available, and all formulations are equally effective. The lowest dose that alleviates symptoms should be used initially, titrating up if needed. Although supporting data are limited, transdermal estrogen may be associated with less thromboembolic risk than oral estrogen because transdermal delivery avoids the hepatic first-pass effect.

A stepwise approach for initiating hormone therapy in women ages 50 to 59 years who have experienced menopause at the median age is presented in **Table 62**. Effectiveness of treatment is based on relief of symptoms. In light of the risks and benefits, hormone therapy may be used to treat troubling menopausal symptoms in healthy women younger than 60 years and within 10 years of menopause, with consideration of symptom severity and risk factors. The low absolute risk of adverse events supports the option to prescribe hormone therapy for women with moderate to severe vasomotor or urogenital symptoms who are at low risk for coronary heart disease, stroke, thromboembolic disease, and breast cancer.

All women with an intact uterus who are treated with hormone therapy must receive progestin to avoid estrogen-induced endometrial proliferation. Several preparations are available and may be given continuously or cyclically to confer endometrial protection. Limited evidence suggests that micronized progesterone confers less risk of thromboembolism than does medroxyprogesterone acetate. Continuous daily estrogen-progestin does not result in cyclic bleeding, an option preferred by most women at midlife. Women treated with cyclic progestin may have withdrawal bleeding and should be counseled regarding this effect. Duration of combined estrogen-progestin use beyond 5 years is associated with increased risk of breast cancer and necessitates individualized risk assessment.

TABLE 62. Initiating Systemic Hormone Therapy in Women Ages 50-59 Years[a]

Step 1: Confirm that hot flushes/night sweats are moderate to severe in intensity and refractory to lifestyle modifications and/or vaginal symptoms have been refractory to local therapies.
Step 2: Assess for contraindications to systemic hormone therapy.
Step 3: Assess the patient's baseline risk for stroke, cardiovascular disease, and breast cancer (consider using the 10-year ASCVD risk calculator, Framingham stroke risk score, Framingham CHD risk score, and Gail model risk score to quantify this risk). If the Framingham stroke or CHD risk score is >10% or Gail model risk score is elevated, consider alternatives to systemic hormone therapy.[b,c]
Step 4: Use the lowest dose of estrogen that relieves menopausal symptoms.
Step 5: Add systemic progesterone therapy to estrogen therapy in women who have an intact uterus.
Step 6: Assess symptoms and side effects after initiating therapy and adjust the dose of estrogen if symptoms are persistent.
Step 7: Reassess symptoms and risk factors for cardiovascular disease, stroke, and breast cancer annually.
Step 8: Discontinue systemic hormone therapy if the risks of treatment outweigh the benefits.

ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease.

[a]According to the North American Menopause Society, systemic hormone therapy should be avoided in women 60 years and older who have experienced menopause at the median age (51 years). If a woman has experienced menopause later than the median age, these guidelines apply within the first 10 years of menopause.

[b]Some experts indicate that systemic hormone therapy is safe in women who have experienced menopause within the last 5 years and have a Framingham CHD risk score of 10% to 20%.

[c]The majority of participants in the Women's Health Initiative had a Gail model risk score of less than 2%.

Absolute contraindications to hormone therapy include pregnancy, unexplained vaginal bleeding, prolonged immobilization, coronary heart disease or high risk for cardiovascular disease, or history of stroke, thromboembolic disease, or breast or endometrial cancer. Discontinuation should be individualized based on clinical symptoms and risk-to-benefit ratio. The need for continued treatment should be reevaluated annually as many women will experience diminished symptoms over time.

KEY POINTS

- Systemic hormone therapy is the most effective treatment of moderate to severe vasomotor symptoms during menopause and also provides contraception.

(Continued)

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KEY POINTS *(continued)*

- All women with an intact uterus who are treated with estrogen therapy must also receive progestin to avoid estrogen-induced endometrial proliferation.
- Hormone therapy should not be initiated in women 60 years of age and older.
- Duration of combined estrogen-progestin use beyond 5 years is associated with an increased risk of breast cancer and necessitates individualized risk assessment.

Management of Genitourinary Symptoms

Mild to moderate genitourinary symptoms can be effectively treated with vaginal lubricants. Vaginal estrogen therapy is FDA-approved for women who have moderate to severe urogenital symptoms and do not respond to lubricants. Preparations include estrogen creams, vaginal estradiol tablets, and a low-dose estradiol vaginal ring. Low-dose vaginal estradiol tablets (10-25 µg) and the estradiol vaginal ring (8-9 µg) have minimal systemic estrogen absorption. Because estradiol absorption is insufficient to cause endometrial proliferation, concurrent progestin is typically not indicated when low-dose local estrogen is used to treat genitourinary syndrome of menopause.

KEY POINTS

- Vaginal estrogen therapy is indicated for treatment of moderate to severe genitourinary symptoms of menopause that do not respond to initial use of vaginal lubricants.
- Concurrent progestin is typically not indicated when low-dose local estrogen is used to treat genitourinary syndrome of menopause, since estradiol absorption is insufficient to cause endometrial proliferation.

Nonhormonal Therapy

Nonhormonal options for women with contraindications to hormone therapy or who wish to avoid the associated risks include low-dose antidepressant agents and gabapentin, which have been shown to help modulate vasomotor symptoms. Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors in low doses that have been shown to have efficacy greater than placebo include venlafaxine, desvenlafaxine, paroxetine, citalopram, and escitalopram. Data regarding black cohosh are inconclusive, as are studies of other herbs, soy, and other phytoestrogens.

KEY POINT

- Alternatives to hormone therapy for management of menopausal symptoms include low-dose antidepressant agents and gabapentin.

Preconception Care

Preconception counseling can significantly reduce the risk for preterm birth and birth anomalies. Preconception risk should be assessed, including personal and family medical history and psychosocial risk (**Table 63**). An obstetric history of pregnancy-induced hypertension, preeclampsia, or gestational diabetes is strongly predictive of future risk. Discussion should include maintenance of a healthy lifestyle; weight management; and tobacco, alcohol, and illicit drug cessation. Medications should be reviewed in order to minimize teratogenic exposure (**Table 64**). The pregnancy letter categories that have been used by the FDA to characterize the safety of drugs in pregnancy are provided in **Table 65**. The FDA has published changes in pregnancy and lactation labeling for prescription drugs, effective June 30, 2015 (see www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm). The pregnancy letter categories will be removed with the new labeling requirements; however, for prescription drugs that were previously approved, these changes will be phased in gradually. Labeling will include information relevant to the use of the drug in pregnant women (such as dosing and potential risks to the developing fetus), information about using the drug while breastfeeding (such as the amount of drug in breast milk and

TABLE 63. Preconception Risk Assessment

Risk Category	Specific Items to Assess
Reproductive awareness	Desire for pregnancy, number and timing of desired pregnancies, age-related changes in fertility, sexuality, contraception
Environmental hazards and toxins	Exposure to radiation, lead, mercury
Nutrition and folic acid consumption	Healthy diet, daily consumption of folic acid, restricting consumption of shark, swordfish, king mackerel, and tilefish to fewer than 2 servings weekly (owing to high mercury content)
Genetics	Family history of inherited genetic disorders
Substance abuse	Use of tobacco, alcohol, illicit drugs
Medical conditions	Seizure disorder, diabetes mellitus, hypertension, thyroid disease, asthma, HIV infection, systemic lupus erythematosus
Obstetric history	Pregnancy-induced hypertension, preeclampsia, gestational diabetes
Medications	Over-the-counter and prescription medications, potential teratogens
Infectious diseases and vaccinations	Immunity to varicella, rubella, pertussis, tetanus; risk for hepatitis B
Psychosocial concerns	Depression, interpersonal/family relationships, risk for abuse (physical, sexual, emotional)

Based on Johnson K, Posner SF, Biermann J, et al; CDC/ATSDR Preconception Care Work Group; Select Panel on Preconception Care. Recommendations to improve preconception health and health care–United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. MMWR Recomm Rep. 2006 Apr 21;55(RR-6):1-23. [PMID: 16617292]

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TABLE 64. Teratogenic Medications Commonly Prescribed by Internists

ACE inhibitors
Androgens, testosterone derivatives
Carbamazepine
Folic acid antagonists
Lithium
Phenytoin
Primidone
Statins
Tetracycline, doxycycline
Valproic acid
Vitamin A derivatives: isotretinoin, retinoids, etretinate
Warfarin

TABLE 65. FDA Classification of Drugs in Pregnancy[a]

Class	Fetal Effect of Drug During Pregnancy
A	No disclosed fetal effects
B	Animal studies failed to demonstrate fetal risk
C	Animal studies suggest adverse fetal effects
D	Evidence of human fetal risk
X	Documented fetal abnormalities

[a]The FDA has published changes in pregnancy and lactation labeling for prescription drugs, effective June 30, 2015. A summary of these changes is available here: www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm. The pregnancy letter categories will be removed with the new labeling requirements; however, for prescription drugs that were previously approved, these changes will be phased in gradually.

potential effects on the breastfed infant), and information regarding potential risks to females and males of reproductive potential who take the drug.

Measurements of BMI and blood pressure are essential. The pelvic examination may include screening cervical cytology. Testing for STIs and screening for HIV infection are also indicated. All women who are considering pregnancy should be routinely assessed for immunity to varicella and rubella. In nonimmune women, vaccination for rubella and varicella should be administered at least 4 weeks before conception to minimize fetal risk. Other routine immunizations should be current.

Supplementation with folic acid (400 µg/d) reduces the risk of neural tube defects. Because these defects occur very early in gestation, when a woman might not be aware of pregnancy, folic acid supplementation is generally recommended for all women who are of reproductive age. Supplementation with low-dose iron may reduce the risk for maternal anemia. A daily prenatal multivitamin that contains iron and folic acid, while not replacing a healthy diet, is reasonable for all women who are planning pregnancy or who may become pregnant.

KEY POINT

- Women considering pregnancy should be routinely assessed for immunity to varicella and rubella, and other routine immunizations should be current.

Vaginitis

Vaginitis describes infectious and noninfectious conditions that cause vulvovaginal symptoms, including abnormal vaginal discharge, vulvar itching, burning, irritation, and malodor. Although vaginal discharge is frequently reported, it may not be due to infection, since normal vaginal secretions vary in color, amount, and consistency throughout the menstrual cycle. When discharge is associated with abnormal findings, the differential diagnosis most commonly includes bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis (**Table 66**). Vaginal irritation also may be caused by dermatologic conditions or allergic reactions, cervical infections, or genitourinary syndrome of menopause. A woman may have more than one type of infection at a time.

History should include duration of symptoms, relationship to the menstrual cycle, use of douches or other products, sexual activity and risk behavior, dysuria, dyspareunia, and discharge characteristics, including color, consistency, odor, pain, and itching. Risk for STIs should be considered. The vulva and vagina should be inspected for erythema, excoriations, and lesions, and vaginal wall secretions should be collected for pH, amine whiff testing, and saline and 10% potassium hydroxide (KOH) microscopy.

Bacterial Vaginosis

Bacterial vaginosis is the most common cause of vaginal discharge or malodor. It is characterized by an imbalance in the normal vaginal bacterial flora, with a decrease in hydrogen peroxide–producing lactobacilli and an increase in *Gardnerella vaginalis*, *Mycoplasma* species, and other anaerobic bacteria. When vaginal alkalinity increases after intercourse or during menses, the odor becomes stronger and is predictive of bacterial vaginosis. Bacterial vaginosis is associated with increased risk of adverse pregnancy outcomes, including preterm labor and pregnancy loss, and with increased risk for STIs and HIV infection.

Symptomatic patients may report a thin, white or gray homogeneous discharge that has a "fishy" or unpleasant odor. Accepted clinical criteria for diagnosing bacterial vaginosis include the presence of three of four characteristics: vaginal pH greater than 4.5, amine ("fishy") odor on the application of 10% KOH to vaginal secretions (whiff test), the presence of a thin homogeneous vaginal discharge, and the finding of at least 20% clue cells on a microscopic saline wet mount examination. Clue cells are squamous vaginal epithelial cells with a large number of coccobacillary organisms attached to the cell surface, causing stippling and obscuring the cell borders (**Figure 21**). Other point-of-care

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TABLE 66. Clinical Presentation, Evaluation, and Management of Vaginitis

Cause of Vaginitis	Clinical Presentation	Evaluation	Management
Bacterial vaginosis	Malodorous or "fishy" vaginal discharge, often most noticeable after intercourse Increased thin white or gray discharge Symptoms other than malodor may be minimal	pH ≥4.5 KOH amine whiff test positive Saline wet mount >20% epithelial clue cells	Metronidazole: 500 mg orally twice daily for 7 days[a] (avoid alcohol during treatment and for 24 hours after last dose); or vaginal gel (0.75%) 5 g into vagina at bedtime for 5 nights Clindamycin: 300 mg orally twice daily for 7 days; or vaginal cream (2%) 5 g into vagina for 7 nights Note: Use oral regimens in pregnancy.
Vulvovaginal candidiasis	Itching, irritation, dysuria, dyspareunia, vulvodynia, excoriation, erythema, fissures Increased thick white discharge (although may be normal)	pH ≤4.5 KOH amine whiff test negative KOH wet mount with hyphae, pseudohyphae, or yeast	**Uncomplicated[b]** Fluconazole: 150 mg orally as a single dose Butoconazole vaginal: (2% cream) 5 g into vagina at bedtime for 3 nights Clotrimazole vaginal: (1% cream) 5 g into vagina at bedtime for 7-14 nights; or 100 mg vaginal tablet into vagina at bedtime for 7 nights; or 200 mg (two vaginal tablets) into vagina once daily at bedtime for 3 nights Miconazole vaginal: (2% cream) 5 g into vagina at bedtime for 7 nights; or 100 mg vaginal suppository into vagina at bedtime for 7 nights; or 200 mg vaginal suppository into vagina at bedtime for 3 nights Note: Single-dose vaginal preparations and non-imidazoles are available but less effective. **Complicated[c]** Longer duration of initial oral or topical treatment, followed by maintenance therapy: Fluconazole 150 mg orally every 3 days for a total of three doses; or topical imidazole therapy for 7-14 nights Following this, maintenance therapy is based on refractory or recurrent symptoms: Fluconazole 150 mg orally weekly for 6 months; or 200 mg orally weekly for 8 weeks; or 200 mg orally twice weekly for 4 months; or 200 mg orally once monthly for 6 months
Trichomoniasis	Increased discolored discharge (yellowish, gray, and/or frothy) Dyspareunia, dysuria, itch, erythema, postcoital bleeding, abdominal pain Punctate cervical hemorrhages ("strawberry" cervix)	pH ≥4.5 KOH amine whiff test negative Saline wet mount with trichomonads, leukocytes NAAT or rapid assay positive	Metronidazole[a]: 2 g orally as a single dose; or 500 mg orally twice daily for 7 days Note: Avoid alcohol during treatment and for 24 hours after last dose.

KOH = potassium hydroxide; NAAT = nucleic acid amplification test.

[a]Safe in pregnancy.

[b]Uncomplicated vulvovaginal candidiasis: *Candida albicans*, mild to moderate symptom severity, healthy nonpregnant women, four or fewer episodes per year.

[c]Complicated vulvovaginal candidiasis: Severe symptoms, suspected or proven non-albicans *Candida*, more than four episodes a year, uncontrolled diabetes mellitus, or immunosuppression.

tests that can aid in diagnosis utilize nucleic acid testing. Because of their low specificity, vaginal cultures are not recommended.

Treatment is with metronidazole or clindamycin, both of which are available in either oral or topical preparations. Both oral treatments are safe in pregnancy; oral metronidazole is most cost effective. Although the pathogenesis is poorly understood, bacterial vaginosis is associated with high rates of recurrence (30%-60%). Condom use may help prevent recurrence, and douching should be avoided. Data regarding the usefulness of probiotics to increase lactobacilli are inconclusive.

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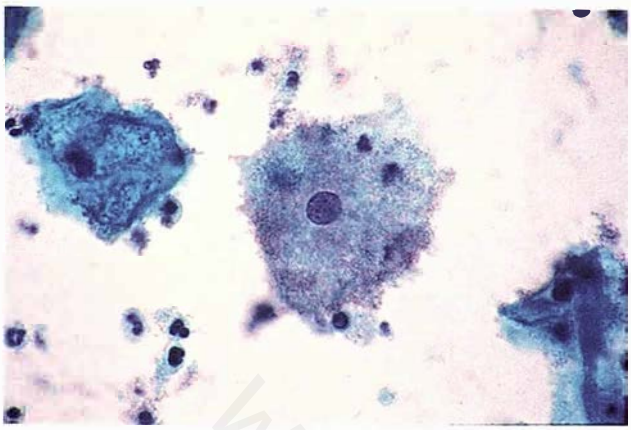

FIGURE 21. Clue cells. Vaginal epithelial cells with bacteria adherent to their surface are termed clue cells and are characteristic of bacterial vaginosis.

KEY POINT

- Clinical criteria for diagnosing bacterial vaginosis include the presence of three of four characteristics: vaginal pH greater than 4.5, positive whiff test, thin homogeneous vaginal discharge, and at least 20% clue cells on saline microscopy.

Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) is a common cause of vaginal symptoms in women and occurs in up to 40% of women who are evaluated for such symptoms in the primary care setting. Uncomplicated VVC develops in immunocompetent women, is sporadic and infrequent, and is likely due to *Candida albicans*. Most healthy women with uncomplicated VVC have no identifiable precipitating factors, although prevalence increases in women who are pregnant, have diabetes mellitus, or require treatment with antibiotics or glucocorticoids. Complicated VVC is recurrent (four or more episodes in 1 year), characterized by more severe symptoms, and may be due to non-albicans *Candida* such as *Candida glabrata*. It may develop in women who have uncontrolled diabetes, are immunosuppressed, or are pregnant.

A diagnosis of VVC is suggested by the presence of external dysuria and vulvar pruritus, pain, irritation, and redness. Signs include vulvar edema; fissures; excoriations; or thick, white, curdy vaginal discharge. The diagnosis can be made when a saline or 10% KOH wet mount of vaginal discharge shows yeast, hyphae, or pseudohyphae. Because VVC is associated with a normal vaginal pH (<4.5), pH testing is not useful.

As the sensitivity of microscopy is low, empiric treatment of VVC can be considered if symptoms are accompanied by characteristic findings. Several therapeutically equivalent topical and oral drugs are available, although among the topically applied drugs, imidazoles (fluconazole, miconazole, clotrimazole) are more effective than nystatin. Short-course over-the-counter intravaginal imidazole therapy may effectively treat uncomplicated VVC, as does prescription fluconazole, 150 mg orally in a single dose. A combined approach is often effective. Severe VVC requires topical therapy, preferably with an imidazole, administered intravaginally daily for 3 to 7 days with or without fluconazole, 150 mg orally every third day for a total of three doses.

Recurrent VVC is common, and retreatment is based on severity and persistence of symptoms. The pathogenesis is poorly understood, and many women have no identifiable predisposing or underlying conditions. Recurrence is treated initially with oral fluconazole every third day for a total of three doses or a 7- to 14-day course of an intravaginal imidazole. Long-term weekly suppressive oral antifungal therapy may be required to control recurrent VVC, and recurrence rates remain high after discontinuation of treatment.

KEY POINTS

- As the sensitivity of microscopy is low, empiric treatment of vulvovaginal candidiasis can be considered if symptoms are accompanied by characteristic findings.
- Short-course, over-the-counter intravaginal imidazole therapy may effectively treat uncomplicated vulvovaginal candidiasis, as does prescription fluconazole, 150 mg orally in a single dose.

Trichomoniasis

Trichomoniasis, which is caused by *Trichomonas vaginalis*, is the most common nonviral STI worldwide. Unlike other STIs that predominate in adolescents and younger adults, rates of trichomoniasis are evenly distributed among women of all age groups.

T. vaginalis is a flagellated protozoan that exclusively infects the urogenital tract, causing inflammatory vaginitis and urethritis. Although the presentation is variable, many women develop a copious, malodorous, pale yellow or gray frothy discharge with vulvar itching, burning, and postcoital bleeding.

The diagnosis has traditionally been made by direct microscopic examination of a wet mount of vaginal fluid to determine the presence of motile trichomonads. Although trichomoniasis is associated with a vaginal pH greater than 4.5, the specificity of an abnormal vaginal pH and the sensitivity of saline microscopy findings are both low. Point-of-care vaginal swab rapid immunoassays and nucleic acid amplification tests (NAATs) for detection of *T. vaginalis* have replaced microscopy or culture as the gold standard for diagnosis. NAATs can be performed on a vaginal (or endocervical) swab, urine sample, or specimens collected for liquid-based Pap tests. Once trichomoniasis is identified, testing for other STIs should be considered. Any patient who tests positive for *T. vaginalis* should be retested 3 months after treatment.

All women with symptoms should be treated with metronidazole, 2 g orally in a single dose, which is associated with high cure rates. In addition, treatment of the sexual partner is essential for preventing reinfection. Metronidazole may be safely given at any stage of pregnancy. Inadequate response to treatment may be caused by reinfection or by diminished responsiveness to metronidazole. If the latter is suspected, a

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7-day course of metronidazole, 500 mg twice daily, usually results in clinical resolution.

KEY POINTS

- Nucleic acid amplification tests for detection of *Trichomonas vaginalis* have replaced microscopy or culture as the gold standard for diagnosis.
- All women with symptoms of trichomoniasis should be treated with metronidazole, 2 g orally in a single dose; treatment of the sexual partner is essential for preventing reinfection.

Eye Disorders

Red Eye

Conjunctivitis

Red eye is the most frequently encountered eye disorder. As a general approach to the patient with red eye, if pain is present, especially in the setting of visual loss, pupillary distortion, or corneal involvement, emergent ophthalmology referral is indicated. In the absence of pain, continuous discharge suggests the presence of conjunctivitis, which is the most common cause of red eye.

Conjunctivitis is categorized as infectious (bacterial or viral) or noninfectious (allergic or nonallergic). History may reveal typical causes, such as allergies, viral or bacterial infections, and contact lens wear. On examination, the conjunctiva (bulbar and tarsal) appears red and vessels may be visible. In general, conjunctivitis is a diagnosis of exclusion; in a patient with red eye and discharge, a diagnosis of conjunctivitis is made only if the vision is normal and there is no evidence of angle closure glaucoma, iritis, or keratitis.

Viral conjunctivitis (**Figure 22**), typically caused by an adenovirus, is often acute, unilateral, and associated with antecedent upper respiratory tract infection and exposure to infected persons. Symptoms are itching, foreign body sensation, and crusting of the eyelids following sleep. Patients are considered contagious for as long as the eye continues to tear and produce discharge, which is usually 3 to 7 days. While contagious, patients should perform careful hand washing. Food handlers and health care providers should not return to work until the eye symptoms subside. Treatment is supportive, including cold compresses and artificial tears.

Bacterial conjunctivitis (**Figure 23**) in adult patients is usually caused by *Staphylococcus aureus* infection. The patient presents with redness in one or both eyes and mucopurulent discharge. In patients with bacterial conjunctivitis, discharge is thick and may be yellow or green in color, whereas discharge appears watery in patients with viral conjunctivitis. Treatment of bacterial conjunctivitis involves broad-spectrum topical antibiotics (erythromycin ophthalmic 0.5% ointment, bacitracin/polymyxin B ophthalmic ointment), which should be used for 5 to 7 days.

Patients with allergic conjunctivitis present with itching, sneezing, and tearing. Inspection may reveal the presence of bilateral redness and chemosis (conjunctival edema). Treatment includes oral antihistamines, topical antihistamines (olopatadine ophthalmic 0.1%, ketotifen ophthalmic), and artificial tears.

Nonallergic conjunctivitis can result from dry eye or insult with a foreign body or chemical. Nonallergic conjunctivitis typically resolves within 24 hours, although topical lubricants may be beneficial.

Episcleritis and Scleritis

Episcleritis (**Figure 24**) is an abrupt inflammation of the superficial vessels of the episclera, a thin membrane that lies just beneath the conjunctiva. The cause is often unclear; rarely, it is associated with systemic rheumatic disease. Patients with episcleritis frequently present without pain or decreased visual acuity. On examination, the inflammation appears



FIGURE 22. Viral conjunctivitis. Diffuse conjunctival injection and erythema, usually with a watery or mucoserous discharge, is characteristic of viral conjunctivitis.

Eye with Viral Conjunctivitis. Digital image. Wikimedia Commons. 1 Feb 2010. Web. 16 May 2012. http://commons.wikimedia.org/wiki/File:An_eye_with_viral_conjunctivitis.jpg.

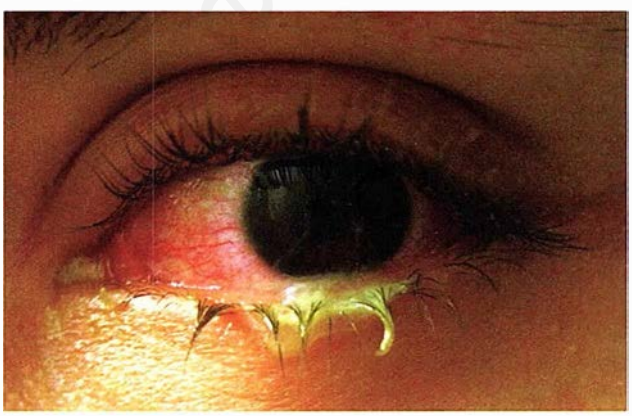

FIGURE 23. Bacterial conjunctivitis. In patients with bacterial conjunctivitis, eye discharge is thick and may be yellow or green in color.

Swollen Eye with Conjunctivitis. Digital image. Wikimedia Commons. 8 Feb 2008. Web. 16 May 2012. http://commons.wikimedia.org/wiki/File:Swollen_eye_with_conjunctivitis.jpg.

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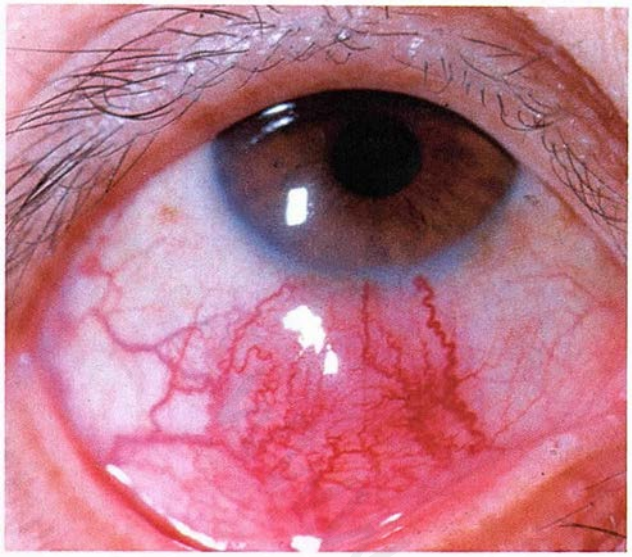

FIGURE 24. Episcleritis. Superficial dilated blood vessels are seen, with white sclera visible between the blood vessels.

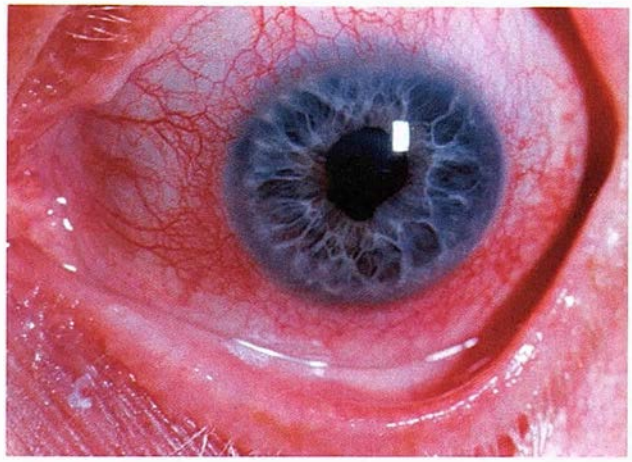

FIGURE 25. Nongranulomatous iritis (anterior uveitis). The conjunctival vessels are most dilated at the corneal edge, resulting in a circumferential redness around the iris, which is termed ciliary flush.

more localized than with conjunctivitis, which is typically diffuse. White sclera can be seen between superficial dilated blood vessels. Episcleritis typically resolves spontaneously.

Scleritis is inflammation of the sclera, the fibrous layers of the eye underlying the episclera and conjunctiva. Anterior scleritis, which is most common, involves the superficial sclera and deep vessels of the episclera. It has several forms, including diffuse, nodular, and necrotizing; the necrotizing form is more often associated with systemic inflammatory disorders. Posterior scleritis involves the deeper structures of the eye. Roughly half of patients with scleritis have an underlying systemic disease, such as an inflammatory connective tissue disorder or infection. Patients may present with severe ocular pain, photophobia, tearing, and vision changes. On examination, the sclera may have a blue or violet coloration and be tender to palpation.

Episcleritis must be distinguished from scleritis, as scleritis can be a sight-threatening condition. Generally, episcleritis is painless and involves no vision changes, whereas scleritis is painful and associated with visual impairment. Patients with scleritis, or any patients in whom the diagnosis is unclear, must be urgently referred to an ophthalmologist.

Uveitis

Uveitis (**Figure 25**) is inflammation of the middle eye, which includes the iris, ciliary body, and choroid (the vascular layer lying between the retina and the sclera). Uveitis can either be idiopathic or occur as part of an underlying systemic condition, such as autoimmune disorders, arthritides associated with HLA-B27 antigen, infection, malignancy, and sarcoidosis. Presenting symptoms of uveal inflammation are eye redness, pain, and photophobia. On examination, the conjunctival vessels are most dilated at the corneal edge, resulting in a circumferential redness around the iris (ciliary flush). The pupil may have an irregular shape because it has become attached to the anterior surface of the lens or the posterior surface of the cornea. Uveitis requires urgent referral to an ophthalmologist.

Blepharitis

Blepharitis (**Figure 26**) is a diffuse inflammation of the sebaceous glands or lash follicles of the eyelids. Common causes are *Staphylococcus aureus* infection, rosacea, and seborrheic dermatitis. The patient may report a gritty, burning sensation and crusting or matting, especially upon awakening. Treatment includes warm compresses, application of diluted shampoo with a cotton tip applicator, topical antibiotics (for staphylococcal infections), and oral tetracyclines (for infections associated with rosacea).



FIGURE 26. Blepharitis. Erythematous, edematous eyelids typically seen in blepharitis.

Blepharitis. Digital image. Wikimedia Commons. 2 May 2012. Web. 13 Nov 2014. https://commons.wikimedia.org/wiki/File:Blepharitis.JPG.

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Subconjunctival Hemorrhage

Subconjunctival hemorrhage (**Figure 27**) is extremely common and usually benign in origin. Examination reveals a blotchy redness (from extravascular blood) that is typically confined to one area of the conjunctiva. Subconjunctival hemorrhage is painless but nonetheless alarming to patients. Most cases resolve within several weeks without intervention.

KEY POINTS

- Viral conjunctivitis is often acute, unilateral, and associated with antecedent upper respiratory tract infection and exposure to infected persons; treatment is supportive.
- Patients with bacterial conjunctivitis present with eye discharge that is thick and yellow or green in color.
- Allergic conjunctivitis presents with itching, sneezing, tearing, bilateral redness, and chemosis (conjunctival edema) and can be treated with oral antihistamines, topical antihistamines, and artificial tears.
- Episcleritis is painless and involves no vision changes, whereas scleritis is painful and associated with visual impairment.

Corneal Disorders

Corneal abrasions are secondary to trauma from foreign bodies and usually heal within 48 hours. Symptoms are pain, foreign body sensation, photophobia, and tearing. Physical examination requires eversion of the lid for inspection and removal of foreign bodies. The cornea can be examined by applying fluorescein dye and examining with a Wood lamp or slit lamp. Management consists of antibiotic ointments that provide comfort. Acute pain control can be achieved with topical NSAIDs, such as diclofenac and ketorolac. Topical anesthetics should be avoided after the initial examination, as they can retard healing and cause further corneal damage. A follow-up examination in 24 hours should be arranged to ensure that the corneal abrasion has healed. Eye patching is not recommended for corneal abrasions.



FIGURE 27. Subconjunctival hemorrhage. A well-localized superficial collection of extravasated blood is visible; the sclera and conjunctiva are not involved.

Subconjunctival hemorrhage. Digital image. Wikimedia Commons. 28 Jun 2011. Web. 16 May 2012. http://commons.wikimedia.org/wiki/File:Subconjunctival_hemorrhage_eye.JPG.

Corneal ulcers (**Figure 28**) are caused by trauma, contact lens wear, herpes simplex virus infection, bacterial infection, and connective tissue disorders (ankylosing spondylitis). On inspection, corneal ulcers are visible with fluorescein dye; herpes infections often manifest as a dendritic-appearing defect. Corneal ulcers can cause permanent visual loss and require referral to an ophthalmologist.

KEY POINT

- Corneal abrasions are managed with topical antibiotic ointments and topical NSAIDs; topical anesthetics and eye patching are not indicated.

Cataract

Cataracts are opacifications of the lens. Cataracts are very common and occur in over 50% of people older than 80 years in the United States. They are a leading cause of visual impairment and blindness worldwide. Risk factors include aging, family history, smoking, diabetes mellitus, ultraviolet B radiation exposure, and use of systemic glucocorticoids. Symptoms are decreased visual acuity, impaired night vision, glare, and diplopia. Ophthalmoscopic examination reveals opacification of the lens and diminished or absent light reflex. Surgery is indicated when symptoms interfere with activities of daily living; however, not all patients with cataracts will require surgery.

Glaucoma

Primary Open Angle Glaucoma

Primary open angle glaucoma (POAG), the most common type of glaucoma, is a progressive optic neuropathy associated with increased intraocular pressure (IOP) without obstruction to the normal drainage pathways of the aqueous humor. POAG is a leading cause of permanent blindness worldwide. Risk factors are age older than 40 years, family history, and race (incidence in blacks is approximately four times higher than in whites). POAG presents with bilateral peripheral visual loss

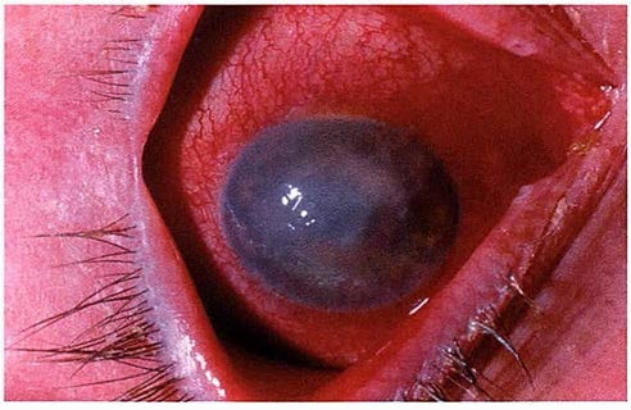

FIGURE 28. Corneal ulcer. Corneal epithelial defect with associated conjunctival injection.

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that occurs gradually and painlessly; it may impair central visual acuity in later stages. Because the onset is gradual and asymptomatic, it often goes unnoticed by the patient. The U.S. Preventive Services Task Force has found that there is insufficient evidence to support the practice of screening for glaucoma. Physical examination reveals increased cup:disc ratio (>0.5), vertical extension of the central cup, and disc hemorrhages. The primary treatment is lowering IOP with medications (**Table 67**). Other interventions include laser therapy and surgical therapy, such as iridectomy or trabeculectomy.

Acute Angle Closure Glaucoma

Acute angle closure glaucoma (AACG) is caused by increased IOP resulting from blocked drainage of the aqueous humor. Symptoms are severe eye pain, headache, and decreased visual acuity. Occasionally, patients experience nausea, vomiting, and visual halos. Ophthalmoscopic examination reveals a mid-dilated (4-6 mm), nonreactive pupil and IOP greater than 50 mm Hg. There is an immediate threat of blindness from optic nerve atrophy in patients with AACG, so urgent referral to an ophthalmologist is required. Additionally, patients with chronic angle closure glaucoma should avoid certain medications that cause pupillary dilatation, including decongestants, anticholinergic agents, adrenergic agents, antidepressants, antipsychotic agents, and motion-sickness medications.

KEY POINTS

- Primary open angle glaucoma presents with bilateral peripheral visual loss that occurs gradually and painlessly.
- Acute angle closure glaucoma presents with severe eye pain, headache, decreased visual acuity, a mid-dilated (4-6 mm) nonreactive pupil, and elevated intraocular pressure; urgent referral to an ophthalmologist is required to prevent blindness.

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a degenerative disease of the macula. It is a leading cause of visual loss among elderly patients. AMD may be classified as either dry or wet (**Figure 29**). Dry AMD, which accounts for approximately 85% of cases, involves the deposition of extracellular material (drusen) in the macular region of one or both eyes. If the drusen become confluent in the macula, visual acuity will decrease but rarely below 20/40. Patients often report a gradual loss of vision.

A small percentage of patients with dry AMD will progress to develop new vessel growth under the retina (wet AMD). Bleeding and exudation result in sudden (or rapid onset over weeks), painless blurring or warping of central vision. Wet AMD, which often involves only one eye, results in severe visual loss.

Risk factors for developing AMD are advanced age, family history, smoking, and cardiovascular disease. Smoking cessation decreases the risk for developing AMD and should be recommended to all patients who smoke.

Dry AMD cannot be reversed with treatment; however, progression to advanced dry AMD may be slowed with the use of zinc or antioxidants. There is no evidence that antioxidants have a role in AMD prevention. Laser photocoagulation is recommended for wet AMD with extrafoveal lesions. Additionally, intraocular injection of inhibitors of vascular endothelial growth factor (VEGF) has been used to slow neovascularization of wet AMD.

KEY POINT

- Progression to advanced dry age-related macular degeneration may be slowed with smoking cessation and the use of zinc or antioxidants.

TABLE 67. Drug Treatment for Primary Open Angle Glaucoma

Agent	Mechanism of Action	Systemic Side Effects
β-Blockers (timolol)	Decreases inflow	Bradycardia, heart block, bronchospasm, decreased libido, central nervous system depression, mood swings
Nonselective adrenergic agonists (epinephrine)	Decreases inflow and increases outflow	Hypertension, headaches, extrasystole
Selective α_2-adrenergic agonists (brimonidine)	Decreases inflow and increases outflow	Hypotension, vasovagal attack, dry mouth, fatigue, insomnia, depression, syncope, dizziness, anxiety
Parasympathomimetic agents (pilocarpine, echothiophate iodide)	Increases outflow	Increased salivation, increased gastric secretion, abdominal cramps, urinary frequency, shock
Oral carbonic anhydrase inhibitors (acetazolamide)	Decreases inflow	Acidosis, depression, malaise, hirsutism, paresthesias, numbness, blood dyscrasias, diarrhea, weight loss, kidney stones, loss of libido, bone marrow suppression, hypokalemia, bad taste, increased serum urate level
Topical carbonic anhydrase inhibitors (dorzolamide)	Decreases inflow	Lower incidence of systemic effects compared with oral carbonic anhydrase inhibitors
Prostaglandin analogues (latanoprost)	Increases outflow	Flu-like symptoms, joint and muscle pain
Hyperosmotic agents (mannitol)	Reduces vitreous and aqueous volume	Headache, heart failure, expansion of blood volume, nausea, vomiting, diarrhea, electrolyte disturbance, kidney failure

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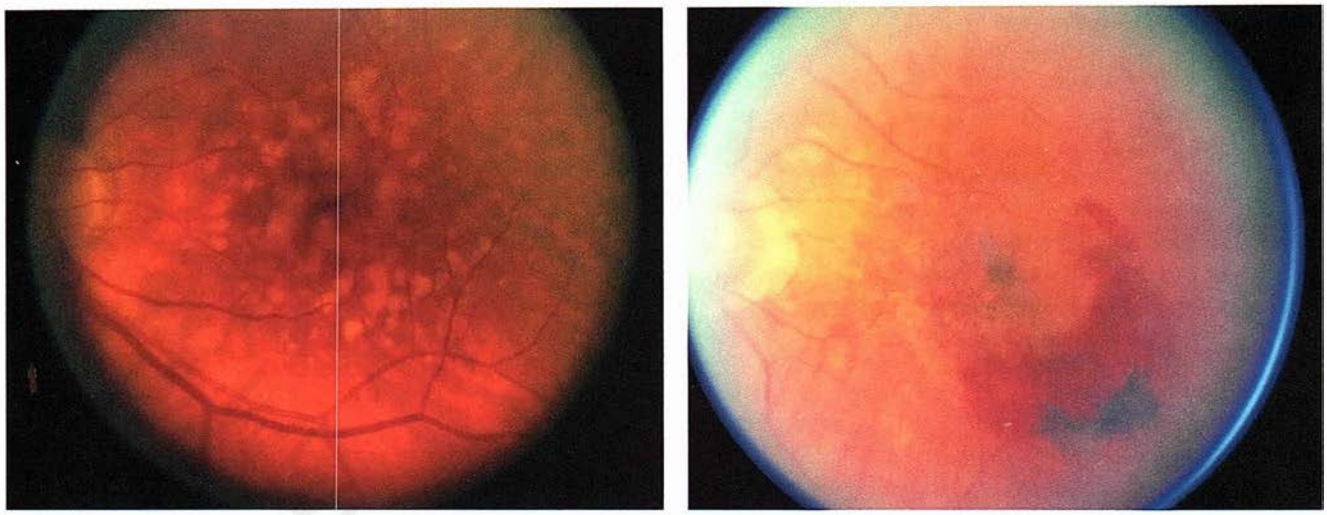

FIGURE 29. Age-related macular degeneration. The dry form (*left*), is characterized by distinct yellow-white lesions (drusen) surrounding the macular region and areas of pigment mottling. The wet form (*right*), is characterized by clumps of hyperpigmentation, hypopigmentation, and evidence of subretinal hemorrhage.

Retinal Detachment

Retinal detachment (**Figure 30**) occurs mainly in patients with myopia. Symptoms are floaters, flashes of light (photopsias), and squiggly lines, followed by a sudden, peripheral visual field defect that resembles a black curtain and progresses across the entire visual field. Emergent ophthalmology referral is crucial, as prognosis depends on the time to surgical treatment.

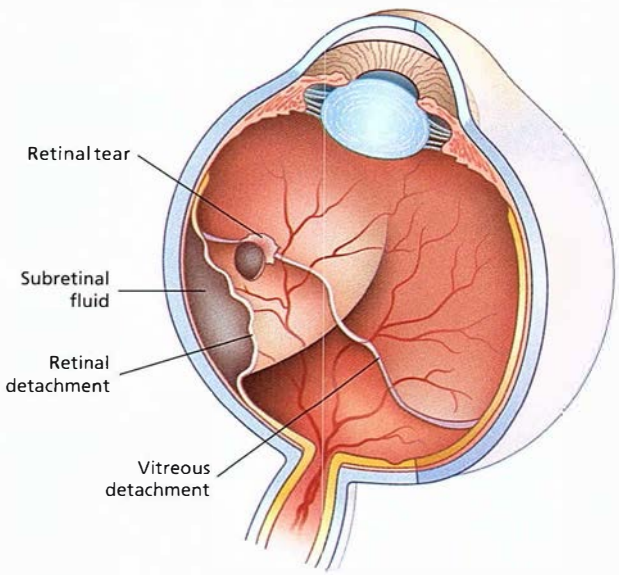

FIGURE 30. Retinal detachment. Retinal detachment occurs when the retina separates from the underlying retinal pigment epithelium and choroid and may be caused by a tear in the retina, leakage or exudation from beneath the retina, or vitreous traction pulling on the retina.

KEY POINT

- Emergent ophthalmology referral is crucial for patients with suspected retinal detachment, as prognosis depends on the time to surgical treatment.

Dry Eye

Dry eye, also called keratoconjunctivitis sicca, includes symptoms of dryness, irritation, and burning that generally worsen throughout the day. Irritants, such as smoke, allergens, and low humidity, may exacerbate symptoms.

The mechanisms of dry eye include disruption of tear secretion and increased tear evaporation. Decreased tear secretion usually results from inflammation of the lacrimal glands and may be related to systemic diseases, such as Sjögren syndrome and rheumatoid arthritis. Increased tear evaporation can be caused by increased size of the palpebral fissure, as seen in Graves ophthalmopathy, or by meibomian gland dysfunction, which reduces the tear film. Sjögren syndrome, Graves disease, and Bell palsy can cause persistent dry eye that results in corneal injury. Other risk factors for dry eye are advanced age, female sex, medications (antihistamines, selective serotonin reuptake inhibitors), diabetes mellitus, or a history of laser-assisted in-situ keratomileusis (LASIK) procedure.

Treatment focuses on reducing inflammation and correcting lid pathology that disrupts the tear film. Common treatments for dry eye are artificial tears and warm compresses. Gentle scrubs with diluted shampoo may be used for meibomianitis. Oral tetracyclines are used to treat lid inflammation. Topical cyclosporine and glucocorticoid drops are reserved for patients with dry eye from systemic illness. Punctal or canalicular plugs, very small devices that are inserted into the tear ducts to decrease tear evaporation, may be used in patients

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who fail to respond to conservative treatment for dry eye. Temporary or semi-permanent plugs are available.

Retinal Vascular Occlusion

Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) is caused by thrombi or emboli. CRAO is most commonly associated with carotid artery atherosclerosis, although it may result from other vascular disease (carotid artery dissection), hematologic disease, or inflammatory disease (giant cell arteritis). Patients are usually elderly and present with profound and sudden painless vision loss.

Funduscopic examination reveals an afferent pupillary defect and cherry red fovea that is accentuated by a pale retinal background (**Figure 31**). Prognosis is based on visual acuity at presentation. Ischemia that lasts 4 hours or longer tends to result in irreversible vision loss. Treatment may include measures to lower IOP. Emergent ophthalmology consultation is required.

Retinal Vein Occlusion

Central retinal vein occlusion (CRVO) is usually caused by occlusion of the central retinal vein by a thrombus, whereas branch retinal vein occlusion (BRVO) is most commonly caused by arterial compression of the vein. Patients with CRVO present with sudden, painless, unilateral visual loss often mixed with "sparkles"; symptoms may be sudden or evolve over hours to days. BRVO is typically asymptomatic. Risk factors for retinal vein occlusion are advanced age, smoking, diabetes mellitus, hypertension, hyperlipidemia, obesity, glaucoma, retinal arteriolar defects, and hypercoagulable states.

Funduscopic examination may reveal an afferent pupillary defect, congested retinal veins, scattered retinal hemorrhages, and cotton wool spots in the region of occlusion (**Figure 32**). Severe visual impairment at presentation signifies the risk of permanent visual loss. Immediate ophthalmology consultation is necessary.

KEY POINT

- Patients with central retinal artery occlusion, caused by thrombi or emboli, present with profound and sudden vision loss; emergent ophthalmology consultation is required.

Eye Emergencies

Eye emergencies may include causes of acute visual loss (retinal detachment, CRAO, CRVO, temporal arteritis, endophthalmitis, orbital cellulitis, optic neuritis, chemical injury) as well as trauma to the globe, eyelid, nasolacrimal system, or tarsal plate.

Endophthalmitis is inflammation of the aqueous and vitreous humors. It is usually caused by bacterial or fungal infection following surgery. Treatment includes intravitreal antibiotics. Prognosis is dependent on how quickly treatment is started and the virulence of the pathogen.

Orbital cellulitis, another ocular emergency, results from infection of tissues posterior to the orbital septum, a membrane that extends from the orbital rims to the eyelids. Preseptal (periorbital) cellulitis originates from the eyelids and facial tissue that is anterior to the orbital septum. Orbital cellulitis often results from contiguous dental or sinus infections.

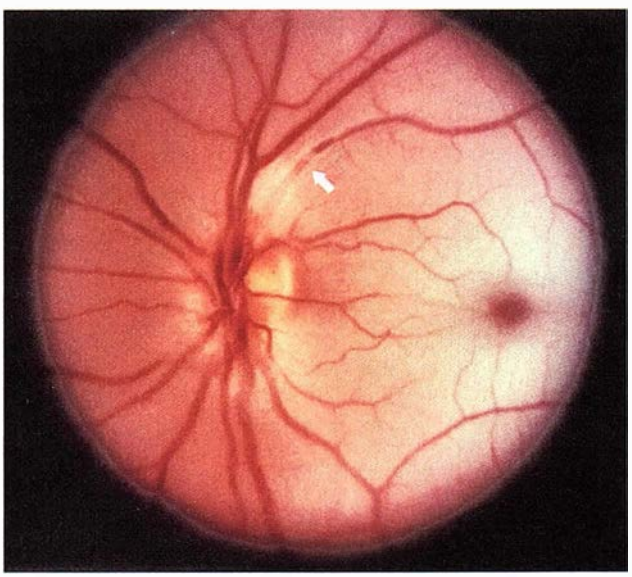

FIGURE 31. Occlusion of the central retinal artery (*arrow*) characterized by the appearance of an opalescent retina, retinal pallor, and "cherry-red spot" defining the fovea.



FIGURE 32. Central retinal vein occlusion characterized by optic disk swelling, dilated and tortuous veins, flame-shaped retinal hemorrhages, and cotton-wool spots ("blood and thunder").

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CONT.

Symptoms are eye swelling, erythema, pain, and fever. Orbital cellulitis may be distinguished from preseptal cellulitis by examining pupillary reflexes and function of the extraocular muscles and obtaining a CT scan to exclude deeper infection.

Herpes zoster involving the trigeminal nerve distribution and especially the tip of the nose (Hutchinson sign) correlates with sight-threatening herpes zoster ophthalmicus. Patients who present with Hutchinson sign require ophthalmologic evaluation.

Optic neuritis, inflammation of the optic nerve, can also result in acute visual loss. It occurs most commonly in people who are middle-aged, white, and female and is often associated with multiple sclerosis. Presenting symptoms include eye pain, blurred vision, visual field defects, and changed color perception. Evaluation includes ophthalmologic evaluation and MRI of the brain. Treatment may include systemic glucocorticoids, although optic neuritis usually resolves spontaneously.

In the case of chemical eye injuries, patients may present with severe pain, decreased visual acuity, eye redness, and photophobia and may not be able to open the eyelids. The eye should be treated with at least 30 minutes of eye irrigation while awaiting ophthalmologic evaluation.

Ear, Nose, Mouth, and Throat Disorders

Hearing Loss

Hearing loss affects 28 million U.S. adults, and it is the third most common chronic health problem in the geriatric population. Hearing loss is generally categorized as conductive or sensorineural, although patients can have mixed hearing disorders (**Table 68**). Conductive hearing loss results from a mechanical problem in the ear canal, tympanic membrane, or ossicles that prevents the transmission of sound to the cochlea. Patients with conductive problems will describe general hearing loss, frequently with associated pain or drainage. Sensorineural hearing loss is caused by damage to the cochlea or acoustic nerve. Patients with sensorineural hearing loss will often describe difficulty hearing people speak, especially if there is background noise. Associated symptoms can include tinnitus or vertigo.

The U.S. Preventive Services Task Force concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for hearing loss in asymptomatic adults

TABLE 68. Common Causes of Hearing Loss

Disease	Notes
Conductive	
Cerumen impaction	Cerumen may completely obstruct ear canal, causing conductive hearing loss. Impacted cerumen can be removed with gentle irrigation or an ear curette. No removal needed if asymptomatic.
Otosclerosis	Bony overgrowth of the stapes footplate with eventual fixation. Family history of otosclerosis is common. Treatment is stapedectomy or stapedotomy. Hearing aid may be helpful.
Tympanic membrane perforation	Often heals without intervention. Ear should be kept dry. Refer for possible repair if associated with significant hearing loss or possible middle ear pathology.
Cholesteatoma	An expanding mass composed of keratinizing squamous epithelial cells that may contain cholesterol crystals. Although histologically benign, it may erode extensively into local structures, including the cochlea, ossicles, tympanic membrane, and facial nerve. Treatment is surgical removal.
Sensorineural	
Presbycusis	Age-related hearing loss; typically symmetric high-frequency hearing loss. Hearing aids are mainstay of treatment.
Sudden sensorineural hearing loss	Unclear etiology; presents as a sudden loss of hearing that is sensorineural in nature. Rapid treatment with glucocorticoids may improve outcome.
Meniere disease	Classically presents as a triad of sensorineural hearing loss, tinnitus, and vertigo, although all three are not necessarily present in each patient. Symptoms may fluctuate, and attacks are often precipitated by high salt intake.
Acoustic neuroma	Benign neoplasm, usually causing sensorineural hearing loss, tinnitus, and sometimes vertigo. A family or personal history of neurofibromatosis type 2 puts patients at high risk for these tumors, often bilaterally.
Noise-induced	History of chronic noise exposure or sudden, short exposure to noise blast. Prevention is mainstay of treatment; hearing aids if condition is already advanced.
Drug-induced	History of ototoxic medication use (aminoglycosides, chemotherapeutic agents [irreversible], aspirin and NSAIDs [partially reversible], antimalarial agents [reversible], loop diuretics [sometimes irreversible]).
Both Conductive and Sensorineural	
Infection	Middle ear infection may impair movement of the tympanic membrane or ossicles, producing reversible conductive hearing loss. Viral cochleitis may cause reversible sensorineural hearing loss. Chronic ear infection may lead to conductive hearing loss.
Head trauma	May produce a conductive hearing loss from ossicular disruption and hemotympanum or a sensorineural hearing loss from cochlear fracture or auditory nerve injury.

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aged 50 years or older. If undertaken, screening can be completed by simply asking the patient if he or she has difficulty hearing. Self-reported hearing loss has been shown to have 90% agreement with audiometric assessment in patients older than age 50 years. Validated screening questionnaires, such as the Hearing Handicap Inventory for the Elderly, have been shown to have high positive likelihood ratios for hearing loss. Additionally, asking close contacts about a patient's hearing impairment is important because patients may not self-perceive hearing loss. The whispered voice test is another reliable screening method for hearing loss. The examiner stands at arm's length behind the patient, and the patient occludes the untested ear canal. The examiner whispers six sets of three letter or number combinations to the patient. Failure to repeat at least three of the six sets correctly constitutes a positive result. The finger rub test involves the examiner gently rubbing his or her fingers together 6 inches (15 cm) from the patient's ear. A positive test result occurs when the patient fails to identify the rubbing in three of six attempts.

Physical examination for hearing loss should focus on differentiating between conductive and sensorineural causes using the Weber and Rinne tests (**Table 69**). During physical examination, visualization of the ear canal is important to determine if a mechanical obstruction or tympanic membrane disorder exists. Formal audiometry should be completed in patients when the etiology of the hearing loss is not evident upon examination. Imaging, usually with MRI, is rarely needed and should be reserved for patients with progressive, unilateral, or accompanying neurologic symptoms.

Sudden sensorineural hearing loss, in which the patient has a 30-dB loss over 3 days or less, requires urgent referral to an otolaryngologist and MRI to determine the underlying cause. Approximately 90% of cases are idiopathic; however, viral infection, bacterial meningitis, Lyme disease, migraine, Meniere disease, acoustic neuroma, head injury, drug reactions, and neurosarcoidosis can be causes. Most cases occur unilaterally. Treatment commonly involves glucocorticoids, although systematic reviews have shown limited success compared with placebo. Most patients recover completely within 2 weeks.

Hearing aids, which amplify environmental sounds, may be beneficial in treating conductive or sensorineural hearing loss in appropriate patients. Studies indicate that approximately 25% of patients who would benefit from hearing aids actually acquire them. Cost can create a barrier for some patients, as hearing aids are expensive and are usually not covered by insurance. Hearing aids are available in multiple styles, including behind-the-ear, in-the-canal models, and some newer hearing aids can be adjusted for only those frequencies requiring amplification.

KEY POINTS

- Screening for hearing loss can be accomplished by questioning the patient, as self-reported hearing loss has been shown to have 90% agreement with audiometric assessment in patients older than age 50 years.
- Sudden sensorineural hearing loss, in which the patient has a 30-dB loss over 3 days or less, requires urgent referral to an otolaryngologist and MRI to determine the underlying cause.

Tinnitus

Tinnitus is the perception of sound (for example, whistling, buzzing, ringing) in one or both ears that is not associated with an external stimulus. Tinnitus is most commonly caused by abnormalities within the auditory system but can occasionally have a vascular etiology. Common causes include excessive noise exposure (both acute and chronic), otosclerosis, barotrauma, infection, vascular insufficiency, Meniere disease, and metabolic disorders. Ototoxic medications may also cause tinnitus (**Table 70**). Most medications associated with ototoxicity are only ototoxic at high doses or toxic levels. Tinnitus due to medication exposure is usually reversible, with the exception of platinum-based chemotherapeutic agents and aminoglycosides.

The characteristics of tinnitus can help facilitate diagnosis and treatment. Tinnitus can be classified as pulsatile (coinciding with the patient's heartbeat) or continuous (nonpulsatile). Pulsatile tinnitus suggests a vascular etiology, such as arteriovenous malformation, atherosclerosis, carotid artery disease, aneurysm, or paraganglioma. For nonpulsatile tinnitus, time of onset, laterality, and other associated symptoms are also helpful in determining the etiology. For example, tinnitus developing in the setting of progressive hearing loss in an older

TABLE 69. Distinguishing between Conductive and Sensorineural Hearing Loss with the Weber and Rinne Tests

Condition	Weber Test[a] Result	Rinne Test[b] Result	Differential Diagnoses
Conductive hearing loss	Louder in the affected ear	Decreased in the affected ear (bone conduction > air conduction)	Cerumen impaction, foreign body, otitis media, otosclerosis, perforated tympanic membrane
Sensorineural hearing loss	Louder in the unaffected ear	As loud or louder in the affected ear (air conduction > bone conduction)	Presbycusis, Meniere disease, acoustic neuroma, sudden sensorineural hearing loss

[a]A 256-Hz vibrating tuning fork (although a 512-Hz tuning fork may be used) is applied to the forehead or scalp at the midline, and the patient is asked if the sound is louder in one ear or the other; a normal test shows no lateralization.

[b]A 512-Hz vibrating tuning fork is applied to the mastoid process of the affected ear until it is no longer heard. The fork is then repositioned outside of the external auditory canal, and the patient is asked if he or she can again hear the tuning fork; with a normal test, air conduction is greater than bone conduction, and the tuning fork can be heard.

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TABLE 70. Drugs Commonly Associated with Tinnitus

Antibiotics (aminoglycosides, erythromycin, vancomycin, neomycin, polymyxin B)
Antimalarial agents (chloroquine, hydroxychloroquine, quinine)
Benzodiazepines
Chemotherapeutic agents (mechlorethamine, vincristine, carboplatin, cisplatin)
Carbamazepine
Loop diuretics
Quinidine
Salicylates
NSAIDs
Tricyclic antidepressants

patient suggests age-related hearing loss (presbycusis); unilateral tinnitus may be caused by otitis media or cerumen impaction; and tinnitus associated with unilateral sensorineural hearing loss is suggestive of acoustic neuroma.

Physical examination for tinnitus is similar to that for hearing loss. Additionally, cranial nerves should be examined for evidence of brainstem involvement. If pulsatile tinnitus is present, auscultation for bruits over the neck, periauricular area, orbits, and mastoid should be performed.

After initial history and examination, the evaluation of patients with tinnitus should include audiometry. Since various metabolic abnormalities may be associated with tinnitus (hypo- and hyperthyroidism, anemia, hyperlipidemia, zinc and vitamin B_{12} deficiencies), obtaining thyroid studies, a complete blood count, lipid studies, and zinc and vitamin B_{12} levels may be considered if clinically appropriate. Most patients with tinnitus do not require neuroimaging; however, patients with unilateral or pulsatile tinnitus, asymmetric hearing loss, or focal neurologic abnormalities should be considered for additional diagnostic imaging.

Mild tinnitus that is minimally bothersome to the patient may not require treatment. Treatment for bothersome tinnitus is directed toward the underlying disorder. Medications are largely ineffective; neurocognitive interventions (including cognitive-behavioral therapy) to help the patient cope with the problem are usually more successful. Sound-masking noise generators are sometimes employed, although limited data exist to support their effectiveness.

KEY POINT

- Medications are largely ineffective in the treatment of tinnitus; neurocognitive interventions to help the patient cope with the problem are usually more successful.

Otitis Media and Otitis Externa

Acute otitis media is characterized by fluid and inflammation in the middle ear accompanied by symptoms of infection. Many patients with acute otitis media will first present with viral upper respiratory tract infection symptoms. Eustachian tube dysfunction, which impairs drainage and causes retention of fluid in the middle ear, is a predisposing factor. In acute otitis media, if the tympanic membrane ruptures, purulent drainage from the ear canal may be present. Otitis media with effusion is defined as fluid in the middle ear but without signs of infection. Otitis media with effusion often occurs after a case of acute otitis media or may be associated with allergies. It is also more likely if eustachian tube dysfunction is present. Evidence to guide treatment of acute otitis media in adults is lacking; however, oral antibiotics (for example, amoxicillin), analgesic therapy, and decongestants are the mainstays of treatment. If there is no response to oral antibiotics within 2 to 3 days, consideration of a broader-spectrum antibiotic is appropriate. Complications include hearing loss, tympanic membrane perforation, meningitis, and mastoiditis. Otitis media with effusion may resolve spontaneously; decongestants, antihistamines, or nasal glucocorticoids are frequently used as therapy, although evidence of their effectiveness is limited.

Otitis externa, which ranges from mild inflammation to severe infection of the external ear canal, can manifest acutely or chronically. Acute otitis externa usually has a bacterial cause, accounting for 90% of cases, whereas chronic otitis externa is frequently the result of fungal infection, allergy, or systemic dermatitis. Swimming can contribute to otitis externa (also known as swimmer's ear) when moisture in the ear canal breaks down the canal's tissue, leading to a favorable environment for bacterial growth. Manipulation or trauma to the ear canal is also a predisposing factor for the development of otitis externa. Treatment for both mild and severe cases includes dilute acetic acid solution and ototopical agents containing neomycin, polymyxin B, and hydrocortisone. Oral antibiotics are indicated for patients whose infection extends beyond the external ear canal, for older patients, for those who have not responded to topical treatment, for immunocompromised patients, and for patients with diabetes mellitus. Patients with malignant otitis externa (a necrotizing infection of the ear canal and osteomyelitis of the skull base) or disease involving the temporal or mastoid bones should be hospitalized and treated with intravenous antibiotics.

Cerumen Impaction

Symptoms of impaction can include itching, pain, hearing loss, odor, or tinnitus. Treatment is only indicated in symptomatic patients or if the tympanic membrane needs to be visualized. Treatment options include ceruminolytic agents, manual removal (with plastic or metal loop or spoon), and irrigation. Suction devices are also available that are useful in removing soft cerumen. No ceruminolytic has been shown to be superior to any other. Manual removal does not subject the ear canal to moisture, so it may be associated with lower rates

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of infection. However, manual removal requires operator skill and a cooperative patient.

Upper Respiratory Tract Infections

Sinusitis

Acute sinusitis can have bacterial or viral causes. In addition to the duration of symptoms, the time course and pattern of disease progression are important in differentiating viral and bacterial rhinosinusitis. Most patients with uncomplicated viral upper respiratory tract infections (URIs) do not have fever. However, if fever is present, it tends to occur early in the illness, often in conjunction with other symptoms, such as myalgia and headache. Fever and constitutional symptoms usually resolve within 24 to 48 hours, after which respiratory tract symptoms become more prominent. In most cases of uncomplicated viral URI, sinus symptoms peak between days 3 and 6 and resolve by day 10. In contrast, patients with acute bacterial sinusitis usually have symptoms (fever, purulent nasal discharge accompanied by nasal obstruction, facial pain/pressure/fullness, tooth pain) that persist without improvement for 10 days from symptom onset. Bacterial sinusitis may also present after a viral URI as a sudden onset of worsening symptoms after typical viral URI symptoms are improving (5–6 days).

Imaging with plain radiographs or CT is rarely needed and does not help in distinguishing bacterial from viral sinusitis. Initial treatment of acute sinusitis (viral and bacterial) is focused on symptom relief. Analgesics, decongestants (systemic or topical), antihistamines, intranasal glucocorticoids, and nasal saline irrigation are frequently prescribed. Although more than 90% of cases of acute sinusitis are viral in origin, antibiotics are frequently prescribed for patients presenting with acute sinusitis symptoms, resulting in inappropriate antibiotic overuse. The Infectious Diseases Society of America (IDSA) recommends initial symptomatic treatment with initiation of antibiotics only in patients with 3 to 4 days of severe symptoms (fever, purulent drainage, and facial pain), worsening of symptoms that were initially improving, or failure to improve with symptomatic treatment after 10 days. Amoxicillin-clavulanate and doxycycline are recommended as first-line antimicrobial therapy. Macrolides, trimethoprim-sulfamethoxazole, and second- and third-generation cephalosporins are no longer recommended because of bacterial resistance. Second-line therapy is higher-dose amoxicillin-clavulanate or doxycycline. Fluoroquinolones should be reserved for those who have failed to respond to initial therapy or those with a history of penicillin allergy, and as second-line therapy for patients at high risk for bacterial resistance. **Figure 33** provides an algorithmic approach for the treatment of acute bacterial rhinosinusitis.

Rhinitis

Allergic rhinitis should be suspected if rhinitis symptoms (sneezing, congestion, rhinorrhea) are associated with a season, environment, or exposure. A thorough history focusing on symptom triggers is necessary for diagnosis. A management algorithm for patients with rhinitis is provided in **Figure 34**. If the history and examination are suggestive of allergic rhinitis, a therapeutic trial for symptom relief is indicated. Pharmacotherapy may include intranasal glucocorticoids, oral antihistamines, intranasal antihistamines, oral leukotriene inhibitors, or intranasal cromolyn. In general, topical agents should be tried before oral agents. Combining therapies may be helpful in patients who have persistent symptoms when using a single agent. If the patient does not respond to these therapies, referral to an allergist-immunologist may be necessary for skin testing, immunotherapy, and medication adjustment.

Nonallergic (vasomotor) rhinitis is defined as chronic rhinitis symptoms without an associated exposure. Patients may describe triggers such as food, odors, or temperature. Treatments include intranasal glucocorticoids, antihistamines, anticholinergics, and nasal saline irrigation. Nasal irrigation can be completed using isotonic saline administered with a specific device (neti pot) that allows the solution to be poured into one nostril with drainage out through the other nostril while keeping the mouth open to breathe. Rhinitis medicamentosa is the syndrome of chronic rhinitis resulting from long-term use of topical nasal decongestants. Treatment involves discontinuing the decongestant; intranasal glucocorticoids may be beneficial.

Pharyngitis

Pharyngitis most frequently has a viral cause (up to 80% of cases). However, group A streptococcal (GAS) pharyngitis, which accounts for approximately 15% of cases, should be detected to prevent potentially serious complications, such as acute rheumatic fever. Diagnosis and treatment of patients with GAS pharyngitis is aided by the four-point Centor criteria: (1) fever, (2) absence of cough, (3) tonsillar exudates, and (4) tender anterior cervical lymphadenopathy. No additional testing or treatment is needed for patients who meet zero or one criterion. Patients who meet two or three criteria should have a confirmatory test (either a rapid antigen detection test for GAS or throat culture) and be treated based on the findings. Rapid antigen detection testing for GAS has a specificity of greater than 95% and a sensitivity of 85% to 95%. Patients with four criteria are at highest risk and can be treated empirically. Penicillin is first-line treatment for GAS pharyngitis, and erythromycin or azithromycin are alternatives in patients who are allergic to penicillin. Complications of GAS pharyngitis include rheumatic fever and peritonsillar abscess.

Pharyngitis can also be caused by group C and group G streptococci. Patients will present with symptoms similar to GAS pharyngitis, although the syndrome is often less severe with groups C and G streptococci. Groups C and G streptococci

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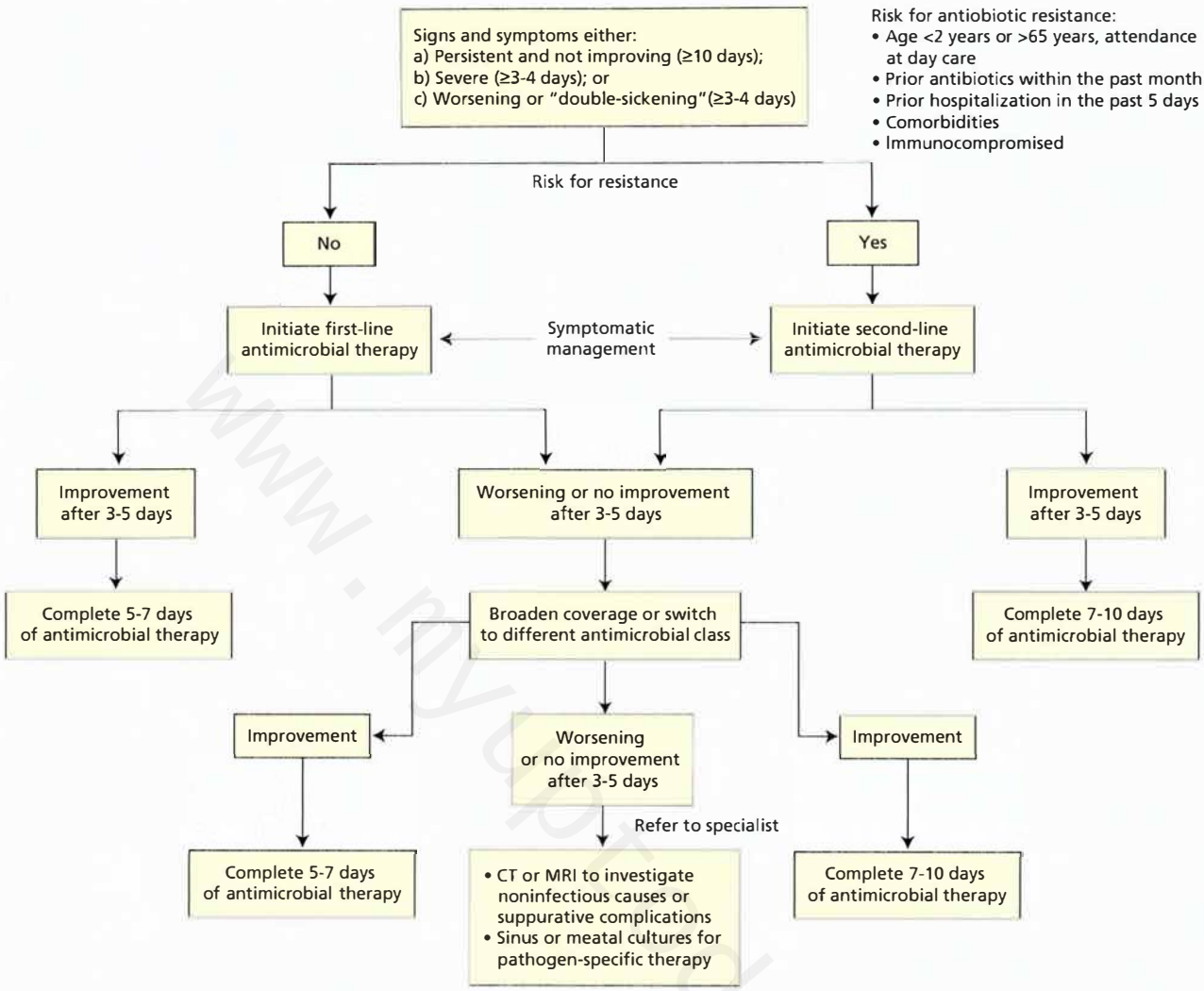

FIGURE 33. Algorithm for the management of acute bacterial rhinosinusitis.

Reprinted from Chow AW, Benninger MS, Brook I, et al; Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012 Apr;54(8):e72-e112. [PMID: 22438350] by permission of Oxford University Press.

are not associated with acute rheumatic fever; however, glomerulonephritis and reactive arthritis may rarely occur. Treatment is with oral antibiotics.

Lemierre syndrome is a rare complication of acute pharyngitis that involves septic thrombosis of the internal jugular vein. The initial infection spreads from the oropharynx into the parapharyngeal space and blood vessels leading to the internal jugular vein. This diagnosis should be considered in patients with antecedent pharyngitis and persistent fever despite antibiotic treatment. Soft-tissue CT of the neck with contrast typically shows a jugular vein thrombus with surrounding tissue enhancement. Treatment of Lemierre syndrome includes intravenous antibiotics. Surgical drainage may become necessary if an abscess forms. The need for anticoagulation should be determined on a case-by-case basis; its use in Lemierre syndrome has not been studied in clinical trials.

KEY POINTS

- In patients with symptoms of acute sinusitis, antibiotics are recommended only for those with 3 to 4 days of severe symptoms (fever, purulent drainage, and facial pain), worsening of symptoms that were initially improving, or failure to improve after 10 days. **HVC**
- Allergic rhinitis is a clinical diagnosis, and effective initial treatments are intranasal glucocorticoids, antihistamines, or cromolyn.
- Diagnosis and treatment of patients with group A streptococcal pharyngitis is aided by the four-point Centor criteria: (1) fever, (2) absence of cough, (3) tonsillar exudates, and (4) tender anterior cervical lymphadenopathy.

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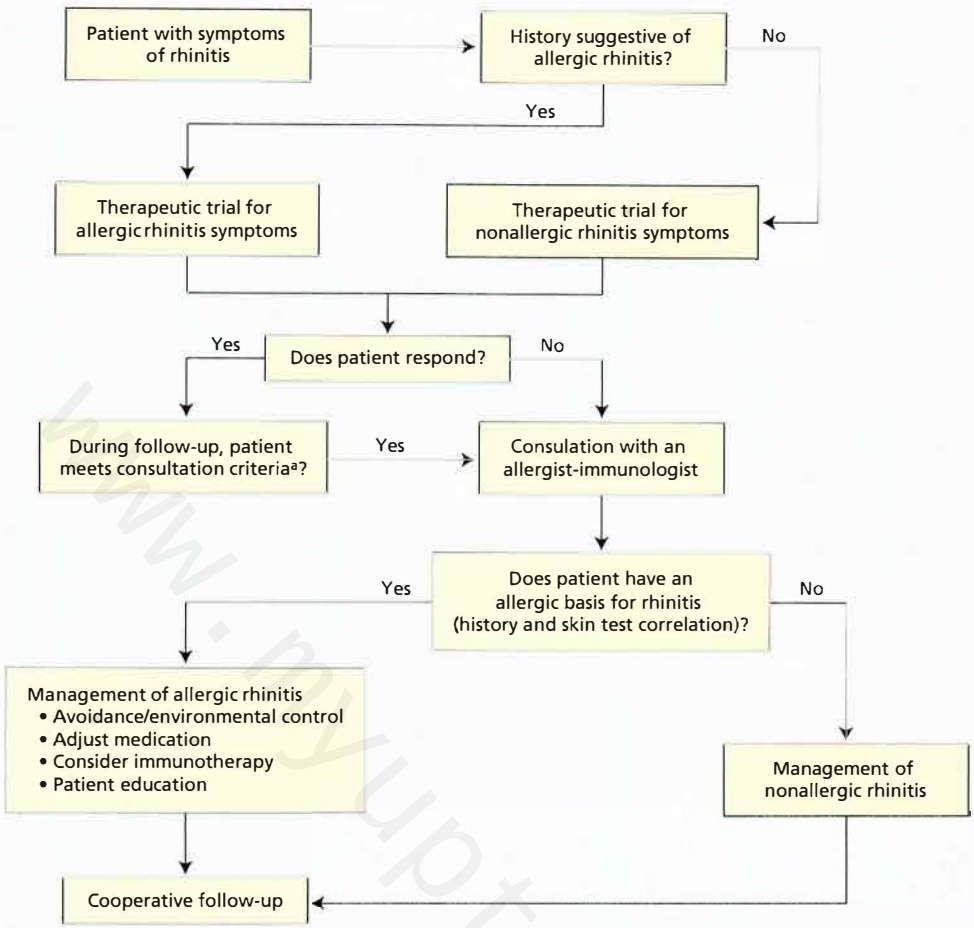

FIGURE 34. Algorithm for the management of rhinitis.

[a]Characteristics that should lead to consideration of consultation with an allergist-immunologist include the following:

- The patient has had prolonged manifestations of rhinitis; complications of rhinitis, such as otitis media, sinusitis, and/or nasal polyposis; and/or a comorbid condition, such as asthma and chronic sinusitis.
- The patient has required a systemic glucocorticoid for the treatment of rhinitis.
- The patient's symptoms or medication side effects interfere with ability to function or significantly decrease quality of life, such as a decrease in comfort and well-being, sleep disturbance, anosmia, or ageusia.
- Treatment with medications for rhinitis is ineffective or produces adverse events.
- The patient has been diagnosed with rhinitis medicamentosa.
- Allergic/environmental triggers causing the patient's rhinitis symptoms need further identification and clarification.
- There is a need for more complete education.
- The patient has required multiple and/or costly medications over a prolonged period.
- Specific allergy immunotherapy is a treatment consideration.

Reprinted from Wallace DV, Dykewicz MS, Bernstein DI, et al; Joint Task Force on Practice; American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol. 2008 Aug;122(2 Suppl):S1-84. Erratum in: J Allergy Clin Immunol. 2008 Dec;122(6):1237. [PMID: 18662584] Copyright 2008, with permission from Elsevier.

Epistaxis

Approximately 90% of nosebleeds originate along the anterior nasal septum, which is where four arterial supplies converge and anastomose as the Kiesselbach plexus. The remaining 10% of epistaxis episodes occur posteriorly (behind the posterior middle turbinate, requiring a nasopharyngoscope for visualization). The presentation of anterior epistaxis is usually obvious, whereas posterior epistaxis can be asymptomatic. Causes of epistaxis may include nose picking, intranasal medication use, dry nasal mucosa, rhinosinusitis, and neoplasms. Hematologic malignancies, hemophilia, acquired bleeding disorders, and anticoagulant or antiplatelet medication use are also associated with epistaxis due to their bleeding diatheses. Routine laboratory testing is not required. If there are symptoms of anemia or significant blood loss, a hemoglobin level should be obtained. A complete blood count, prothrombin time, and activated partial thromboplastin time might be considered in patients with symptoms or signs of a bleeding disorder and those with severe or recurrent epistaxis. CT imaging may be considered if a foreign body, tumor, or sinusitis is a suspected cause.

Initial treatment for anterior epistaxis is patient-exerted compression of the nasal ala against the septum for at least 15

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CONT. minutes, which will stop most anterior bleeds. If direct pressure fails, visualization of the anterior septum should be attempted to find the source of bleeding. Removal of clots or foreign bodies can be done with suction, irrigation, or forceps. If a bleeding site is found, silver nitrate or a topical vasoconstrictor (oxymetolazone or phenylephrine) can be applied to control the bleeding. If the bleeding does not stop, anterior nasal packing should be applied. Electrical cautery by an otorhinolaryngologist may be necessary if these therapies fail. An otorhinolaryngologist should be consulted for patients with posterior bleeds that require packing. Most patients who require posterior packing should be hospitalized for observation and assessed for the need for further intervention. The packing typically remains in place for 4 to 5 days. An antibiotic is typically given to prevent sinusitis and otitis media.

KEY POINT

- Initial treatment for anterior epistaxis is patient-exerted compression of the nasal ala against the septum for at least 15 minutes.

Oral Health

Oral Infections and Ulcers

Oral mucosal findings are discussed in MKSAP 17 Dermatology.

Dental Infection

Dental infections may involve the tooth, bony structures, or gingiva. Infections of the tooth structure are typically asymptomatic until they involve the pulp cavity, at which point an abscess can develop. Dental pulp infection, as a result of caries, is the leading cause of odontogenic infection. Prompt referral to a dental specialist is warranted. Endodontic removal of diseased pulp (root canal) or extraction of the infected tooth is the definitive treatment. If dental care is not immediately available, therapy should focus on pain relief until the appropriate intervention (filling, root canal, local irrigation, incisional drainage) can be performed.

Periodontal disease involves inflammation of the gingiva, with or without accompanying destruction of supportive connective tissue and alveolar bone. Periodontal disease may be linked with an increase in atherosclerotic cardiovascular disease. Therapy should focus on performing proper oral hygiene.

Halitosis

Eighty percent to 90% of cases of halitosis originate in the mouth, principally as a result of microbial breakdown of food, saliva, and other substances. Halitosis can also be associated with sinusitis, nasal polyps, tonsillar stones, esophageal diverticula, and chronic pulmonary infections, as well as other systemic diseases leading to alterations in the odor of the breath, such as ketoacidosis or advanced liver disease or kidney failure. Treatment includes good oral hygiene, including daily flossing and scraping the posterior tongue. A chlorhexidine mouthwash used nightly may also be effective in reducing odor. Patients with dental caries, abscesses, or periodontal disease should receive dental care.

Temporomandibular Disorders

Temporomandibular disorders include articular disorders (derangements of the intra-articular disk of the temporomandibular joint [TMJ]) and masticatory muscle disorders (myofascial pain syndrome). TMJ disorder can present with jaw pain, headache, and clicking. Most TMJ symptoms are self-limited. Evaluation should involve exclusion of other disorders such as trigeminal neuralgia, mastoiditis, dental pain, temporal arteritis, or herpes zoster. Palpation of the TMJ may reveal tenderness, clicking, or crepitus. Generally, imaging is not indicated; however, CT is useful in diagnosing osteoarthritis of the TMJ, and MRI can provide information about soft tissues and vasculature. Treatment involves jaw relaxation with physical therapy exercises, cognitive-behavioral therapy, jaw appliances, and analgesic medications. In patients with osteoarthritis of the TMJ, glucocorticoid injection may be beneficial. In refractory cases, referral for arthrocentesis, arthroscopy, or joint replacement may be warranted.

Mental and Behavioral Health

Mood Disorders

Mood disorders are characterized by disturbed mood accompanied by cognitive, psychomotor, and vegetative symptoms and interpersonal difficulties. Mood disorders include depressive disorders and bipolar disorder.

Depressive Disorders

About 20% of women and 12% of men experience depression during their lifetimes; peak onset is approximately age 40 years for women and age 55 years for men. Depression is a leading cause of disability and a risk factor for suicide. Depression is common in persons with medical diseases; its presence adversely affects outcomes of the diseases.

Depression is a common reason for primary care visits but is often underrecognized. The U.S. Preventive Services Task Force recommends screening adults for depression when appropriate support for definitive diagnosis, effective treatment, and follow-up is available. Validated depression screening tools are available, the simplest being a two-question instrument ("Over the past 2 weeks, have you felt down, depressed, or hopeless?" and "Over the past 2 weeks, have you felt little interest or pleasure in doing things?"). A positive response to either question warrants further evaluation.

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Some nonpsychiatric conditions manifest symptoms that mimic depression, including chronic infectious diseases (such as HIV), endocrine diseases and conditions (such as thyroid and adrenal gland diseases, androgen deficiency, or menopause), cancer, heart failure, neurologic diseases (such as Parkinson disease or multiple sclerosis), and sleep apnea. Medications can also cause symptoms of depression (such as glucocorticoids, hormone therapies, interferons, or anticancer drugs).

Diagnosis

Major Depressive Disorder

Major depressive disorder is diagnosed according to the DSM-5 by the presence of at least five of the following symptoms during the same 2-week period, at least one of which is depressed mood or loss of interest or pleasure:

1. Depressed mood most of the day, nearly every day by self-report (for example, feels sad, blue, or hopeless) or observed by others (for example, frequently tearful)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
3. Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive inappropriate guilt nearly every day
8. Diminished ability to think or concentrate nearly every day
9. Recurrent thoughts of death (not just fear of dying); recurrent suicidal ideation with or without a specific plan; suicide attempt

Depressive symptoms cause work-related and social impairment and cannot be attributed to a medical condition, drug, or substance abuse. A tool for identifying and assessing the severity of depression is the PHQ-9 (www.integration.samhsa.gov/images/res/PHQ%20-%20Questions.pdf); the items correlate with the DSM-5 criteria. Each item is scored from 0 (not bothered by the symptom) to 3 (bothered by the symptom every day); the maximum score is 27. A score of 5 to 9 indicates mild, 10 to 14 moderate, 15 to 19 moderately severe, and ≥20 severe depression. Physicians should determine whether the depressed patient has a history of abnormal elevation of mood (termed mania or hypomania based on the degree); this may indicate bipolar disorder, which is treated differently than depressive disorders. Notably, treating a patient with bipolar depression with an antidepressant drug alone (that is, without a mood stabilizer) may "switch" the patient's depression to mania.

Persistent Depressive Disorder

Symptoms of persistent depressive disorder (formerly known as dysthymia) are milder than those of major depressive disorder. DSM-5 diagnostic criteria are 1) depressed mood most of the day, more days than not, for at least 2 years and 2) the presence, while depressed, of two or more of the following symptoms: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness. Symptoms do not abate for more than 2 months.

Seasonal Affective Disorder

Seasonal affective disorder is a subtype of major depressive disorder characterized by the onset of symptoms during autumn or winter, which resolve during the subsequent spring. It is more common in women than in men. Affected patients experience psychomotor retardation, overeating, and hypersomnia. Diagnosis requires 3 consecutive years of symptoms.

Premenstrual Dysphoric Disorder

Premenstrual dysphoric disorder affects 3% to 5% of menstruating women. It is characterized by the presence of specific symptoms occurring during the final week before the onset of menses, which improve within a few days after the onset of menses and become minimal or absent the week after menses. Primary symptoms required for diagnosis include one of the following: affective lability, irritability or anger with interpersonal conflict, depressed mood, or anxiety. Additional symptoms include decreased interest in usual activities, difficulty concentrating, lack of energy, appetite changes, sleep disturbance, a sense of loss of control, and other physical symptoms (such as breast tenderness, bloating, weight gain).

Peripartum Depression

The DSM-5 has changed the term *postpartum depression* to *peripartum depression* because nearly 50% of women develop these symptoms during pregnancy. Peripartum depression affects 10% to 15% of women within 6 months of giving birth. Single and poor mothers are at greatest risk. Although not considered an independent disorder, it is specified by DSM-5 as major depressive disorder that occurs during pregnancy or within 4 weeks following delivery, although clinical symptoms may not be recognized until after this period.

Persistent Complex Bereavement Disorder

Grief and bereavement are normal responses after the death of a loved one. Emotional lability, sadness, loneliness, sense of numbness, dreams of the deceased, and fleeting visual or auditory hallucinations of the deceased are all common during the normal grieving process. Normal grieving often occurs in fits and starts but gradually becomes less intense over time. Grieving that lasts for more than 12 months (6 months in children): is associated with persistent yearning, sorrow, or preoccupation with the deceased; disrupts normal function or social

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relationships; and is out of proportion to cultural norms is considered pathologic and is termed persistent complex bereavement disorder, formerly complicated grief disorder. Nearly 20% of all bereaved persons experience persistent complex bereavement disorder. Risk factors for the development of persistent complex bereavement disorder include pre-existing psychiatric illness, excess caregiver burden, and ongoing significant life stressors. The death of a loved one can also precipitate a true major depressive episode in a vulnerable individual, and the presence of grief does not necessarily exclude the existence of concomitant major depression.

Management

Most patients with mild or moderate depression (for example, PHQ-9 score <15) are treated by primary care physicians. In the United States, generalists prescribe 75% of all antidepressant medications; psychiatric referral is reserved for those with complex psychiatric comorbid conditions or when initial antidepressant treatments fail to achieve desired results. Before initiating treatment, medical illnesses, medications, and drug use that cause symptoms of depression and bipolar disorder should be ruled out. Psychotherapy (cognitive-behavioral therapy [CBT], psychodynamic therapy, and interpersonal therapy) and psychopharmacology, alone or in combination, are mainstays of treatment and can prove synergistic. In addition to those refractory to initial treatment, referral to a psychiatrist is indicated for patients with homicidal or suicidal ideation, psychotic symptoms, or evidence of bipolar disorder. Diet, exercise, spiritual support, and other measures are adjuncts.

Several classes of antidepressant drugs are available (**Table 71**). Choice of drug is based on the patient's symptoms, the drug's side effects, and the patient's personal and family history of responses to antidepressant drugs. The initial dose should be low and subsequently increased based on clinical response. Patients should be informed of potential side effects and that side effects will likely occur before benefits. Patients who do not respond to full-dose antidepressant monotherapy for 6 weeks may respond to a different antidepressant drug, either from the same or a different class, or the addition of a second antidepressant drug. Another strategy is to add an antipsychotic drug. The FDA has approved

TABLE 71. Characteristics of Selected Antidepressants

Drug	Advantages	Disadvantages
SSRIs		
Citalopram	Few drug interactions	GI and sexual side effects
Escitalopram	Few drug interactions	GI and sexual side effects
Fluoxetine	Long half-life reduces risk for withdrawal syndrome; effective for anxiety disorders, OCD, PMDD	Long half-life increases risk for drug accumulation; drug interactions common; CYP2D6 substrate
Fluvoxamine	OCD, SAD, panic disorder	GI and sexual side effects; sleep disturbance
Paroxetine	Effective for anxiety disorders, panic disorder, PTSD, OCD	FDA pregnancy category D; weight gain; constipation; sedation; drug interaction; high risk for withdrawal syndrome
Sertraline	Few drug interactions; effective for panic disorder, PTSD, OCD, PMDD	GI and sexual side effects; sleep disturbance
SNRIs		
Venlafaxine	Effective for anxiety disorders	Nausea; elevated heart rate and blood pressure
Desvenlafaxine	Effective for anxiety disorders	Nausea; elevated blood pressure
Duloxetine	Effective for pain syndromes and GAD	Nausea; urinary retention
Tricyclic Antidepressants		
Nortriptyline	Analgesic effect; sedating	Cardiac toxicity with overdose; anticholinergic effects
Amitriptyline	Analgesic effect; sedating	Cardiac toxicity with overdose; anticholinergic effects; weight gain
Other Agents		
Bupropion	Fewer sexual side effects than SSRIs; energizing; improved concentration; less weight gain	Seizure risk; elevated blood pressure
Mirtazapine	Sedating; increased appetite	Sedation; weight gain
Trazodone	Sedating; increased sexual function	Sedation; orthostatic hypotension; priapism

GAD = generalized anxiety disorder; GI = gastrointestinal; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = posttraumatic stress disorder; SAD = seasonal affective disorder; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

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the following combinations of antidepressant and antipsychotic drugs for the treatment of depression: aripiprazole or quetiapine extended-release with any antidepressant, and olanzapine with fluoxetine.

About 50% of patients with unipolar depression successfully treated with acute pharmacotherapy followed by placebo and about 40% of patients successfully treated with acute CBT followed by no subsequent treatment experience relapse and recurrence of depression after 1 year. To prevent relapse, an American Psychiatric Association guideline recommends continuation therapy (4 to 9 months) for patients with unipolar depression who respond to acute therapy. In general, the dose of antidepressant drug used in the acute phase should be used in the continuation phase and depression-focused psychotherapy should be continued for those receiving it. Patients with severe depression or those who have experienced more than two depressive episodes are at increased risk for recurrent depression and should be considered for life-long treatment.

Antidepressant drugs should not be stopped abruptly; they should be tapered gradually to avoid discontinuation syndromes. Although some antidepressant drugs have been associated with precipitating suicidal ideation, the risk of suicide in untreated depression is likely greater.

The most widely prescribed antidepressant drugs are selective serotonin reuptake inhibitors (SSRIs). SSRIs have excellent safety profiles compared with tricyclic antidepressant drugs, but adverse sexual side effects (such as reduced libido, anorgasmia, or delayed orgasm) are common. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are helpful in patients who also have pain syndromes. Bupropion is an alternative agent for patients with SSRI- or SNRI-associated sexual side effects; however, this agent is contraindicated in patients with seizure disorders. Monoamine oxidase inhibitors (MAOIs) are seldom used. SSRIs, SNRIs, and MAOIs, particularly if used in combination, can cause serotonin syndrome, which is characterized by altered mental status, autonomic instability, and neuromuscular hyperactivity and is potentially lethal. Patients who do not respond to a single SSRI may respond to another antidepressant drug from the same or different class, adding a second antidepressant, or adding psychotherapy. For some patients, electroconvulsive therapy may be indicated, which is safe (low mortality risk) and effective.

Treatment of seasonal affective disorder involves daily therapeutic exposure (30-60 minutes) to 10,000 lux of visible light; antidepressant drugs and CBT are also used.

Treatment of premenstrual and peripartum depression is similar to that of other forms of depression. Notably, there are no contraindications to breastfeeding while taking antidepressant drugs. However, SSRIs and SNRIs are FDA pregnancy category C (paroxetine is category D).

Persistent complex bereavement disorder does not usually require pharmacologic treatment; medications, when used, should target specific symptoms (such as hypnotics for sleep). Pastoral care, support groups, and counseling may be helpful.

KEY POINTS

- About 20% of women and 12% of men experience depression during their lifetimes; depression is a leading cause of disability and a risk factor for suicide.
- Depression is common in persons with medical diseases; its presence adversely affects outcomes of the diseases.
- The U.S. Preventive Services Task Force recommends screening adults for depression when appropriate support for definitive diagnosis, effective treatment, and follow-up is available.
- Psychotherapy (cognitive-behavioral therapy, psychodynamic therapy, and interpersonal therapy) and psychopharmacology, alone or in combination, are mainstays of treatment of depression.
- Referral to a psychiatrist is indicated in patients with depression refractory to initial treatment, homicidal or suicidal ideation, psychotic symptoms, or evidence of bipolar disorder.

Bipolar Disorder

Bipolar disorder is a mood disorder characterized by episodes of mania or hypomania. Prevalence is about 1%. Men and women are equally affected; onset is usually during early adulthood. It is rare for patients with bipolar disorder to have mania or hypomania only; most have recurrent depressive episodes. Lifetime risk for suicide is high (6%-15%).

Bipolar I disorder is defined as one or more manic episodes. A manic episode is characterized by at least 7 days of severe, abnormally expansive, euphoric, or irritable mood associated with at least three of the following symptoms (four if irritable mood only): grandiosity or inflated self-esteem, pressured speech, flight of ideas, distractibility, increased goal-directed activity or psychomotor agitation, excessive involvement in pleasurable activities with high potential for adverse consequences (for example, spending sprees, sexual encounters), and lessened need for sleep. Dysfunction is substantial. The episode is not attributable to the physiologic effects of a substance (for example, a drug of abuse, a medication, other treatment) or to another medical condition. Most patients with bipolar I disorder experience depressive episodes. Bipolar II disorder is defined as major depression and hypomania. Compared with mania, hypomania is less severe, results in less dysfunction, and is present for at least 4 days.

Psychiatrists should be involved in the management of patients suspected of having bipolar disorder. Pharmacotherapy involves mood stabilizers (such as lithium, valproic acid, and carbamazepine) or lamotrigine; these drugs are essential because risk for recurrent manic or depressive episodes in affected patients is high. Lithium has a narrow therapeutic window and may adversely affect kidney and thyroid

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function. Acute manic episodes are usually treated with lithium or valproic acid and an atypical antipsychotic drug (such as olanzapine, quetiapine, or aripiprazole). FDA-approved pharmacologic treatments for bipolar depression are quetiapine and combination olanzapine-fluoxetine. Psychotherapy is adjunctive.

KEY POINT

- Mood stabilizers are essential in the treatment of bipolar disorder because risk for recurrent manic or depressive episodes in affected patients is high.

Anxiety Disorders

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is relatively common; the lifetime prevalence in U.S. adults is between 4% and 7%. GAD affects women more than men. Patients with GAD often experience sweats, dyspnea, palpitations, difficulty swallowing, nausea, chest and abdominal pain, loose stools, muscle tension, insomnia, fatigue, tachycardia, and tremor. Diagnosis should be considered in patients with multiple unexplained physical symptoms.

The DSM-5 diagnostic criteria for GAD are as follows: 1) excessive anxiety or worry about a number of events or activities (for example, school or work) occurring more days than not for 6 months or longer; 2) the patient recognizes it is difficult to control the worry; 3) the anxiety or worry is associated with three or more of the following symptoms: restlessness, easy fatigability, difficulty concentrating, irritability, muscle tension, and sleep disturbance; 4) the anxiety, worry, or symptoms cause impairment at school, work, or other settings and cannot be attributable to medical or other psychiatric conditions, medications, or substance use.

A tool for identifying and assessing the severity of GAD is the GAD-7 (www.adaa.org/sites/default/files/GAD-7_Anxiety-updated.pdf). Treatment options include psychotherapy and medications. CBT is the most effective psychotherapy for GAD and in trials has been shown to be as effective as medications. SSRIs, SNRIs, and tricyclic antidepressant agents are effective if needed. Benzodiazepines are often used for GAD but carry a risk for dependence. Nonetheless, benzodiazepines can be useful in the early stages (for example, the first 6 weeks) of SSRI treatment—the time often necessary for SSRIs to take effect. The GAD-7 can be used to monitor symptom severity over time, allowing clinicians to monitor treatment effectiveness.

Panic Disorder

The lifetime prevalence of panic attack is 10% to 30%. However, the prevalence of panic disorder is much lower (about 2% in women and 1% in men); onset usually occurs during early adulthood. Not all patients with panic attacks have panic disorder. Panic attacks occur in patients with panic disorder but can also occur in other depressive or anxiety disorders as well.

Panic disorder is characterized by recurrent, unexpected, and abrupt surges of extreme anxiety that peak within minutes and is accompanied by four or more of the following symptoms: palpitations, sweating, trembling, dyspnea, choking sensation, chest pain, nausea or abdominal pain, lightheadedness, chills or heat sensations, numbness or tingling, feeling detached from oneself, and fear of losing control or dying. Diagnosis requires that an attack be followed by at least 1 month of worry by the patient that he or she will experience a recurrent attack. Because of physical symptoms, patients with panic disorder often present to primary care physicians or emergency departments after a panic attack; however, panic disorder is often unrecognized. The diagnosis should be considered if medical mimics (for example, hyperthyroidism, pheochromocytoma, substance use) are unlikely or have been excluded.

The recommended treatment of panic disorder is an antidepressant (SSRI or SNRI) in combination with CBT. If needed, a short course of a long-acting benzodiazepine (clonazepam) can be used in the first few weeks as the antidepressant is escalated. Shorter-acting benzodiazepines should be used with caution and for short periods because there is increased addiction potential. Treatment duration for panic disorder is about 1 year after symptom control is achieved, then reassessed.

Social Anxiety Disorder

Social anxiety disorder (formerly known as social phobia) has a lifetime prevalence of about 2.5%. Social anxiety disorder is characterized by severe, persistent anxiety or fear of social or performance situations (public speaking, meeting unfamiliar people) lasting 6 months or longer. In these situations, affected patients experience anxiety and physical symptoms such as palpitations, dyspnea, and flushing. Patients recognize their anxiety is excessive but nonetheless avoid trigger situations (or endure them with extreme anxiety), resulting in impairments at home, work, and other settings.

Treatment of social anxiety disorder includes CBT and medications. SSRIs and the SNRI venlafaxine are first-line therapy for social anxiety disorder.

Posttraumatic Stress Disorder

The DSM-5 diagnostic criteria for posttraumatic stress disorder (PTSD) are complex. In general, PTSD occurs in response to directly experiencing or witnessing traumatic events (actual or threatened death, injury, or sexual violence), learning that such an event has occurred to a loved one, or experiencing repeated or extreme exposures to "aversive details" of traumatic events. PTSD is characterized as at least 1 month of symptoms, including intrusive memories of the traumatic event, recurrent nightmares or flashbacks, persistent avoidance of reminders, persistent negative changes in thoughts and mood associated with the event, and alterations in arousal and reactivity (exaggerated startle, hypervigilance, sleep disturbance,

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reckless behavior). PTSD usually presents within 1 month of the traumatic event, but symptoms can be delayed.

Risk factors for PTSD include greater severity of the stressor, poor social support in general and especially after the stressor, subsequent life stressors (for example, loss of employment), parental neglect, and family and personal history of psychiatric disorder. Among veterans, those with traumatic brain injury (TBI) have a higher prevalence of PTSD than veterans without TBI; information about evaluating for PTSD in veterans is available from the Veterans Administration (www.mentalhealth.va.gov/communityproviders/miniclinics.asp). Comorbid psychiatric conditions may include depression, anxiety, and substance abuse. Patients with PTSD are at increased risk for occupational and marital discord and suicide.

Treatment of PTSD includes psychotherapy and medications. A psychotherapist with experience in treating survivors of trauma can be very helpful. Antidepressant drugs, especially SSRIs, are useful. Trazodone is useful for insomnia and nightmares (usually used in combination with another drug such as an SSRI). Benzodiazepines are not effective for PTSD.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is characterized by obsessions (persistent and intrusive thoughts, images, or impulses that are associated with distress) and compulsions (repetitive behaviors such as hand washing, counting, and inspecting that are done in order to decrease distress caused by the obsession), resulting in wasted time, marked distress, or impaired social function. Obsessive traits often precede the disorder. Prevalence is 2% to 3%; men and women are affected equally.

CBT is the primary treatment for OCD. Medications for OCD include SSRIs (sertraline, paroxetine, fluoxetine, and fluvoxamine) and clomipramine. Benzodiazepines are sometimes used for acute exacerbations but not as monotherapy. Treatment should continue for 1 to 2 years, then be reassessed.

KEY POINTS

- Cognitive-behavioral therapy has been shown to be as effective as medications in the treatment of generalized anxiety disorder.
- Panic disorder should be considered as a diagnosis in patients who present to the emergency department with physical symptoms of a panic attack if medical mimics (for example, hyperthyroidism, pheochromocytoma, substance use) are unlikely or have been excluded.
- Cognitive-behavioral therapy is the primary treatment for obsessive-compulsive disorder.

Substance Abuse Disorders

Tobacco

At least 70% of smokers will visit a physician each year, thus providing a key opportunity for tobacco cessation interventions. Patients should be asked about tobacco use at each visit, as it has been shown to increase the frequency of tobacco cessation discussions in the clinical setting and to increase tobacco cessation rates. The Agency for Healthcare Research and Quality (AHRQ) and others have endorsed using the "5 A's" approach to office tobacco counseling (see Screening Recommendations for Adults in Routine Care of the Healthy Patient). For smokers not ready to quit, motivational interviewing, with emphasis on nonconfrontational strategies and discussion of patient choices, has shown higher cessation rates than use of brief advice or usual care. High-intensity counseling (greater time and number of sessions) is more effective than low-intensity strategies; for clinicians with limited time, recommendations are to use adjunctive telephone counseling, as every state in the United States has telephone counseling quit line services (1-800-Quit-Now).

Pharmacotherapy has proven to be effective and should be offered to those without contraindications (**Table 72**). Bupropion is contraindicated in patients with seizures and other conditions that can lower seizure threshold. Varenicline should be dose adjusted in patients with severe kidney impairment. Both bupropion and varenicline can cause vivid dreams and can increase suicidality. Bupropion can be used with long-acting (nicotine patches) or short-acting (nicotine gum, lozenges, inhalers, nasal spray) nicotine replacement. Varenicline can be used with a short-acting nicotine replacement, although a few studies have demonstrated safety and efficacy in combining varenicline and long-acting nicotine replacement. Bupropion and varenicline can also be combined. Referral to a specialist is appropriate, especially in cases of relapse.

Alcohol

The DSM-5 combined alcohol abuse and alcohol dependence as a single entity, termed alcohol use disorder, which is characterized as problematic alcohol use causing significant distress or impairment within a 12-month period. Common features include continued alcohol use despite recurrent adverse consequences, craving and impaired control of alcohol use, tolerance, and withdrawal. Alcohol use disorder should be treated as a chronic disease. Excessive alcohol use is the third-leading preventable cause of death, behind smoking and obesity. Much of the mortality risk is related to an increased risk of accidental death, including motor-vehicle accidents and drowning. Suicide rates are also higher among frequent alcohol users. Given the health risks associated with alcohol use, screening all adults is recommended (see Screening Recommendations for Adults in Routine Care of the Healthy Patient). The primary treatment of alcohol use disorder is psychosocial interventions (counseling, motivational interviewing, CBT, residential care, peer support groups such as Alcoholics Anonymous). Pharmacotherapy (naltrexone and acamprosate) can be used in combination with psychosocial treatment. Naltrexone is contraindicated in patients receiving or withdrawing from any opioid and in those with liver failure or hepatitis. Acamprosate enhances abstinence but is contraindicated in kidney disease.

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TABLE 72. Commonly Used Pharmacologic Therapies for Smoking Cessation

Agent	Mechanism	Effectiveness	Initial Prescription	Advantages	Disadvantages
Nicotine gum[a]	Prevents nicotine withdrawal[b]	Increases cessation rates about 1.5-2 times at 6 mo.	1 piece (2 mg) whenever urge to smoke, up to 30 pieces/d. Continuous use for >3 mo not recommended. Max dose: 24 pieces/d	Less expensive than other forms of nicotine replacement. Chewing replaces smoking habit. No prescription required. Associated with delay in weight gain.	Some patients find taste unpleasant.
Nicotine patch (24 h)[a,c]	Prevents nicotine withdrawal[b]	Increases cessation rates about 1.5-2 times at 6 mo.	Most patients: 21-mg patch for 4-8 wk (remove and replace every 24 h), then 14-mg patch for 2-4 wk, followed by 7-mg patch for 2-4 wk. Max dose: 22 mg/d. Adults weighing <100 lb (45.5 kg), smoking fewer than 10 cigarettes/d, and/or with cardiovascular disease: 14-mg patch for 4-8 wk, then 7-mg patch for 2-4 wk.	Less expensive than other forms of nicotine replacement. No prescription required.	Can cause skin irritation.
Nicotine nasal spray[a]	Prevents nicotine withdrawal[b]	Increases cessation rates about 1.5-2 times at 6 mo.	1 spray (0.5 mg) in each nostril 1-2 times/h whenever urge to smoke, up to 10 sprays/h or 80 sprays/d. Initially, encourage use of at least 16 sprays/d, the minimum effective dose. Recommended duration of therapy is 3 mo. Max dose: 80 sprays/d; do not exceed 10 sprays/h.	Some patients prefer this delivery method.	More expensive than other forms of nicotine replacement. Requires a prescription. Safety not established for use >6 mo.
Nicotine inhaler[a]	Prevents nicotine withdrawal[b]	Increases cessation rates about 1.5-2 times at 6 mo.	6-16 cartridges (containing 4 mg)/d for up to 12 wk, followed by gradual reduction in dosage over a period up to 12 wk.	Some patients prefer this delivery method.	More expensive than other forms of nicotine replacement. Requires a prescription. Use >6 mo not recommended.
Nicotine lozenge[a]	Prevents nicotine withdrawal[b]	Increases cessation rates about 1.5-2 times at 6 mo.	1 lozenge (2 mg or 4 mg) every 1-2 h during weeks 1-6, then 1 lozenge every 2-4 h during weeks 7-9, then 1 lozenge every 4-8 h during weeks 10-12. Patients who smoke within 30 min of waking require 4-mg lozenge; those who have first cigarette later in the day require 2-mg lozenge. Recommended duration of therapy is 12 wk.	Some patients prefer this delivery method.	Some patients find the taste unpleasant. Side effects include nausea, dyspepsia, and mouth tingling. Avoid acidic beverages (juice, soda) 15 min before use.

(Continued on the next page)

Alcohol withdrawal occurs with chronic heavy alcohol use within hours to days after alcohol cessation. Early withdrawal symptoms occur within a few hours of abstinence and include agitation, anxiety, tremulousness, headache, and symptoms of autonomic hyperactivity (fever, diaphoresis, tachycardia, hypertension). Generalized tonic-clonic seizures occur within 6 to 24 hours and should be treated with benzodiazepines because if left untreated, up to one third of patients may progress to delirium tremens. In general, antiepileptic drugs are not required. Delirium tremens is characterized by fluctuating levels of consciousness, confusion, and agitation with marked auto- ...ality rate.

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TABLE 72. Commonly Used Pharmacologic Therapies for Smoking Cessation *(Continued)*

Agent	Mechanism	Effectiveness	Initial Prescription	Advantages	Disadvantages
Bupropion	Unclear	Increases cessation rates about 2 times at 1 y.	Begin 1-2 wk before quit date; start with 150 mg once daily for 3 days, then 150 mg twice daily through end of therapy (7-12 wk max). Max dose: 150 mg twice daily.	Some antidepressant activity; may be a good option for patients with a history of depression. Associated with a delay in weight gain.	Requires a prescription. Can interact with other drugs. Safety in pregnancy is unclear. Associated with hypertension. Avoid in patients with eating disorders, patients with seizure disorder or at risk for seizure, and in patients taking MAOIs. May cause vivid dreams and increase suicidality.
Varenicline	Reduces cravings via nicotine receptor agonist.	Increases cessation rates >3.5 times and almost 2 times over bupropion at 12 wk.	Begin 0.5 mg once daily on days 1-3, then 0.5 mg twice daily on days 4-7, then 1 mg twice daily through end of therapy (12 wk). Consider additional 12 wk of therapy to prevent relapse. Max dose: 1 mg twice daily.	No hepatic clearance. No clinically significant drug interactions reported.	Requires a prescription. Associated with hypertension. Safety in pregnancy is unclear. Caution in severe kidney disease. May cause nausea, insomnia, vivid dreams, and increased suicidality.

[a]Avoid nicotine replacement in patients with recent myocardial infarction, arrhythmia, or unstable angina. Safety of nicotine replacement in pregnancy is unclear.

[b]A standard cigarette contains approximately 1 mg of nicotine.

[c]Several formulations of patches are available. Dosing guidelines are for patches designed to stay in place for 24 h and that come in doses of 21 mg, 14 mg, and 7 mg. Clinicians should check prescribing information on nicotine patches that come in other doses or that are designed for use <24 h/d.

Adapted with permission from Wilson JF. In the clinic. Smoking cessation. Ann Intern Med. 2007 Feb 6;146(3):ITC2-1-ICT2-16. [PMID: 17283345]

Treatment of alcohol withdrawal includes thiamine and glucose to prevent Wernicke encephalopathy, intravenous fluids, multivitamins with folate, correction of electrolyte abnormalities, and long-acting benzodiazepines (short-acting benzodiazepines if there is severe liver disease). Benzodiazepines should be given as needed, rather than by scheduled dosing or continuous infusion.

The Clinical Institute Withdrawal Assessment (CIWA) scale may be useful to help monitor symptoms and deliver treatment. Patients with low CIWA scores can be monitored as an outpatient and may not require medication, whereas those with moderate scores should receive medication. Those with high CIWA scores, history of an alcohol withdrawal seizure or delirium tremens, or suicidal ideation should be hospitalized and in some cases require intensive care.

Drugs

Illicit drug use is common and affects 9% of the U.S. population yet often goes undetected. Any illicit drug use should be considered harmful given potential health and legal consequences of even infrequent use. Asking about illicit drug use and prescription drug misuse is recommended during initial medical visits and when clinically relevant (see Routine Care of the Healthy Patient). The approach to treatment is similar to that for tobacco and alcohol misuse, consisting primarily of behavioral interventions. Prevalence of co-occurring serious mental illnesses with substance abuse, high-risk sexual behavior, and polysubstance abuse is increased among illicit drug users. Veterans who have experienced combat, multiple deployments, and those with PTSD are at higher risk for substance abuse. The Veterans' Administration has created a series of veteran-focused mini clinics to help clinicians optimize mental health and wellness among veterans. Module topics include tobacco use, substance abuse, PTSD, mental illness, and suicide prevention and are available at www.mentalhealth.va.gov/communityproviders/miniclinics.asp.

KEY POINTS

- For smokers not ready to quit, motivational interviewing, with emphasis on nonconfrontational strategies and discussion of patient choices, has shown higher cessation rates than use of brief advice or usual care.
- Pharmacotherapy with nicotine replacement, bupropion, and/or varenicline has proven to be effective for smoking cessation and should be offered to those without contraindications.
- The primary treatment of alcohol use disorder is psychosocial interventions.

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Personality Disorders

A personality disorder is characterized by persistent patterns of inner experiences and behaviors that digress substantially from the expectations of the affected person's culture. These disorders are entrenched, rigid, and stable over time, and lead to substantial impairment and distress. Onset is usually during adolescence or early adulthood. There are 10 specific personality disorders, which are grouped into 3 clusters based on symptoms (**Table 73**). Persons with personality disorders usually do not recognize their interactions with others as abnormal.

Patients with personality disorders often interface with the health care system. Physicians should balance the patient's need to be seen (for example, frequent, yet brief, visits) with clear boundaries. Patients with personality disorders often require more time than the primary care physician can realistically provide and may benefit from referral to a mental health professional. Affected persons may benefit from psychotherapy. There are no FDA-approved medications for personality disorders; medications are used to relieve symptoms (for example, mood stabilizers for mood swings and impulsivity).

TABLE 73. Personality Disorders

Cluster A: Odd or Eccentric Thinking and Behaviors
Paranoid: pervasive distrust of others; unjustified suspicion of others; unjustified suspicions regarding their partners or spouses; overly hostile reactions to perceived insults
Schizoid: prefer to be alone and lack interest in relationships; seem indifferent, cold, and unresponsive to social cues; take pleasure in few activities
Schizotypal: manifest odd thinking, beliefs (e.g., their thoughts are magical and can influence others, events have hidden meaning), dress, and other behaviors
Cluster B: Dramatic or Unpredictable Thinking and Behaviors, Emotional
Antisocial: engage in behaviors such as lying, stealing, and other aggressive and violent behaviors; disregard others' feelings, rights, and safety; lack remorse for these behaviors; often experience recurrent legal problems
Borderline: have chaotic relationships (idealized and devalued) and a fragile self-image; fear abandonment; experience labile and intense emotions (e.g., anger), sense of emptiness; engage in impulsive and risky behaviors (e.g., gambling, sex); may manifest self-injury and suicidality
Histrionic: excessive emotionality and attention-seeking behavior; dramatic; often seductive or sexually provocative; melodramatic
Narcissistic: grandiose and inflated self-perceptions; desire attention
Cluster C: Anxious and Fearful Thinking and Behaviors
Avoidant: feel inadequate and are sensitive to criticism; extremely shy and socially inhibited and avoid activities that involve interactions with others, especially strangers
Dependent: excessively dependent on others ("clingy") and fear being alone; lack self-confidence and tolerate poor treatment by others
Obsessive-compulsive: perfectionistic and preoccupied with orderliness and rules; controlling of situations and others; rigid regarding values; not the same as obsessive-compulsive disorder, which is an anxiety disorder

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Somatic Symptom and Related Disorders

The DSM-5 has reclassified the somatoform disorders under the term somatic symptom and related disorders (SSRDs). More commonly encountered in nonpsychiatric settings, these disorders may be seen in up to 20% of patients in primary care settings. Such patients have very high utilization of health care despite overall dissatisfaction with their medical care. Although patients with these disorders typically present with medically unexplained symptoms, this should not be used as the key diagnostic feature. Instead, the patient's interpretation of the symptoms causes functional impairment.

Diagnostic criteria for somatic symptom disorder are as follows: at least one somatic symptom causing distress or interference with daily life; excessive thoughts, behaviors, and feelings related to the somatic symptom(s) (disproportionate or persistent concern about seriousness of symptoms, persistent high level of anxiety about health, or excessive focus of time and energy on health concerns); and persistent somatic symptoms for at least 6 months (does not have to be the same symptom for 6 months).

When this disorder has pain as the main symptom, the specifier "with predominant pain" should be used because this diagnosis has replaced pain disorder. Illness anxiety disorder (previously known as hypochondriasis) is characterized by excessive worry about general health and preoccupation with health-related activities (such as measuring pulse). Unlike somatic symptom disorder, patients with illness anxiety disorder have no or only mild somatic symptoms. Conversion disorder (functional neurologic symptom disorder) involves one or more symptoms of abnormal sensation or motor function (such as limb weakness) that are not explained by a medical condition and are inconsistent with physical examination findings. Factitious disorder is a deliberate falsification of symptoms or infliction of injury on oneself or another, even in the absence of clear external benefit. Prior to diagnosing any of the somatic symptom and related disorders, excluding or optimizing treatment of organic disease or other psychiatric disorders (such as depression and generalized anxiety) is indicated.

These patients are challenging and difficult to treat. The symptoms are often chronic in nature and patients frequently undergo repetitive and unnecessary diagnostic testing, which often leads to unnecessary invasive medical and surgical interventions. Management begins with an open discussion of the diagnosis, scheduling of regular follow-up visits, and coordi-

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avoided as a means of reassurance. Antidepressants may be beneficial, but CBT has greater potential for managing the underlying behavioral disorder.

KEY POINT

- Management of patients with somatic symptom and related disorders begins with an open discussion of the diagnosis, scheduling of regular follow-up visits, and coordination of care with a psychiatrist.

Eating Disorders

Types

The DSM-5 has reshaped the classification for eating disorders. Binge eating disorder (BED), now formally recognized as a separate entity, is defined as recurring episodes (on average ≥1 per week for 3 months) of eating significantly more food in a short period than most people would under similar circumstances while feeling a lack of control. Common features include eating more rapidly than normal, feeling uncomfortably full, eating large amounts when not hungry, eating alone due to embarrassment, and feeling disgust or guilt afterward. These features can help differentiate BED from the common occurrence of overeating.

Compared with BED, bulimia nervosa is characterized by frequent episodes (≥1 per week) of binge eating followed by inappropriate compensatory behaviors (self-induced vomiting or misuse of laxatives, diuretics, and enemas) due to fear of weight gain. Physical examination may reveal erosion of dental enamel, parotid gland swelling, xerosis, and Russell sign (scarring or calluses on the dorsum of the hand if used to induce vomiting).

Anorexia nervosa is an important entity to recognize because it is associated with high mortality. It is characterized by persistent caloric intake restriction leading to significantly low body weight, a distorted body image, and an intense fear of gaining weight or becoming fat. Subtypes include restricting type (no binge eating or purging behaviors) and binge eating/purging type (purging with or without binging). It primarily affects adolescent girls and young women but can also affect men and older women. In the DSM-5, amenorrhea is no longer included in the diagnostic criteria, although this still commonly occurs. Physical examination may reveal emaciation, brittle hair and nails, lanugo, xerosis, yellow skin especially of the palms (from hypercarotenemia), and edema.

Medical Complications

Anorexia nervosa is associated with multiple medical complications, nearly all of which are reversible with restoration of ideal body weight. Loss of bone density, seen in ≥30% of patients, often is not completely reversible, in part because anorexia nervosa often affects adolescents before peak bone mass is reached. Bone density measurement is often suggested after 6 to 12 months of continued symptoms. Vital sign abnormalities may also occur and are reflective of a hypometabolic state, including sinus bradycardia, hypotension, and hypothermia. Electrolyte abnormalities (hypokalemia, hypomagnesemia, hypophosphatemia) are often seen and can contribute to life-threatening arrhythmias and prolonged corrected QT intervals. Other laboratory abnormalities include anemia, leukopenia, and elevation of liver chemistry tests. Refeeding syndrome is another serious complication and can be avoided by gradually increasing caloric intake according to basal metabolic rate during the first few weeks of the refeeding.

Bulimia nervosa can also cause electrolyte derangements leading to arrhythmias but also involves gastrointestinal-related complications, including esophagitis, Mallory-Weiss tears, and esophageal rupture. Purging and misuse of laxatives, diuretics, and enemas can cause electrolyte abnormalities.

Both anorexia nervosa and bulimia nervosa also impart an increased risk of depression, anxiety, substance abuse, and suicide risk.

Treatment

The primary treatment of eating disorders is restoration of normal weight and eating behaviors. This can be done in a combination of outpatient, residential, or inpatient settings involving a multidisciplinary team, including a primary care physician, dieticians, and mental health specialists.

Treatment of anorexia nervosa involves psychotherapy (including family therapy, especially in adolescents) and nutritional restoration (supervised meals, medical monitoring, and hospitalization in severe cases). Intense psychological support is often needed during the process of regaining weight. In bulimia nervosa and BED, CBT has been consistently shown to be beneficial. Antidepressants can be useful in bulimia nervosa (fluoxetine is FDA approved for bulimia nervosa) but have not demonstrated benefit in the treatment of anorexia nervosa. Olanzapine has shown recent promise in reducing obsessive-compulsive tendencies and improving weight gain in anorexia nervosa. Antidepressants and topiramate have shown benefit in BED.

KEY POINTS

- Treatment of anorexia nervosa involves psychotherapy and nutritional restoration.
- Cognitive-behavioral therapy has been consistently shown to be beneficial in the treatment of bulimia nervosa and binge eating disorder.

Schizophrenia

Schizophrenia often begins in late adolescence and is characterized by at least two of the following symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms (affective flattening, alogia, or avolition). These symptoms must affect one or more major areas of functioning (work, interpersonal relations, or self-care) and have been present for 6 months (including at least 1 month of active symptoms).

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Schizophrenia is associated with a 2- to 3-fold increase in mortality, which is due to a 13-fold increased risk of suicide and greater than 2-fold increase in cardiovascular disease mortality. Rates of hypertension, dyslipidemia, diabetes mellitus, obesity, smoking, and metabolic syndrome are significantly increased. Atypical antipsychotics may contribute to metabolic complications. Furthermore, schizophrenia is often associated with undertreatment of chronic medical disorders and low rates of obtaining screening and preventive care.

Antipsychotic medications are first-line therapy for schizophrenia. Typical antipsychotics have a higher risk of sedation, anticholinergic effects, extrapyramidal symptoms, and hyperprolactinemia. Second-generation antipsychotics have fewer extrapyramidal symptoms and are more effective than typical antipsychotics. Clozapine has proved more effective than other antipsychotics but requires routine blood monitoring because it can cause agranulocytosis. Both clozapine and olanzapine are associated with high risk of weight gain and metabolic complications.

KEY POINT

- Antipsychotic medications are first-line therapy for schizophrenia; clozapine has proven more effective than other antipsychotics but requires routine blood monitoring because of the potential for agranulocytosis.

Attention-Deficit/Hyperactivity Disorder

The diagnosis of attention-deficit/hyperactivity disorder (ADHD) requires persistent inattention and/or hyperactivity-impulsivity that interfere with functioning or development in at least two areas of life (home, work, school, peer relationships). Although symptoms need to be present by the age of 12 years, a diagnosis is often not made until later. Up to 60% of children with ADHD continue to have symptoms as an adult, although adult ADHD remains underdiagnosed and undertreated. Symptoms of hyperactivity and impulsivity often lessen over time; adults with ADHD may be easily distracted, disorganized, and feel restless. Many adults have comorbid psychiatric problems such as sleep disorders, depression, anxiety, and substance abuse. Stimulants are first-line therapy in adults without a substance abuse history; given their cardiovascular side effects (hypertension, arrhythmias, cardiac arrest), routine blood pressure monitoring is necessary. In those with a history of substance abuse, the selective norepinephrine reuptake inhibitor atomoxetine may be useful. CBT is a useful adjunctive treatment.

Autism Spectrum Disorder

The DSM-5 has eliminated the subclassifications of autism (including Asperger syndrome) and merged these entities into autism spectrum disorder (ASD). ASD describes heterogeneous conditions characterized by repetitive behaviors and persistent deficits in communication and social interaction associated with impairment in function. Symptoms must be present in early childhood but may not manifest or may be masked by compensatory skills until later in life. ASD may be associated with intellectual or language impairment (some may have specific exceptional abilities). It is also associated with seizures, sleep disorders, and gastrointestinal and feeding problems. Acute changes in behavior may signal an underlying medical issue rather than a behavioral issue. If possible, internists should involve the patient's caregiver to optimize communication during the visit. Use of clear, brief language, visual aids, or alternative modes of communication may be helpful. Treatment involves specialists and community resources consisting of sustained behavioral and educational interventions, which may include speech, language, and occupational therapy, and should also involve caregivers. Pharmacotherapy (antipsychotics) and complementary therapies (diet modification, music therapy) can also be used. Early intervention improves outcomes. Adults with autism have normal life expectancies, but most continue to require at least some assistance, with some requiring life-long residential care. Follow-up care should be life-long.

Geriatric Medicine

Comprehensive Geriatric Assessment

The evaluation of geriatric patients must emphasize functional ability, independence, and quality of life. The comprehensive geriatric assessment prioritizes these outcomes through multidisciplinary review of physical health, functional status, sensory capacity, cognition, mental health, and environmental factors that affect patients and their caregivers. Performance of comprehensive geriatric assessment in the home and in dedicated geriatric inpatient hospital units has demonstrated improved morbidity and mortality and decreased rates of institutionalization. The impact of outpatient or inpatient consultative comprehensive geriatric assessment on outcomes is less clear.

Functional Assessment

Functional status can be evaluated by assessing basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs). Basic ADLs refer to self-care tasks necessary to provide one's own personal care. IADLs are tasks necessary to maintain an independent household, such as using the telephone, preparing meals, and managing one's own medications. Identifying deficiencies in ADLs and IADLs allows for the provision of appropriate support services. There are several screening tools available that may be used to measure functional status in the older adult (**Table 74**).

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TABLE 74. Indices to Assess Basic and Instrumental Activities of Daily Living

Index	Assessed Functional Activity	Scoring	Comments
Katz Index of Independence in Activities of Daily Living	Bathing Dressing Toileting Transferring Continence Feeding	The Katz Index is scored by assigning a score of 1 point to each activity if it can be performed independently, which is defined as requiring no supervision, direction, or personal assistance; scores are then added for a range of 0 to 6. (6 = fully functional; 4 = moderately impaired; 2 = severely impaired)	Simple to use/score; brief, takes only a few minutes to complete. Less discriminative at low levels of disability.
Modified Barthel Index	Feeding Bathing Grooming Dressing Bowels Bladder Toilet use Transfers Mobility Stairs	Each item in the Modified Barthel Index is scored on a range from 0 to 15, depending on how much the patient is able to do. Total scores range from 0 to 100, with 100 being fully independent. In stroke patients, a score of less than 60 is considered a poor outcome.	A form must be filled out; takes approximately 10 minutes to complete. Highly validated in multiple settings. Better discriminative function and very sensitive to change.
Lawton and Brody Instrumental Activities of Daily Living (IADL) Scale	Ability to use telephone Shopping Food preparation Housekeeping Laundry Transportation Medication management Ability to handle finances	The Lawton and Brody IADL Scale is scored by assigning a score of 1 point to each activity if it can be performed at all; scores are then added for a range of 0 to 8, with a score of 8 representing independence and 0 representing total dependence for IADLs.	Simple to use; brief, takes only a few minutes to complete.

Vision

Visual impairment, often resulting from cataracts, macular degeneration, presbyopia, glaucoma, or diabetic retinopathy, is common in the elderly, but frequently underrecognized by patient and physician alike. There is little evidence that standard vision screening tests actually improve outcomes in older adults. Vision screening tests, such as the Snellen eye chart, primarily measure visual acuity, which may help identify presbyopia but may miss visual deficits due to the other previously mentioned ocular disorders. Glaucoma and macular degeneration are difficult to detect in the primary care setting. A functional assessment of vision, such as having the patient read a paragraph of newsprint, seems reasonable, but there is no evidence to support its use as a screening measure. Therefore, although visual acuity screening is inexpensive and simple to perform, it may be insufficient alone to adequately assess elderly patients. Although the U.S. Preventive Services Task Force (USPSTF) has found inconclusive evidence to justify routine vision screening in older adults, the American Academy of Ophthalmology recommends a comprehensive medical eye examination by an eye professional in asymptomatic adults aged 65 years and older every 1 to 2 years; more frequent screening is recommended for patients with risk factors for diabetes mellitus or glaucoma.

Hearing

Hearing loss is common in the elderly, with a prevalence as high as 80% in those over 80 years of age. In this population, hearing loss results in significant impairment in quality of life and potentially leads to depression and social isolation, which may be further exacerbated by feelings of frustration that hearing loss can engender in caregivers. Because the patient may experience difficulties in understanding and communication, hearing loss in the elderly is frequently misdiagnosed as cognitive dysfunction. Presbycusis, age-related hearing loss, is the most common etiology, and its onset is subtle. Presbycusis begins as high-frequency hearing loss but progresses over time to encroach on frequencies important to hearing people speak. Often, patients report inability to understand speech rather than an inability to hear.

The USPSTF does not make a recommendation regarding screening for hearing loss in asymptomatic older patients.

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However, patients who have cognitive or affective concerns that may be related to hearing should be evaluated for hearing loss. No one screening test has been shown to be superior to another. Whispered voice test, finger rub test, hearing loss questionnaire, and hand-held audiometry are all reasonable screening tests (see Ear, Nose, Mouth, and Throat Disorders). Patients who test positive in this clinical scenario or who report hearing loss should be referred for formal audiologic testing and consideration of hearing aids.

Hearing aids may improve communication abilities in older adults; however, they require considerable patient motivation to be used effectively, and cost may be a significant issue for many patients. In studies, the patients who have benefited from hearing aids have predominantly self-identified as having hearing loss. There is limited evidence suggesting that hearing aids may improve quality of life and mood and decrease social isolation.

Depression

Depression is common in older adults, although it is both underrecognized and undertreated. In the United States, depression is present in 5% of men aged 60 years and older and 7% of women aged 60 years and older. Additionally, older persons have higher rates of completed suicide than younger adults, although older adults attempt suicide less often. Depression should be suspected in the older adult if there are mood symptoms more intense than expected, poor response to medical therapy, low motivation, and lack of engagement with providers. In the elderly, depression can frequently masquerade as cognitive impairment or multiple somatic complaints, resulting in delayed diagnosis.

A simple two-question screen is highly sensitive (97%) but less specific (67%) for depression in the elderly. Using this tool, the clinician asks, "During the past month, have you been bothered by feeling down, depressed, or hopeless?" and "During the past month, have you been bothered by little interest or pleasure in doing things?" A positive response to either question constitutes a positive screening result. Because the specificity of the two-question screen is low, a positive result should be further evaluated with a more extensive diagnostic instrument, such as the Geriatric Depression Scale (GDS) or PHQ-9. Both the GDS and PHQ-9 have been validated in the elderly population and have similar positive predictive values for the diagnosis of depression. The GDS relies less on somatic symptoms and has a simplified yes-or-no format, which may be more conducive to screening those with cognitive impairment.

Selective serotonin reuptake inhibitors are considered first-line pharmacotherapy for the elderly. Further discussion on diagnosing and treating depression can be found in Mental and Behavioral Health.

Cognitive Function

Dementia affects more than 35% of persons age 90 years and older. It is characterized by a progressive decline in at least two cognitive domains (memory, attention, language, visuospatial, executive) that is severe enough to impair functioning. Mild cognitive impairment (MCI) represents cognitive deficits that do not affect daily functioning. In older patients who are asymptomatic, there is currently insufficient evidence to support routine screening for cognitive impairment. However, since patients with cognitive dysfunction are at increased risk for accidents, medical nonadherence, and behavioral disturbances, physicians should maintain a very low threshold for screening patients if there is any suspicion of cognitive impairment.

There are many simple, effective screening tests available. The Mini-Mental State Examination (MMSE) has the strongest evidence base, but recent proprietary restrictions have complicated its use clinically. The Mini-Cog screening tool is a simple, validated test that assesses both memory and executive function with a high degree of sensitivity and specificity across multiple settings. The Mini-Cog is also copyright protected, although it is available to clinicians for free use as a clinical and educational tool. The Mini-Cog involves a three-item recall and clock drawing test. Recall of all three items is normal, whereas recall of none of the items indicates dementia. If only one to two items are recalled, the results of the clock drawing test are used to classify the patient, with a normal clock drawing result indicating no dementia and an abnormal result indicating dementia. For further discussion of MCI and discussion of pharmacologic therapies for cognitive symptoms, see MKSAP 17 Neurology.

Fall Prevention

Thirty percent to 40% of community-dwelling adults older than 65 years experience a fall in a given year. The prevalence of falls increases to 50% for persons in long-term care facilities and to 60% for persons with cognitive dysfunction. In older adults, falls are a source of morbidity, mortality, decreased functionality, and premature institutionalization. Risk factors for falling are myriad; the strongest associations include lower extremity weakness, history of falls, gait or balance deficits, polypharmacy, low vitamin D level, and visual impairments. Many risk factors are amenable to remediation. **Figure 35** presents the American Geriatric Society's recommended algorithm for preventing falls in older persons.

Older patients should be routinely asked about falls. Patients who present with a fall, have a history of recurrent falls, or acknowledge gait or balance concerns should undergo a full fall evaluation. Patients with a history of one fall in the last year should be screened for balance or gait disturbance with a Timed Up and Go test, in which the patient is timed in the activity of rising from a chair, walking 10 feet (3 m), turning around, and returning to the chair. A time of longer than 20 seconds is abnormal, and the patient should be referred for full fall evaluation.

The full fall evaluation is a multidisciplinary assessment of risk, followed by a multicomponent intervention based on risk factor identification. Studies suggest that with intensive

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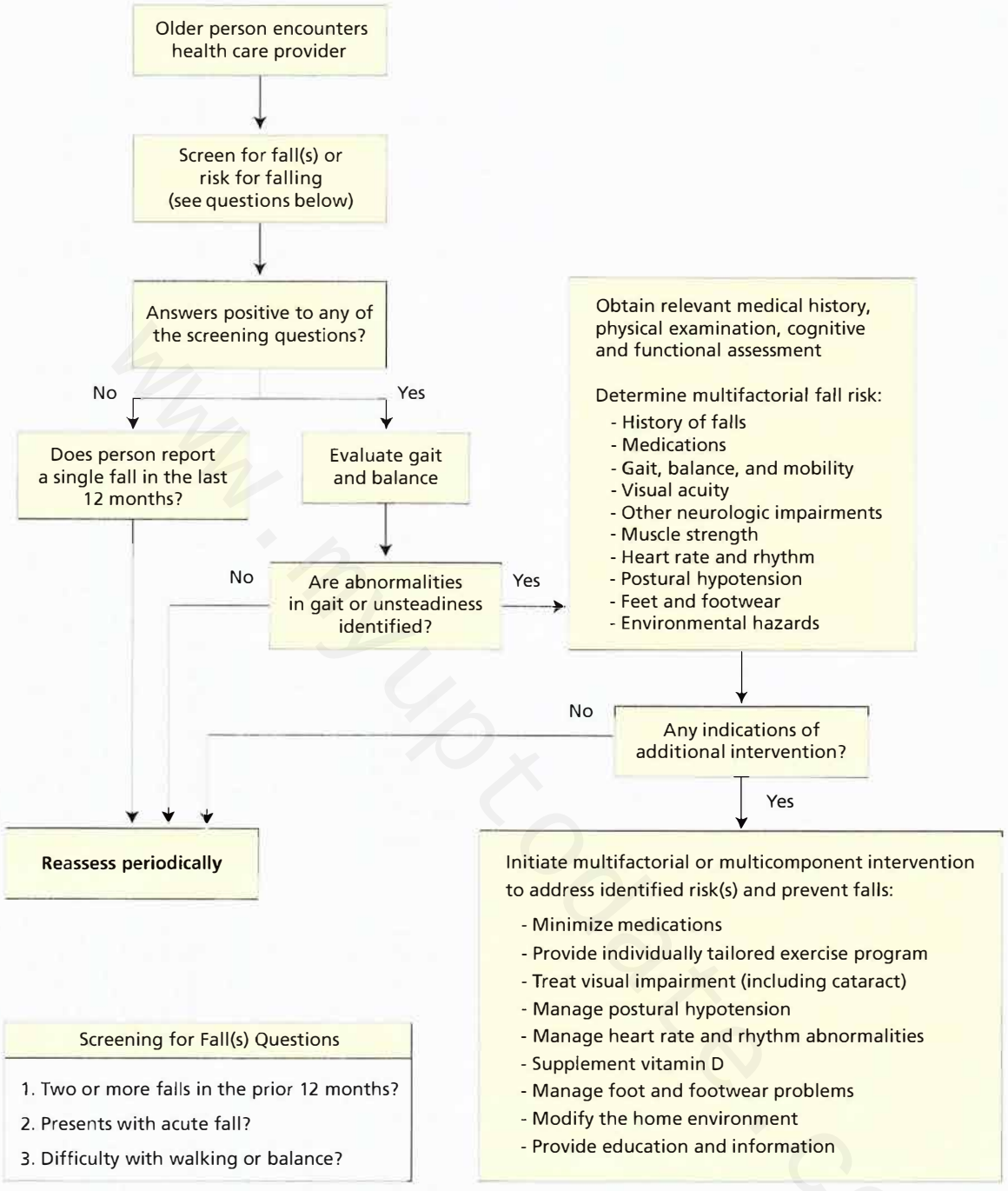

FIGURE 35. Prevention of falls in older persons living in a community.

Reprinted with permission from Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc. 2011 Jan;59(1):148-57. [PMID: 21226685] Copyright 2011, John Wiley & Sons, Inc.

intervention, those community-dwelling adults at the highest risk of falling can decrease their fall rates by 20%. Interventions for community-dwelling older adults include individualized exercise programs that emphasize balance, gait, and strength training, such as physical therapy or tai chi. Exercise programs do not seem to benefit institutionalized residents, however. Limiting polypharmacy (particularly psychoactive medications), addressing orthostasis, and assessing footwear and providing appropriate adaptive equipment should also be stressed. Ample evidence exists to support supplementation with 800 U/d of vitamin D to decrease fall risk in older adults, with a number needed to treat of only 15 irrespective of vitamin deficiency. Given that vitamin D is safe, inexpensive, and highly effective, some experts believe that vitamin D supplementation should be routine for all older adults. There is currently insufficient evidence to support any recommendations to

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reduce fall risk in the cognitively impaired. Modification of the home environment in isolation is ineffective, but when performed in addition to the previously mentioned interventions as part of a multimodal fall prevention program, it has been shown to be beneficial.

Assessment of the Older Driver

Older drivers are involved in more fatal car crashes per mile driven than any other age group excepting those under age 25 years. In older drivers, the accident rate can be at least partially attributed to physical or mental changes associated with aging or disease. The American Medical Association recommends that physicians assess older patients for physical or mental impairments that might adversely affect driving abilities. This is a qualitative assessment that relies heavily on physician clinical judgment. It is important to note that family assessment of driving ability is more reliable than patient self-assessment when gathering information. The more risk factors (**Table 75**) that a patient has, the higher the risk of an adverse event while driving. Drivers at highest risk should be counseled to retire from driving. Experts suggest using the terminology "retiring from driving" when counseling patients as this normalizes the process. Experts also suggest helping patients brainstorm alternative transportation options when counseling them against driving. A formal assessment by a driver rehabilitation specialist (associated with hospital occupational therapy departments) can be considered if the situation is unclear. Physician reporting responsibilities vary from state to state, and physicians should be aware of the laws in their own state.

KEY POINTS

H/C • Whispered voice test, finger rub test, hearing loss questionnaire, and hand-held audiometry are all reasonable screening tests for hearing loss.

H/C • Interventions that decrease fall risk in community-dwelling older adults include implementing individualized exercise programs (physical therapy, tai chi), limiting polypharmacy, addressing orthostasis, assessing footwear, and adding vitamin D supplements.

TABLE 75. Risk Factors for Impaired Driving

Cognitive dysfunction
Caregiver report of marginal or unsafe skills
History of citations or accidents
Driving <60 miles/week
Emotional aggression or impulsivity
Use of alcohol and/or medications that affect the central nervous system
Impaired mobility or coordination of neck or extremities
Medical disorders that predispose to loss of consciousness
Visual impairment

Levels of Care

In the United States, there are more than 43 million persons older than 65 years and more than 1.4 million nursing home residents. The economics of providing comprehensive, high-quality care for aging adults has led to an expansion of care options for this population.

Acutely ill elderly patients are cared for primarily in a hospital setting. Home hospital care is a service in which health care professionals provide active treatment in the home setting of a condition that otherwise would have required an inpatient hospital stay, and although the feasibility and safety of home hospital care have been established, the intensive resources required are not widely available. For patients with ongoing, high-intensity care needs who require regular physician input, such as chronic mechanical ventilation, multiple intravenous therapies, or complex wound care needs, a long-term acute care hospital (LTACH) is often the most appropriate site for care. When the patient no longer requires high-acuity care, there are a multitude of care options with varying levels of intensity depending on patient need.

Elderly patients often require posthospital rehabilitation, which can be performed in many different settings. The purpose of rehabilitation is to maximize functional recovery and independence. Conceptually, disability involves two domains—the patient's disease and the patient's environment. Both need to be addressed in order to maximize independent functioning. Free-standing rehabilitation hospitals provide intensive rehabilitation services under the direction of specialized physiatrists. To qualify, patients must require active, intensive rehabilitation services, usually defined as 3 hours per day, 5 days per week, from multiple therapy disciplines (physical therapy, occupational therapy, speech therapy, prosthetics services). Medicare covers the expense of this rehabilitation for patients who qualify. For patients unable to tolerate that level of therapy intensity, rehabilitation may be performed at a skilled nursing facility (SNF). Medicare covers all or part of the cost of rehabilitation in a SNF for 100 days if the patient has had a 3-day inpatient hospital stay before admission and makes continued progress towards rehabilitation goals during the stay. For patients who are more functional, rehabilitation services can be provided on an outpatient basis, either in the patient's own home if the patient is homebound or at an outpatient rehabilitation clinic. If the patient needs rehabilitation services for a specific disease, such as cardiac rehabilitation after acute myocardial infarction or pulmonary rehabilitation for chronic lung disease, this type of rehabilitation is generally done on an outpatient basis.

For patients who require increased assistance with ADLs, custodial services are available in many settings. Custodial care services are nonskilled personal care services such as bathing, dressing, toileting, and mobility services; they are not covered by Medicare but may be covered by Medicaid in some cases. Nursing homes, which may provide either skilled rehabilitation services or nonskilled custodial

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CONT. services, are the most familiar custodial care in the United States. Most patients in a nursing home require substantial assistance with several ADLs. Assisted living is a home-like living environment that provides some custodial services to residents. Types and intensity of services vary widely and may include meals, transportation, ADL assistance, and social interaction. Typically, residents in assisted living facilities are more functional than those in a nursing home but are not able to live independently. Adult foster care and group homes provide custodial care in a home-like setting for a smaller number of residents.

For some patients, care in the home is most ideal. Persons with financial means may hire full-time or part-time custodial care providers (skilled or unskilled, depending on need) to provide respite for family caregivers. For patients who are homebound and have a skilled care need such as medication management, wound care, intravenous infusions, or physical therapy, home care services are a covered medical benefit. Multidisciplinary services, with physician oversight, are provided in the home on an intermittent basis for patients who meet these criteria.

Adult day care is a community-based option that provides care for patients who require supervision while their primary caregiver is at work. Adult day care may also be used to provide caregiver respite. The adult day care model is often an alternative to in-home or nursing home care, and it is much less costly.

Complex patients with many comorbid conditions often require care in more than one setting, or may move between different settings depending on the status of their medical issues. This movement between settings of care increases the number of transfers of care between institutions and providers, and increases the risk of medication errors, duplication of services, or failure to understand the patient's medical conditions and treatments. Therefore, careful attention to these care transitions is extremely important. Information that should be conveyed during transitions includes a summary of the hospital course, list of problems and diagnoses, baseline and discharge functional and cognitive status, reconciled medication list, outstanding test results, follow-up appointments, and information about goals of care and advance directives. Direct communication between discharge and receiving physician should occur when there are critical test results pending or complexities in family dynamics or goals of care. Checklists are helpful to assure completion.

KEY POINT

HVC
- The economics of providing comprehensive, high-quality care for aging adults has led to an expansion of care options for this population; complex patients with many comorbid conditions often require care in more than one setting or may move between different settings, and careful attention to these care transitions is essential.

Polypharmacy

Approximately 50% of patients over age 65 years take five or more medications each week. In a recent nationwide study, older adults frequently had multiple drugs started, stopped, or otherwise changed, with a median of four medication changes per patient in a 1-year period. The use of multiple medications increases the risk for inappropriate use, drug-drug interactions, duplication of therapy, adverse reactions, and medication errors. Polypharmacy is clearly associated with increased outpatient visits, increased risk for hospitalization, increased health care costs, and decreased functional status. Additionally, the risk for nonadherence increases, which can lead to treatment failure and disease progression.

In the elderly, drug dosing must be adjusted for age as well as kidney function, as drug metabolism may be altered due to decreased glomerular filtration, underlying illness, or altered pharmacokinetics related to aging. Certain medications have been found to particularly incur high risk for geriatric patients. In an effort to improve the care of older adults by reducing the use of potentially inappropriate medications, the American Geriatrics Society has compiled a list of high-risk drugs that must be carefully considered in terms of risk-to-benefit ratio in the elderly (available at http://geriatricscareonline.org/ProductAbstract/american-geriatrics-society-updated-beers-criteria-for-potentially-inappropriate-medication-use-in-older-adults/CL001).

Although treatment of multiple comorbid conditions often requires multiple medications, evidence shows that half of older adults take one or more medications that are not medically necessary (that is, not indicated, not effective, or therapeutically duplicative). Frequent, routine review to verify need for medication and appropriate dosing is an essential aspect of optimal geriatric care.

KEY POINT

- Polypharmacy increases the risk for inappropriate drug use, drug-drug interactions, duplication of therapy, nonadherence, adverse reactions, and medication errors.

Urinary Incontinence

Epidemiology

Urinary incontinence affects 25% to 45% of women, with 9% to 39% of women over age 60 years reporting daily urinary incontinence. The prevalence of urinary incontinence in men is roughly half of that in women; 11% to 34% of older men experience urinary incontinence, with 2% to 9% of older men experiencing daily incontinence. The true prevalence, however, may be higher, as many patients do not report incontinence due to embarrassment.

Urinary incontinence has a strong impact on quality of life, affecting the patient's psychological state, social and work functioning, and sexual activity. It increases the risk of falls

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and may lead to nursing home admission. Risk factors for urinary incontinence include age, female sex, obesity, parity, gynecologic surgery, benign prostatic hyperplasia, prostate surgery, pelvic floor muscle weakness, diabetes mellitus, high caffeine intake, tobacco use, and impairment in cognition or mobility. Most evidence on the management of urinary incontinence has been produced from studies on women, although principles can generally be applied to men.

Evaluation

There are four main classifications of urinary incontinence: (1) urge incontinence, characterized by loss of urine accompanied by sense of urgency; (2) stress incontinence, in which coughing, sneezing, or exertion causes urine loss; (3) mixed urge and stress incontinence; and (4) overflow incontinence, typified by continuous leakage or dribbling. Overflow incontinence is rare in women; it more frequently occurs in men due to prostate enlargement. Functional incontinence, which occurs in patients who cannot reach and use the toilet in a timely manner, may occur in patients with significant mobility or cognitive impairments. Classifying the type(s) of incontinence helps guide management.

Asking the older adult about urinary incontinence is recommended, as patients may be hesitant to openly discuss symptoms of urinary incontinence with their physician. A brief standardized questionnaire can be used to distinguish urge from stress incontinence (**Figure 36**). Voiding symptom diaries are helpful in determining symptom patterns and severity.

Before embarking on a more complicated path to diagnosis, reversible or transient causes of incontinence should be identified. A review of medications is essential, with attention to diuretic use, along with a review of possible situational, metabolic, cognitive, or infectious causes. Evaluation should incorporate a targeted history, including surgeries, instrumentations, and radiation. In women, an obstetric history should be obtained, and a pelvic examination should be performed to rule out atrophy or prolapse. Men should be asked about prostate symptoms and should undergo a digital rectal examination. Additionally, urinalysis should be performed. Post-void residual urine volume need not be determined unless there is high clinical suspicion for neurologic disease or bladder outlet obstruction. When possible, ultrasound bladder volume measurement is preferred to urethral catheterization.

Treatment

The treatment of urinary incontinence generally progresses in a stepwise manner. Lifestyle changes and behavioral therapy should be initiated first, followed by pharmacologic therapy and devices, and finally surgery if all other therapies have

1. During the last 3 months, have you leaked urine (even a small amount)?

❑ Yes ❑ No

↓

Questionnaire completed.

2. During the last 3 months, did you leak urine:
(Check all that apply.)

❑ a. When you were performing some physical activity, such as coughing, sneezing, lifting, or exercise?
❑ b. When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?
❑ c. Without physical activity and without a sense of urgency?

3. During the last 3 months, did you leak urine *most often*:
(Check only one.)

❑ a. When you were performing some physical activity, such as coughing, sneezing, lifting, or exercise?
❑ b. When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?
❑ c. Without physical activity and without a sense of urgency?
❑ d. About equally as often with physical activity as with a sense of urgency?

Definitions of type of urinary incontinence are based on responses to question 3:

Response to Question 3	Type of Incontinence
a. Most often with physical activity	Stress only or stress predominant
b. Most often with the urge to empty the bladder	Urge only or urge predominant
c. Without physical activity or sense of urgency	Other cause only or other cause predominant
d. About equally with physical activity and sense of urgency	Mixed

FIGURE 36. The 3 Incontinence Questions (3IQ) for evaluation of urinary incontinence.

Reprinted with permission from Brown JS, Bradley CS, Subak LL, et al; Diagnostic Aspects of Incontinence Study (DAISy) Research Group. The sensitivity and specificity of a simple test to distinguish between urge and stress urinary incontinence. Ann Intern Med. 2006;144:715-723. [PMID: 16702587] Copyright 2006, American College of Physicians.

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failed. First-line lifestyle modifications, which may be used for all types of incontinence, include fluid and food management (avoidance of caffeine and alcohol) and weight loss. Excess fluid intake should be avoided, especially at nighttime. Any underlying causes should also be addressed. Subsequent treatment is guided by the type of urinary incontinence.

Behavioral Therapy

The two most effective behavioral therapies are pelvic floor muscle training (PFMT, or Kegel exercises) and bladder training/urge suppression techniques. The American College of Physicians (ACP) recommends PFMT as first-line therapy for women with stress incontinence and may also be of benefit in patients with mixed urge and stress incontinence. In men, PFMT may also be beneficial in those with postmicturition dribble. If performed correctly and diligently, PFMT exercises may strengthen the pelvic floor muscles and enhance urinary retention. The patient is advised to tighten the pelvic muscles as if trying to interrupt urination, although it should be emphasized to the patient that he or she should not habitually interrupt urine flow. Best results require three or four sets of ten contractions daily, with contractions lasting 10 seconds. The regimen should be continued for a minimum of 15 to 20 weeks. The ACP recommends bladder training and suppressive therapy for urge and mixed incontinence. With bladder training, patients are instructed to void regularly throughout the day, regardless of urge, and progressively increase the interval between voids. Suppression techniques are used to manage urge to void outside of the schedule. The patient is instructed to contract pelvic floor muscles quickly three or four times, use a distraction technique (counting backwards from 100), and, when the urge passes, walk to the bathroom to urinate. The ACP recommends weight loss and exercise for all obese women with urinary incontinence.

Prompted voiding is a useful technique for patients with cognitive impairment and is usually implemented in nursing homes. Prompted voiding involves regularly asking the patient to report on incontinence, asking the patient if he or she needs to void and providing assistance, and praising the patient for continence.

Pharmacologic Therapy

No drugs are recommended for the treatment of stress urinary incontinence. The ACP recommends antimuscarinic medications (oxybutynin, tolterodine, fesoterodine, darifenacin, solifenacin, and trospium) for urge incontinence if bladder training was unsuccessful. All of these drugs appear therapeutically equivalent and provide similar small benefits in continence rates, and choice should be guided by cost and side effect profile. There is a high incidence of anticholinergic adverse effects, including constipation and dry mouth, necessitating careful consideration of risk-to-benefit ratio. Anticholinergic agents are contraindicated in patients with angle-closure glaucoma.

Pharmacologic therapy for prostate-related lower urinary tract symptoms is addressed in further detail in Men's Health.

Devices, Injectable Agents, and Surgery

Patients who fail to respond to conservative behavioral and/or pharmacologic interventions should be referred to a urologist or urogynecologist for consideration of other treatment options. For patients with stress incontinence, medical devices, including pessaries and urethral plugs, can be considered as adjunctive treatments. Pessaries may be effective for stress incontinence and are safe and low cost, although they are underused and require fitting by experienced practitioners. Periurethral injection of bulking agents, such as collagen, silicone microparticles, or carbon beads, is a minimally invasive treatment for stress incontinence, with cure rates between 18% and 40% and improvement rates between 33% and 39%. Repeated injections are needed to maintain effectiveness. Urinary urgency, urinary tract infection, difficulty voiding, and urinary retention are possible adverse effects.

In women, the most beneficial surgeries for stress incontinence are sling procedures for intrinsic sphincter deficiency. The mid-urethral sling procedure is associated with objective and patient-perceived improvement of stress incontinence and fewer complications than other surgical approaches. The advent of laparoscopic procedures allows for speedier recovery, but relative safety and long-term effectiveness are not yet known. In men with stress incontinence, placement of an artificial urinary sphincter may be effective when other measures fail.

For the treatment of urge incontinence, injection of botulinum toxin into the detrusor muscle can be considered in patients who are unresponsive to conservative or pharmacologic measures. In a recent Cochrane review, botulinum toxin injection demonstrated superiority over placebo in reducing incontinence. Symptoms are typically reduced for a period of 3 to 6 months. Another option is continuous neuromodulation with transcutaneous tibial or surgically implanted sacral nerve stimulators, which inhibit detrusor muscle activity and have demonstrated efficacy. High cost is a deterrent, however, and long-term efficacy data are limited.

Chronic indwelling catheters are generally not advised, except as a palliative or temporizing measure, as they are associated with urethral injury, urinary tract infection, and kidney stones. Condom catheters have fewer associated complications than indwelling catheters; however, an incorrectly fitting condom catheter can result in skin irritation, leakage, and infection. H

KEY POINTS

- Pelvic floor muscle training is recommended as first-line therapy for stress urinary incontinence. HVC
- Bladder training is recommended as first-line therapy for urge urinary incontinence. HVC
- Antimuscarinic medications are recommended for urge urinary incontinence when bladder training is unsuccessful.
- Weight loss and exercise are recommended for obese women with urinary incontinence. HVC

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Pressure Ulcers

Clinical Presentation

Pressure ulcers are a common occurrence in hospitals and long-term care settings, affecting up to 3 million patients and costing nearly $11 billion per year in the United States. In addition to the accompanying high costs, pressure ulcers can result in decreased quality of life, with associated depression, impaired mobility, and social isolation. The Centers for Medicare and Medicaid Services have selected the development of pressure ulcers as a sentinel health event (unexpected and preventable occurrences that result in serious patient injury) for health care facilities. In addition, Medicare no longer offers reimbursement for the treatment of stage III and IV pressure ulcers that develop in the inpatient setting.

Pressure ulcers are characterized by localized injury to the skin or soft tissue as a result of pressure and shear forces. Risk factors for the development of pressure ulcers include advanced age, cognitive impairment, reduced mobility, sensory impairment, and comorbid conditions that affect skin integrity (such as low body weight, incontinence, edema, poor microcirculation, and hypoalbuminemia). Pressure ulcers may be classified by use of a staging system (**Table 76**), with each stage distinguished by the amount of tissue loss.

Prevention and Management

In 2015, the American College of Physicians published a clinical practice guideline for risk assessment and prevention of pressure ulcers. This guideline recommends risk assessment to identify patients at risk for developing pressure ulcers; the National Pressure Ulcer Advisory Panel Guideline additionally recommends use of a validated risk assessment tool for this purpose. For those found to be at risk, skin inspection should occur regularly. Prevention of pressure ulcers should begin with a support surface that ensures pressure redistribution, shear reduction, and microclimate control. There is moderate evidence that the use of advanced static mattresses and overlays (such as foam, gel, or air mattresses/overlays) is associated with a lower risk for pressure ulcers compared with conventional bedding. No one advanced static mattress or overlay has been shown to be superior to another. There is no evidence to support the use of more sophisticated bed systems, such as alternating-pressure air mattresses or low-air-loss systems, in prevention of pressure ulcers, although they can be beneficial in the treatment of existing pressure ulcers. Although there is insufficient evidence to support repositioning, nutritional supplementation, creams, or dressings in prevention of pressure ulcers, these interventions are standard in most guidelines.

The ACP has also issued a clinical practice guideline for treatment of pressure ulcers. Treatment of pressure ulcers is aimed at addressing the factors that predisposed the patient to the development of the ulcer. Air-fluidized beds have been shown to enhance healing of pressure ulcers compared with standard hospital mattresses. Dressings, such as hydrocolloid dressings, are used to maintain a moist wound environment while also controlling exudate. Debridement of nonviable tissue via surgical or nonsurgical techniques (for example, wet-to-dry dressings) is also indicated. Nutritional supplementation to enhance wound healing remains controversial; however, there is weak evidence that protein or amino acid supplementation improves wound healing. There is insufficient evidence to support vitamin supplementation or zinc supplementation, although these interventions are considered very low risk. Conversely, at least in patients with advanced dementia, enteral feeding worsened pressure ulcers. There is low-level evidence supporting electrical stimulation and vacuum wound devices in reducing wound size, although the potential harms of vacuum wound devices are unclear. Evidence is insufficient to support electromagnetic, ultrasound, or hyperbaric treatment of pressure ulcers, even though these treatments remain widely utilized. Overall, the evidence for treating pressure ulcers is limited. H

TABLE 76. Classification of Pressure Ulcers

Stage	Description
I	Intact skin with nonblanchable redness
II	Partial-thickness loss of dermis. Shallow open ulcer with red-pink wound bed without slough. May also present as intact or ruptured serum-filled blister.
III	Full-thickness tissue loss. Visible subcutaneous fat but not bone, tendon, or muscle. May include undermining or tunneling.
IV	Full-thickness tissue loss with exposed bone, tendon, or muscle.
Unstageable	Full-thickness tissue loss in which the base of the ulcer is covered by slough or eschar.
Suspected deep-tissue injury	Purple or maroon localized area of discolored but intact skin or a blood-filled blister due to damage of underlying soft tissue from pressure or shear.

Adapted from National Pressure Ulcer Advisory Panel. National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel, and Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers: Quick Reference Guide. Cambridge Media: Perth, Australia; 2014.

KEY POINTS

- Prevention of pressure ulcers should begin with a support surface that ensures pressure redistribution, shear reduction, and microclimate control; special attention to patient positioning is also paramount. HVC
- Air-fluidized beds and surgical or nonsurgical debridement may enhance healing rates of pressure ulcers.

Perioperative Medicine

General Recommendations H

Rather than providing "clearance" for surgery, a comprehensive preoperative evaluation achieves three important

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objectives. First, it provides an opportunity to reassess and optimize the patient's baseline general health and chronic disease management. Second, risk assessment and subsequent discussion with the patient ensure that an informed choice is made about surgery. Third, a preoperative evaluation can identify potential postoperative risks and forms the basis of a care "handover" to those treating the patient after surgery.

Preoperative Testing

Routine diagnostic testing is not indicated preoperatively. Multiple studies have demonstrated low yield and poor risk correlation of routine preoperative diagnostic tests. The American Board of Internal Medicine Foundation's Choosing Wisely initiative (www.choosingwisely.org) and the American College of Physicians' (ACP) High Value Care initiative (http://hvc.acponline.org) include several recommendations against practices such as obtaining routine preoperative laboratory studies in healthy patients undergoing elective or low-risk surgery (such as eye surgery) or obtaining preoperative chest radiography in the absence of cardiopulmonary symptoms.

In most circumstances, patient-specific factors determine diagnostic testing needs. For example, serum electrolytes in patients who will undergo diuresis, and kidney function studies in those with chronic kidney disease (CKD), are reasonable testing indications. The American Society of Anesthesiology (ASA) does not recommend repeating laboratory studies obtained within 6 months of surgery in the absence of a clinical change.

A few studies may be indicated for surgery-related reasons. Pregnancy testing should be offered to women of childbearing age, and preoperative urinalysis should be performed in patients undergoing urologic procedures.

Perioperative Medication Management

Detailed medication reconciliation, the process of creating the most accurate list of medications a patient is actually taking (including over-the-counter medications) and comparing it with the list of medications currently ordered, can prevent complications as well as allow for reassessment of long-term benefits and risks.

Perioperative medication management begins with determination of medication indications. For agents with no clear benefit, the medication should be stopped before surgery (as long as there is no concern for withdrawal symptoms) and long-term use reconsidered. Unless specific surgery-related risks are identified, medications with a clear indication should be continued uninterrupted, with the patient taking the medications with sips of water while fasting for surgery. If risk outweighs benefit, the medication should be stopped long enough before surgery to ensure adequate clearance (usually 3-5 half-lives) and should not be restarted until the risk subsides.

Management of immunomodulators and disease-modifying antirheumatic drugs (DMARDs) is particularly challenging. Risks of infection and poor wound healing need to be carefully balanced. Solid organ transplant recipients should generally have no medication changes, but an important exception to this is sirolimus, which has been associated with wound dehiscence and should be discontinued before surgery. For non-transplant patients, DMARDs and biologic agents should be stopped for at least 4 half-lives prior to surgery and not restarted until after wound healing is complete (usually 2-4 weeks after surgery); however, methotrexate and hydroxychloroquine are typically safe to continue perioperatively.

It is also important to consider specific drugs and their potential effect in certain clinical circumstances. For example, intraoperative floppy iris syndrome is a complication affecting 2% to 3% of patients undergoing cataract surgery who are taking α_1-antagonists (in particular, tamsulosin). This complication increases the risk of retinal detachment and endophthalmitis; therefore, the management of this agent in patients being evaluated for a cataract procedure should be discussed with the eye surgeon preoperatively.

Table 77 lists other medications with potential surgery-related risk and recommended time frames for withholding them.

KEY POINTS

- Several organizations recommend against obtaining routine preoperative laboratory studies in healthy patients undergoing elective or low-risk surgery and against obtaining preoperative chest radiography in the absence of cardiopulmonary symptoms. HVC
- Unless specific surgery-related risks are identified, medications with a clear indication should be continued uninterrupted; if risk outweighs benefit, medications should be stopped long enough before surgery to assure adequate clearance.

Cardiovascular Perioperative Management

Cardiovascular Risk Assessment

The 2014 American College of Cardiology (ACC) and American Heart Association (AHA) perioperative cardiovascular guidelines provide comprehensive recommendations for managing noncardiac surgery in patients with all types of cardiac disease and those with unclear cardiovascular risk (**Figure 37**). Patients requiring emergency surgery cannot afford any delay for cardiac testing, whereas those experiencing an acute coronary syndrome (ACS) should not undergo surgery until they have received appropriate cardiac assessment and treatment. If a patient has no history, symptoms, or risk factors for coronary artery disease (CAD), no preoperative coronary evaluation is necessary.

For patients with risk factors for cardiovascular disease, the guidelines recommend determination of risk for a major adverse cardiac event (MACE). The Revised Cardiac Risk Index (RCRI)

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TABLE 77. Suggested Perioperative Medication Management

Medication Class	Recommendation	Comments
Anticoagulant	Continue for minor surgery. Discontinue before major surgery: IV heparin: 4-6 h LMWH: 24 h (12 h for prophylactic dose) Warfarin: 5 days TSOAC: 1-2 d (normal kidney function), 3-6 d (eGFR <50 mL/min/1.73 m^2) (discontinue earlier for high bleeding risk procedures).	Bridging with heparin indicated for high-risk patients and possibly moderate-risk patients.
Antiplatelet	Clopidogrel: discontinue 5-7 d before surgery; patients with cardiac stent may require continuation. Aspirin: continue if minor surgery. Continue if indication is recent myocardial infarction (up to 6 months), cardiac stent, or high risk for coronary event; otherwise, discontinue 7-10 d before major surgery (other than CABG).	Aspirin and clopidogrel use in patients with cardiac stent and/or at high risk is controversial. Aspirin should be started before CABG.
Cardiovascular	Continue β-blockers, calcium channel blockers, nitrates, antiarrhythmia agents. ACE inhibitors and ARBs should be used with caution. Diuretics usually withheld on day of surgery.	ACE inhibitors and ARBs can promote intraoperative hypotension, especially in patients with hypovolemia; perioperative use, especially in persons with left ventricular dysfunction, is controversial.
Lipid lowering	Continue statins; withhold all other lipid-lowering agents on day of surgery.	
Pulmonary	Continue controller and rescue inhalers as well as systemic glucocorticoids (if used). Probably continue leukotriene antagonists and lipoxygenase inhibitors.	
Gastrointestinal	Continue H_2 receptor blockers and proton pump inhibitors.	
Hypoglycemic agents	Oral hypoglycemic agents: discontinue 12-72 h before surgery depending upon half-life of the drug and risk of hypoglycemia. Short-acting insulin: withhold morning of surgery; may need dose reduction preoperatively if modified diet (e.g., gastrointestinal surgery). Intermediate-acting insulin: reduce dose, typically to one half of usual dose. Long-acting insulin: continue at previous dose or reduce dose to two thirds.	Hypoglycemia is more dangerous than hyperglycemia; caution to always have some basal insulin present in patients with type 1 diabetes.
Thyroid	Continue thyroid replacement, propylthiouracil, methimazole.	
Glucocorticoids	Continue; increase to stress doses if indicated.	Stress-dose glucocorticoids for patients taking >10 mg/d prednisone for >3 weeks.
Estrogen	Discontinue several weeks before surgery if feasible; if continued, increase level of deep venous thrombosis prophylaxis.	
Psychiatric	Discontinue MAOIs 10-14 d before surgery; SSRIs and TCAs can either be continued or tapered 2-3 weeks before surgery. Continue antipsychotic medications. Can continue lithium, although some experts taper and discontinue several days before surgery.	Paucity of evidence, although most psychiatric agents confer at least some theoretical risk. Risk of serotonin syndrome with some anesthetic agents. Must weigh risks of continuing versus stopping. May wish to consult with psychiatrist.
Neurologic	Continue antiepileptic drugs. May continue antiparkinsonian agents, although some experts may discontinue the night before surgery. Discontinue dementia drugs.	
Herbal	Discontinue up to 1 week before surgery.	
Analgesic	NSAIDs and COX-2 inhibitors are usually discontinued 7 d before surgery. Long-acting narcotics continued or dose reduced.	

(Continued on the next page)

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TABLE 77. Suggested Perioperative Medication Management *(Continued)*

Medication Class	Recommendation	Comments
Immunomodulators	For transplant recipients, continue all except sirolimus without interruption. For non-transplant patients, discontinue for at least 4 half-lives before and 2 weeks after surgery.	Paucity of data; risk of disease flare balanced against risk of adverse reaction from medication. Risk of perioperative wound complications may be lower for methotrexate, hydroxychloroquine, and sulfasalazine.

ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; COX-2 = cyclooxygenase-2; eGFR = estimated glomerular filtration rate; IV = intravenous; LMWH = low-molecular-weight heparin; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TSOAC = target-specific oral anticoagulant.

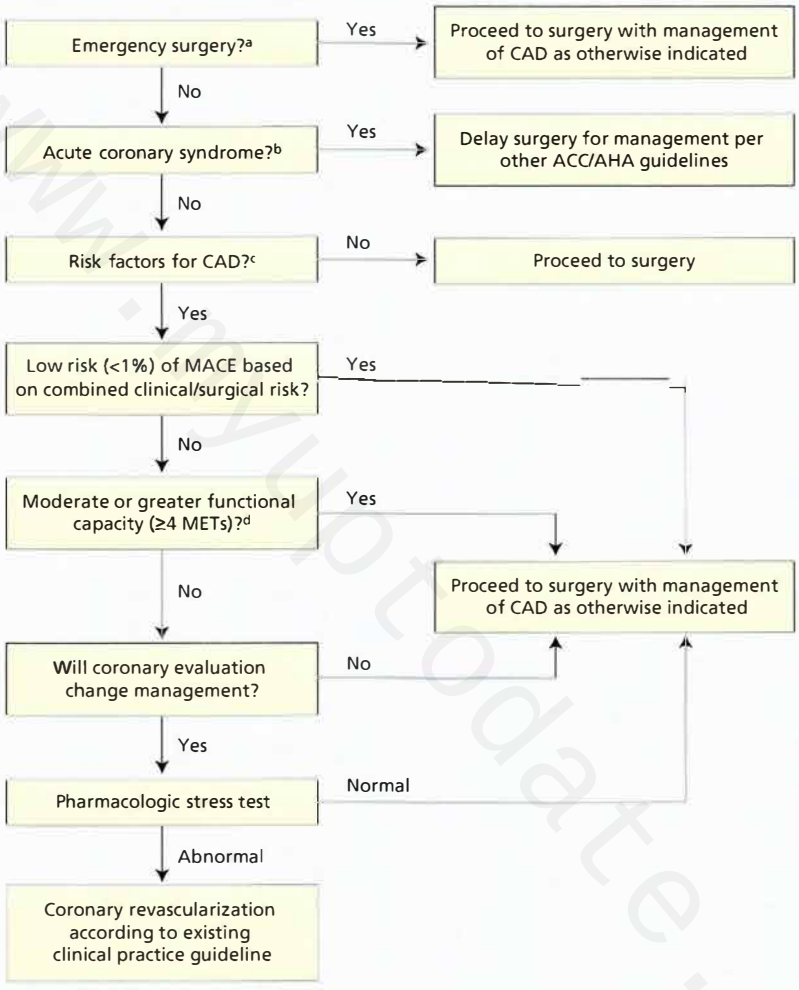

FIGURE 37. Perioperative ischemic cardiac disease evaluation for noncardiac surgery.

ACC = American College of Cardiology; AHA = American Heart Association; CAD = coronary artery disease; MACE = major adverse cardiac events; MET = metabolic equivalents.

[a]Emergency surgery required within 6 hours to avoid loss of life or limb.

[b]Acute coronary syndromes: myocardial infarction <30 days ago, unstable or severe angina.

[c]Risk factors for CAD: not specifically defined in ACC/AHA guidelines; examples include known CAD, cerebrovascular disease (that is, stroke or transient ischemic attack), chronic kidney disease, diabetes mellitus, and heart failure.

[d]Examples of activities requiring ≥4 METs include climbing a flight of stairs, walking up a hill, walking on level ground at 4 miles per hour, running for a short distance, and playing tennis.

Recommendations from Fleisher LA, Fleischmann KE, Auerbach A, et al. 2014 ACC/AHAguideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. J Am Coll Cardiol. 2014 Dec 9;64(22):e77-137. [PMID: 25091544]

CONT.

has been the most utilized risk prediction model due to its simplicity and fairly effective risk stratification for major cardiac complications (**Table 78**). However, it was not developed or validated for use in low-risk or ambulatory surgery and significantly overestimates risk for these procedures. Additionally, the RCRI has been shown to underestimate the risk in vascular surgery procedures. The RCRI may be used to estimate MACE risk, but it is important to recognize low-risk surgeries for which further cardiac testing is unnecessary even if the RCRI score is elevated (2 or higher). Low-risk procedures

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TABLE 78. Revised Cardiac Risk Index and Predicted Rate of Major Cardiac Complications Perioperatively

Risk Factor (1 point for each)	
High-risk surgery (intrathoracic, intraperitoneal, suprainguinal vascular)	
Ischemic heart disease	
Heart failure (compensated)	
Diabetes mellitus (requiring insulin)	
Cerebrovascular disease	
Chronic kidney disease (serum creatinine >2.0 mg/dL [176.8 µmol/L])[a]	
Number of Points	**Risk of Major Cardiac Complications[b]**
0	0.5%
1	2.6%
2	7.2%
≥3	14.4%

[a]Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 also shown to predict cardiovascular risk.

[b]Defined as myocardial infarction, pulmonary edema, or primary cardiac arrest.

Data from Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10):1043-9. [PMID: 10477528] and Davis C, Tait G, Carroll J, et al. The Revised Cardiac Risk Index in the new millennium: a single-centre prospective cohort re-evaluation of the original variables in 9,519 consecutive elective surgical patients. Can J Anesth. 2013 Sept;60(9):855-63. [PMID: 23813289]

CONT. include cataract extraction, carpal tunnel release, breast biopsy, and inguinal hernia repair. Although not externally validated like the RCRI, the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) Surgical Risk Calculator (http://riskcalculator.facs.org) has the potential to provide a procedure-specific estimate of MACE risk.

For patients with an elevated MACE risk (≥1%), an estimated functional capacity of <4 metabolic equivalents (METs) suggests that pharmacologic stress testing be considered if the results will change management. Examples of activities requiring the equivalent of ≥4 METs include climbing a flight of stairs or walking up a hill without stopping, running a short distance, lifting or moving heavy furniture, and participating in moderate-exertion sporting activities such as bowling or golf.

Prior to proceeding with pharmacologic stress testing in an asymptomatic patient undergoing noncardiac surgery, the purpose of testing and how it might change management must be carefully considered. In most instances, preoperative coronary evaluation will not influence medical management. However, for patients faced with different surgical options (higher versus lower risk) or in whom the risk-benefit ratio for elective surgery is uncertain, coronary evaluation may provide useful data for decision-making. Studies have failed to demonstrate survival benefit with percutaneous coronary intervention (PCI) in stable patients or improved postoperative outcomes in most patients who undergo preoperative coronary revascularization. Instead, for stable (including asymptomatic) patients with ischemia on stress testing, the ACC/AHA recommend that revascularization prior to noncardiac surgery be reserved for the same indications as in the general setting according to existing guidelines.

Echocardiography may also be beneficial in specific circumstances for assessment of left ventricular function or valvular heart disease. For patients with symptoms suggestive of undiagnosed heart failure or with a history of heart failure and a change in symptoms, the ACC/AHA recommend obtaining an echocardiogram. Reassessment of left ventricular function in patients with clinically stable heart failure who have not had an echocardiogram within the past year is also reasonable. The ACC/AHA also recommend echocardiography for patients with suspected or known moderate to severe valvular disease if the patient has had a change in clinical status (or physical examination findings) or if there is no echocardiogram within the past year.

The ACC/AHA state that it is reasonable to obtain an electrocardiogram (ECG) within 1 to 3 months of surgery in any patient with CAD, significant arrhythmias, cerebrovascular disease (stroke or transient ischemic attack), peripheral arterial disease, or other structural heart disease unless they are undergoing low-risk surgery. A preoperative ECG may also be considered in asymptomatic patients without known CAD, except in those undergoing low-risk surgery. Routine ECG is not useful in asymptomatic patients undergoing low-risk surgical procedures.

At this time, it is still unclear what role cardiac biomarkers (troponin and B-type natriuretic peptides) and CT coronary angiography should play in perioperative cardiovascular care.

Cardiovascular Risk Management

Patients with known CAD should not undergo elective noncardiac surgery within 30 days of bare metal stent implantation or 12 months of drug-eluting stent (DES) placement, and dual antiplatelet therapy should not be interrupted during this time frame. Optimally, surgery should be delayed for 12 months after DES placement. However, if the risk of further surgical delay is thought to be greater than the expected risk of ischemia and stent thrombosis, noncardiac surgery after DES implantation may be considered after 180 days; in this case, aspirin should be continued and if the second antiplatelet agent is withheld, the window of time off the agent should be as short as possible. Antiplatelet therapy must also be managed carefully to balance the bleeding risks of perioperative continuation and the thrombotic risks of cessation (see Perioperative Management of Antiplatelet Medications).

Perioperative β-blocker therapy remains controversial. At present, the strongest ACC/AHA recommendation for perioperative β-blockade indicates that it should be continued uninterrupted in patients who are already on a β-blocker. For patients who have moderate- to high-risk ischemia on preoperative testing or three or more RCRI factors, starting a β-blocker at least 1 day (preferably ≥1 week) prior to surgery is reasonable

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CONT. after consideration of potential adverse effects (for example, increased stroke risk and heart failure decompensation).

Statins may also provide perioperative cardiac risk reduction, and limited data suggest this benefit can be seen even when initiated shortly before surgery. Individuals who qualify for statin therapy according to the 2013 ACC/AHA cholesterol treatment guidelines (see Dyslipidemia) should begin this therapy preoperatively. Statins should also be continued perioperatively in patients already taking them.

ACC/AHA guidelines do not recommend routine postoperative surveillance with ECG or measurement of cardiac biomarkers unless symptoms of an acute coronary syndrome are present. This recommendation is based upon the lack of data supporting specific risk reduction measures for patients with perioperative asymptomatic myocardial infarction or isolated cardiac biomarker elevation.

ACC/AHA guidelines also provide suggestions and evidence-based recommendations for other forms of cardiac disease, including cardiomyopathies, pulmonary hypertension, valvular heart disease, and arrhythmias. In general, these conditions should be medically optimized as much as possible prior to surgery and need careful attention to postoperative hemodynamic management. Perioperative care planning for patients with congenital heart disease, cardiomyopathy, or significant arrhythmias should include collaboration with the appropriate subspecialists (cardiology and electrophysiology), and a specific perioperative management plan should be obtained from the clinician who manages the patient's implanted cardiac devices. Severe valvular disease should be repaired if intervention criteria are met; if repair is not indicated, elective noncardiac surgery is reasonable to perform with close perioperative hemodynamic monitoring.

KEY POINTS

HVC
- Patients without coronary artery disease (CAD) or CAD risk factors with an estimated major adverse cardiac event risk of <1% or with a functional capacity ≥4 metabolic equivalents do not require preoperative coronary evaluation.

HVC
- Preoperative coronary revascularization in asymptomatic patients has not been shown to reduce postoperative cardiac complications and should be reserved for the same indications as in the general setting.
- Current recommendations indicate that perioperative β-blockade should be continued uninterrupted in patients who are already on a β-blocker.

Pulmonary Perioperative Management

Pulmonary complications account for more than 50% of adverse perioperative events and have higher mortality and cost than postoperative cardiac problems. The pulmonary complications of greatest clinical concern are respiratory failure and pneumonia; risk factors can be divided into procedure-specific and patient-specific factors (**Table 79**).

TABLE 79. Major Risk Factors for Postoperative Pulmonary Complications

Procedure-Specific
Emergency surgery
Prolonged surgery (>3 h)
Thoracic surgery
Abdominal surgery
Head and neck surgery
Aortic surgery (open)
General anesthesia
Patient-Specific
Advanced age[a]
ADL functional limitations
ASA class 2 or higher[b]
COPD
Smoking within past year
Preoperative sepsis; obstructive sleep apnea; pulmonary hypertension

ADL = activities of daily living; ASA = American Society of Anesthesiologists.

[a]Incremental risk increase with every decade above age 50 years.

[b]ASA classes are as follows: class 1, normal healthy patient; class 2, patient with mild systemic disease; class 3, patient with severe systemic disease; class 4, patient with systemic disease that is a constant threat to life; and class 5, moribund patient who is not expected to survive for 24 hours with or without operation.

Several models and risk calculators have been developed for predicting pulmonary risk. Although these calculators may provide a fairly reliable estimate of general pulmonary complications, they have limitations because they were derived from surgical data that did not capture information on obstructive sleep apnea (OSA) or pulmonary hypertension, both of which have been shown to significantly increase the risk of postoperative pulmonary complications. Most interventions for pulmonary risk reduction have minimal potential adverse effects and are not specific for any particular level of risk or risk factor. Therefore, clinical assessment of risk factors without a validated risk calculator is likely sufficient in most clinical situations. The exception is assessment of OSA risk, for which there are specific perioperative considerations. All surgical patients should be screened for OSA with a validated tool such as the STOP-BANG survey (**Table 80**).

Spirometry is no more predictive of complications than clinical assessment alone and should be performed only for dyspnea or hypoxia of uncertain cause. Arterial blood gas analysis and chest radiograph results rarely alter perioperative management when obtained in clinically stable patients.

Surgery should be delayed whenever possible to treat acute respiratory disease, and medical management of chronic pulmonary problems should be fully optimized. Smoking cessation should be strongly encouraged; the greatest benefit comes from quitting more than 8 weeks before surgery. The ASA suggests pursuing polysomnography and initiation of

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TABLE 80. STOP-BANG Obstructive Sleep Apnea Screening Tool

Survey Items (1 point for each)	
Snoring	
Tiredness or sleepiness during the day	
Observed apnea during sleep	
Pressure, high blood	
BMI >35	
Age >50 years	
Neck circumference >40 cm	
Gender = male	
STOP-BANG Score	**Risk Correlation**
0-2	Low risk of OSA
≥3	Increased risk of OSA
≥5	Increased risk of moderate-severe OSA

OSA = obstructive sleep apnea.

Adapted with permission from Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology. 2008 May;108(5):812-21. [PMID: 18431116] and Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. Br J Anaesth. 2012 May;108(5):768-75. [PMID: 22401881]

CONT.

continuous positive airway pressure (CPAP) therapy for patients with presumed severe OSA. For a patient with suspected OSA who is scheduled for outpatient surgery, discussion with the anesthesiologist and surgeon is important to determine whether the surgical procedure is most appropriately performed on an inpatient or outpatient basis.

The mainstay of risk management is lung expansion maneuvers, including deep breathing exercises, incentive spirometry, intermittent positive pressure breathing, and CPAP therapy. Each of these is equally effective, and a combination of modalities provides no additive benefit. Selective use of nasogastric intubation is also effective at preventing pulmonary complications. Regional and neuraxial anesthesia and analgesia, intraoperative protective lung ventilation, and laparoscopic surgical approaches are other available risk reduction methods. Patients with suspected or diagnosed OSA should receive nonsupine positioning (unless contraindicated) and continuous pulse oximetry. H

KEY POINTS

- All surgical patients must be screened for obstructive sleep apnea with a validated tool such as the STOP-BANG survey.
- HVC Preoperative spirometry should be performed only for dyspnea or hypoxia of uncertain cause.
- HVC The mainstay of perioperative pulmonary risk management is lung expansion maneuvers, including deep breathing exercises and incentive spirometry.

Hematologic Perioperative Management H

Venous Thromboembolism Prophylaxis

Venous thromboembolism (VTE) is estimated to cause more than 50,000 postoperative deaths per year in the United States. The American College of Chest Physicians (ACCP) antithrombotic guidelines provide recommendations for VTE prophylaxis after many types of surgery and incorporate use of the Caprini model for perioperative VTE risk stratification (**Table 81** and **Table 82**). The Caprini model has been validated in multiple types of surgery (excluding orthopedic and gynecologic oncology surgery) and provides a relatively simple objective assessment of postoperative VTE risk. Prophylactic antithrombotic agents should be withheld until the risk of surgical bleeding has sufficiently subsided (at least 12 hours after surgery) and should be continued until hospital discharge. Major orthopedic and abdominal-pelvic surgery for cancer carries especially high VTE risk and requires extended-duration prophylaxis (up to 35 days after surgery).

Evidence does not support the use of inferior vena cava (IVC) filters for primary prophylaxis. Instead, IVC filters should be reserved for patients with an acute VTE event and an absolute contraindication for anticoagulation. This includes patients with VTE within 3 months before necessary surgery for which anticoagulation must be withheld. Removable IVC filters are preferred, and the perioperative management plan should include a timeline for when anticoagulation can be resumed and the filter extracted.

Perioperative Management of Anticoagulant Therapy

Surgical patients on chronic anticoagulant therapy confront the challenge of balancing their baseline thrombotic risk with the added thromboembolic and bleeding risks associated with invasive procedures. Anticoagulation management must address the following: (1) need for temporary anticoagulant cessation, (2) potential benefit of bridging anticoagulation if cessation is necessary, and (3) appropriate timing for anticoagulant resumption after surgery.

Anticoagulation must be stopped for most surgical procedures except those with minimal expected blood loss (for example, cataract surgery, dermatologic procedures, dental procedures, and endoscopic procedures without biopsy). If temporary cessation is warranted, therapy should be withheld for a sufficient period of time to leave minimal residual anticoagulant activity. Stopping warfarin 5 days prior to surgery usually achieves the standard target of an INR of less than 1.5. Much less data are available for the perioperative management of target-specific oral anticoagulants. Most experts recommend a conservative approach to ensure elimination by the time of surgery (**Table 83**). Although normal activated partial thromboplastin time (aPTT) in patients taking dabigatran and normal INR in patients taking apixaban or rivaroxaban correlate with minimal residual activity, such

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TABLE 81. Postoperative Venous Thromboembolism Prophylaxis Recommendations for Common Noncardiothoracic Surgeries

	Surgery and Risks		Recommended Prophylaxis[a]
General, abdominal-pelvic, urologic, plastic, vascular	Caprini[b] score 0		Early ambulation
	Caprini score 1-2		IPC
	Caprini score 3-4	Average bleeding risk	LMWH, LDUH, IPC
		High bleeding risk[c]	IPC
	Caprini score ≥5	Average bleeding risk	LMWH or LDUH (+ IPC)
		High bleeding risk[c]	IPC
	Cancer surgery		LMWH for 4 weeks
Orthopedic	Hip or knee arthroplasty[d]		IPC + LMWH, LDUH, aspirin, TSOAC, fondaparinux, warfarin, or IPC alone if high bleeding risk; continue for 10-35 d
	Hip fracture repair[c]		IPC + LMWH, LDUH, warfarin, fondaparinux, or IPC alone if high bleeding risk; continue for 10-35 d
	Isolated lower leg fracture repairs		None
	Knee arthroscopy with no previous VTE		Early ambulation
Spine (elective)	Average VTE risk		IPC
	High VTE risk (e.g., malignancy, anterior-posterior approach)		IPC + LMWH (when bleeding risk sufficiently low)
Major trauma	Average VTE risk		LMWH, LDUH, IPC
	High VTE risk (e.g., spinal cord or brain injury)		LMWH or LDUH (+ IPC)
	High bleeding risk[c]		IPC
Intracranial	Average VTE risk		IPC
	High VTE risk (e.g., malignancy)		LMWH or LDUH (+ IPC)

IPC = intermittent pneumatic compression; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; TSOAC = target-specific oral anticoagulant (dabigatran, rivaroxaban, apixaban); VTE = venous thromboembolism.

[a]Duration is for postoperative hospitalization unless noted otherwise.

[b]See Table 82 for the Caprini Risk Assessment Scoring method.

[c]Risk factors suggesting high bleeding risk: concurrent antithrombotic therapy (e.g., aspirin for cardiac disease), known or suspected bleeding disorder, active bleeding, liver or kidney disease, and sepsis.

[d]LMWH is preferred.

Recommendations from Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e227S-e277S. [PMID: 22315263] and Falck-Ytter Y, Francis CW, Johanson NA, et al; American College of Chest Physicians. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e278S-325S. [PMID: 22315265]

CONT.

testing is not routinely recommended. There are no approved reversal strategies for these agents. Rapid reversal of warfarin for urgent surgery can be accomplished with vitamin K, fresh frozen plasma, or prothrombin complex concentrates, but the potential thrombotic complications of this approach must be considered.

Bridging anticoagulation is not currently recommended for patients stopping dabigatran, rivaroxaban, or apixaban. For patients chronically taking warfarin, the decision to provide alternative anticoagulation while off this drug is based upon the indication for chronic anticoagulation and level of thromboembolic risk (**Table 84**). For patients with low thromboembolic risk, warfarin therapy is stopped with no bridging anticoagulation, whereas high-risk patients should receive bridging anticoagulation with intravenous unfractionated heparin (UFH) or therapeutic-dose low-molecular-weight heparin (LMWH). For all other patients, the decision for bridging is individualized based on patient and surgical considerations. Although the CHA_2DS_2-VASc risk score is the preferred method for long-term thromboembolic risk stratification in atrial fibrillation patients, its utility for perioperative risk stratification is unknown, and current ACCP guidelines for perioperative anticoagulation management utilize the $CHADS_2$ system for perioperative risk stratification (see MKSAP 17 Cardiovascular Medicine). LMWH should be avoided in patients with an estimated glomerular filtration

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TABLE 82. Caprini Venous Thromboembolism Risk Assessment Scoring Method

Number of Points for Each Risk Factor	Risk Factors
1	Age 41-60 y; minor surgery; BMI >25; leg edema; varicose veins; recent or current pregnancy; estrogen use; recurrent spontaneous abortion; recent sepsis (<1 mo)/pneumonia (<1 mo); severe lung disease; abnormal pulmonary function; inflammatory bowel disease; acute MI; recent HF (<1 mo); medical patient at bed rest
2	Age 61-74 y; arthroscopic surgery; major surgery lasting >45 min; malignancy; bed rest for >72 h; immobilizing cast; central venous access
3	Age ≥75 y; personal history of VTE; family history of VTE; congenital or acquired thrombophilia; HIT
5	Stroke or spinal cord injury within 1 mo; elective arthroplasty; hip, pelvis, or leg fracture

HF = heart failure; HIT = heparin-induced thrombocytopenia; MI = myocardial infarction; VTE = venous thromboembolism.

Adapted from Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell DA Jr, Caprini JA. A validation study of a retrospective venous thromboembolism risk scoring method. Ann Surg. 2010 Feb;251(2):344-50. [PMID: 19779324]

TABLE 83. Cessation of Target-Specific Oral Anticoagulants Before Surgery

Agent	Duration of Preoperative Cessation by Kidney Function[a]		
	eGFR >50 mL/min/1.73 m²	eGFR 31-50 mL/min/1.73 m²	eGFR ≤30 mL/min/1.73 m²
Apixaban	1-2 d	2-3 d	>3 d
Rivaroxaban	1-2 d	1-2 d	2-3 d
Dabigatran	1-2 d	2-4 d	>4 d

eGFR = estimated glomerular filtration rate.

[a]For surgeries with high bleeding risk, use longer duration. All target-specific oral anticoagulants should not be restarted postoperatively until 24 hours after low bleeding risk surgery and 48 to 72 hours after high bleeding risk procedures.

CONT.

rate <30 mL/min/1.73 m². If bridging is utilized, UFH or LMWH should be started approximately 36 hours after the last dose of warfarin. In patients receiving bridging with UFH, the last presurgical dose should be 4 to 6 hours before surgery. In those being bridged with LMWH, the last dose should be given no sooner than 12 hours before surgery if being dosed at prophylactic levels, or no sooner than 24 hours if being given at therapeutic dosing levels.

Warfarin can be safely restarted 12 to 24 hours after surgery if there are no major bleeding concerns. Therapeutic-dose LMWH and UFH may be started 24 hours after surgery with low operative blood loss (<500 mL) but should be withheld for at least 48 to 72 hours after surgery with greater blood loss. In the latter situation, it may be advisable to provide prophylactic-dose LMWH (which can be resumed within 12 hours after surgery) until therapeutic doses are possible. Dabigatran, rivaroxaban, and apixaban all have rapid onset of action and should be restarted using the same guidelines as LMWH.

TABLE 84. Perioperative Warfarin Bridging Strategies

TE Risk (rate per year)	Patient Characteristics	Bridging Strategy
Low (<5%)	Bileaflet mechanical aortic valve without atrial fibrillation, CVA, or other risk factors	No bridging
	Atrial fibrillation with $CHADS_2$ score ≤2 and no prior CVA	No bridging
	VTE >12 mo previously with no other risk factors	No bridging
Intermediate (5%-10%)	Bileaflet mechanical aortic valve with atrial fibrillation or $CHADS_2$ score >0	Bridging on case-by-case basis; use therapeutic- or prophylactic-dose[a] LMWH or UFH
	Atrial fibrillation with $CHADS_2$ score 3-4	Bridging on case-by-case basis; use therapeutic- or prophylactic-dose[a] LMWH or UFH
	Recurrent VTE or VTE within past 3-12 mo or associated with nonsevere thrombophilia or active cancer	Bridging on case-by-case basis; use therapeutic- or prophylactic-dose[a] LMWH or UFH
High (>10%)	Mitral or caged ball or tilting disc mechanical aortic valve, or bileaflet mechanical aortic valve with recent CVA	Bridge with therapeutic LMWH or UFH
	Atrial fibrillation with $CHADS_2$ score >4, rheumatic valvular heart disease, or recent CVA or TIA	Bridge with therapeutic LMWH or UFH
	VTE within past 3 mo or with severe thrombophilia	Bridge with therapeutic LMWH or UFH

CVA = cerebrovascular accident; LMWH = low-molecular-weight heparin; TE = thromboembolism; TIA = transient ischemic attack; UFH = unfractionated heparin; VTE = venous thromboembolism.

[a]Prophylactic-dose LMWH is only an option in patients with VTE as their indication for chronic anticoagulation.

Adapted from Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e326S-e350S. [PMID: 22315266]

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Perioperative Management of Antiplatelet Medications

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For patients who take aspirin for primary prevention or analgesia, the risks of surgical bleeding most likely outweigh any benefits, and aspirin should be stopped 7 to 10 days before surgery. In patients with CAD on dual antiplatelet therapy with aspirin and another agent (clopidogrel, ticagrelor, ticlopidine, or prasugrel), neither should be stopped within 12 months of drug-eluting stent placement or 4 to 6 weeks of bare metal stent placement. If a patient requires surgery during these intervals, dual antiplatelet therapy, or at least aspirin alone, should be continued perioperatively. Following these time periods, the non-aspirin antiplatelet can be temporarily discontinued 5 to 7 days before surgery, but aspirin should be continued uninterrupted unless the risk of surgical bleeding is excessive (such as intracranial surgery). The timing and safety of antiplatelet cessation for surgery within 1 year after acute myocardial infarction or surgical coronary revascularization should be discussed with a cardiologist. Management of patients taking antiplatelet agents for other secondary prevention (such as history of stroke) is less clear, but the ACC/AHA and ACCP suggest considering the perioperative continuation of aspirin based on assessment if the ischemic risk is considered greater than the bleeding risk.

If antiplatelet therapy is withheld for surgery, it can be safely restarted 24 hours after surgery unless there is persistent risk for surgical bleeding. However, careful consideration should be given to the benefits and risks of restarting dual antiplatelet therapy for patients who will receive concomitant postoperative anticoagulation.

Perioperative Management of Anemia, Coagulopathies, and Thrombocytopenia

All patients should undergo a thorough personal and family history and physical examination to identify underlying anemia or bleeding diatheses. Laboratory testing for coagulation and platelet disorders should not be done routinely due to very low yield and poor correlation with surgical bleeding risk. Hemoglobin and hematocrit should be measured in the setting of signs or symptoms of anemia or surgery with a large expected blood loss. For the patient with a history suggestive of a bleeding disorder, preoperative prothrombin time, activated partial thromboplastin time, and platelet count measurements are indicated.

Preoperative anemia is associated with increased surgical morbidity and mortality and reversible causes, such as iron or vitamin B_{12} deficiency, and should be treated whenever possible. Preoperative autologous blood donation is rarely used because it increases the risk of preoperative anemia and results in the waste of up to 50% of donated units.

Erythrocyte transfusion thresholds have been the focus of much recent research. For multiple types of surgeries and patient characteristics (including those with cardiovascular disease), studies have shown that a conservative transfusion protocol (transfusing for signs or symptoms attributable to anemia or a hemoglobin level <7-8 g/dL [70-80 g/L]) is as good, if not better, than transfusing at a higher hemoglobin level. Studies of patients with cardiovascular disease have also suggested no benefit from more liberal transfusion strategies. One specific exception to a conservative blood management approach is patients with sickle cell disease who benefit from perioperative maintenance of a hemoglobin level of 10 g/dL (100 g/L), either through exchange or traditional erythrocyte transfusions.

A platelet count of greater than 50,000/μL (50×10^9/L) is sufficient to achieve hemostasis in most surgeries. In patients with immune-mediated thrombocytopenia, glucocorticoids and intravenous immune globulin can temporarily boost platelet counts. Patients with platelet function defects may be given prophylactic desmopressin, factor VIII/von Willebrand factor concentrates, or platelet transfusions, depending on their specific disorder. Known coagulation factor deficiencies are treated with specific factor replacement (hemophilia A and B) or fresh frozen plasma (factor XI deficiency). The complexity of platelet function disorders and coagulopathies makes consultation with a hematologist advised in most cases.

KEY POINTS

- Anticoagulation must be stopped prior to most surgical procedures except those with minimal expected blood loss.
- Preoperatively, for patients with low thromboembolic risk, warfarin therapy is stopped with no bridging anticoagulation, whereas high-risk patients should receive bridging anticoagulation. HVC
- In patients with coronary artery disease on dual antiplatelet therapy, neither agent should be stopped within 12 months of drug-eluting stent placement or 4 to 6 weeks of bare metal stent placement, acute myocardial infarction, or surgical coronary revascularization.

Perioperative Management of Endocrine Diseases

Diabetes Mellitus

Diabetes mellitus is a risk factor for several perioperative complications, although the link between glucose levels and risk remains indistinct. In cardiac surgery, poor glycemic control, both preoperatively and postoperatively, has been associated with worse cardiovascular, infectious, and neurologic outcomes. For other types of surgery, hyperglycemia is an inconsistent risk factor for complications, and postoperative hyperglycemia (even in patients without a preoperative diagnosis of diabetes) appears to be most predictive of adverse events.

Preoperatively, the status of glycemic control and diabetic complications in patients with diabetes should be assessed, which includes obtaining a hemoglobin A_{1c} measurement and

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kidney function assay if not tested recently. Although no evidence-based hemoglobin A_{1c} cutoff for elective surgery exists, reasonably good glycemic control (hemoglobin A_{1c} <8%-9%) should be achieved before nonurgent surgery.

Patients on insulin will likely have different insulin needs postoperatively and need close perioperative monitoring. Long-acting insulins (glargine or detemir) should be continued unchanged or at two thirds of their usual dose, depending on risk factors for hypoglycemia and duration of fasting state and procedure. On the morning of surgery and while fasting, neutral protamine Hagedorn (NPH) insulin can be given at half of the usual dose. Short-acting insulins should usually be withheld on the morning of surgery. Patients with type 1 diabetes require at least some insulin at all times to prevent ketoacidosis.

Oral hypoglycemic agents (OHAs) should be withheld for 12 to 72 hours depending on the half-life of the medication. Due to potential side effects and unpredictable postoperative nutrition, these agents should be withheld until the patient has resumed a normal diet. Insulin is the preferred therapy and likely the safest choice for achieving inpatient glycemic control. The recommended insulin regimen should incorporate both basal and prandial coverage. In the setting of preprandial hyperglycemia, prandial coverage can be supplemented with additional insulin (correction factor insulin). Sliding scale insulin is not recommended. Patients with good preoperative glycemic control (hemoglobin A_{1c} <7%) can resume OHAs on discharge, even if they required significant amounts of insulin while hospitalized. Patients with poor preoperative glycemic control on OHAs meet American Diabetes Association (ADA) criteria for insulin therapy, and the postoperative period can be used to transition to long-term insulin therapy.

Specific postoperative glycemic control targets remain unclear. Recent literature has demonstrated that intensive insulin therapy may not necessarily improve outcomes in hospitalized patients. The ADA and ACP guidelines for managing hyperglycemia in the hospital setting are described in MKSAP 17 Endocrinology and Metabolism.

Thyroid Disease

For patients with stable thyroid disease, thyroid function testing within 6 months before surgery is usually sufficient for preoperative evaluation. Clinicians should order thyroid function tests for any patient with symptoms suggestive of unstable or new thyroid disease. Patients with mild to moderate hypothyroidism generally tolerate surgery well, but those with severe hypothyroidism (overt symptoms related to thyroid hormone deficiency and/or free thyroxine [T_4] level <1.0 ng/dL [12.9 pmol/L]) are at risk for multiple complications. Elective surgery should be postponed for patients who have severe hypothyroidism or those with hypothyroidism who are undergoing high-risk elective surgery. Hyperthyroidism is problematic in the perioperative setting because it is more likely to cause arrhythmias and heart failure. Elective surgery should be delayed to achieve a euthyroid state in patients with clinical hyperthyroidism. If surgery is urgently required, patients should be managed with aggressive β-blocker therapy. Consultation with an endocrine specialist is also warranted to determine other appropriate therapy.

Adrenal Insufficiency

There is minimal evidence on best management of patients at risk for adrenal insufficiency. A practical approach utilizes risk stratification based upon assessment of the physiologic stress of surgery and patient characteristics (**Table 85**). Patients with no risk factors and those undergoing low-risk procedures (such as surgery lasting <45 minutes or without general or neuraxial anesthesia) require only their usual dose of glucocorticoid on the day of surgery. If such patients develop signs or symptoms of adrenal insufficiency, increased doses of glucocorticoids should be provided. Even for those patients at high risk for adrenal insufficiency or undergoing high-risk procedures (such as intrathoracic and intra-abdominal surgery), "stress-dose" glucocorticoids should be rapidly de-escalated within the first few days after surgery. Although adrenocorticotropin hormone stimulation testing can be used to objectively assess the responsiveness of the hypothalamic-pituitary-adrenal axis to surgical stress, such testing is generally not employed because it is expensive and logistically difficult.

KEY POINTS

- In patients with diabetes mellitus, short-acting insulins should usually be withheld on the morning of surgery, and long-acting insulins should usually be continued at two thirds to 100% of the usual dose.
- Elective surgery should be postponed for patients with severe hypothyroidism or those with hypothyroidism undergoing high-risk elective surgery.
- Patient-related risk factors for perioperative adrenal insufficiency include primary adrenal insufficiency and a daily prednisone dose of ≥10 mg for ≥3 weeks in the previous year.

TABLE 85. Management of Perioperative Adrenal Insufficiency Risk

Patient Risk		Management Based on Surgical Risk: High	Management Based on Surgical Risk: Low
High	Primary adrenal insufficiency; ≥10 mg of daily prednisone[a] for ≥3 weeks in past year	Hydrocortisone, 50-100 mg IV, before surgery, then 25-50 mg IV every 8 h for 24-48 h	Give usual dose of glucocorticoid on day of surgery
Low	Any other glucocorticoid exposure	Give usual dose of glucocorticoid on day of surgery	Give usual dose of glucocorticoid on day of surgery

[a]Or other glucocorticoid of equivalent dose.

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Perioperative Management of Kidney Disease

Up to 7% of surgical patients with chronic kidney disease (CKD) experience acute kidney injury (AKI), and even small decrements in kidney function increase morbidity and mortality. Patients should be counseled on these risks.

All patients with CKD should have a recent basic metabolic panel and optimization of blood pressure control and volume status preoperatively. Patients on chronic dialysis should have the timing of dialysis and surgery carefully coordinated. Ideally, dialysis should be performed the day before surgery to allow for re-equilibration of electrolytes and stabilization of blood pressure; dialysis the day after surgery is often necessary if intravascular volume is an issue.

A recent Cochrane systematic review found no significant evidence that specific interventions preserve kidney function perioperatively. However, adequate preoperative hydration, avoidance of nephrotoxic agents (such as NSAIDs), and minimization of perioperative hypotension are useful for patients with kidney disease. It is also important to emphasize the need to maintain adequate hydration during perioperative fasting. ASA fasting guidelines permit clear liquid intake until up to 2 hours before the surgical procedure.

In the postoperative period, kidney function, blood pressure, electrolyte levels, and volume status should be monitored closely in patients with CKD. Urine output poorly correlates with kidney function and should not be used as the sole means of assessing intravascular volume status. Medications should be appropriately dosed for kidney function; morphine, LMWH, and other agents highly dependent on kidney clearance should be used with caution or avoided completely.

KEY POINT

- Patients on chronic dialysis should ideally have dialysis performed the day before surgery to allow for re-equilibration of electrolytes and stabilization of blood pressure.

Perioperative Management of Liver Disease

Abnormal liver function predisposes patients to bleeding, poor wound healing, and infections, and many common perioperative medications, including anesthetics and sedatives, are hepatically metabolized and prone to prolonged effects. Patients with newly diagnosed or worsened liver disease should have elective surgery postponed. If elective surgery is undertaken, patients with stable viral hepatitis and cirrhosis need to be fully apprised of the risks, including the potential for further liver decompensation. For patients with cirrhosis, postoperative mortality is up to 10% for patients with Child-Turcotte-Pugh class A disease and 80% for class C disease. Postoperative mortality for major surgery in patients with cirrhosis can be estimated using a calculator incorporating the Mayo End-stage Liver Disease (MELD) score, patient age, and ASA classification (www.mayoclinic.org/meld/mayomodel9.html). In general, elective surgeries are safe in patients with a MELD score of less than 8 and are generally not recommended in patients with a MELD score ≥15.

For patients with cirrhosis who do proceed to surgery, liver disease management should be fully optimized (see MKSAP 17 Gastroenterology and Hepatology, Disorders of the Liver). It is advisable to enlist the help of a hepatologist or gastroenterologist in the perioperative management of these patients due to the high perioperative risk of sepsis, kidney failure, liver failure, bleeding, encephalopathy, hypotension, cholestasis, ascites, and pulmonary edema.

KEY POINTS

- Patients with newly diagnosed or worsened liver disease should have elective surgery postponed.
- In general, elective surgeries are safe in patients with a Mayo End-stage Liver Disease (MELD) score of less than 8 and are not recommended in patients with a MELD score ≥15.

Perioperative Management of Neurologic Disease

Patients with chronic neurologic disease are at risk for decompensation in the surgical setting. In general, all medications for chronic neurologic disease should be continued uninterrupted. This is especially important for antiepileptic drugs and Parkinson disease agents. Missing doses of the latter can precipitate a syndrome similar to the neuroleptic malignant syndrome, with severe muscle rigidity and respiratory compromise. For patients likely to be unable to take oral medications, preoperative planning for alternative routes of administration (nasogastric, parenteral, sublingual, transdermal, rectal) should be coordinated with a neurologist.

Even with proper medication management, patients with neuromuscular disease or Parkinson disease remain at risk for complications. Respiratory and oropharyngeal muscle weakness is common in these conditions and may be exacerbated by surgery. Close monitoring for respiratory failure, aspiration, and pneumonia are necessary. Delirium is particularly common in elderly surgical patients, but perioperative risk factors and treatment are similar to those for delirium in the general hospital setting (see MKSAP 17 Neurology).

Postoperative stroke occurs in 0.5% of major surgical procedures and is most common in patients with other cardiovascular risk factors. The contribution of asymptomatic carotid stenosis to the risk of perioperative stroke remains unclear, and prophylactic intervention is not advised prior to noncardiac surgery. Further information on perioperative stroke management is covered in MKSAP 17 Neurology.

KEY POINT

- In general, all medications for chronic neurologic disease should be continued uninterrupted perioperatively.

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 58-year-old woman is evaluated during a routine examination. She is asymptomatic. Medical history is unremarkable. She smoked cigarettes socially in her 20s but is currently a nonsmoker. Family history is significant for her mother who had a hip fracture in her 70s and two cousins who have hypothyroidism. She takes no medications.

On physical examination, temperature is normal, blood pressure is 118/72 mm Hg, and pulse rate is 72/min. BMI is 24. The remainder of the physical examination is normal.

A lipid panel and fasting plasma glucose level obtained 1 year ago were normal. Pap smear and human papillomavirus testing performed 3 years ago were negative. Her Fracture Risk Assessment Tool (FRAX) score indicates a 13% risk for major osteoporotic fracture over the next 10 years.

Which of the following is the most appropriate screening test for this patient?

(A) Dual-energy x-ray absorptiometry scan
(B) Fasting lipid panel
(C) Fasting plasma glucose level
(D) Pap smear
(E) Thyroid-stimulating hormone level

Item 2

A 38-year-old woman is evaluated during a routine examination. She is a mother of two children and works full time at a high-stress job. She smokes 10 cigarettes daily, eats fast food three times per week, and drinks two alcoholic beverages most nights. She does not exercise. Family history is noncontributory. She takes no medications.

On physical examination, the patient is afebrile, blood pressure is 122/76 mm Hg, and pulse rate is 80/min. BMI is 26. The remainder of the physical examination is normal.

Which of the following interventions will have the largest impact on this patient's health?

(A) Decrease alcohol consumption
(B) Exercise 30 minutes daily, 5 days per week
(C) Healthful diet including fruits and vegetables
(D) Smoking cessation
(E) Stress management and relaxation techniques

Item 3

A 62-year-old woman is evaluated for a 4-hour episode of dizziness. Upon arising from bed in the morning, she noted the abrupt onset of a spinning sensation and imbalance. She has moderate nausea but no vomiting. Symptoms are markedly accentuated when she positions her head backward or forward, such as when bending down to tie her shoe. She reports no dysarthria, diplopia, dysphagia, weakness, numbness, tinnitus, headache, recent head trauma, otalgia, or recent upper respiratory tract infection. She had a similar episode several years ago. Medical history is remarkable for osteoporosis. Her medications are alendronate, calcium, and vitamin D.

On physical examination, the patient is afebrile, blood pressure is 137/84 mm Hg and pulse rate is 78/min without orthostasis, and respiration rate is 13/min. BMI is 25. Tympanic membranes, external auditory canals, and gross auditory acuity are normal. Cardiopulmonary and neurologic examinations are normal. The Dix-Hallpike maneuver results in mild vertigo with nausea, and after 10 seconds, there are five beats of upbeat nystagmus with a rotatory component with the upper pole of the eyes beating toward the lower ear. The nystagmus lasts for 10 seconds and then abates.

Which of the following is the most appropriate next step in management?

(A) Diazepam
(B) Epley maneuver
(C) Meclizine
(D) Vestibular rehabilitation therapy

Item 4

A 52-year-old woman is seen for preoperative evaluation for open total abdominal hysterectomy. She is an active smoker with a 30-pack-year smoking history but no cough, dyspnea, or chest pain. She reports no daytime fatigue and has never been told she snores or stops breathing in her sleep. She exercises by running for 2 miles on a treadmill every other day. She takes no medications.

On physical examination, respiration rate is 14/min. Oxygen saturation on pulse oximetry is 98% with the patient breathing ambient air. BMI is 28. Cardiovascular examination is normal. Lungs are clear to auscultation and percussion. There is no clubbing or cyanosis of the digits.

In addition to smoking cessation counseling, which of the following is the most appropriate diagnostic test to perform next?

(A) Chest radiography
(B) Chest radiography and spirometry
(C) Chest radiography, spirometry, and arterial blood gas analysis
(D) No further diagnostic tests

Item 5

A 42-year-old woman is evaluated for a 6-day history of right elbow pain that started after lifting a heavy box. The pain is often worse at night and sometimes radiates to the wrist. Her medical and family histories are unremarkable. Her only medication is ibuprofen as needed for the elbow pain, and she has no allergies.

On physical examination, vital signs are normal. There is tenderness over the right lateral epicondyle, but there is normal elbow range of motion and no elbow swelling.

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Pain is elicited with resisted wrist extension. The neck and shoulder examinations are normal.

Which of the following is the most appropriate management?

(A) Advise limiting pain-inducing activities
(B) Evaluation for surgical treatment
(C) Glucocorticoid injection
(D) MRI of the right elbow

Item 6

In recent patient satisfaction surveys, a clinical laboratory scored poorly with regard to waiting times for patients. A quality improvement team is created to study the problem and reduce patient waiting times.

Which of the following quality improvement methods would be most useful to help reduce waiting times?

(A) Define, Measure, Analyze, Improve, Control (DMAIC) process
(B) Lean
(C) Plan, Do, Study, Act (PDSA) cycle
(D) Six Sigma

Item 7

A 24-year-old woman is evaluated for severe cramps associated with her menstrual periods. The cramps have worsened over the past year, and the discomfort is severe enough that she has periodically missed work. She reports no abnormal vaginal discharge. Menses are unchanged from her baseline pattern. She has tried ibuprofen and naproxen for pain relief, but these medications cause stomach upset. The patient is sexually active with several male partners. She has no history of sexually transmitted infection and is up to date with her immunizations and gynecologic screening. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. On pelvic examination, there is no cervical motion tenderness, adnexal tenderness, masses, or abnormal discharge. The cervix appears normal. Bimanual examination is unremarkable, and the remainder of the physical examination is normal.

A urine pregnancy test is negative. Tests for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are negative.

Which of the following is the most appropriate treatment for this patient's dysmenorrhea?

(A) Combined estrogen-progestin contraceptive pill
(B) Depot medroxyprogesterone acetate
(C) Low-dose selective serotonin reuptake inhibitor
(D) Progestin-only contraceptive pill
(E) Tranexamic acid

Item 8

A 91-year-old woman with advanced dementia is examined in her extended-care facility for a routine evaluation. She is nonverbal, incontinent of urine and stool, largely bedbound, and dependent on others for all activities of daily living. The patient's nurse notes that the patient has continued to lose weight despite being actively fed but raises no other concerns. Medical history is significant for hypertension, and her only medication is amlodipine.

On physical examination, blood pressure is 132/87 mm Hg; other vital signs are normal. The patient appears cachectic with temporal wasting. She is awake but is unresponsive to questions. Mucous membranes are moist. She does not appear to have any pain. There are mild early contractures of her ankles and hips. The remainder of the examination, including skin examination, is unremarkable.

Which of the following is the most appropriate intervention for preventing pressure ulcers in this patient?

(A) Alternating-air mattress
(B) Enteral nutrition
(C) Foam mattress overlay
(D) Frequent repositioning

Item 9

A 75-year-old woman is evaluated during a follow-up examination. Medical history is significant for hypertension, type 2 diabetes mellitus, and end-stage kidney disease. She has been treated with hemodialysis for the past year and is not considered a candidate for kidney transplantation. She is currently asymptomatic. Family history is significant for a maternal aunt who was diagnosed with breast cancer at age 70 years. Current medications are lisinopril, nifedipine, sevelamer, aspirin, and regular and neutral protamine Hagedorn (NPH) insulin.

On physical examination, the patient is afebrile, blood pressure is 142/76 mm Hg, and pulse rate is 82/min. An arteriovenous hemodialysis graft is present in the left upper extremity. The remainder of her examination is unremarkable.

The patient's last mammogram, performed 1 year ago, was normal.

Which of the following is the most appropriate management of this patient's breast cancer screening?

(A) Begin annual mammography with breast MRI
(B) Continue annual mammography
(C) Switch to biennial mammography
(D) Discontinue breast cancer screening

Item 10

A 17-year-old teenager is evaluated during an office visit. She is brought in by her mother who is concerned about her focus on diet and weight. The patient states that she believes that she is obese and feels as though she needs to diet to achieve a more appropriate body weight. She also reports exercising on a daily basis to help her lose weight. Dietary history suggests that most of the time she consumes very little food, but at least twice per week she will eat large amounts of high-calorie desserts over the course of 1 to 2 hours. She describes feeling guilty after doing so and will make herself vomit. Medical history is otherwise

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unremarkable, although she indicates that her menstrual periods are highly irregular.

On physical examination, vital signs are normal. BMI is 23. The parotid glands are enlarged, but the remainder of the examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Anorexia, purging subtype
(B) Anorexia, restricting subtype
(C) Binge eating disorder
(D) Bulimia nervosa

Item 11

A 28-year-old man is evaluated for a 3-week history of "stuffiness," decreased hearing, and discomfort in his left ear. He has no other symptoms and otherwise feels well except for mild nasal congestion that he attributes to seasonal allergies. Medical history is unremarkable, and he takes no medications.

On physical examination, temperature is normal, blood pressure is 122/62 mm Hg, pulse rate is 90/min, and respiration rate is 11/min. Examination of the left ear is shown. There is no lymphadenopathy. The remainder of the examination is unremarkable.



Which of the following is the most appropriate next step in management?

(A) Amoxicillin
(B) Neomycin, polymyxin B, and hydrocortisone ear drops
(C) Tympanostomy tube placement
(D) Clinical observation

Item 12

An 86-year-old woman is evaluated in her assisted-living facility for pain. Four weeks ago, she developed herpetic lesions on her right posterior thorax in a T7 distribution. She was treated with acyclovir, and the lesions healed; however, she has persistent severe burning pain. The pain is so severe that she is unable to leave her bed to attend meals. Medical history is remarkable for hypertension, mild cognitive impairment, and osteoporosis. She ambulates short distances but uses a walker for longer distances. Medications are amlodipine and as-needed acetaminophen. She cannot tolerate opioid medications because they have caused delirium in the past.

On physical examination, the patient is afebrile, blood pressure is 140/86 mm Hg, pulse rate is 62/min, and respiration rate is 14/min. BMI is 18. Examination of the back reveals allodynia and hyperalgesia in the right posterior T7 dermatome. All zoster skin lesions have resolved. On neurologic examination, she exhibits short-term memory impairment, which her family reports is her baseline. The remainder of the examination is unremarkable.

Which of the following medications is the most appropriate pharmacologic therapy for this patient's pain?

(A) Fentanyl patch
(B) Oral gabapentin
(C) Oral tramadol
(D) Topical lidocaine

Item 13

A 26-year-old woman is evaluated for a 3-day history of pain and redness of the left eye. She also notes increased pain when looking at bright objects with that eye. Her symptoms have been progressively worsening since onset. Medical history is unremarkable, although she reports generalized fatigue, chronic low back pain, and stiffness over the past several months. The back pain awakens her at night and improves throughout the day with activity. Her only medication is as-needed ibuprofen for her back pain, which provides some relief.

On physical examination, temperature is normal, blood pressure is 126/64 mm Hg, and pulse rate is 54/min. BMI is 27. On ophthalmologic examination, extraocular muscle movements and visual acuity are normal. There is pronounced redness of the sclera surrounding the border where it meets the cornea in the left eye. The left pupil is constricted, and there is photophobia with illumination of the left eye. The right eye is normal. The physical examination is normal except for tenderness to palpation over the buttocks in the region of the sacroiliac joints.

Which of the following is the most likely diagnosis?

(A) Corneal ulcer
(B) Episcleritis
(C) Scleritis
(D) Uveitis

Item 14

A 49-year-old woman is evaluated during a follow-up visit. She is overweight and has hypertension and type 2 diabetes mellitus, both of which are well controlled. For several years, she has attempted to lose weight through various commercial diets; dietician-monitored, calorie-restricted diets; and physical activity. She has worked with a behavioral therapist, and although she has not achieved weight

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loss, her weight has remained stable. She exercises 30 minutes daily. Medical history is also remarkable for glaucoma, generalized anxiety disorder, and chronic constipation. Medications are lisinopril, metformin, timolol eye drops, and sertraline.

On physical examination, temperature is normal, blood pressure is 128/74 mm Hg, pulse rate is 70/min, and respiration rate is 12/min. BMI is 29. Waist circumference is 92 cm (36 in). Head, neck, lung, and heart examinations are normal. The abdomen is obese without striae.

In addition to continuing calorie restriction and exercise, which of the following is the most appropriate management to help this patient achieve weight loss?

(A) Lorcaserin
(B) Orlistat
(C) Phentermine-topiramate
(D) Roux-en-Y gastric bypass

Item 15

A 94-year-old woman is brought to the office by her two daughters, who are concerned about her ability to drive. The patient lives independently and drives fewer than 30 miles per week, only during daylight hours. She has no history of traffic tickets or accidents. She feels that she is a very capable driver, although her daughters cite several "near misses," which she dismisses as irrelevant. Medical history is remarkable for mild cognitive impairment, osteoarthritis, and macular degeneration. She sees an ophthalmologist every 3 months, and her corrected vision was stable at her last visit, allowing her to pass the driver's vision test with a restriction to daytime driving at low speeds. She consumes alcohol only occasionally and does not smoke. Her only medication is as-needed acetaminophen.

On physical examination, vital signs and general examination are normal. On musculoskeletal examination, the lateral range of motion of her neck is mildly limited. Gait is antalgic, and she is slow to arise from a seated position. Mini-Mental State Examination score is 24/30.

Which of the following is the most appropriate management of this patient's driving?

(A) Accept the patient's assessment of her ability to drive safely
(B) Advise the patient that she should no longer drive
(C) Ask the patient's ophthalmologist for an assessment of her ability to drive safely
(D) Obtain formal neuropsychiatric testing

Item 16

A 35-year-old woman is evaluated for a several-year history of multiple symptoms, including chronic headaches, dizziness, lightheadedness, shortness of breath, back pain, insomnia, generalized abdominal pain, and numbness. She reports no depressed mood, anhedonia, or problems with concentration or memory. She has been seen by multiple physicians for her symptoms and has been treated in the past with paroxetine, sumatriptan, gabapentin, and an as-needed albuterol inhaler without improvement of her symptoms.

Review of previous records shows laboratory studies significant for normal comprehensive metabolic profile, complete blood count, thyroid function tests, and antinuclear antibody test. Other studies include an unremarkable mammogram, chest radiograph, abdominal and pelvic CT scans, and MRI of the lumbar spine. Upper endoscopy is unremarkable, and pulmonary function tests are normal.

Medical history is significant for depression in college. She does not smoke, drink alcohol, or use illicit drugs. She is currently unemployed and on disability due to her symptoms. She reports allergies to multiple medications, including penicillin, sulfa-containing drugs, and macrolide and fluoroquinolone antibiotics. Medications are as-needed ibuprofen and multiple herbal preparations.

Physical examination is unremarkable.

Which of the following is the most appropriate management of this patient?

(A) Brain MRI
(B) Citalopram
(C) Cognitive-behavioral therapy
(D) Evaluation by a neurologist
(E) Follow-up in 6 months

Item 17

A 56-year-old woman is evaluated for a painless lump in her right breast that she first noticed 6 weeks ago. She has not had any nipple discharge. She has no history of breast lumps or abnormal mammograms; her last screening mammogram was 8 months ago and was negative. Medical history is unremarkable. She experienced menarche at age 12 years and menopause at age 53 years, and she is gravida 4, para 3. There is no breast, ovarian, or colon cancer in her family history. She takes no medications.

On physical examination, she is afebrile, blood pressure is 134/82 mm Hg, pulse rate is 72/min, and respiration rate is 12/min. BMI is 25. Examination of the breasts reveals a firm, nontender, 1-cm mass on the right upper outer quadrant 3 cm from the areolar edge. There is no nipple discharge or skin change, and no supraclavicular or axillary lymphadenopathy.

A mammogram is obtained and is read as benign (Breast Imaging Reporting and Data System [BI-RADS] category 1).

Which of the following is the most appropriate management?

(A) Breast MRI
(B) Clinical reassessment in 4 weeks
(C) Core needle biopsy
(D) Resume regular mammographic screening

Item 18

An 88-year-old woman living in a nursing home is evaluated for worsening dizziness, weakness, and gait unsteadiness of several weeks' duration. She also reports occasional vague lightheadedness and feeling like her legs are "wobbly." She reports no vertigo, chest pain, palpitations,

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H CONT.

loss of consciousness, leg or arm weakness, numbness, tingling, tinnitus, headaches, neck or other joint pain, or falls or head trauma. She was provided with a cane, but she feels too weak to use it. Medical history is also remarkable for cataract, hearing loss, osteoporosis, and hypertension. Medications are alendronate, lisinopril, and vitamin D.

On physical examination, the patient is alert and oriented. She is afebrile. Blood pressure is 142/70 mm Hg supine and 136/70 mm Hg standing, precipitating symptoms of lightheadedness; pulse rate is 86/min supine and 88/min standing; and respiration rate is 16/min. BMI is 20. On neurologic examination, she has 20/200 vision, diminished hearing, and 4/5 motor strength in both upper and lower extremities. The remainder of the examination is normal.

Laboratory studies reveal a hemoglobin level of 11.6 g/dL (116 g/L) and normal vitamin B_{12} and thyroid-stimulating hormone levels. Results of a comprehensive metabolic profile are normal.

Electrocardiogram shows normal sinus rhythm with first-degree atrioventricular block and left ventricular hypertrophy.

Referrals are made to address her auditory and visual impairments.

Which of the following is the most appropriate additional management?

(A) CT scan of the head
(B) 24-Hour ambulatory electrocardiography
(C) Physical therapy
(D) Provide a walker

H Item 19

A 66-year-old man is evaluated following a multilevel lumbar spine laminectomy and fusion 2 days ago. He tolerated general anesthesia well and had approximately 1200 mL of intraoperative blood loss. Postoperative recovery has been uneventful. He has been fully participating in physical therapy without symptoms of lightheadedness, shortness of breath, or chest pain. His surgical site pain is well controlled and gradually receding. Medical history is notable for hypertension, hyperlipidemia, anemia of chronic disease, and coronary artery disease with placement of a bare metal stent 4 years ago. Medications are carvedilol, atorvastatin, aspirin, and as-needed oxycodone and acetaminophen.

On physical examination, the patient is afebrile. Blood pressure is 140/86 mm Hg, and pulse rate is 60/min. The surgical site is intact with no surrounding erythema, tenderness, or induration. The remainder of the examination is normal.

Laboratory studies are significant for a hemoglobin level of 9.1 g/dL (91 g/L). Prior to surgery, the hemoglobin level was 13.1 g/dL (131 g/L). Leukocyte count and platelet count are normal.

Which of the following is the most appropriate management of this patient's anemia?

(A) Administer intravenous iron
(B) Transfusion of one unit of packed red blood cells
(C) Transfusion of two units of packed red blood cells
(D) Clinical observation

Item 20

A 68-year-old man is evaluated for a 3-month history of pain on the superior aspect of the right shoulder. The pain developed insidiously and has progressively worsened. He reports no trauma or other symptoms. Medical history is unremarkable. The patient has tried both acetaminophen and ibuprofen, with only minimal pain relief.

On physical examination, the patient is afebrile, blood pressure is 134/84 mm Hg, pulse rate is 92/min, and respiration rate is 16/min. BMI is 28. The right shoulder is normal in appearance. Pain is reproduced with adduction of the right arm across the body. The painful arc test and drop-arm test are negative. There is full active and passive range of motion; strength is 5/5 throughout the right arm. The remainder of the examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Acromioclavicular joint degeneration
(B) Adhesive capsulitis
(C) Rotator cuff tear
(D) Supraspinatus tendinitis

Item 21

A 77-year-old man is evaluated in follow-up for prostate cancer. He is asymptomatic and feels well. He was diagnosed with high-grade prostate cancer 3 years ago and was treated with external-beam radiation therapy. Since that time, he has undergone regular surveillance.

His most recent serum prostate-specific antigen level rose from undetectable to 120 ng/mL (120 µg/L). A subsequent abdominopelvic CT scan showed an increase in regional lymphadenopathy and multiple sclerotic bony lesions in the visualized pelvis and spine.

The patient has been actively engaged in his medical care and has expressed a desire to be made aware of all information about his health status. The patient has scheduled this visit to discuss the results of his prostate cancer surveillance testing, and the physician indicates to the patient that, unfortunately, he has bad news to convey.

Which of the following is the most appropriate approach to conveying this news to the patient?

(A) Explain that the planned surveillance has done what was intended and that it has led to the finding of possible recurrent tumors
(B) Indicate that there are several abnormal lesions in his bones that will require further evaluation
(C) Note that the cancer has likely returned but that hormonal therapy and chemotherapy are usually effective treatments
(D) State that the cancer has returned

Item 22

A 59-year-old man is evaluated during a health maintenance visit. He is asymptomatic. He has a 35-pack-year smoking history, but he quit smoking 5 years ago. He takes no medications.

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Vital signs and the results of the physical examination are normal.

Which of the following is the most appropriate screening test to obtain?

(A) Abdominal ultrasonography
(B) Chest radiography
(C) Low-dose chest CT
(D) Spirometry

Item 23

A 78-year-old man is evaluated for low back pain that has worsened over the past 24 hours. The patient has had chronic low back pain localized to the lumbar spine without radiation for many years. He reports no trauma but notes that his low back pain has rapidly increased in intensity and that he now has a "pins and needles" sensation over the inner thighs and intermittent radiation of pain down both legs. Treatment with over-the-counter analgesics and anti-inflammatory agents usually resolves his pain, but these medications have not helped his current symptoms. He has not had fever, chills, or other systemic symptoms. He has had urinary retention but no bowel incontinence. Medical history is significant for hypertension and hyperlipidemia. Current medications are hydrochlorothiazide, atorvastatin, and as-needed acetaminophen and naproxen.

On physical examination, temperature is 37.1 °C (98.7 °F), blood pressure is 148/70 mm Hg, and pulse rate is 95/min. BMI is 26. The general medical examination is unremarkable. On musculoskeletal examination, the major lower extremity muscle groups show normal bulk and tone with normal or slightly decreased strength. Neurologic examination shows a decrease in anal tone and saddle anesthesia. The patellar reflexes are normal, but ankle reflexes are absent bilaterally.

MRI of the lumbosacral spine shows vertebral endplate osteophytosis, facet joint hypertrophy, and thickening of the ligamentum flavum resulting in narrowing of the spinal canal at multiple levels but without evidence of mass or hemorrhage.

Which of the following is the most appropriate management?

(A) Epidural glucocorticoid injection
(B) High-dose intravenous glucocorticoid therapy
(C) Lumbar puncture
(D) Surgical evaluation

Item 24

A 55-year-old man is evaluated for the gradual onset of erectile dysfunction over the past year. He reports a satisfying marriage, but during most sexual encounters, he is unable to achieve an erection that is satisfactory for vaginal penetration. He has been spending longer hours at work, and he no longer exercises regularly. Nonetheless, he describes his mood as excellent and continues to enjoy time with his family. He sleeps well, and his energy level is good. He reports no chest pain or dyspnea. He does not have nocturnal erections. He does not smoke cigarettes.

On physical examination, the patient appears alert and comfortable. Blood pressure is 134/60 mm Hg. BMI is 32. Cardiopulmonary examination is normal. The penis, testicles, and prostate are normal.

Which of the following is the most appropriate next step in management?

(A) Intraurethral alprostadil
(B) Marriage counseling
(C) Venlafaxine
(D) Weight loss

Item 25

An 80-year-old man was hospitalized 1 week ago for a 5-day history of acute leg ischemia treated with angioplasty and stenting. He is now asymptomatic. The patient has a history of stage 3 chronic kidney disease and hypertension that is well controlled with diltiazem and lisinopril. Other medications are aspirin and clopidogrel.

On physical examination, the patient is afebrile, and blood pressure is 130/78 mm Hg. The remainder of the examination is unremarkable.

Laboratory studies:

Alanine aminotransferase	20 U/L
Total cholesterol	170 mg/dL (4.40 mmol/L)
LDL cholesterol	97 mg/dL (2.51 mmol/L)
HDL cholesterol	44 mg/dL (1.14 mmol/L)
Serum creatinine	1.8 mg/dL (159 µmol/L)
Triglycerides	147 mg/dL (1.67 mmol/L)
Estimated glomerular filtration rate	35 mL/min/1.73 m^2

Which of the following is the most appropriate therapy for secondary prevention of cardiovascular disease in this patient?

(A) High-intensity rosuvastatin
(B) Moderate-intensity rosuvastatin
(C) Niacin
(D) No additional treatment

Item 26

A physician reviews a study in which investigators attempted to determine whether tadalafil improved erectile function following radiation treatment for prostate cancer. The researchers reviewed the records of 940 patients with prostate cancer who had undergone radiation therapy. Three hundred patients received daily tadalafil following radiation, and 640 patients did not receive tadalafil. There was no significant difference in the overall International Index of Erectile Function scores ($P < 0.15$) between the two groups.

Which of the following would be the most appropriate outcome measure for this study?

(A) Confidence interval
(B) Number needed to treat
(C) Odds ratio
(D) Relative risk

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Item 27

An 88-year-old man is evaluated at an assisted-living facility. Staff members have noticed that the patient seems more withdrawn than usual, is less interactive with other residents, and no longer attends social functions. At times, he seems confused and answers questions nonsensically or has difficulty navigating simple conversations. At other times, he seems normal and cheerful. The staff has not observed any crying spells. He appropriately manages his own medications and finances. There have been no recent changes in his medications. He has had no recent falls, illness, or fever.

On physical examination, vital signs are normal. The patient is appropriately conversant. The general medical examination is unremarkable. On neurologic examination, Mini-Mental State Examination score is 25/30, which is unchanged over the past 18 months. A two-question depression screen is negative. The remainder of the neurologic examination is unremarkable.

Which of the following is the most appropriate management of this patient?

(A) Donepezil
(B) PHQ-9 depression assessment
(C) Whispered voice test
(D) Clinical observation

Item 28

A 79-year-old man is evaluated for a 3-month history of right hip pain. He points to the center of his right buttock when asked to identify the location of the pain. He has no radicular symptoms. He reports no focal trauma but believes his symptoms began after he stepped off a curb that was higher than anticipated. Medical history is otherwise unremarkable. His only medication is as-needed acetaminophen for pain.

On physical examination, vital signs are normal. The general medical examination is unremarkable. There is no tenderness to palpation over the lateral right hip, and he notes mild discomfort when the "dimple" areas of the posterior surface of the buttocks are palpated. There is no pain with passive range of motion of both hips. Straight-leg raise test is negative. When either hip is flexed, abducted, and externally rotated with downward pressure applied to the knee, his pain is reproduced.

Which of the following is the most likely diagnosis?

(A) Hip joint osteoarthritis
(B) Piriformis syndrome
(C) Sacroiliitis
(D) Trochanteric bursitis

Item 29

A 26-year-old woman is evaluated during a routine follow-up visit. She recently underwent direct-to-consumer genetic testing that offered risk screening for more than 200 different conditions. Her results indicate that her genetic breast cancer risk is 52.5% greater than that of the average woman, and she is interested in discussing what should be done next. She feels well and has no symptoms. Three-generation family history is negative for breast and ovarian cancer. She takes no medications.

The physical examination is normal.

Which of the following is the most appropriate next diagnostic test?

(A) Biennial breast MRI screening
(B) *BRCA* genetic testing
(C) Monthly breast self-examination
(D) No further testing

Item 30

H

An 88-year-old woman with severe emphysema is evaluated in the hospital for dyspnea. This is her seventh hospitalization in the last 6 months for similar symptoms. Her ability to perform basic daily activities between hospitalizations is markedly limited, and she reports uncomfortable shortness of breath both at rest and with minimal activity. Medical history is otherwise significant only for hypertension. Medications are tiotropium, mometasone/formoterol, as-needed albuterol, hydrochlorothiazide, and supplemental oxygen.

On physical examination, the patient is notably dyspneic with increased work of breathing at rest. She is afebrile, blood pressure is 148/84 mm Hg, pulse rate is 98/min, and respiration rate is 22/min. Oxygen saturation is 86% breathing 6 L of oxygen by nasal cannula. BMI is 17. There is no jugular venous distention. The lungs show markedly decreased air movement but no focal findings. There is trace bipedal edema. The remainder of the examination is unremarkable.

Following extensive discussion with the patient, she indicates a desire to pursue a palliative approach with a focus on symptom control given her advanced disease and lack of response to maximal medical therapy.

Which of the following is the most appropriate treatment of this patient's dyspnea?

(A) Nebulized lidocaine
(B) Nebulized morphine
(C) Oral lorazepam
(D) Oral morphine

Item 31

H

A 68-year-old man is evaluated in the hospital for a right intertrochanteric fracture sustained in a mechanical fall. He reports right hip pain but no other symptoms. He has hypertension and type 2 diabetes mellitus and was in his usual state of health prior to the fall. He checks his blood glucose level several times daily; his average blood glucose level is 150 mg/dL (8.3 mmol/L), with a low of 92 mg/dL (5.1 mmol/L) and a high of 208 mg/dL (11.5 mmol/L). Surgical repair is scheduled for tomorrow at 7:00 AM with an anticipated length of surgery of 1.5 hours; use of spinal anesthesia is planned. Medications are enalapril; extended-release metformin; insulin glargine, 20 units nightly; and insulin lispro, 8 units with each meal. It is 8:00 PM, and

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H CONT.

the patient took his usual morning medications and insulin lispro prior to dinner but has not yet taken insulin glargine.

On physical examination, vital signs are normal. An ecchymosis is noted over the right hip. The right leg is externally rotated. The remainder of the examination is unremarkable.

Laboratory studies are significant for a hemoglobin A_{1c} level of 8.2% and a plasma glucose level of 182 mg/dL (10.1 mmol/L).

In addition to discontinuing metformin, which of the following is the most appropriate preoperative diabetic management for this patient?

(A) Administer insulin glargine as usual; withhold scheduled insulin lispro
(B) Continue both insulin glargine and insulin lispro uninterrupted
(C) Stop insulin glargine and insulin lispro; start intravenous insulin infusion
(D) No further insulin until after surgery

Item 32

A 26-year-old man is evaluated for a 3-month history of depressed mood, poor concentration, decreased energy, increased sleep, and weight gain. He reports missing many days at work and that his work performance has lagged. He has no suicidal ideation. He states that his current symptoms differ markedly from his usual state of being "highly upbeat and energetic" and having high job performance. He has experienced several 30- to 40-day periods of high energy during which he sleeps little and makes "bad choices" (such as spending sprees and "one-night stands"). He has not experienced hallucinations. Medical history is notable for treatment of depression during college with a 6-month course of sertraline. He stopped the drug when he felt "energetic." He is currently taking no medications.

Physical examination is unremarkable.

Laboratory studies are normal.

Which of the following is the most appropriate treatment?

(A) Desipramine
(B) Paroxetine
(C) Quetiapine
(D) Venlafaxine

H

Item 33

A 66-year-old man who was admitted to the hospital after undergoing urgent sigmoid colectomy for a perforated diverticulum is evaluated for co-management of his medical problems. He tolerated general anesthesia well and had no immediate perioperative complications. He is fully awake, alert, and breathing comfortably with adequate control of postoperative pain. Additional history provided by his wife indicates that he snores loudly when sleeping and occasionally seems to gag and stop breathing. He reports no daytime somnolence. Medical history includes hypertension and hyperlipidemia. Medications are lisinopril, simvastatin, and as-needed oxycodone.

On physical examination, blood pressure is 156/94 mm Hg, and respiration rate is 18/min. Oxygen saturation on pulse oximetry is 97% with the patient breathing ambient air. BMI is 45. Cardiovascular examination is normal. The lungs are clear to auscultation. The left lower quadrant surgical incision is intact with minimal tenderness to palpation; bowel sounds are present, and the abdomen is not distended.

Laboratory studies on admission were significant for a hemoglobin level of 14.6 g/dL (146 g/L), a leukocyte count of 18,000/μL (18×10^9/L) with 95% neutrophils, and a normal basic metabolic panel.

In addition to continuous pulse oximetry, which of the following is the most appropriate respiratory management of this patient?

(A) Insert a nasogastric tube
(B) Keep the head of the bed elevated at 30 degrees
(C) Start nebulized albuterol
(D) Start nocturnal continuous positive airway pressure ventilation

Item 34

A 65-year-old man is scheduled to undergo staged bilateral cataract extractions under conscious sedation. Medical history is notable for hypertension and asthma. Medications are amlodipine, an albuterol inhaler as needed, and a fluticasone inhaler.

On physical examination, blood pressure is 122/74 mm Hg. The cardiac examination is normal. The lungs are clear.

Laboratory studies from 1 year ago show normal serum electrolyte and serum creatinine levels.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Chest radiography
(B) Complete blood count, prothrombin time, and activated partial thromboplastin time
(C) Electrocardiography
(D) Serum electrolytes and creatinine
(E) No diagnostic studies

Item 35

A 29-year-old woman is evaluated for a 2-week history of a tender lump in the left breast. She has not noticed skin changes, swollen glands, or nipple discharge, and there is no history of trauma to the breast. She had a similar problem last year with a breast biopsy that was negative for cancer and was told she has fibrocystic breasts. She takes a monocyclic oral contraceptive and her menses are regular, with her last menstrual period starting 1 week ago. She underwent menarche at age 12 years, and she has never been pregnant. She has no family history of breast cancer.

On physical examination, all vital signs are normal. BMI is 25. Examination of the breasts reveals a 2-cm round, mobile, tender mass in the upper outer quadrant of the left breast. There are no skin changes and no supraclavicular or axillary lymphadenopathy. The remainder of the physical examination is unremarkable.

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Which of the following is the most appropriate management?

(A) Diagnostic ultrasonography
(B) Digital diagnostic mammography
(C) Fine needle aspiration biopsy
(D) Stop hormonal contraception

Item 36

A 39-year-old woman presents for a second opinion following a recent diagnosis of systemic exertion intolerance disease (formerly known as chronic fatigue syndrome), which was made after a thorough evaluation. Her symptoms are interfering with her daily personal and professional activities. She reports generalized myalgia, arthralgia, difficulty concentrating, unrefreshing sleep, and chronic headaches but no anhedonia or thoughts of self-harm. Review of previous records shows a normal physical examination. Complete blood count, erythrocyte sedimentation rate, thyroid function tests, electrolytes, kidney function tests, glucose level, creatine kinase level, serum creatinine level, liver chemistry studies, antinuclear antibody test, and urine drug screen were all normal within the past several months. A sleep study and imaging studies of the chest, abdomen, and pelvis were normal. Medical history is significant for hypertension. Family history is remarkable for hypertension in both parents. Her only medication is ramipril.

Physical examination is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Citalopram
(B) Cognitive-behavioral therapy
(C) Methylphenidate
(D) Valacyclovir

Item 37

A 28-year-old woman visits to discuss her contraceptive options. She is sexually active and is in a monogamous relationship with a new partner. She has been using depot medroxyprogesterone acetate for the past 2 years but has unpredictable breakthrough bleeding, which she finds unacceptable; in addition, she reports mood changes and weight gain. She does not plan to have children for several years and is interested in trying birth control pills. Medical history is significant for episodic migraine associated with photophobia and visual aura. She has never smoked. Her only medication is as-needed sumatriptan.

On physical examination, vital signs are normal. BMI is 21. The general medical examination is unremarkable.

In addition to recommending condom use to reduce risk of sexually transmitted infections, which of the following is the most appropriate contraceptive method to recommend?

(A) Estrogen-progestin oral contraceptive
(B) Estrogen-progestin vaginal ring
(C) Intrauterine device
(D) Progestin-only oral contraceptive
(E) Progestin subcutaneous implant

Item 38

A 65-year-old man is evaluated during a follow-up examination. The patient is asymptomatic. He expresses interest in being screened for prostate cancer with a new screening test. The patient brings in a printout of a study of the screening test, which used a randomly selected population of men and divided them into two groups: one that was screened for prostate cancer using the new test and another that did not undergo screening and in whom any cases of prostate cancer were diagnosed by detection of symptoms and signs of the disease. The researchers, including outcome assessors, were blinded.

The study found that prostate cancer survival was increased by 2 years in the screened group compared with the non-screened group. The study mostly included healthy white men with an average age of 66 years. There was little crossover between groups. In the group that was screened for prostate cancer, there were more cases of prostate cancer diagnosed overall, most of which were low-grade cancers. In the group that was not screened, there were significantly fewer cases of prostate cancer diagnosed overall; however, those that were diagnosed were more aggressive.

Which of the following is the most likely cause of the increased survival in the screen-detected cohort?

(A) Contamination bias
(B) Length-time bias
(C) Observer bias
(D) Selection bias

Item 39

A 48-year-old man is evaluated for a 2-day history of right anterior knee pain and swelling. The pain began suddenly and has increased in intensity. He currently rates his pain as an 8 on a 10-point scale. He has no knee instability and reports no fever or chills. He has no history of trauma and has never had this problem before. Other than his right knee pain and swelling, he feels well. He is employed as a carpet layer. His only medication is ibuprofen, which provides minimal relief.

On physical examination, vital signs are normal. BMI is 28. On examination of the right knee, there is a palpable fluid collection that is located anterior to the patella. The right knee has full range of motion. There is no medial or lateral joint line tenderness or laxity with varus or valgus forces. Anterior drawer, posterior drawer, and Lachman tests are all negative.

Which of the following is the most appropriate next step in management?

(A) Aspiration
(B) Compression
(C) Glucocorticoid injection
(D) Right knee radiographs
(E) Ultrasound

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Item 40

A 35-year-old woman is scheduled for right carpal tunnel release to be performed with local anesthesia and mild sedation. Anticipated duration of surgery is less than 1 hour. She is physically active and otherwise feels well with no lightheadedness, weight changes, fatigue, or shortness of breath. She received a living-related kidney transplant 5 years ago for polycystic kidney disease; she also has hypertension. Medications are amlodipine, tacrolimus, mycophenolate, and prednisone, 5 mg/d. She has not had any recent changes in her medications.

On physical examination, she is afebrile. Blood pressure is 128/80 mm Hg, and pulse rate is 68/min. Except for paresthesias in the right hand following the distribution of the median nerve, the physical examination is unremarkable.

Laboratory studies show a normal basic chemistry panel and kidney function tests.

Which of the following is the most appropriate preoperative management of this patient's glucocorticoid therapy on the day of surgery?

(A) Continue current prednisone dose
(B) Double the current prednisone dose
(C) Substitute intravenous hydrocortisone, 50 mg, for daily prednisone
(D) Withhold prednisone

Item 41

An 81-year-old man is admitted to the hospital with an acute coronary syndrome. Immediate coronary angiography with possible angioplasty and stent placement is indicated. The patient has mild dementia treated with donepezil. He is married, and his wife is his designated surrogate decision maker. The patient is informed of the risks, benefits, and alternatives to the procedure. He expresses understanding of these elements in basic terms and is able to reflect back the risks, benefits, and alternatives to the procedure. He consents to coronary angiography, and when asked again, his decision is unchanged. His wife is currently unavailable.

Which of the following is the most appropriate next step?

(A) Obtain consent from the patient's spouse
(B) Perform a Mini-Mental State Examination
(C) Proceed with coronary angiography
(D) Request that a colleague assess and confirm the patient's decision-making capacity

Item 42

A 27-year-old man is evaluated in the emergency department for dull, throbbing, left testicular pain occurring over the past week. He also notes urinary frequency and dysuria, but no penile discharge. He reports no back pain, weight loss, or fever. Medical history is unremarkable. His only medication is ibuprofen, which he takes as needed for pain. He is sexually active with several different partners and uses barrier protection only intermittently. He reports no testicular trauma.

On physical examination, blood pressure is 126/64 mm Hg, and pulse rate is 90/min. BMI is 22. The penis appears normal without discharge at the meatus. The left testicle is boggy and exquisitely tender to palpation over the superior pole. The testicular pain lessens with elevation of the testis.

Laboratory studies reveal a normal complete blood count, and urinalysis with microscopy shows 2 leukocytes/hpf.

Which of the following is the most likely diagnosis?

(A) Epididymitis
(B) Testicular torsion
(C) Urinary tract infection
(D) Varicocele

Item 43

A 64-year-old woman is evaluated for difficulty controlling her urine. The patient works and maintains a very active lifestyle; the urinary leakage is restricting her activities. She needs to wear pads because of involuntary loss of urine with coughing, sneezing, and laughing, and occasionally with physical exertion. There is no dysuria or increased urinary frequency. She does not smoke and does not drink alcoholic beverages. Medical history is remarkable for hypertension, and her only medication is lisinopril.

On physical examination, temperature is normal, blood pressure is 130/78 mm Hg, pulse rate is 72/min, and respiration rate is 14/min; BMI is 29. General examination is unremarkable. Pelvic examination is normal except for mild anterior wall prolapse.

Urinalysis is normal.

In addition to suggesting weight loss, which of the following is the most appropriate management?

(A) Oxybutynin
(B) Pelvic floor muscle training
(C) Postvoid residual urine volume measurement
(D) Prompted voiding
(E) Urodynamic study

Item 44

A 26-year-old woman is evaluated during a routine examination. Her last Pap smear was performed 1 year ago and was normal. She has received a complete human papillomavirus (HPV) quadrivalent vaccine series. Medical history is unremarkable. Family history is noncontributory. She takes no medications.

On physical examination, temperature is normal, blood pressure is 110/72 mm Hg, and pulse rate is 78/min. The remainder of the physical examination is normal.

Which of the following is the most appropriate management of this patient's cervical cancer screening?

(A) Obtain HPV testing in 2 years
(B) Obtain Pap smear in 2 years
(C) Obtain Pap smear and HPV testing now
(D) Obtain Pap smear and HPV testing in 2 years

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Item 45

A 67-year-old man is evaluated following a recent diagnosis of type 2 diabetes mellitus. He is sedentary but is without cardiopulmonary symptoms. Family history is significant for myocardial infarction in his father at age 50 years and stroke in his mother at age 54 years. He takes no medications.

On physical examination, the patient is afebrile, and blood pressure is 144/96 mm Hg. BMI is 40. Other than obesity, his physical examination is normal.

Laboratory studies:

Alanine aminotransferase	31 U/L
Total cholesterol	203 mg/dL (5.26 mmol/L)
LDL cholesterol	123 mg/dL (3.19 mmol/L)
HDL cholesterol	40 mg/dL (1.04 mmol/L)
Serum creatinine	0.75 mg/dL (66.3 µmol/L)
Glucose	194 mg/dL (10.8 mmol/L)
Triglycerides	201 mg/dL (2.27 mmol/L)
Hemoglobin A_{1c}	6.7%

Electrocardiogram is normal.

His 10-year atherosclerotic cardiovascular disease risk based on the Pooled Cohort Equations is 25%.

The patient is counseled on lifestyle changes to reduce cardiovascular risk, and management of his diabetes and hypertension is initiated with metformin and ramipril.

Which of the following is the most appropriate treatment of this patient's hyperlipidemia?

(A) Gemfibrozil
(B) High-intensity atorvastatin
(C) Moderate-intensity simvastatin
(D) No additional treatment

Item 46

A 49-year-old man is evaluated during a routine examination. He is asymptomatic but is concerned about his risk for cardiovascular disease. Medical history is notable for hypertension. He is a nonsmoker, and he works as an executive at a highly successful company. Family history is noncontributory. His only medication is hydrochlorothiazide.

On physical examination, the patient is afebrile, blood pressure is 118/78 mm Hg, and pulse rate is 78/min. BMI is 31. The remainder of the physical examination is normal.

Results of laboratory studies show a serum total cholesterol level of 190 mg/dL (4.92 mmol/L) and a serum HDL cholesterol level of 46 mg/dL (1.19 mmol/L). Fasting plasma glucose level is 95 mg/dL (5.27 mmol/L).

His estimated 10-year risk of atherosclerotic cardiovascular disease using the Pooled Cohort Equations is 3.2%.

In addition to diet and exercise, which of the following is the most appropriate next step in management?

(A) Coronary artery calcium scoring
(B) Exercise electrocardiography
(C) Resting electrocardiography
(D) No further testing

Item 47

A 91-year-old man is brought to the office by his daughter following two recent falls. He lives independently in his own home, and both falls occurred at home while the patient was using a walker. He had no serious injuries with either fall. He cannot recall what led to the falls, but he was able to get himself up after each one. He has a known multifactorial gait disturbance and has routinely used a walker for the last 2 years. He reports that his balance has worsened in the last few months and that his activity level has been "slowing down." He reports no lightheadedness or specific weakness. His cognition is normal. Medical history is remarkable for diffuse osteoarthritis with minimal discomfort and a small stroke 10 years ago without any residual deficits. He does not drink alcohol. Medications are daily aspirin, as-needed acetaminophen, and topical menthol ointment for occasional joint pain.

On physical examination, the patient is afebrile. Blood pressure is 138/82 mm Hg sitting and 140/84 mm Hg standing, and pulse rate is 84/min sitting and 80/min standing. His corrected vision is 20/25 in both eyes. He has a slow, wide-based gait with use of his walker. Neurologic examination is normal with no parkinsonian features. No detectable asymmetries in muscle strength are noted. He is wearing flip flops, which are his preferred footwear.

A multimodal intervention to prevent falls is initiated, and the patient is referred to physical therapy for an individualized exercise program. A home safety evaluation is ordered to optimize his home environment, and he is educated on proper footwear.

Which of the following additional treatments is most likely to decrease this patient's risk of falls?

(A) Compression stockings
(B) Hip protectors
(C) Mineralocorticoid supplementation
(D) Vitamin D supplementation

Item 48

A 39-year-old man in hospice is evaluated for depressed mood. He has progressive amyotrophic lateral sclerosis, with an estimated life expectancy of weeks to months. His wife is his primary caregiver, and he has two teenage sons still at home. The patient is tearful and reports feeling sad and overwhelmed at times. He is fatigued, his appetite is poor, and he has lost weight. He admits to sometimes wishing death would come quickly but has no plan to act on these feelings. He attributes his illness to past illicit drug use and feels guilty that his sons will come of age without their father.

Which of the following is the most likely diagnosis?

(A) Adjustment disorder with depressed mood
(B) Anticipatory grief
(C) Major depression
(D) Persistent complex bereavement disorder

Item 49

A 77-year-old man is evaluated for a 6-month history of fatigue, weakness, and erectile dysfunction. He previously

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had an enjoyable sex life with his wife but more recently has experienced low interest in sexual activity. He is unable to engage in his regular exercise routine due to reduced energy and muscle weakness. He reports no weight loss or depressed mood.

On physical examination, the patient is afebrile, blood pressure is 142/88 mm Hg, and pulse rate is 90/min. BMI is 32. Examination of the heart and lungs is normal. Musculoskeletal and nervous system examinations are normal. Normal-appearing testes and circumcised penis are noted.

Laboratory studies show an 8:00 AM serum total testosterone level of 195 ng/dL (6.8 nmol/L). Serum thyroid-stimulating hormone level is within normal limits.

Which of the following is the most appropriate next step in management?

(A) Begin testosterone replacement therapy
(B) Measure follicle-stimulating hormone and luteinizing hormone levels
(C) Measure prolactin level
(D) Obtain a pituitary MRI
(E) Repeat 8:00 AM testosterone level

Item 50

A 46-year-old man is evaluated for a 3-week history of right foot pain. The pain is located near the medial inferior heel without radiation. He describes the pain as sharp and occurring with the first few steps taken after awakening in the morning or after prolonged rest. The pain improves with continued walking. He reports no edema, erythema, or ecchymoses in this area, and he has no history of trauma. Medical history is significant for obesity. He has tried ibuprofen without pain relief.

On physical examination, vital signs are normal. BMI is 35. Strength and sensation in the foot are normal. There is pain on palpation of the medial tubercle of the calcaneus. Pain is also reproduced with passive dorsiflexion of the toes. Pain is not present on palpation of the posterior heel or with tapping inferior to the medial malleolus. There is no atrophy of the heel fat pad. Pes planus is present.

Which of the following is the most likely diagnosis?

(A) Achilles tendinopathy
(B) Heel pad syndrome
(C) Plantar fasciitis
(D) Stress fracture of the tarsal navicular bone

Item 51

A 48-year-old woman is evaluated for a 6-week history of persistent low back pain. The patient is a nurse and has had continuous pain ever since helping lift a patient. The pain is localized to the lumbar back, is bilateral, and does not radiate. She has not had fever or bowel or bladder dysfunction. The patient was involved in a motor vehicle accident 10 years ago and sustained a back injury that has subsequently healed. Medical history is otherwise unremarkable, and her only medication is as-needed naproxen for pain control.

On physical examination, vital signs are normal. BMI is 27. The general medical examination is normal. Musculoskeletal examination shows pain induced with palpation over the lumbar paraspinal muscles. Range of motion with back flexion and extension is limited. Results of the straight-leg raise test are negative bilaterally. Lower extremity muscle strength and reflexes are normal.

Which of the following is the most appropriate treatment?

(A) Bed rest
(B) Glucocorticoid taper
(C) Lumbar support
(D) Massage therapy

Item 52

A 50-year-old man is evaluated in the emergency department after sustaining a complex right tibia fracture in a motor vehicle accident at 9:00 PM. He underwent splinting of the fracture and was admitted to the hospital for wound debridement and internal fixation to occur the next morning. Medical history is notable for hypertension, hyperlipidemia, and type 2 diabetes mellitus. Medications are extended-release metoprolol every morning, pravastatin every evening, and metformin twice daily. He took all of his usual medications today (both morning and evening doses). He was in his usual state of health with no symptoms prior to the accident.

On physical examination, the patient has a splint on the right lower extremity. Blood pressure is 138/86 mm Hg, and pulse rate is 78/min. The remainder of the physical examination is normal.

Laboratory studies show normal serum bicarbonate, blood urea nitrogen, serum creatinine, and serum potassium levels; random plasma glucose level is 119 mg/dL (6.6 mmol/L).

Which of the patient's medications should be taken the morning of surgery?

(A) Metformin
(B) Metoprolol
(C) Metoprolol and metformin
(D) No medications

Item 53

A 28-year-old man is evaluated for right knee pain that began 2 days ago. He was playing football when he stopped suddenly and pivoted to make a catch. He heard a popping sound and immediately developed severe pain in his right knee. Within 30 minutes, the knee became swollen. Since the injury, he has been able to bear weight, but he has discomfort with ambulation and reports feeling that his right knee is going to buckle. He has also been unable to participate in any further sports activities. Medical history is unremarkable. He takes no medications.

On physical examination, vital signs are normal. BMI is 24. The right knee is swollen with a palpable effusion. There is no overlying erythema, medial or lateral joint line tenderness, or increased laxity with varus and valgus forces. Anterior drawer and Lachman tests are positive. Posterior drawer test is negative.

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Which of the following is the most likely diagnosis?

(A) Anterior cruciate ligament tear
(B) Lateral collateral ligament tear
(C) Medial collateral ligament tear
(D) Meniscal tear

Item 54

At a morbidity and mortality conference, a case is presented in which an older man died because of a delay in the diagnosis of cholecystitis. He was admitted to the medical service for evaluation of abdominal discomfort. The care team diagnosed constipation based on the history of abdominal bloating and an abdominal radiograph showing a large amount of stool. Treatment with stool softeners and laxatives was initiated. The patient later developed vomiting, fever, escalating abdominal pain, and leukocytosis; however, no additional studies were performed, and his treatment was not significantly altered. He subsequently died.

Which of the following cognitive errors contributed most to the outcome?

(A) Anchoring
(B) Confirmation bias
(C) Framing bias
(D) Triage cueing

Item 55

A 68-year-old woman is evaluated for sinus symptoms of 2 to 3 days' duration. She reports nasal congestion and a whitish nasal discharge, a full sensation over both maxillary sinuses, and pain in her upper teeth. She does not have fever or ear or throat pain and has had no sick contacts. Medical history is significant for hypertension and type 2 diabetes mellitus. She has no known drug allergies. Her medications are fosinopril and metformin.

On physical examination, temperature is 37.2 °C (98.9 °F), blood pressure is 122/72 mm Hg, and pulse rate is 68/min. BMI is 26. There is tenderness to palpation over both maxillary sinuses. Dentition and tympanic membranes are normal. The oropharynx is mildly erythematous without exudates. There is no cervical lymphadenopathy. The lungs are clear. The remainder of the examination is normal.

Which of the following is the most appropriate management?

(A) Amoxicillin-clavulanate
(B) Doxycycline
(C) Sinus CT scan
(D) Supportive care

Item 56

A 57-year-old woman is evaluated for a 2-month history of bothersome hot flushes multiple times daily, with night sweats disrupting sleep about two to three times nightly. She also reports irritability and mood lability and reports worsening vaginal dryness with dyspareunia. Her last menstrual period was 13 months ago. Medical history is significant only for hypothyroidism. Personal and family histories are negative for breast and ovarian cancer. Her only medication is levothyroxine. Mammography and cervical cancer screening are up to date.

On physical examination, vital signs are normal. The general medical examination is unremarkable. Breast examination is negative. On pelvic examination, the vaginal mucosa is pale with decreased rugae with petechial hemorrhages present. Decreased vaginal lubrication is noted.

Which of the following is the most appropriate next step in management?

(A) Measure serum follicle-stimulating hormone level
(B) Measure serum estradiol level
(C) Prescribe estradiol-progestin combination
(D) Prescribe low-dose paroxetine
(E) Prescribe vaginal estradiol cream

Item 57

A nursing care facility is noted to have a higher than expected rate of infections related to use of urinary catheters. To address this finding, a quality improvement team performs a root cause analysis that discovers multiple issues that are possibly contributing to the high rate of infection.

Which of the following quality improvement tools should be used to organize the results of the root cause analysis?

(A) Cause-and-effect (fishbone) diagram
(B) Control chart
(C) Pareto chart
(D) Spaghetti diagram

Item 58

A 68-year-old man is seen for a preoperative evaluation for a total left knee arthroplasty. He engages in no exercise and does minimal walking due to his knee pain. He reports no other symptoms. Medical history is notable for hypertension, for which he takes losartan.

On physical examination, blood pressure is 130/74 mm Hg. Cardiovascular examination is normal. The left knee shows changes compatible with severe osteoarthritis.

Laboratory studies show a normal serum creatinine level.

Which of the following should be performed preoperatively?

(A) Noninvasive pharmacologic cardiac stress testing
(B) Resting echocardiography
(C) Serum troponin measurement
(D) No further diagnostic testing

Item 59

A 42-year-old woman is evaluated in the emergency department for an episode of transient loss of consciousness. Two hours ago, she was standing in line at the grocery store and began to feel warm, flushed, and nauseated. After

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about a minute, she remembers becoming lightheaded with "graying" of her vision, after which she fell to the ground. She immediately regained consciousness and had no residual symptoms. She reports no chest pain, palpitations, nausea, numbness, tingling, weakness, vertigo, or headache. There was no apparent seizure activity or bowel or bladder incontinence.

On physical examination, temperature is 36.8 °C (98.2 °F). Blood pressure is 110/80 mm Hg supine and 102/68 mm Hg standing, pulse rate is 78/min supine and 88/min standing, and respiration rate is 14/min. BMI is 28. The lungs are clear, and examination of the heart is normal and without murmurs. The remainder of the general medical examination is unremarkable. Neurologic examination is normal.

Laboratory test results reveal a hemoglobin level of 13.2 g/dL (132 g/L). Pregnancy test is negative.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Echocardiography
(B) Electrocardiography
(C) Head CT
(D) No additional testing

Item 60

A 61-year-old man is seen for preoperative evaluation before left total hip arthroplasty scheduled in 2 weeks. He was hospitalized 4 months ago for an ST-elevation myocardial infarction related to a completely occluded proximal left circumflex artery. He underwent percutaneous coronary intervention and stenting with an everolimus-eluting coronary stent. He has since done well with no symptoms with daily activities, and an echocardiogram 1 month ago showed preserved left ventricular function and no structural heart disease. Medical history is also notable for hypertension and hyperlipidemia. Medications are aspirin, clopidogrel, carvedilol, atorvastatin, and lisinopril.

On physical examination, blood pressure is 126/76 mm Hg, and pulse rate is 64/min. Central venous pressure is normal. Cardiac and pulmonary examinations are normal. There is no peripheral edema.

Laboratory studies show a normal basic metabolic panel and complete blood count.

Electrocardiogram shows normal sinus rhythm.

Which of the following is the optimal preoperative management?

(A) Continue clopidogrel and aspirin throughout surgery
(B) Delay surgery for at least 8 months
(C) Stop aspirin and clopidogrel 5 to 7 days before surgery
(D) Stop clopidogrel 5 to 7 days before surgery; continue aspirin

Item 61

A 26-year-old man is evaluated for almost daily unexpected episodes of sweating, palpitations, tremulousness, shortness of breath, and numbness in his fingers and toes. During these episodes, he feels as if he is going to die. Episodes have occurred during lectures at medical school and while watching films in movie theaters; symptoms can be so severe that he must leave "to get air." All of the episodes resolve after 15 to 20 minutes. Because of fear of future episodes, he has withdrawn from social activities. His sleep has been poor, and he is fatigued. Medical history is otherwise unremarkable. He does not smoke, drink alcohol, or use illicit drugs.

On physical examination, the patient appears anxious. Blood pressure is 124/76 mm Hg, pulse rate is 94/min, and respiration rate is 16/min. BMI is 23. The remainder of the physical examination, including heart, lung, and nervous system examinations, is unremarkable.

Laboratory studies, including thyroid function tests, are normal.

In addition to cognitive-behavioral therapy, which of the following is the most appropriate long-term pharmacologic treatment for this patient?

(A) Alprazolam
(B) Buspirone
(C) Propranolol
(D) Sertraline

Item 62

A 40-year-old woman is evaluated during a routine visit and asks to start on contraception. She had been sexually inactive since her divorce several years ago but is in a new sexual relationship and is interested in starting an oral contraceptive. Medical history is unremarkable, with no history of thromboembolism, heart disease, or headache. She is a never-smoker and takes no medications. Her last Pap smear was 1 year ago and was normal. Menses are regular; her most recent period began approximately 3 weeks ago.

On physical examination, vital signs are normal. BMI is 27. The general medical examination, including breast examination, is unremarkable.

Which of the following is the most appropriate management prior to starting hormonal contraception in this patient?

(A) Lipid profile
(B) Mammogram
(C) Pelvic examination and Pap smear
(D) Pregnancy test
(E) No additional testing

Item 63

A 28-year-old man is evaluated for a 3-day history of cough, rhinorrhea, sore throat, generalized malaise, and low-grade fever. His nasal discharge is slightly yellow, and his cough is productive of small amounts of yellow sputum. He reports no wheezing or shortness of breath. He does not smoke cigarettes and has no new environmental exposures. He is an elementary school teacher, and many of his students have had similar symptoms over the previous week. Medications are acetaminophen and ibuprofen as needed. He has no allergies. The patient requests a prescription for a medication that will help manage his symptoms.

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On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 132/70 mm Hg, pulse rate is 90/min, and respiration rate is 18/min. BMI is 24. There is mild bilateral conjunctival injection. Ear examination is normal. The posterior pharynx is erythematous without tonsillar enlargement or exudate. Nasal turbinates are mildly swollen, and there is a copious amount of clear nasal drainage. Lung examination reveals no wheezing or rhonchi, and there is no dullness to percussion. The remainder of the examination is normal.

Which of the following is the most appropriate treatment?

(A) Azithromycin
(B) Chlorpheniramine-pseudoephedrine
(C) Codeine
(D) Inhaled albuterol

Item 64

A 38-year-old woman is evaluated in the emergency department for a 1-day history of right shoulder pain, which began after she fell on her right shoulder while running. She reports no shoulder problems before the fall. She is a highly active athlete who enjoys running, biking, and playing racquetball. Medical history is unremarkable. Her only medication is acetaminophen as needed for pain.

On physical examination, vital signs are normal. BMI is 21. Findings on general medical examination are unremarkable. On musculoskeletal examination, the neck is normal. The right shoulder is normal in appearance, and there is no tenderness to palpation of bony structures. The patient is unable to actively abduct her right shoulder beyond 90 degrees. When asked to lower her arm progressively once it has been passively abducted to 90 degrees, her arm falls to her waist. When her arm is passively abducted to 20 degrees and externally rotated, she is unable to maintain external rotation. There is no pain with internal or external rotation. Grip strength and sensation in the hand are normal.

Plain radiographs of the right shoulder show no dislocation or fracture.

Which of the following is the most appropriate next step in management?

(A) Glucocorticoid injection
(B) MRI of the right shoulder
(C) Physical therapy
(D) Right upper extremity nerve conduction study

Item 65

A 38-year-old man is evaluated during a follow-up visit. Eight weeks ago, he was diagnosed with a first episode of depression based on symptoms of depressed mood, fatigue, increased sleep, anhedonia, and weight gain. His score on the PHQ-9 was 15 (moderately severe depression). Citalopram, 20 mg/d, was initiated at that time. Six weeks ago, he was tolerating the medication with no significant side effects but without improvement of symptoms; citalopram was therefore increased to the maximum dose of 40 mg/d. Currently, he reports no improvement of his depressive symptoms, and his PHQ-9 score remains 15. He has no suicidal ideation.

On physical examination, the patient has a mildly depressed affect but responds appropriately. Vital signs are normal, and the remainder of the examination is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Add liothyronine
(B) Discontinue citalopram and begin bupropion
(C) Discontinue citalopram and begin olanzapine
(D) Refer for electroconvulsive therapy

Item 66

A physician group practice recently hired a new graduate of an internal medicine residency training program. The new physician had excellent references, and her performance in the practice has been exemplary. She is well liked by patients, her clinical care is considered excellent, and staff members indicate that she is an outstanding team player.

A physician colleague in the practice discovers that the new physician's social media page contains disparaging comments about obese patients, patients with somatoform disorders, and nonadherent patients, although there is no mention of specific patients in the practice. Her social media page also contains photographs of her drinking alcohol at various parties.

Which of the following is the most appropriate course of action for this physician to take regarding the colleague's social media use?

(A) Meet with the colleague and advise that she remove the inappropriate content
(B) Notify the head physician in the practice of the inappropriate posts
(C) Post a comment on the colleague's social media page indicating that the content is unprofessional
(D) No action is required

Item 67

A 45-year-old man is evaluated for a 1-year history of cough. The cough is described as episodic throughout the day and nonproductive. He believes his cough may worsen after a heavy meal. He reports no postnasal drip, shortness of breath, wheezing, chest pain, paroxysmal nocturnal dyspnea, or lower extremity edema, although he experiences occasional heartburn. He smokes one pack of cigarettes per day with a 15-pack-year history, and he drinks one alcoholic beverage and three cups of coffee daily. He has no history of environmental exposures. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, temperature is 37.2 °C (98.9 °F), blood pressure is 140/70 mm Hg, pulse rate is 70/min, and respiration rate is 16/min. BMI is 35. Lung examination reveals normal breath sounds. Cardiovascular examination is normal; there is no S_3. Abdomen is obese, and no pedal edema is noted.

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A posteroanterior/lateral chest radiograph is normal.

In addition to smoking cessation and weight reduction counseling, which of the following is the most appropriate management of this patient?

(A) Antihistamine-decongestant
(B) Bronchoscopy
(C) Echocardiography
(D) Proton pump inhibitor

Item 68

A 65-year-old man is evaluated during a routine examination. He is asymptomatic. The patient has a 15-pack-year smoking history, and family history is noncontributory. He takes no medications.

Which of the following is the most effective screening maneuver?

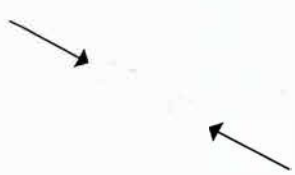
(A) Abdominal aorta palpation
(B) Carotid artery auscultation
(C) Pulse palpation
(D) Testicular examination

Item 69

A 63-year-old woman is evaluated for a 3-week history of vaginal discharge. The discharge is described as yellowish and malodorous and is accompanied by burning and dyspareunia. She is postmenopausal and is sexually active with a new male partner. Her last Pap smear was 2 years ago and was normal. Medical history is significant for hypertension, and her only medication is hydrochlorothiazide.

On physical examination, the patient is afebrile, blood pressure is 128/78 mm Hg, pulse rate is 72/min, and respiration rate is 12/min. BMI is 26. On pelvic examination, a frothy, yellowish discharge is present in the vaginal vault. The cervix is without lesions, although there is contact bleeding with speculum placement. There is no cervical motion tenderness or adnexal tenderness. The remainder of the examination is unremarkable.

Laboratory studies show a vaginal pH is 6.0; whiff test is negative. Saline microscopy is shown. Potassium hydroxide microscopy is negative. Testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* is negative.



Treatment with single-dose metronidazole is planned.

Which of the following is the most appropriate additional intervention?

(A) Confirm infection with a nucleic acid amplification test
(B) Perform repeat Pap smear following treatment
(C) Test for cure following treatment
(D) Treat the patient's sexual partner

Item 70

A 55-year-old man is evaluated during a new patient visit. He feels well and has no specific symptoms, but he asks for advice on reducing his risk for cardiovascular disease because his younger brother recently had a myocardial infarction. He leads a sedentary lifestyle but has no cardiopulmonary symptoms. Medical history is significant for obesity and hypertension. Medications are hydrochlorothiazide and lisinopril.

On physical examination, he is afebrile, and blood pressure is 136/82 mm Hg. BMI is 34. Waist circumference is 99 cm (39 in). The remainder of the physical examination is normal.

Laboratory studies:

Alanine aminotransferase	Normal
Total cholesterol	207 mg/dL (5.36 mmol/L)
LDL cholesterol	137 mg/dL (3.55 mmol/L)
HDL cholesterol	34 mg/dL (0.88 mmol/L)
Creatine kinase	Normal
Serum creatinine	Normal
Triglycerides	180 mg/dL (2.03 mmol/L)
Hemoglobin A_{1c}	Normal

His 10-year risk for a major cardiovascular event based on the Framingham risk calculator is 12%.

The patient is instructed on lifestyle modifications and is started on moderate-intensity simvastatin.

Which of the following is the most appropriate additional treatment for reduction of this patient's cardiovascular risk?

(A) Aspirin
(B) Diltiazem
(C) Fenofibrate
(D) Metformin

Item 71

A 54-year-old woman is evaluated for severe hot flushes that started about 12 months ago. They occur several times each night, waking her from sleep. They also occur throughout the day, disturbing her concentration at work. She reports being tired with emotional lability. She does not feel depressed but is very frustrated by her symptoms and moodiness. She also reports vaginal dryness with intermittent dyspareunia and is using lubricants with minimal relief. She does not have dysuria and has not noted any abnormal vaginal discharge. She has tried black cohosh, yoga, and increased exercise, but her discomfort

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persists. Medical history is otherwise significant for hypertension and negative for thromboembolism or cardiac disease. She underwent hysterectomy 5 years ago for fibroids. She is up to date with scheduled health screening interventions, including mammography. Her only medication is hydrochlorothiazide.

On physical examination, blood pressure is 136/80 mm Hg, and her other vital signs are normal. Speculum examination shows pale vaginal mucosa with decreased rugae. The remainder of the physical examination, including the breast examination, is normal.

Which of the following is the most appropriate treatment?

(A) Oral estradiol-progestin
(B) Oral progestin
(C) Transdermal estradiol
(D) Vaginal estradiol

Item 72

A 32-year-old woman is evaluated during a follow-up visit. She indicates that she and her husband are contemplating pregnancy, and she discontinued her oral contraceptive 2 months ago. Medical history is significant for hypertension, type 2 diabetes mellitus, and severe depression, which is currently in remission. Medications are lisinopril, metformin, atorvastatin, and sertraline. She does not smoke or use alcohol or illicit drugs. A normal Pap smear was obtained 1 year ago, no high-risk behaviors are identified, and her vaccinations are up to date.

On physical examination, blood pressure is 114/70 mm Hg. BMI is 24. The remainder of the examination is unremarkable.

A urine pregnancy test is negative.

Her lisinopril is discontinued, and she is started on a prenatal vitamin with folate.

Which of the following medications also needs to be discontinued?

(A) Atorvastatin
(B) Metformin
(C) Sertraline
(D) No additional changes needed

Item 73

A 27-year-old woman is evaluated for overweight. Her weight has steadily increased over the past 10 years, and she has attempted weight loss through commercial diets and increased physical activity. Additionally, she has met with a dietician for nutritional guidance. She frequently eats fast food, and she snacks at work, before meals, and especially when she is under stress. She currently exercises 30 minutes daily. She does not smoke and rarely consumes alcohol. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, the patient is afebrile, blood pressure is 138/74 mm Hg, and pulse rate is 76/min. BMI is 29. Waist circumference is 92 cm (36 in). Head, neck, lung, and heart examinations are normal. The abdomen is obese without striae.

Laboratory studies, including fasting plasma glucose, total cholesterol, and thyroid-stimulating hormone levels, are normal.

In addition to calorie restriction and continued regular exercise, which of the following is the most appropriate next step to help this patient achieve sustained weight loss?

(A) Behavioral therapy
(B) Laparoscopic adjustable gastric banding
(C) Orlistat
(D) Phentermine

Item 74

A 47-year-old woman is evaluated for a 2-year history of cramping lower abdominal pain that is not associated with nausea or changes in bowel movements. She also notes a 1-year history of right-sided chest pain that is intermittent, lasting for 2 to 3 hours and resolving spontaneously. Her chest pain is not associated with exertion but is sometimes triggered by stress. She has seen six different physicians for these symptoms and has undergone multiple examinations and diagnostic studies, which have been unrevealing. She has taken several sick days from work and almost daily researches her symptoms online. She voices frustration over her previous medical care and is afraid that she has cancer or some other serious illness that no one can diagnose. She has no family history of cancer. Medications are acetaminophen and probiotic tablets.

A complete physical examination, including vital signs and pelvic examination, is normal.

Which of the following is the most likely diagnosis?

(A) Conversion disorder
(B) Factitious disorder
(C) Illness anxiety disorder
(D) Somatic symptom disorder

Item 75

A 40-year-old woman presents for a second opinion for her chronic pain. She has had widespread pain consistent with fibromyalgia for several years. She describes her pain as achy in nature, constant, and worsening with strenuous activity. It is associated with poor sleep quality and "foggy" thinking but no clear deficits on cognitive testing. She has not responded to adequate trials of gabapentin, pregabalin, topiramate, amitriptyline, nortriptyline, duloxetine, and venlafaxine. Additionally, she has tried many complementary and integrative therapies to help manage her pain, and she has not responded to numerous herbal supplements and bioidentical hormones. She finds acupuncture helpful for short periods of time, but she cannot afford it in the long term. She is frustrated by the inability of her previous physicians to find a medication that relieves her pain. Her only medication is trazodone for sleep.

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Physical examination is unremarkable except for widespread muscle tenderness.

Which of the following is the most appropriate treatment for this patient?

(A) Cognitive-behavioral therapy
(B) Lidocaine patch
(C) NSAID therapy
(D) Opioid therapy

Item 76

A 32-year-old woman visits to discuss genetic testing. She inquires whether she should be tested for the *BRCA* gene mutation after having read a magazine article that recommended testing. She feels well with no symptoms. She reports no palpable breast masses, nipple discharge, or breast skin changes. She takes no medications.

On physical examination, the patient is afebrile, blood pressure is 112/72 mm Hg, pulse rate is 66/min, and respiration rate is 16/min. BMI is 23. The remainder of the physical examination, including breast examination, is normal.

Which of the following is the most appropriate management?

(A) Obtain a three-generation family history
(B) Order screening mammography
(C) Perform *BRCA* genetic testing
(D) Refer for genetic counseling

Item 77

A 98-year-old woman is evaluated in the emergency department after falling on her left hip at home. The patient lives with her daughter, and she uses a walker and requires assistance for most of her activities of daily living. Her daughter cares for the patient full time and is very conscientious and attentive. Medical history is significant for moderate dementia, osteoarthritis, and osteoporosis. She has mild vision loss that is maximally corrected with glasses. Medications are supplemental calcium, vitamin D, and as-needed acetaminophen.

On physical examination, she is pleasant but frail appearing. Vital signs are normal without orthostatic changes. BMI is 17. She is oriented only to person but can name her daughter. Her general physical examination, including skin examination, is unremarkable. Her vision is maximally corrected. On musculoskeletal examination, there is bruising about her left hip, but otherwise she has full painless range of motion of the hip. Her gait is antalgic and unsteady, and she requires one-person assist for transfers.

Pelvic and left hip and leg radiographs show joint osteoarthritis but are negative for fracture.

Which of the following is the most appropriate management of this patient to decrease future falls?

(A) Initiate an individualized exercise program
(B) Initiate risperidone
(C) Recommend nursing home placement
(D) Continue current care

Item 78

A 62-year-old man is evaluated during a new patient visit. He reports never having received influenza vaccination because of an egg allergy. The allergy was diagnosed many years ago after he developed hives upon eating eggs. His medical history is otherwise unremarkable. He currently feels well and takes no medications.

Physical examination, including vital signs, is normal.

Which of the following is the most appropriate management of this patient's influenza vaccination?

(A) Administer inactivated influenza vaccine
(B) Administer live attenuated influenza vaccine
(C) Perform influenza vaccine skin testing
(D) Do not vaccinate the patient against influenza

Item 79

A 45-year-old man is evaluated during a routine examination. He is interested in quitting smoking. He has a history of seizures but has not had a seizure in 15 years and discontinued his seizure medication 4 years ago. He also has hypertension. His only medication is amlodipine.

Physical examination is unremarkable.

Which of the following will most likely give this patient the greatest chance of success in quitting smoking?

(A) Bupropion
(B) Electronic cigarettes
(C) Nicotine replacement patches
(D) Varenicline

Item 80

A 78-year-old man is evaluated for vertigo that began abruptly 2 days ago. The vertigo waxes and wanes in severity, with each episode lasting several hours, and is accompanied by visual blurring, nausea, low-grade headache, and unsteadiness on his feet. He reports no chest pain, shortness of breath, or recent head trauma. He does not smoke cigarettes and drinks one 4-ounce glass of wine daily. Medical history is remarkable for myocardial infarction 5 years ago, type 1 diabetes mellitus, hypertension, and hyperlipidemia. Medications are insulin glargine, lisinopril, atorvastatin, and aspirin.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 162/80 mm Hg, pulse rate is 78/min, and respiration rate is 15/min. BMI is 24. The neurologic examination is notable for impaired near vision, a Dix-Hallpike maneuver that reveals 8 beats of lateral nystagmus without delay, and an unsteady gait with leaning to his right side. The remainder of the physical examination is normal.

Laboratory studies show a plasma glucose level of 244 mg/dL (13.5 mmol/L).

Electrocardiogram reveals a normal sinus rhythm, evidence of an old inferior myocardial infarction, and no acute ST- or T-wave changes.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Carotid Doppler ultrasonography
(B) CT scan of the head

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(C) Lumbar puncture
(D) MRI of the brain

Item 81

A 26-year-old man is evaluated during a routine follow-up visit. He inquires about undergoing genetic testing because his father and paternal grandfather both died of Huntington disease. His older brother recently underwent genetic testing, which confirmed the *HD* gene mutation; however, his older brother is not yet manifesting any symptoms. His younger brother was also tested, but the results were negative for the mutant gene. The patient is asymptomatic and takes no medications.

The physical examination is normal.

Which of the following is the most appropriate management of this patient?

(A) Obtain electromyogram
(B) Obtain genetic testing
(C) Refer the patient for genetic counseling
(D) Tell the patient that testing is unnecessary

Item 82

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An 83-year-old man is admitted to the hospital with fever, severe dyspnea, and hypoxemia due to pneumonia. He is lethargic, disoriented, and lacks capacity to make decisions. Medical history is significant for chronic bronchitis. Respiratory failure and need for mechanical ventilation are imminent. There is no advance directive. Two surviving adult children are struggling with making decisions about his care, especially regarding mechanical ventilation.

Which of the following is the most appropriate course of action to facilitate a decision on this patient's care?

(A) Ask the patient's children to make a decision based on the patient's best interests
(B) Ask the patient's children to make a decision based on what they feel is correct
(C) Ask the patient's children what the patient would do if he were able to make a decision
(D) Encourage the patient's children to speak to a social worker
(E) Wait for the court to appoint a guardian who will make a decision

Item 83

A 52-year-old woman is evaluated during a routine examination. She is healthy with no symptoms. The patient underwent menarche at age 14 years. She is gravida 1, para 1, with pregnancy at age 30 years. She has no family history of breast or ovarian cancer. Medical history is otherwise negative, and she takes no medications.

Vital signs are normal, and the remainder of the physical examination is unremarkable.

A film screening mammogram shows heterogeneously dense breast tissue using the Breast Imaging Reporting and Data System (BI-RADS) breast density categories; the mammogram is otherwise normal.

Which of the following imaging modalities is the most appropriate for subsequent breast cancer screening in this patient?

(A) Breast MRI
(B) Digital mammography
(C) Film mammography
(D) Whole breast ultrasonography

Item 84

A 58-year-old man is evaluated for a 1-year history of slowly progressive bilateral leg swelling. He notes that the swelling is minimal in the morning and is most pronounced at the end of the day. He reports no calf pain but does note a sensation of heaviness in both legs that is worse at night. He has no dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or abdominal distention. He uses alcohol socially and is a never-smoker. He works as a police officer. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, the patient is afebrile, blood pressure is 112/76 mm Hg, pulse rate is 76/min, and respiration rate is 16/min. BMI is 31. There is no elevation in central venous pressure. The lungs are clear. No murmurs or extra heart sounds are noted on cardiac examination. The abdominal examination is normal. There is no inguinal lymphadenopathy. Pitting edema of the lower extremities extends to approximately 3 inches above the ankles.

Laboratory studies are significant for normal kidney function and liver chemistry tests; the serum albumin level is 4.0 g/dL (40 g/L). Urinalysis is normal.

Which of the following is the most appropriate next diagnostic study?

(A) Abdominal/pelvic CT
(B) Lower extremity venous duplex ultrasonography
(C) Transthoracic echocardiogram
(D) No additional testing

Item 85

An 86-year-old woman is evaluated for increasing urinary incontinence. The patient has dementia and lives with her daughter, who is her primary caregiver. She previously had occasional urinary incontinence but now needs to wear a diaper. Her daughter is concerned about mild skin irritation she has noticed on the patient's buttocks. In addition to dementia, the patient has osteoarthritis and hypothyroidism. Medications are levothyroxine and as-needed acetaminophen.

On physical examination, vital signs are normal. BMI is 21. The patient is confused but cooperative. She appears frail and uses a walker for balance when standing and ambulating. Cardiopulmonary examination is normal. The abdomen shows no tenderness or suprapubic fullness. Erythema is present around the groin and buttocks, but no pressure ulcers are seen.

Urinalysis is normal.

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Which of the following is the most appropriate management?

(A) Antimuscarinic agent
(B) Pelvic floor muscle training
(C) Prompted voiding
(D) Transdermal estradiol

Item 86

A 79-year-old man is evaluated for pain in the buttocks region. He was diagnosed with non-Hodgkin large B-cell lymphoma 6 months ago. Although his lymphoma has responded well to therapy and he is without evidence of active disease, he required hospitalization three times for chemotherapy-associated complications during his treatment course. He has been bedbound at home during his lymphoma treatment. He describes the pain as severe when sitting and has difficulty finding a comfortable position lying down as well. He has the least pain when standing, but he is unable to stand for very long. He has had no fever. Medical history is otherwise remarkable for hypertension, hyperlipidemia, type 2 diabetes mellitus, and advanced chronic kidney disease being treated with in-center hemodialysis. Medications are felodipine, insulin, calcium carbonate, calcitriol, and erythropoietin.

On physical examination, the patient is afebrile, blood pressure is 104/58 mm Hg, and pulse rate is 64/min supine. BMI is 18. Weight is 58 kg (128 lb), decreased from 77 kg (170 lb) 5 months ago. He appears cachectic with temporal wasting. Examination of his back shows no vertebral tenderness to palpation. There is wasting of the gluteal muscles. Examination of the sacrum reveals a shallow ulcer that is 5 cm in diameter with a hard black eschar covering the base. There is no wound drainage and no surrounding erythema.

Which of the following is the most appropriate management of this patient's lesion?

(A) Biopsy of the lesion
(B) Intravenous antibiotics
(C) Leave the wound open to air
(D) Surgical debridement

Item 87

A 25-year-old man is evaluated during a follow-up visit for a diagnosis of schizophrenia. He was diagnosed after his affect became increasingly flat, he would express little emotion, and he developed a feeling that his thoughts were actively being broadcast over the radio. He was started on chlorpromazine 3 months ago with improvement in his psychiatric symptoms. However, his family notes that he has started exhibiting involuntary, repetitive body movements. His medical history is otherwise normal, and his family history is notable for his father who also has schizophrenia.

On physical examination, the patient is afebrile, blood pressure is 125/76 mm Hg, and pulse rate is 82/min. BMI is 24. He looks unkempt and has little facial expression, poor eye contact, monotone speech, and occasional grimacing and lip smacking. The remainder of his examination is unremarkable.

Which of the following is the most appropriate management of this patient's medication?

(A) Continue chlorpromazine
(B) Switch chlorpromazine to clozapine
(C) Switch chlorpromazine to haloperidol
(D) Switch chlorpromazine to thioridazine

Item 88

A 53-year-old woman is evaluated for increasing vaginal dryness, itching, and dyspareunia. She notes a slight vaginal discharge, sometimes yellowish, but reports no odor, dysuria, urinary frequency, or abnormal bleeding. She has tried vaginal lubricants, but they offer minimal relief. Intercourse is so uncomfortable that she is avoiding sex, and this is putting a strain on her marriage.

Medical history is unremarkable, and she takes no medications. She is gravida 3, para 2, and has been menopausal since age 51 years. She reports occasional hot flushes, but they do not wake her at night. Her last cervical cancer screening was 2 years ago and was negative.

On physical examination, vital signs are normal. The general medical examination is unremarkable. Pelvic examination demonstrates pale vaginal mucosa with decreased rugae. There is scant yellow-orange discharge. The cervix appears normal. Bimanual examination is normal with no tenderness or masses.

Vaginal pH is 5.5. Microscopy shows 3 to 5 leukocytes and 2 to 3 erythrocytes/hpf and is negative for clue cells, and a potassium hydroxide preparation is negative for yeast. Whiff test is negative.

Which of the following is the most appropriate treatment?

(A) Estradiol vaginal tablets
(B) Metronidazole vaginal gel
(C) Miconazole vaginal cream
(D) Transdermal estradiol with oral progestin

Item 89

H

A 97-year-old woman is evaluated in the emergency department for acute abdominal pain radiating to her back. She is found to have a ruptured aortic aneurysm. Following discussion with the patient and her family, she declines any attempt at endovascular or surgical intervention and requests that care be focused on keeping her comfortable. Her estimated life expectancy is hours to days. Medical history is significant for hypertension, and her only medication prior to admission was felodipine.

On physical examination, temperature is normal, blood pressure is 90/48 mm Hg, pulse rate is 115/min, and respiration rate is 24/min. BMI is 22. She is awake, alert, and able to answer questions. She appears frail and is in obvious pain. Her abdomen is tender to palpation with guarding. No bowel sounds are detected.

Laboratory studies are significant for a hemoglobin level of 8.0 g/dL (80 g/L) and serum creatinine level of 5.9 mg/dL (521 µmol/L).

Her antihypertensive medication is held.

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H CONT.

Which of the following is the most appropriate treatment of this patient's pain?

(A) Fentanyl, transdermally
(B) Hydromorphone, intravenously
(C) Morphine, intravenously
(D) Tramadol, orally

Item 90

A physician has observed that a colleague with whom he has worked for many years has arrived late for and been absent from work with increasing frequency in recent months. While at work, the colleague appears disengaged, distracted, moody, and forgetful. The physician has also noticed lapses in his colleague's judgment and errors which, if unnoticed, might have resulted in patient harm. The physician met with the colleague in private and told him of his observations. He asked his colleague if something is wrong and was rebuffed, being told that he is fine.

Which of the following is the most appropriate course of action for the physician to take regarding his colleague?

(A) Ask other physicians if they have made similar observations of the colleague
(B) Inform the colleague's supervisor of the observations and outcome of the private meeting
(C) Review the colleague's patient care notes for evidence of negligent care
(D) Continue close observation of the colleague

Item 91

A 40-year-old woman is evaluated following several recurrent witnessed episodes of syncope. The patient is an orthopedic surgeon and has experienced loss of consciousness on three separate occasions over the past 6 months after prolonged standing in the operating room. Each episode was brief, was preceded by darkening of peripheral vision, and occurred approximately 2 hours into each surgical procedure. She reports no chest pain, palpitations, weakness, headache, sensory symptoms, flushing, or nausea before the episodes, and no bladder or bowel incontinence or postevent confusion were seen following syncope. She had a normal evaluation in the emergency department after each episode with a normal physical examination, laboratory studies, and electrocardiogram. A 24-hour electrocardiographic monitor placed after her second episode was normal. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, the patient is afebrile. Blood pressure is 132/74 mm Hg supine and 128/68 mm Hg standing, pulse rate is 66/min supine and 76/min standing, and respiration rate is 14/min. BMI is 22. Cardiac, pulmonary, abdominal, and neurologic examinations are normal.

Laboratory studies are significant for a normal complete blood count and comprehensive metabolic profile, including a fasting plasma glucose level and kidney function studies. A urine pregnancy test is negative.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Brain MRI
(B) Echocardiography
(C) 48-Hour ambulatory electrocardiography
(D) Tilt-table testing
(E) No further testing

Item 92

A 31-year-old man is evaluated for a 9-month history of worry, irritability, restlessness, poor sleep, and fatigue. He feels "keyed up," has difficulty concentrating on tasks, and worries constantly about his health, job performance, and financial matters. In a recent job performance evaluation, his work was rated "poor." He has withdrawn from social circles and is sedentary. He experiences frequent headaches, loose stools, and rapid heartbeat. Because of his symptoms, he worries that he has an undiagnosed medical condition. His PHQ-9 score is 9, and his Generalized Anxiety Disorder 7-item scale score is 13. When asked about the impact of his symptoms on his ability to work, take care of things at home, or get along with other people, he indicates that they have made these activities very difficult. He does not smoke cigarettes or use illicit drugs; he drinks one alcoholic beverage per day.

On physical examination, blood pressure is 138/84 mm Hg, and pulse rate 100/min. BMI is 28. The remainder of the physical examination is unremarkable.

Laboratory studies, including thyroid function tests, are normal.

Which of the following is the most likely diagnosis?

(A) Attention-deficit/hyperactivity disorder
(B) Generalized anxiety disorder
(C) Major depression
(D) Obsessive-compulsive disorder

Item 93

A 27-year-old woman is evaluated during a follow-up visit. She is planning a trip to China, and her immunization status is being reviewed. She received the first dose of the hepatitis B virus (HBV) vaccine series 18 months ago and the second dose 1 month thereafter. However, she has not received the third dose, which was scheduled for administration 3 months ago. Medical history is unremarkable, and she takes no medications.

Results of the physical examination are unremarkable.

Which of the following is the most appropriate management?

(A) Administer the third dose of the HBV vaccine series now
(B) Order hepatitis B surface antibody titers to assess for immunity
(C) Restart the HBV vaccine series
(D) No additional HBV vaccination is required

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Item 94

A 43-year-old man is evaluated for pain and swelling of the left elbow of several weeks' duration. He is a taxi driver and has been working more than usual. When driving, he tends to move his elbow back and forth across the armrest, and the swelling has developed progressively. He notes no acute trauma, skin breaks, rash, or fever. He also reports no history of gout or alcohol use. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. BMI is 26. The left olecranon bursa is fluctuant but nontender, and there is no redness or warmth. The left elbow has full range of motion. The remainder of the examination is normal.

In addition to protection of the elbow area, which of the following is the most appropriate therapy?

(A) Glucocorticoid injection
(B) NSAID therapy
(C) Topical lidocaine
(D) Tramadol

Item 95

A 36-year-old woman is evaluated for a 5-year history of multiple symptoms, including back pain, food intolerances, headaches, pelvic pain, nausea, myalgia, joint stiffness, lightheadedness, and fatigue. She reports that her most bothersome symptom is mid/low back pain. She reports no trauma, fever, weight loss, rash, or bladder or bowel incontinence. She notes that if she removes highly processed foods from her diet, her symptoms seem to improve, especially the fatigue.

During the past 3 years, the patient has been evaluated by an orthopedic surgeon, allergist, neurologist, gastroenterologist, gynecologist, and rheumatologist, along with three different internists. She is married with no history of intimate partner violence. She does not smoke, drink alcohol, or use illicit drugs. Medications are citalopram, gabapentin, tramadol, and several herbal preparations.

On physical examination, vital signs are normal. BMI is 21. Back examination shows mild tenderness to palpation along the paraspinal muscles. Straight-leg raise test is negative for radicular symptoms but does reproduce her low back discomfort. The remainder of the examination is unremarkable.

Previous records show a normal comprehensive metabolic profile, creatine kinase level, complete blood count, and thyroid-stimulating hormone level within the past year. An erythrocyte sedimentation rate measured 1 month ago was 25 mm/h, and Lyme serology performed at the same time was negative. A lumbosacral spine radiograph 6 months ago was normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Food allergy testing
(B) MRI of the lumbosacral spine
(C) Repeat Lyme serology
(D) No additional testing

Item 96

A 59-year-old man is evaluated in the emergency department for an episode of syncope. He experienced lightheadedness upon arising from a chair, which was followed by a witnessed transient loss of consciousness. He was immediately arousable and alert within 10 seconds. There was no loss of bladder or bowel function. He was otherwise asymptomatic prior to the event. Medical history is significant for hypertension and poorly controlled type 2 diabetes mellitus. Medications are benazepril, insulin glargine, and rosuvastatin.

On physical examination, the patient is afebrile. Blood pressure is 147/72 mm Hg supine and 120/76 mm Hg standing, pulse rate is 72/min supine and 94/min standing, and respiration rate is 14/min. BMI is 27. There is no jugular venous distention. Cardiopulmonary and abdominal examinations are normal. On neurologic examination, he is alert and oriented. Neurologic examination is unremarkable except for decreased sensation to touch in the feet bilaterally.

Laboratory studies are significant for a plasma glucose level of 338 mg/dL (18.8 mmol/L).

A 12-lead electrocardiogram shows normal sinus rhythm with normal axis and intervals and no acute ST- or T-wave changes.

Which of the following is the most likely cause of this patient's syncope?

(A) Orthostatic hypotension
(B) Seizure
(C) Silent cardiac ischemia
(D) Ventricular arrhythmia

Item 97

A 62-year-old woman is evaluated during a routine examination. She is asymptomatic. Her most recent Pap smear and human papillomavirus test were performed 3 years ago and were negative. A lipid panel and fasting plasma glucose level obtained last year were normal. She has never smoked cigarettes. Family history is noncontributory. She takes no medications.

On physical examination, the patient is afebrile, blood pressure is 116/78 mm Hg, and pulse rate is 78/min. BMI is 24. The remainder of the physical examination is normal.

Which of the following is the most appropriate screening test for this patient?

(A) Fasting lipid panel
(B) Fasting plasma glucose
(C) HIV testing
(D) Pap smear

Item 98

An 85-year-old woman is evaluated during a follow-up examination. She lives independently and is the primary caretaker of her elderly husband, who has dementia. Over the last 6 months, she has noticed increased difficulty reading the print on her husband's prescription pill bottles. She

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has worn glasses for many years and has had stable corrected vision, with her last prescription for glasses around 9 months ago. She reports no headache, jaw claudication, or muscle aches. Medical history is significant for hypertension and osteoporosis. She has never smoked and does not use alcohol. Medications are amlodipine, calcium, vitamin D, and alendronate.

On physical examination, she is afebrile, blood pressure is 137/82 mm Hg, pulse rate is 77/min, and respiration rate is 13/min. BMI is 23. The general physical examination is unremarkable, and there are no focal neurologic findings. There are no findings on undilated ophthalmoscopic examination.

Which of the following is the most appropriate next step in managing this patient's vision?

(A) Erythrocyte sedimentation rate
(B) Pinhole testing
(C) Referral to an eye professional
(D) Snellen eye chart testing

Item 99

A 37-year-old woman is evaluated for a 4-month history of anterior left knee pain that developed after she started training for a marathon. The pain was gradual in onset and has slowly worsened. She rates the pain as a 5 on a 10-point scale when at its worst. The pain increases when she climbs stairs or when she sits for an extended period of time. She reports no knee instability or recent trauma. Due to her pain, she has cut back on her running. Medical history is unremarkable. Her only medication is ibuprofen as needed for pain.

On physical examination, vital signs are normal. BMI is 25. Pain is reproduced by applying direct pressure to the left patella, and there is increased patellar laxity with lateral and medial displacement. There is no varus or valgus laxity, medial or lateral joint line tenderness, palpable joint effusion or swelling, or other tenderness to palpation. Anterior drawer, posterior drawer, and Lachman tests are negative. The remainder of the examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Iliotibial band syndrome
(B) Patellofemoral pain syndrome
(C) Pes anserine bursitis
(D) Prepatellar bursitis

Item 100

A 68-year-old woman in hospice care is evaluated for cachexia. She has widely metastatic breast cancer, which has progressed through multiple cycles of chemotherapy. Her estimated life expectancy is months. She reports anorexia and has lost 8% of her body weight despite attempts to increase her caloric intake with dietary measures and high-calorie supplements. Her pain is well controlled, and she reports no symptoms of sedation, depression, nausea, or constipation. The patient, her husband, and her daughter all express concern about her loss of appetite and weight loss, and they request information on pharmacologic options for weight gain. Current medications are extended-release morphine and bisacodyl.

On physical examination, the patient appears comfortable but very thin with notable temporal wasting. Temperature is normal, blood pressure is 112/72 mm Hg, and pulse rate is 66/min. BMI is 17. The mucous membranes are moist. Abdominal examination shows an enlarged liver that is nontender to palpation. Bowel sounds are normal. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management of this patient's cachexia?

(A) Dronabinol
(B) Enteral nutrition
(C) Megestrol
(D) Continue current care

Item 101

A 29-year-old woman is evaluated for a 5-month history of widespread muscle aching. The pain was insidious in onset and has gradually worsened over time. The patient describes the pain as aching in nature and worsening after prolonged activity. She reports no sensations of burning, tingling, or numbness. Her symptoms have interfered with her ability to do household chores as well as her job as a bank teller because she is unable to stand for long periods of time due to the pain. She notes that her sleep is poor and that she awakens feeling unrefreshed. She reports no depressed mood, and her PHQ-9 score is not indicative of depression. She has not had any recent stressors in her life, and she enjoys her job. Medical history is otherwise unremarkable. There is no family history of rheumatologic diseases. She takes no medications.

On physical examination, vital signs are normal. On musculoskeletal examination, there is widespread muscle tenderness involving her deltoid, rhomboid, trapezius, paraspinal, and gluteal muscles, and thighs and calves bilaterally. There is no pain with joint range of motion and no joint synovitis. Strength is normal in all muscle groups. Reflexes are normal throughout. No rash is present.

Laboratory testing reveals a normal erythrocyte sedimentation rate and normal C-reactive protein level.

Which of the following types of pain is responsible for the patient's condition?

(A) Central pain
(B) Neuropathic pain
(C) Nociceptive pain
(D) Psychological pain

Item 102

A 35-year-old man is evaluated in the emergency department following a motor vehicle accident. The patient experienced significant abdominal trauma and multiple lacerations and contusions. Abdominal imaging shows a splenic laceration with intra-abdominal bleeding. Urgent

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laparotomy for splenectomy is planned. Medical history is unremarkable, and he has no known allergies. He takes no medications.

On physical examination, the patient is alert and oriented and reports moderate pain. He is afebrile, blood pressure is 124/76 mm Hg, pulse rate is 105/min, and respiration rate is 16/min. BMI is 23. Cardiopulmonary examination is normal. There is significant abdominal tenderness in the left upper quadrant. Scattered lacerations are noted across the chest and abdomen. The remainder of the physical examination is unremarkable.

Which of the following is the most appropriate pneumococcal vaccination strategy in this patient?

(A) Administer pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23) now
(B) Administer PCV13 now, followed by PPSV23 in 8 weeks
(C) Administer PPSV23 now
(D) Administer PPSV23 now, followed by PCV13 in 8 weeks

Item 103

A 29-year-old woman is evaluated for increasing nervousness associated with public speaking. She recently was promoted to a leadership position at work; her previous position required little interaction with others and no public speaking. When required to speak to a group of people, she becomes extremely anxious and is increasingly seeking ways to avoid this responsibility. When she must do so, she becomes sweaty and tachycardic, and she worries that she will be seen as appearing nervous and incompetent. She states that she "would rather die" than speak publicly and "does not want to be the center of attention." She relates that she has always been uncomfortable around others, avoiding social gatherings and rarely dating. She recognizes her fear of public speaking is excessive. Her PHQ-9 score is 2, and her Generalized Anxiety Disorder 7-item scale score is 4. She otherwise has no worries or health concerns.

On physical examination, blood pressure is 118/72 mm Hg, and pulse rate is 84/min. BMI is 23. The remainder of the physical examination is unremarkable.

Which of the following is the most appropriate pharmacologic treatment for this patient?

(A) Clonazepam
(B) Diazepam
(C) Propranolol
(D) Sertraline

Item 104

A 74-year-old woman is seen for preoperative evaluation for arthroscopic repair of a right rotator cuff tear. The pain and weakness significantly limit her activities of daily living and have been unresponsive to acetaminophen, NSAIDs, and physical therapy. Medical history is notable for severe aortic stenosis diagnosed 6 months ago. She reports no cardiac symptoms, and her functional status has not changed in the last 6 months. She does not currently meet criteria for aortic valve replacement. Current medications are acetaminophen and ibuprofen.

On physical examination, blood pressure is 142/78 mm Hg, and pulse rate is 76/min. There is a grade 3/6 crescendo-decrescendo murmur at the cardiac base with radiation to the carotid arteries and a diminished S_2. Right shoulder findings include supraspinatus muscle weakness, weakness with external rotation, and a positive drop-arm test in the right arm.

An echocardiogram from 6 months ago reveals an ejection fraction of 65% and severe aortic stenosis (aortic valve area: 1 cm^2; aortic valve mean gradient: 42 mm Hg; aortic valve peak velocity: 4.1 m/s).

An electrocardiogram from 5 months ago is normal. Treadmill exercise stress testing as part of aortic stenosis evaluation and risk stratification 5 months ago showed the patient achieving 4 metabolic equivalents (METs) and 90% of maximum predicted heart rate; she stopped the test due to knee pain but had normal blood pressure response to exercise and no symptoms or electrocardiographic changes with exercise.

Which of the following is the most appropriate management?

(A) Cancel surgery
(B) Perform dobutamine stress echocardiography
(C) Proceed to surgery
(D) Repeat echocardiography

Item 105

A 48-year-old man is evaluated for a 3-month history of bilateral lower extremity edema, mostly of the ankles. The edema does not seem to vary during the day and has been getting progressively worse. He reports no leg pain. He notes no dyspnea, orthopnea, abdominal distention, or constitutional symptoms. He has not had any recent surgical procedures or travel. Medical history is significant for hypertension. His current medications are amlodipine and hydrochlorothiazide.

On physical examination, the patient is afebrile, blood pressure is 132/76 mm Hg, pulse rate is 76/min, and respiration rate is 16/min. BMI is 28. There is no elevation in central venous pressure. The lungs are clear. No extra heart sounds or murmurs are noted. The abdomen shows no hepatomegaly, shifting dullness, fluid wave, or bulging flanks. No inguinal lymphadenopathy is present. There is pitting edema to the level of the ankles bilaterally.

Laboratory studies are significant for normal liver chemistry and kidney function tests; the serum albumin level is 4.1 g/dL (41 g/L). Urinalysis is normal.

Which of the following is the most appropriate next step in management?

(A) Compression stockings
(B) Lower extremity venous duplex ultrasonography
(C) Switch amlodipine to lisinopril
(D) Switch hydrochlorothiazide to furosemide

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Item 106

A 30-year-old woman is evaluated for severe breast discomfort that is worse in the week before her menstrual periods. Both breasts ache and hurt with movement, and to the touch, the left breast is more painful than the right. She has not noted any lumps, skin changes, or nipple discharge. She otherwise feels well with no fever, cough, or joint pain. Her menses are regular. She has never been pregnant, and she does not smoke or use illicit drugs. She drinks one to two cups of coffee each morning. Her maternal aunt had breast cancer at age 52 years. She takes vitamin D daily but no other medications.

On physical examination, vital signs are normal. BMI is 27. Except for diffuse tenderness, the results of the breast examination are normal bilaterally, with no skin changes or dimpling, no focal abnormalities or masses, no nipple discharge, and no supraclavicular, cervical, or axillary lymphadenopathy. There is diffuse symmetric nodularity, which is most prominent in the upper outer quadrant of both breasts. There is no chest wall tenderness, and the heart and lungs are normal to examination.

Which of the following is the most appropriate management?

(A) Breast ultrasonography
(B) Caffeine-free diet
(C) Combined hormonal oral contraceptive
(D) Danazol
(E) Support bra

Item 107

A 72-year-old man is evaluated in the emergency department for a witnessed syncopal episode. The patient was sitting in church when he noted acute onset lightheadedness accompanied by a rapid heartbeat. He abruptly lost consciousness and was unresponsive for 1 minute. There was no apparent seizure activity, bladder or bowel incontinence, or tongue biting. Upon regaining consciousness, he was groggy but alert with no retrograde amnesia, chest pain, shortness of breath, or weakness. He is a current smoker with a 50-pack-year history. Medical history is remarkable for type 2 diabetes mellitus, hypertension, and hyperlipidemia. Medications are metformin, lisinopril, and simvastatin.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 138/86 mm Hg without orthostatic change, pulse rate is 56/min and regular, and respiration rate is 15/min. BMI is 33. Oxygen saturation is 93% with the patient breathing ambient air. Carotid upstrokes are normal and without bruits. The lungs are clear. Cardiac examination shows occasional premature beats but is otherwise normal.

Electrocardiogram reveals normal sinus rhythm with a left axis shift, QRS interval of 140 ms, and complete left bundle branch block pattern (unchanged from 1 year ago). Chest radiograph is normal.

Which of the following is the most appropriate next step in management?

(A) 24-Hour ambulatory event monitor
(B) Implantable loop recorder
(C) Inpatient cardiac monitoring
(D) Pacemaker insertion

Item 108

A 46-year-old man is evaluated for left shoulder pain that began suddenly 2 weeks ago. The pain worsens with overhead activities and at night. He notes limited range of motion and pain with lifting his arm. He reports no trauma to his shoulder and has never had this pain before. He is employed as a painter, and the pain is interfering with his ability to work. Medical history is unremarkable. His only medication is ibuprofen, which provides modest relief.

On physical examination, vital signs are normal. The left shoulder is normal in appearance, and there is no tenderness to palpation of bony structures. Examination reveals a positive painful arc test. Pain is elicited over the anterolateral aspect of his left shoulder with active but not passive shoulder abduction. External rotation resistance, external rotation lag, and internal rotation lag tests are negative. He has no pain with his left arm in full flexion, and he is able to slowly and smoothly lower his left arm to his waist. When the patient is asked to hold the arm flexed at 90 degrees with the forearm bent to 90 degrees (at 12 o'clock), he does not have pain with the arm internally rotated to cross in front of the body (negative Hawkins test). When his left shoulder is abducted to 90 degrees and then adducted 30 degrees in the scapular plane with the thumb pointed downward and downward pressure is applied at the elbow against resistance, he does not have any pain or weakness (negative empty can test). Strength is 5/5 throughout.

Which of the following is the most appropriate next step in management?

(A) Conservative therapy
(B) MRI of the left shoulder
(C) Orthopedic surgery evaluation
(D) Radiographs of the left shoulder

Item 109

A 32-year-old man is evaluated for a 2-week history of nonradiating low back pain. He notes that the pain developed insidiously and worsens with increased physical activity, such as playing basketball. He has no morning stiffness. He has not had any trauma and reports no weakness or abnormal sensation in the lower extremities. He otherwise feels well and has no other symptoms. Medical history is unremarkable. He does not use alcohol excessively, and he does not smoke or use illicit drugs. He takes no medications except for as-needed ibuprofen, which provides only modest pain relief.

On physical examination, vital signs are normal. BMI is 23. The general medical evaluation, including eye and

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skin examinations, is unremarkable. Musculoskeletal examination shows no scoliosis or kyphosis and no tenderness to palpation across the lower back and spine. There is normal muscle bulk and tone and normal sensation in the lower extremities. Flexion and extension of the back are limited by pain. Straight-leg raise test is negative. Examination of the joints is unremarkable, and deep tendon reflexes are normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Erythrocyte sedimentation rate
(B) HLA-B27 testing
(C) Radiography of the lumbar spine
(D) No additional testing

Item 110

A 64-year-old man is evaluated for the gradual onset of lower urinary tract symptoms over the past year. He notes a weak urinary stream and nocturia once nightly. He drinks two cups of coffee each morning and does not drink fluids within 3 hours of retiring to sleep. He reports no dysuria, hematuria, or fever. Medical history is notable for hyperlipidemia and osteoarthritis. He drinks two alcoholic beverages each week, and his social history is otherwise noncontributory. Medications are simvastatin and aspirin.

On physical examination, the patient is afebrile, blood pressure is 100/54 mm Hg, and pulse rate is 60/min. BMI is 27. The prostate is diffusely enlarged to approximately 30 mL in volume (normal, 20 mL); no nodules are detected. Cardiac and pulmonary examinations are normal. The penis is normal. The patient's American Urological Association Symptom Index score is 4.

Urinalysis with microscopy shows 2 leukocytes/hpf and is otherwise unremarkable.

Which of the following is the most appropriate management?

(A) Ciprofloxacin
(B) Finasteride
(C) Tamsulosin
(D) Observation

Item 111

A 52-year-old man is evaluated for the sudden onset of erectile dysfunction that has persisted for 6 months. He reports having erections that are inadequate for vaginal penetration. He feels guilty about not being able to satisfy his wife's requests for sexual intercourse, although he still has sexual desires. He has been sleeping poorly and feeling fatigued throughout the day. He reports no snoring or daytime somnolence, and his review of systems is otherwise negative. His wife does not report that the patient has episodes of nocturnal gasping or apnea. He has firm erections upon waking in the morning. For years, he has run 2 miles daily without chest pain or exercise-limiting dyspnea, although he has not been interested in exercise over recent weeks. Medical history is notable for hypertension. Family history is notable for his father who died of a myocardial infarction at age 70 years and his mother who died of complications from a stroke at the age of 94 years. He has never smoked cigarettes. His 10-year risk of atherosclerotic cardiovascular disease is calculated to be 5% using the Pooled Cohort Equations. Medications are hydrochlorothiazide and lisinopril. He has taken these medications for 6 years without interruption.

On physical examination, the patient is afebrile, and blood pressure is 132/64 mm Hg. BMI is 26. Heart, lung, and abdominal examinations are normal. The penis is uncircumcised without abnormalities, and the testes are normal size.

Laboratory studies show a fasting plasma glucose level of 98 mg/dL (5.4 mmol/L).

Which of the following is the most likely cause of this patient's erectile dysfunction?

(A) Hypogonadism
(B) Mood disorder
(C) Obstructive sleep apnea
(D) Prolactinoma

Item 112

A study in which researchers randomized 150 patients with asthma to a program of mindfulness meditation and 150 patients with asthma to a mock intervention of reading in a quiet room is reviewed. All subjects were patients at the same academic medical center. The intervention group was enrolled in a meditation program that was administered in July, whereas the control group participated in the mock intervention during the months of January through March. Outcomes, which were measured 1 hour after meditation and mock intervention, included peak-flow rates and validated health care quality-of-life scores. The researchers found that patients with asthma randomized to meditation had significantly better peak-flow rates and quality-of-life scores than control subjects.

Which of the following would improve the validity of this study's results?

(A) Include patients with COPD
(B) Increase the sample size
(C) Measure the outcomes of both study groups concurrently
(D) Use a more precise measure of airway function

Item 113

A 43-year-old woman is evaluated for acute-onset vertigo of 3 days' duration. She reports that severe vertigo accompanied by nausea and vomiting began abruptly and has been persistent. There are no maneuvers that accentuate or totally relieve her symptoms, and the severity of the vertigo prevents her from conducting her usual activities at work and home. She prefers to lie in bed with her eyes closed. She has had neither head trauma nor headaches and reports no motor weakness, numbness, tingling,

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otalgia, dysarthria, diplopia, hearing loss, tinnitus, fevers, or chills. Ten days ago, she had an upper respiratory tract infection. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, the patient is afebrile, blood pressure is 135/80 mm Hg, pulse rate is 98/min, and respiration rate is 14/min. BMI is 22. She appears uncomfortable and is lying down on the examination table with her eyes closed. She is unable to walk because of the vertigo. Hearing is normal. Pupils are equal, round, and reactive to light. Funduscopic examination reveals normal discs and vasculature. The remainder of the general medical examination is normal. On neurologic examination, finger-to-nose, rapid alternating movements, and heel-to-knee-to-shin tests are normal. The Dix-Hallpike maneuver evokes mixed upbeat-torsional nystagmus after 6 seconds that lasts for about 30 seconds; she then becomes very symptomatic and vomits. The remainder of the neurologic examination is normal.

Which of the following is the most likely diagnosis?

(A) Benign paroxysmal positional vertigo
(B) Brainstem infarction
(C) Labyrinthitis
(D) Vestibular neuronitis

Item 114

A 46-year-old man visits to discuss preventive measures. He feels well and has no current symptoms, although he asks whether he should be taking vitamin supplements to decrease his risk for cardiovascular disease and cancer. He reports exercising regularly and eating a healthy diet that includes fruits and vegetables. Family history is significant for his father who had a myocardial infarction at age 72 years and a paternal uncle who developed colon cancer in his 70s. He takes no medications.

On physical examination, the patient is afebrile, blood pressure is 118/78 mm Hg, pulse rate is 76/min, and respiration rate is 16/min. BMI is 25. The remainder of the examination is unremarkable.

Which of the following is the most appropriate recommendation for this patient to reduce his risk for cardiovascular disease and cancer?

(A) β-Carotene
(B) Multivitamin with minerals
(C) Vitamin C
(D) No vitamin supplementation

Item 115

A 28-year-old woman is evaluated for bilateral eye pain and redness of 3 months' duration, which has recently worsened. She describes the pain as deep and constant and notes that it worsens at night. She also reports photophobia. She does not wear contact lenses. She has tried several types of over-the-counter eye drops without improvement in her symptoms. She is otherwise healthy and takes no medications.

On physical examination, the patient is afebrile, blood pressure is 100/62 mm Hg, and pulse rate is 94/min. BMI is 24. Ophthalmologic examination shows diffuse redness bilaterally, sparing the lids and iris. Visual acuity is normal. A nondilated funduscopic examination is unremarkable. The remainder of the examination is normal.

Which of the following is the most likely diagnosis?

(A) Episcleritis
(B) Keratoconjunctivitis sicca
(C) Scleritis
(D) Subconjunctival hemorrhage

Item 116

A 30-year-old woman is evaluated for a 2-week history of irritability, inability to sleep, feelings of emptiness, and suicidal thoughts. Just prior to the onset of her symptoms, her boyfriend, whom she describes as a "loser," broke up with her. The patient was seen 1 month ago for a preventive services evaluation, including a pelvic examination and Pap smear. At that time, she described her then-new boyfriend, whom she met online, as "perfect" even though he was unemployed and had previously been incarcerated. Immediately after meeting, they spent nearly all of their time together, and she described herself as the happiest she has ever been. However, they quickly engaged in arguments, and he broke up with her. Over the years, she has had similar relationships associated with emotional ups and downs. Medical history is notable for previous hospitalizations for suicide attempts.

Which of the following is the most likely primary diagnosis?

(A) Bipolar disorder
(B) Borderline personality disorder
(C) Depression
(D) Generalized anxiety disorder

Item 117

A 61-year-old man is evaluated for a gradual onset of difficulty achieving erections over the past year. He reports a good relationship with his wife and a strong interest in having sexual intercourse and does not have a depressed mood. He no longer has nocturnal erections. Over the past several months, he becomes fatigued and dyspneic with any regular exertion; these symptoms resolve after 10 minutes of rest. He normally has a sedentary lifestyle. He is a lifetime nonsmoker. Medical history is notable for hyperlipidemia treated with diet only and benign prostatic hyperplasia treated with tamsulosin.

On physical examination, the patient's affect is normal. Blood pressure is 104/64 mm Hg. BMI is 25. Examination of the heart, lungs, prostate, penis, and testicles is normal.

Electrocardiogram shows normal sinus rhythm and is otherwise normal. Chest radiograph is normal.

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Which of the following is the most appropriate next step in management?

(A) Initiate tadalafil
(B) Obtain cardiac stress test
(C) Psychiatric evaluation
(D) Recommend weight loss through diet and exercise

Item 118

A 16-year-old teenager is evaluated during an office visit. He was brought to the office by his mother who has concerns about his behavior. She has noticed that since he was a toddler, he has been unable to make friends and prefers to be alone. He has difficulty engaging in social conversation and reading nonverbal cues and thus avoids social interactions. He has had significant difficulty with school because of his hesitation to communicate with others. She also describes that he is adamant about sticking to routines and gets frustrated with change. As an example, she states that he has to turn the light on and off three times before closing the door to his room. He also has a collection of shoelaces that he lines up nightly before bed and carries his teddy bear with him everywhere.

On physical examination, the patient is awake and alert but minimally communicative. Vital signs are normal, and the remainder of the physical examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Antisocial personality disorder
(B) Autism spectrum disorder
(C) Obsessive-compulsive disorder
(D) Social anxiety disorder

Item 119

A 35-year-old woman is evaluated in follow-up after treatment of her fourth episode of vulvovaginal candidiasis within the past year. Her usual symptoms include a thick, white vaginal discharge associated with severe itching, burning, and dyspareunia. Her last episode was 2 weeks ago and was treated with a single dose of oral fluconazole with complete resolution of symptoms. However, she wishes to discuss her options for avoiding future infections. Medical and gynecologic histories are otherwise unremarkable, and she takes no medications. She has one male sexual partner and uses an oral contraceptive.

On physical examination, vital signs are normal. BMI is 24. The general medical and gynecologic examinations are unremarkable.

Which of the following is the most appropriate recommendation to decrease recurrent infections?

(A) Antifungal treatment of her sexual partner
(B) Extended-course antifungal therapy
(C) *Lactobacillus* recolonization
(D) Switch to an alternative contraceptive method

Item 120

A 55-year-old man is evaluated for a 2-week history of visual symptoms in the left eye. He reports seeing black spots that move across his eye and flashes of light, followed by a progressive loss of vision over the lateral field, as if half of his vision is covered by a shadow. He reports no headaches or trauma. He does not wear contact lenses; however, he does wear glasses for the correction of myopia. He is a nonsmoker. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. BMI is 28. Visual acuity is intact. The pupils appear normal and are equally reactive to light. On dilated ophthalmoscopy, the left fundus is undulating and out of focus. There is no retinal pallor, and there are no cotton wool spots or hemorrhages. The remainder of the physical examination is normal.

Which of the following is the most likely diagnosis?

(A) Age-related macular degeneration
(B) Branch retinal vein occlusion
(C) Central retinal artery occlusion
(D) Retinal detachment

Item 121

A 78-year-old man is evaluated for low back and leg pain. He first noticed symptoms about 2 years ago, and they have steadily worsened. He describes a dull ache in the low back and pain that radiates down both legs. The leg pain is worse when ambulating and absent when seated, and his symptoms are particularly noticeable when walking up steps. He notes no previous trauma, weakness, or systemic symptoms. Medical history is significant for hypertension, hyperlipidemia, and obesity. He is a retired carpenter. Medications are ramipril, rosuvastatin, and as-needed acetaminophen and naproxen.

On physical examination, vital signs are normal. BMI is 31. The general medical examination is unremarkable. There is normal muscle bulk and tone in the lower extremities, and the distal extremities are warm with palpable dorsalis pedis and posterior tibialis pulses. No point tenderness is detected with palpation of the spine. Hyperextension of the back exacerbates the pain. There is no lower extremity weakness, and reflexes and sensory examination findings are normal.

Which of the following is the most likely cause of this patient's symptoms?

(A) Compression fracture
(B) Hip osteoarthritis
(C) Peripheral arterial disease
(D) Spinal stenosis

Item 122

A 40-year-old woman is evaluated during a follow-up visit for a 4-year history of medically unexplained symptoms. She reports shortness of breath, generalized pain, fatigue,

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arthralgia, nausea, headaches, and migratory dysesthesia. She has been evaluated by multiple primary care and specialty physicians and has had more than 20 emergency department visits during this time; all studies have been normal. Trials of two different antidepressant medications were unsuccessful. Her quality of life has significantly declined over the past several years. Medical history is otherwise unremarkable. Family history is significant for fibromyalgia in her mother. Medications are tramadol, albuterol, and ibuprofen, all taken as needed.

On physical examination, temperature is 36.0 °C (96.8 °F), blood pressure is 125/80 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. BMI is 28. The remainder of the physical examination is normal.

Which of the following is the most appropriate management of this patient?

(A) Long-acting benzodiazepine
(B) Neuropsychological testing
(C) Physical therapy
(D) Regular primary care visits

Item 123

A 45-year-old man is hospitalized for fever and cough and started on appropriate antibiotic treatment for community-acquired pneumonia. While in the hospital, he develops a headache and begins to feel restless and agitated. He drinks four beers nightly on weekdays and eight beers daily on weekends. He has chronic liver disease and has had alcohol withdrawal seizures in the past. His last drink was 12 hours ago. Outpatient medications are lactulose and propranolol, but he has not been adherent with this regimen. He is given thiamine, glucose, intravenous fluids, and multivitamins.

On physical examination, the patient is diaphoretic. He is alert and oriented but tremulous. Temperature is 38.4 °C (101.1 °F), blood pressure is 182/94 mm Hg, pulse rate is 118/min, and respiration rate is 20/min. Jaundice is present. Numerous spider angiomas and palmar erythema are present. Other than tachycardia, the cardiac examination is normal. Crackles are heard in the left lower lung field. There is a small amount of ascites. The liver is not palpable, but the spleen tip is easily palpable. The deep tendon reflexes are brisk. There is no clonus.

Which of the following is the most appropriate treatment of this patient's current symptoms?

(A) Chlordiazepoxide
(B) Clonidine
(C) Lorazepam
(D) Propranolol

Item 124

A 35-year-old man is evaluated during a routine examination. He is asymptomatic but is interested in starting a diet and exercise program. In high school, he was athletic, thin, and fit, but since then, he has gradually gained weight. He works very long hours in a sedentary job, does not exercise, and occasionally smokes a cigar. He drinks two to three alcoholic beverages per day on weekends, and he often eats fast food. He reports occasional snoring, but he feels refreshed when awaking in the morning. He reports no daytime somnolence or sleep intrusions. He does not have exertion-associated symptoms suggestive of cardiac ischemia. Medical history is unremarkable. He takes no medications.

On physical examination, the patient is afebrile, blood pressure is 126/76 mm Hg, and pulse rate is 78/min. BMI is 31. The abdomen is protuberant without pathologic striae. The remainder of the examination is normal.

Which of the following is the most appropriate cardiovascular risk stratification strategy?

(A) Exercise stress testing
(B) Overnight oximetry
(C) Resting electrocardiography
(D) Waist circumference measurement

Item 125

A 48-year-old man is evaluated during a follow-up appointment. Three months ago, he sustained an ST-elevation myocardial infarction and underwent percutaneous coronary intervention and bare metal stenting of his left circumflex artery. He was started on high-intensity rosuvastatin at the time of his myocardial infarction; his alanine aminotransferase and serum creatinine levels were normal. His recovery has been uneventful. He follows a heart-healthy diet and exercises regularly with no chest pain, dyspnea, palpitations, or lightheadedness. He reports no fatigue, muscle pains, abdominal pain, or changes in skin color. Medical history is significant for hypertension. Medications are aspirin, metoprolol, lisinopril, and rosuvastatin.

On physical examination, vital signs are normal. There is no muscle or abdominal tenderness. The remainder of the physical examination is unremarkable.

Which of the following is the most appropriate laboratory study to obtain at this visit?

(A) Alanine aminotransferase level
(B) Creatine kinase level
(C) Fasting lipid panel
(D) High-sensitivity C-reactive protein level

Item 126

A 65-year-old woman is evaluated during a routine examination. She is asymptomatic. Her most recent cervical cancer screening was 2 years ago at age 63 years and included a normal Pap smear. She has received regular Pap smears for the past 30 years, and all previous Pap smears have been negative. She is a widow and has had one new sexual partner in the last 2 years. Medical history is unremarkable. Family history is noncontributory. She takes no medications.

On physical examination, the patient is afebrile, blood pressure is 122/74 mm Hg, and pulse rate is 82/min. BMI is 28. The remainder of the physical examination is normal.

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Which of the following is the most appropriate recommendation for cervical cancer screening?

(A) Obtain Pap smear in 1 year
(B) Obtain Pap smear in 3 years
(C) Obtain Pap smear now
(D) Discontinue screening

Item 127

A 58-year-old woman is evaluated for an 8-week history of persistent posterior neck pain. The patient describes the pain as a burning and tingling sensation that will occasionally radiate down both arms. She reports no headache, changes in vision, or upper extremity muscle weakness. There is no history of trauma. Medical history is otherwise unremarkable. Her only medications are acetaminophen and naproxen, which do not effectively relieve the pain.

On physical examination, vital signs are normal. The general medical examination is unremarkable. On musculoskeletal examination, range of motion of the neck is limited. There is no pain to palpation over the neck and upper back. Upper extremity muscle strength is normal, and there is no upper extremity spasticity or hyperreflexia. Extension and rotation of the patient's neck toward either side with pressure applied to the top of her head reproduces the discomfort. The remainder of the examination is unremarkable.

A plain radiograph of the neck shows osteoarthritis. Cervical spine MRI shows evidence of extensive degenerative changes, facet hypertrophy, and disk space narrowing.

Which of the following is the most appropriate next step in management?

(A) Diazepam
(B) Epidural glucocorticoid injections
(C) Erythrocyte sedimentation rate
(D) Gabapentin

Item 128

An 87-year-old woman is admitted to the hospital with altered mental status. Prior to her illness, she lived in an assisted-living facility. She has a history of mild cognitive impairment, and she now lacks the capacity to make decisions. The patient has an advance directive that names her daughter as the surrogate decision maker. The patient's daughter requests a do-not-resuscitate (DNR) order in accordance with the patient's previously expressed preferences.

Urinalysis reveals greater than 100 leukocytes/hpf and bacteria. The findings suggest that the patient's altered mental status may be due to a urinary tract infection and therefore may be reversible. Blood and urine cultures and intravenous fluids and antibiotics are recommended; however, the patient's daughter refuses, stating that her mother has a DNR order.

Which of the following is the most appropriate next step in management?

(A) Assess the daughter's understanding of her mother's condition and wishes
(B) Obtain an emergency court-appointed guardian
(C) Request an ethics consultation
(D) Withhold further testing and treatment

Item 129

A 59-year-old man is evaluated for hyperlipidemia. The physician suggests initiating a statin medication, and the patient asks how effective the medication will be at preventing myocardial infarction (MI). The physician reviews a randomized controlled trial that was conducted to determine whether statin medications reduce the risk of death from MI. A total of 2146 patients were randomized to receive a statin medication or placebo. After 5 years, the researchers determined the number of deaths from MI in each study group. The findings revealed that 93 of 1093 patients in the placebo group died of MI, whereas only 53 of 1053 patients in the statin group died of MI.

Based on the study results, what is the absolute risk reduction in mortality from a myocardial infarction after taking a statin medication for 5 years?

(A) 4%
(B) 14%
(C) 24%
(D) 94%

Item 130

A 48-year-old woman is evaluated during a routine gynecologic examination. Menstruation is generally regular; her last period was 3 weeks ago. She has had no abnormal bleeding or discharge and no dysuria. She is gravida 2, para 2. She has no history of sexual trauma or pelvic surgery.

When asked an open-ended screening question about sexual concerns, she hesitantly admits that she has been having a hard time in her marriage because she has lost interest in sex over the past 2 years. She engages in sexual activity to keep her partner happy but she does not enjoy intercourse. She has been increasingly avoiding sexual intimacy, and this has become a source of friction in her marriage. She uses a lubricant for intercourse, which has been adequate for reducing discomfort.

Results of the physical examination, including the pelvic examination, are unremarkable.

Which of the following is the most likely diagnosis?

(A) Genitopelvic pain/penetration disorder
(B) Orgasmic disorder
(C) Sexual interest/arousal disorder
(D) Vulvodynia

Item 131

An 18-year-old man is seen for a preparticipation sports evaluation. The patient has no specific symptoms. He has played varsity basketball for the past 3 years without any limitation and remains active in the off-season by participating in cross-country running and soccer.

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Hypertension was recently diagnosed in his father; his two younger siblings are both healthy. He has no family history of cardiomyopathy or unexplained sudden death.

On physical examination, blood pressure is 112/62 mm Hg, and pulse rate is 52/min. The lungs are clear to auscultation. The jugular venous pulse shows a normal contour, and the carotid upstroke is normal. Precordial examination shows a prominent apical impulse that is not sustained or enlarged. The intensity of S_1 is slightly increased, and S_2 is normally split. No murmurs, rubs, or gallops are present. The remainder of the physical examination is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Echocardiography
(B) Electrocardiographic stress testing
(C) Electrocardiography
(D) No further testing

Item 132

A 52-year-old man is evaluated during a follow-up visit for chronic back pain due to spinal injuries sustained in a motor vehicle accident 1 year ago. He underwent spinal stabilization surgery at the time of the accident and has experienced significant pain since recovery. His pain has not responded to appropriate trials of nonopioid pain medications, glucocorticoid injections, and physical therapy. Repeat orthopedic and neurosurgical evaluations indicate that no additional surgical interventions are indicated. He attended an intensive, multimodal pain rehabilitation program and continues to practice mindfulness-based stress reduction techniques. He exercises daily in the form of swimming. Although these interventions have helped to some degree, he remains functionally impaired due to his pain. He fears he will lose his job as a computer programmer due to his inability to sit in a chair all day. The patient has been reliable and engaged.

On physical examination, vital signs are normal. The general physical examination is unremarkable except for postsurgical changes in the back. The neurologic examination is normal.

The patient scores in the low-risk category for opioid therapy on DIRE (Diagnosis, Intractability, Risk, and Efficacy) risk assessment. Baseline screening urine drug testing is negative. The patient and physician both sign an opioid treatment agreement, and the patient is started on long-term opioid therapy.

Which of the following is the most appropriate method for monitoring the patient's opioid therapy?

(A) Documentation of functional assessment twice annually
(B) Office visits monthly for 3 months, followed by as-needed visits
(C) Regular 3-month office visits with urine drug testing at every office visit
(D) Use of a prescription drug monitoring program at every visit

Item 133

A 41-year-old man is evaluated during an examination to establish care. The patient reports being generally healthy and has no symptoms, although he leads a sedentary lifestyle and is obese. Medical and family histories are noncontributory. He does not smoke, drink alcohol excessively, or use illicit drugs. He takes no medications.

On physical examination, the patient is afebrile, blood pressure is 132/82 mm Hg, pulse rate is 80/min, and respiration rate is 11/min. BMI is 32. The remainder of the physical examination is unremarkable.

Laboratory studies:

Total cholesterol	251 mg/dL (6.50 mmol/L)
LDL cholesterol	172 mg/dL (4.45 mmol/L)
HDL cholesterol	35 mg/dL (0.91 mmol/L)
Triglycerides	220 mg/dL (2.49 mmol/L)
Hemoglobin A_{1c}	5%

The patient's estimated 10-year risk for atherosclerotic cardiovascular disease using the Pooled Cohort Equations is 3.4%.

Which of the following is the most appropriate management of this patient's hyperlipidemia?

(A) Ezetimibe
(B) High-intensity rosuvastatin
(C) Moderate-intensity rosuvastatin
(D) Niacin
(E) Therapeutic lifestyle modification

Item 134

A 28-year-old woman is admitted to the hospital with toxic epidermal necrolysis. Two weeks prior to admission, the patient was seen in the outpatient setting by the attending physician's colleague, and she was prescribed trimethoprim-sulfamethoxazole for a urinary tract infection. The patient's medical record indicates that she has a sulfa allergy. In the hospital, the patient is informed of the new findings and treatment plan, and the patient expresses concern that she was initially prescribed a sulfa drug. She asks if the attending physician's colleague made a mistake.

In addition to acknowledging that an error occurred, which of the following is the most appropriate course of action?

(A) Advise the patient to share her concerns with the physician who committed the error
(B) Inform the patient that the pharmacy was at fault for not preventing the error
(C) Offer to transfer the patient's care to a physician at another hospital
(D) Tell the patient that the colleague will be informed of the error and steps will be taken to prevent future errors

Item 135

A 58-year-old man is seen for preoperative evaluation prior to umbilical hernia repair scheduled in 1 week. He has

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been in good health except for increasing pain at the site of his umbilical hernia. He has experienced no incarceration of his hernia. He exercises regularly without symptoms. He has no history of stroke or transient ischemic attack. Medical history is notable for aortic valve replacement with bileaflet mechanical prosthesis performed 3 years ago for a bicuspid aortic valve and decreasing exercise capacity. Medications are warfarin and low-dose aspirin.

On physical examination, blood pressure is 124/72 mm Hg, and pulse rate is 70/min. Cardiovascular examination reveals a regular rhythm, a mechanical S_2, and a grade 1/6 early systolic crescendo-decrescendo murmur at the cardiac base without radiation.

Laboratory studies show a normal serum creatinine level.

An electrocardiogram performed 2 months ago showed normal sinus rhythm with normal intervals. An echocardiogram from 2 months ago showed normal left ventricular function and normal function of the mechanical aortic valve prosthesis.

In addition to continuing aspirin and stopping warfarin 5 days before surgery, which of the following is the most appropriate management for preoperative anticoagulation bridging?

(A) Intravenous unfractionated heparin
(B) Prophylactic-dose subcutaneous enoxaparin
(C) Therapeutic-dose subcutaneous enoxaparin
(D) No bridging anticoagulation

Item 136

A 42-year-old man is evaluated for a 3-month history of cough. He describes the cough as nonproductive and associated with sinus congestion. He also notes increased mucus production with frequent throat clearing. He has no shortness of breath, wheezing, hemoptysis, or chest pain. He does not notice any change in cough with exercise. He reports that he has had similar extended periods of cough in the past, usually in either the fall or spring. He has tried over-the-counter dextromethorphan and decongestants, alone and in combination, without noticeable improvement. Medical history is otherwise unremarkable. He is a never-smoker and takes no medications.

On physical examination, the patient is afebrile, blood pressure is 124/84 mm Hg, pulse rate is 68/min, and respiration rate is 15/min. Nasal turbinates are boggy. The lungs are clear to auscultation. The remainder of the examination is normal.

Which of the following is the most appropriate treatment?

(A) Antibiotic therapy
(B) Antihistamine-decongestant
(C) Inhaled bronchodilator
(D) Intranasal glucocorticoid

Item 137

A 38-year-old man is evaluated during a routine examination. Since high school, the patient has gradually gained 25 kg (55 lb). He has a sedentary job, does not exercise, and eats fast food for lunch and dinner and snacks throughout the day. The patient has never been treated with pharmacologic agents for weight loss, and he wonders if he is a candidate for gastric banding bariatric surgery. He reports no exertion-associated symptoms suggestive of cardiac ischemia and is otherwise healthy. Medical history and review of systems are unremarkable. He takes no medications.

On physical examination, temperature is normal, blood pressure is 122/70 mm Hg, pulse rate is 78/min, and respiration rate is 12/min. BMI is 36. Waist circumference is 106 cm (42 in). Head, neck, lung, and heart examinations are normal. The abdomen is protuberant without pathologic striae.

In addition to increasing physical activity, which of the following is the most appropriate next step in management?

(A) Laparoscopic adjustable gastric banding
(B) Lorcaserin
(C) Orlistat
(D) Reduce caloric intake to maintain a deficit of 500 kcal/d

Item 138

A 60-year-old man is evaluated for urinary frequency of several years' duration. His symptoms have worsened over the past 6 to 12 months, and he notes several episodes of nocturia over the past 3 months. He reports no fever or dysuria. Medical history is notable for hypertension, and his only medication is amlodipine; he takes no over-the-counter medications.

On physical examination, blood pressure is 140/60 mm Hg, and pulse rate is 64/min. BMI is 30. There is no evidence of suprapubic bladder distention. The prostate is diffusely enlarged, firm, and nontender without nodules. The penis appears normal. The remainder of the examination is normal.

Which of the following is the most appropriate next step in management?

(A) Postvoid residual urine volume
(B) Prostate ultrasonography
(C) Urinalysis
(D) Urine flow studies

Item 139

A 42-year-old man is evaluated for a lifelong history of insomnia. He reports always having had trouble sleeping, but sleep initiation and maintenance have become more difficult over the past few years. He experiences daytime sleepiness but does not have the opportunity to nap. He reports no depressed mood or anhedonia. His wife has not noticed excessive snoring or abnormal or absent breathing during sleep. He drinks one cup of coffee in the morning and drinks one alcoholic beverage 3 to 4 nights per week. Medical history is otherwise unremarkable. He takes no medications.

On physical examination, the patient is afebrile, blood pressure is 142/82 mm Hg, pulse rate is 78/min, and respiration rate is 14/min. BMI is 27. The remainder of the physical examination is normal.

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Which of the following is the most appropriate next step in management?

(A) Alcohol cessation counseling
(B) Sleep hygiene counseling
(C) Trazodone
(D) Zolpidem

Item 140

A 27-year-old man is evaluated during a pre-employment examination. He is asymptomatic. Review of systems is negative, including no hearing loss, tinnitus, or ear pain. Medical history is otherwise unremarkable. He takes no medications.

On physical examination, vital signs are normal. BMI is 21. General examination is normal except for cerumen impaction of both auditory canals. The tympanic membranes cannot be visualized. Gross auditory acuity is normal. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Ceruminolytic agent
(B) Ear irrigation
(C) Manual cerumen removal
(D) Clinical observation

Item 141

A 52-year-old man is evaluated in follow-up for a large, inoperable pelvic osteosarcoma that is currently being treated palliatively. He reports increasingly worsening pelvic and abdominal pain. His pain had previously been controlled with as-needed nonopioid analgesics, although he is experiencing increased pain with tumor growth. Except for pain, he has no other symptoms. Medical history is otherwise unremarkable, and his current medications are as-needed naproxen and acetaminophen.

On physical examination, the patient appears to be in mild painful distress. Vital signs are normal. BMI is 22. There is a mass in the right pelvis that is moderately tender to palpation. The remainder of the examination is unremarkable.

Scheduled oral hydromorphone is prescribed for pain control.

Which of the following daily adjunctive treatments should be given to this patient?

(A) Docusate
(B) Fiber supplementation
(C) Methylnaltrexone
(D) Senna

Item 142

A 66-year-old man was diagnosed with stage III colon cancer and underwent laparotomy with resection of the tumor and colostomy placement yesterday. He tolerated general anesthesia without complications and had approximately 100 mL of blood loss during the procedure. He is ambulating, eating, and voiding without problems. He has been wearing intermittent pneumatic compression devices on his legs when in bed since admission. He is also prescribed acetaminophen and oxycodone as needed for postoperative pain.

On physical examination, vital signs are normal. The abdominal incision is intact with no surrounding erythema, induration, tenderness, or exudate. The abdomen is soft and nontender with normal bowel sounds. There is no peripheral edema.

Laboratory studies are significant for a hemoglobin level of 13.8 g/dL (138 g/L) (14.2 g/dL [142 g/L] before surgery), a platelet count of 308,000/μL (308×10^9/L), and a normal serum creatinine level.

Which of the following is the most appropriate management for venous thromboembolism prophylaxis?

(A) Continue intermittent pneumatic compression only until hospital discharge
(B) Initiate aspirin for up to 35 days after surgery
(C) Initiate prophylactic-dose enoxaparin for up to 28 days after surgery
(D) Initiate prophylactic-dose enoxaparin only until hospital discharge
(E) Initiate therapeutic warfarin for up to 35 days after surgery

Item 143

A 50-year-old man with a new diagnosis of non–small cell lung cancer is seen in follow-up. At the time of diagnosis, his disease was found to be metastatic to the liver, bone, and brain. He has completed whole-brain radiation for his brain metastases, and he is scheduled to begin chemotherapy. He states that he currently feels well, and his bone pain is well controlled with as-needed acetaminophen and NSAIDs.

In discussing his management, he indicates that he understands that his disease is incurable, and his overall goal is to live as long as possible comfortably so that he can spend as much quality time with his children as he can.

Which of the following is the most appropriate approach to management of this patient's care?

(A) Admit the patient to hospice
(B) Begin palliative care following completion of active treatment
(C) Begin palliative care if pain control becomes ineffective
(D) Begin palliative care now
(E) Continue current management

Item 144

An 88-year-old woman was admitted to the hospital 17 days ago with a small-bowel obstruction due to adhesions. She did not respond to conservative management

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H CONT.

and required surgical intervention. Her hospital course was complicated by atrial fibrillation, non–ST-elevation myocardial infarction, and acute kidney injury that is improving without the need for renal replacement therapy. Her bowel function has been slowly recovering, and she is increasingly taking food and fluids by mouth. Before admission, she had been living at home independently. The patient's children checked on her daily and brought her most meals. She used a walker but spent most of her day in a chair watching television or reading. She had a home health nurse who assisted with her medications.

In the hospital, she is fatigued and weak; she is participating in therapy but tires after 30 minutes. She requires one-person assist for transfers and to reach the bedside commode. The patient's family is not able to accommodate her in their home during her recovery but would be able to continue their previous level of support following discharge.

Which of the following discharge options is most appropriate for this patient?

(A) Home with family care and in-home rehabilitation services
(B) Rehabilitation at a long-term acute care hospital
(C) Short-term rehabilitation in a skilled nursing facility
(D) Short-term rehabilitation in a specialized rehabilitation hospital

Item 145

An 82-year-old man is evaluated during a follow-up visit. He was initially evaluated for a report of difficulty with his vision when he drives, which he describes as blurriness in both eyes, but reports no other vision problems. Medical history is significant for a 45-pack-year smoking history, and he is a current smoker. His only medication is a daily low-dose aspirin.

On physical examination, the patient is afebrile, blood pressure is 134/82 mm Hg, pulse rate is 82/min, and respiration rate is 16/min. BMI is 32. Large drusen are present bilaterally on funduscopic examination. There are no other ophthalmologic findings. The remainder of the physical examination is normal.

An ophthalmologic evaluation confirms bilateral moderate dry age-related macular degeneration.

In addition to encouraging the patient to stop smoking, which of the following is the most appropriate therapy?

(A) High-dose antioxidant vitamins
(B) Laser therapy
(C) Vascular endothelial growth factor inhibitor therapy
(D) Clinical observation

Item 146

H

A 79-year-old woman is admitted to the hospital with shortness of breath due to volume overload, hyperkalemia, and acidemia. She has stage 4 chronic kidney disease. Based on her history and physical examination, urgent hemodialysis is clinically indicated, and this is discussed with the patient. She articulates an understanding of the indications for hemodialysis and the consequences of refusing treatment, including possible death. She decides to decline hemodialysis, stating that she is at peace with her life and her God. The patient has an advance directive, which names her son as her surrogate decision maker.

Which of the following is the most appropriate management of this patient?

(A) Obtain a psychiatric assessment to determine competency
(B) Order hemodialysis
(C) Seek permission from the patient's son to perform hemodialysis
(D) Withhold hemodialysis

Item 147

A 24-year-old man is evaluated for a 1-week history of left posterior heel pain and stiffness. The pain developed gradually, and the patient rates the pain as an 8 on a 10-point scale when at its worst. He describes the pain as burning in character and notes that it worsens with activity and improves with rest. He reports no recent trauma but does note that he has been running more in preparation for a marathon. Medical history is unremarkable. His only medication is ibuprofen, which provides some improvement in his pain.

On physical examination, vital signs are normal. BMI is 23. There is tenderness to palpation approximately 2 to 3 cm proximal to the left calcaneus. No Achilles tendon defect is appreciated. Dorsiflexion and plantar flexion of the foot are intact. When the patient's calf is squeezed while the patient kneels with the feet hanging over the edge of the examining table, there is plantar flexion (negative Thompson test). There is no tenderness to palpation of the medial plantar surface. There is no pain with medial-lateral compression of the left leg at the mid-calf (negative squeeze test) or when the patient crosses his legs and places the mid-calf of the left leg on the right knee (negative crossed-leg test).

Which of the following is the most likely diagnosis?

(A) Achilles tendinopathy
(B) Achilles tendon rupture
(C) High ankle sprain
(D) Tarsal tunnel syndrome

Item 148

A 53-year-old woman is evaluated for a 1-year history of dyspareunia. She has tried using lubricants, but she still has discomfort and has lost interest in sexual intercourse. She reports vaginal itching but no vaginal discharge, bleeding, or odor. She reached menopause 2 years ago and notes occasional hot flushes, but they are not troublesome. There is no history of sexual trauma, sexually transmitted infection, or pelvic surgery. She reports no marital problems. Medical history is otherwise remarkable for hypertension. Her only medication is benazepril.

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On physical examination, the patient is afebrile, blood pressure is 130/78 mm Hg, pulse rate is 72/min, and respiration rate is 14/min. BMI is 27. The general medical examination is unremarkable. On pelvic examination, she can only tolerate insertion of a narrow speculum, and the vaginal mucosa is pale and dry with smooth vaginal walls and decreased rugae. There is scant vaginal discharge. Bimanual examination is normal.

Microscopic evaluation of a vaginal preparation reveals no hyphae, yeast, or clue cells.

Which of the following is the most appropriate management?

(A) Discontinue benazepril
(B) Systemic estrogen and progestin therapy
(C) Topical testosterone
(D) Topical vaginal estradiol

Item 149

A 78-year-old man is evaluated for a 6-month history of bilateral tinnitus. The tinnitus is high-pitched, continuous, and nonpulsatile and does not disturb his sleep. There is no associated fever, dizziness, vertigo, or headache. The patient is now retired but has a history of occupational noise exposure after working in a factory for 30 years. He has some difficulty hearing conversations if there is background noise. Medical history is significant for hypertension and hyperlipidemia, and his only medications are benazepril and pravastatin.

On physical examination, vital signs are normal. BMI is 28. Examination of the ears shows normal tympanic membranes and no cerumen impaction. When a vibrating tuning fork is placed at the midline of the patient's forehead (Weber test), the vibration is heard equally in both ears. When placed against the mastoid process until it can no longer be heard and then moved to directly outside the ear (Rinne test), the tuning fork is best heard after removal from the mastoid.

The remainder of the physical and neurologic examinations is unremarkable.

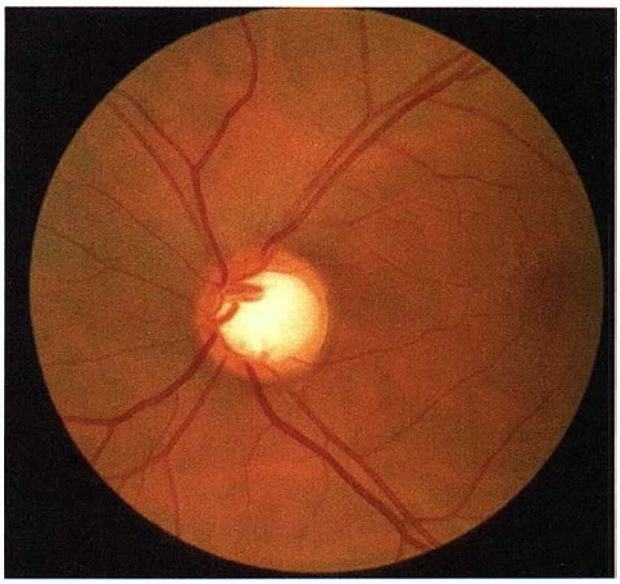
Which of the following is the most likely cause of this patient's tinnitus?

(A) Acoustic neuroma
(B) Meniere disease
(C) Otosclerosis
(D) Sensorineural hearing loss

Item 150

A 50-year-old man is evaluated for a 1-year history of reduced vision in both eyes. Over the course of this time, he has noticed a decrease in peripheral vision, most apparent when driving his car. He has no eye pain, redness, or other symptoms. He wears only reading glasses and does not wear contact lenses. Medical history is remarkable for hypertension and hyperlipidemia. He has a 35-pack-year smoking history and is a current smoker. Medications are losartan and simvastatin.

On physical examination, temperature is normal, blood pressure is 138/88 mm Hg, and pulse rate is 84/min. BMI is 32. The eyes appear normal upon inspection. There is mild loss of peripheral vision on clinical visual field testing. Funduscopic examination findings are shown. Intraocular pressure is 35 mm Hg bilaterally. The remainder of the examination is unremarkable.



Which of the following is the most likely diagnosis?

(A) Ophthalmic artery occlusion
(B) Optic neuritis
(C) Papilledema
(D) Primary open angle glaucoma

Item 151

A 56-year-old woman is evaluated for an 8-month history of insomnia. She has difficulty falling asleep and maintaining sleep for longer than 3 hours; once she awakens, she often lies in bed for as long as 1 hour trying to fall back asleep. Her symptoms seem worse during the work week and are impairing her wakefulness during the day. She reports no new stressful events in her life or symptoms suggestive of sleep-disordered breathing or restless legs syndrome. She does not drink caffeinated beverages or alcohol. She exercises for 30 minutes five times weekly on her way home from work. She does not take daytime naps, has tried a relaxing bedtime regimen, does not watch television or use electronic devices in bed, and keeps the room quiet and dark at bedtime without improvement of her insomnia. Medical history is otherwise unremarkable, and she takes no medications.

Physical examination is normal.

Which of the following is the most appropriate next step in the management of this patient's insomnia?

(A) Diphenhydramine
(B) Shift exercise regimen to before bedtime
(C) Sleep restriction counseling
(D) Zolpidem

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Item 152

A 32-year-old woman is evaluated for a 4-week history of eye symptoms. She notes redness of both eyes with itchiness and irritation. There is a watery discharge and mild crusting, mostly in the morning. Vision is normal, and she notes no other symptoms except for intermittent sneezing. She has not had contact with anyone who has similar symptoms or is ill. She does not wear contact lenses. Medical history is remarkable for hypothyroidism. Her medications are levothyroxine and an oral contraceptive.

On physical examination, she is afebrile, blood pressure is 124/60 mm Hg, and pulse rate is 62/min. Skin examination is normal. There is redness with edematous swelling of the conjunctivae in both eyes. A watery discharge is present, and there is mild swelling of the upper eyelids bilaterally. Visual acuity is normal. The remainder of the physical examination is normal.

Which of the following is the most likely diagnosis?

(A) Allergic conjunctivitis
(B) Bacterial conjunctivitis
(C) Blepharitis
(D) Viral conjunctivitis

Item 153

A 70-year-old man is admitted to the hospital with a 1-hour episode of left arm and left leg weakness. He is diagnosed with a transient ischemic attack. The patient has a history of hypertension and type 2 diabetes mellitus and a 30-pack-year history of smoking. Family history is noncontributory. His medications are metformin and lisinopril.

On physical examination, the patient is afebrile, and blood pressure is 148/88 mm Hg. The remainder of the examination is unremarkable.

Laboratory studies:

Alanine aminotransferase	28 U/L
Total cholesterol	239 mg/dL (6.19 mmol/L)
LDL cholesterol	140 mg/dL (3.63 mmol/L)
HDL cholesterol	38 mg/dL (0.98 mmol/L)
Serum creatinine	0.8 mg/dL (70.7 µmol/L)
Triglycerides	302 mg/dL (3.41 mmol/L)

In addition to aspirin, which of the following is the most appropriate treatment?

(A) Atorvastatin, high-intensity dosage
(B) Atorvastatin, moderate-intensity dosage
(C) Fenofibrate
(D) Fenofibrate and atorvastatin, high-intensity dosage

Item 154

A 27-year-old man is evaluated for a 4-day history of sore throat, malaise, rhinitis, and fever. He reports no cough, diarrhea, or vomiting. His 4-year-old daughter, who attends preschool, has similar symptoms. Medical history is noncontributory, and he has no allergies. His only medication is ibuprofen.

On physical examination, the patient is in no distress and has no shortness of breath. Temperature is 38.1 °C (100.6 °F), blood pressure is 112/52 mm Hg, pulse rate is 99/min, and respiration rate is 12/min. BMI is 23. The tympanic membranes are normal. The oropharynx shows tonsillar exudates. Tender anterior cervical lymphadenopathy is present. The lungs are clear with no evidence of consolidation. Abdominal examination is normal. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Penicillin
(B) Rapid streptococcal antigen test
(C) Throat culture
(D) Clinical observation

Item 155

An 81-year-old woman is admitted to the hospital with intractable pain in the setting of metastatic breast cancer. Medical history is significant for ischemic cardiomyopathy. She has an implantable cardioverter-defibrillator (ICD) for the prevention of sudden cardiac death, and the ICD has fired in the past. The patient is started on intravenous morphine, and her pain diminishes. The patient knows that she is dying, and she requests comfort care only. She also requests that her ICD be deactivated so that it cannot deliver shocks. She understands the consequences of ICD deactivation and is steadfast in her decision. The patient has an advance directive, which names her daughter as her surrogate decision maker.

Which of the following is the most appropriate management of this patient's request?

(A) Continue the ICD
(B) Deactivate the ICD
(C) Obtain psychiatric assessment of competence prior to ICD deactivation
(D) Seek permission from the patient's daughter to continue the ICD

Item 156

A 27-year-old woman at 30 weeks' gestation is evaluated during a routine examination. She is gravida 2, para 1, and delivered her first child vaginally without complications 20 months ago. During her first pregnancy, she received the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine. Her only medication is a daily prenatal vitamin.

Findings on physical examination are unremarkable.

Which of the following is the most appropriate management of this patient's vaccination status?

(A) Administer the Tdap vaccine after 36 weeks' gestation
(B) Administer the Tdap vaccine now
(C) Administer the tetanus and diphtheria (Td) vaccine now
(D) Administer the Td vaccine after 36 weeks' gestation
(E) Do not administer the Td or Tdap vaccines during this pregnancy

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Item 157

A 36-year-old man is evaluated for a 1-year history of fatigue, intermittent headaches, sore throat, and joint and muscle pain. He reports no difficulties falling asleep and gets 10 hours of uninterrupted but nonrestorative sleep each night. He has seen several physicians over the past year. Evaluation has included a complete blood count with differential, thyroid-stimulating hormone level, and plasma glucose level that were normal at the time of initial presentation and again 2 months ago. HIV testing performed 4 months ago was negative. He is in a monogamous heterosexual relationship, and there is no history of blood transfusions or injection drug use. Medical history is otherwise unremarkable. Family history is significant for depression and type 2 diabetes mellitus. He takes no medications.

On physical examination, the patient appears anxious. Vital signs and the remainder of the physical examination are normal. The patient's evaluation for sleep disorders is normal. A screening test for depression is negative.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Epstein-Barr virus titer
(B) Lyme disease titer
(C) Repeat HIV testing
(D) No further testing

Item 158

A 78-year-old man is evaluated for gradual hearing loss in the left ear over the past several years. Although hearing in his right ear seems normal, he has noticed that it is more difficult to hear men's voices or lower voices with his left ear. He reports no dizziness, tinnitus, or previous infection or exposure to loud noise in that ear. Medical history is significant for hypertension, hyperlipidemia, and coronary artery disease. Medications are losartan, rosuvastatin, and low-dose aspirin.

On physical examination, the patient is afebrile, blood pressure is 134/82 mm Hg, pulse rate is 85/min, and respiration rate is 13/min. BMI is 29. The tympanic membranes are normal. The remainder of the general medical examination is unremarkable. On neurologic examination, a vibrating tuning fork placed in contact with the patient's forehead at the midline results in vibrations being heard more loudly in the left ear.

Which of the following is the most likely diagnosis?

(A) Drug-induced hearing loss
(B) Meniere disease
(C) Otosclerosis
(D) Presbycusis

Item 159

A 47-year-old man is evaluated during a follow-up examination. He is obese and has hypertension, type 2 diabetes mellitus, and obstructive sleep apnea. He reports that he has always has been overweight, and over the years, his weight has gradually increased to 123 kg (271 lb). During the past 2 years, he has tried several commercial diets; a dietician-monitored, calorie-restricted diet; increased physical activity; orlistat; and a combination of these interventions, all without achieving sustained weight loss. Medical history is also significant for bilateral knee pain and depression. He uses continuous positive airway pressure for his obstructive sleep apnea, and his medications are lisinopril, amlodipine, metformin, paroxetine, and as-needed ibuprofen.

On physical examination, the patient is afebrile, blood pressure is 144/78 mm Hg, pulse rate is 86/min, and respiration rate is 18/min. BMI is 36. Cardiovascular and pulmonary examinations are normal. The abdomen is protuberant without pathologic striae. The knees show bony hypertrophy with crepitus, and there is trace bilateral lower extremity edema.

Laboratory studies are significant for a hemoglobin A_{1c} level of 9.1%.

Which of the following is the most appropriate management to help this patient achieve sustained weight loss?

(A) Bariatric surgery
(B) Hypnosis
(C) Lorcaserin
(D) Very-low-calorie, physician-monitored diet

Item 160

A 90-year-old woman is brought to the emergency department by her son for a 1-week history of worsening cognition, weakness, dizziness, and anorexia. She lives in an assisted-care facility and is generally alert. She is ambulatory when using a cane. Medical history includes hypertension, chronic heart failure, chronic kidney disease, osteoarthritis, allergic rhinitis, hyperlipidemia, and urinary stress incontinence. Current medications are lisinopril, bisoprolol, oxybutynin, loratadine, acetaminophen, pravastatin, and omeprazole.

On physical examination, she appears frail but is in no acute distress. Temperature is normal, blood pressure is 100/60 mm Hg, pulse rate is 88/min, and respiration rate is 14/min. BMI is 20. Oxygen saturation is 97% with the patient breathing ambient air. There is no orthostasis. Cardiac examination discloses an irregularly irregular rate. Pulmonary examination reveals slightly diminished breath sounds bilaterally but no crackles. The abdomen is mildly distended but nontender. Rectal examination reveals hard stool that is negative for occult blood. There is no edema. Neurologic examination is nonfocal, and the patient scores 24/30 on the Mini-Mental State Examination.

Laboratory studies:

Hematocrit	34%
Leukocyte count	7100/μl (7.1×10^9/L); normal differential
Creatinine	1.6 mg/dL (141 μmol/L) (2 months ago: 1.3 mg/dL [114 μmol/L])
Electrolytes	Normal
Glucose	78 mg/dL (4.3 mmol/L)
Urinalysis	Trace protein, trace ketones, no cells

Chest radiograph shows no evidence of heart failure or pulmonary infiltrates.

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Which of the following is the most likely cause of this patient's recent symptoms?

(A) Acute kidney injury
(B) Adverse medication effects
(C) Occult pneumonia
(D) Urinary tract infection

Item 161

A 32-year-old woman is evaluated during a follow-up visit for treatment of depression. She presented 3 months ago with depressed mood, decreased energy, increased sleep, and anhedonia but without suicidal ideation. Her PHQ-9 score was 13, indicating moderate depression. Citalopram, 20 mg/d, was initiated and titrated upward to 40 mg/d 6 weeks ago. She notes improved mood, energy, and sleep with a 6-point improvement in her PHQ-9 score. However, she reports persistent nausea and heartburn coupled with complete anorgasmia while taking this medication. Her medical history is notable for being overweight but is otherwise unremarkable. She takes no other medications.

On physical examination, blood pressure is 126/78 mm Hg. BMI is 29. Examination of the heart reveals physiologic splitting of the S_2. The abdomen is soft and nontender with normal bowel sounds. The remainder of the examination is normal.

Which of the following is the most appropriate alternative antidepressant to recommend for this patient?

(A) Amitriptyline
(B) Bupropion
(C) Buspirone
(D) Mirtazapine

Item 162

A 62-year-old man is evaluated during a routine follow-up visit. He expresses concern about developing prostate cancer because his father was diagnosed with the disease at age 55 years. He has read that the 5α-reductase inhibitor finasteride may prevent prostate cancer and asks whether he would be an appropriate candidate for treatment with this drug.

The physician reviews a study to determine whether finasteride prevents prostate cancer. In the study, investigators randomized 2000 patients equally to treatment with finasteride or placebo. Seven years later, all patients underwent a prostate biopsy. Results showed that prostate cancer occurred in 200 of 1000 (20%) patients taking finasteride compared with 300 of 1000 (30%) patients taking placebo.

Based on this study, how many patients need to be treated (number needed to treat) with finasteride for 7 years to prevent one case of prostate cancer?

(A) 2
(B) 3
(C) 5
(D) 10

Item 163

A 54-year-old man is seen for preoperative evaluation. Cervical spine laminectomy is planned. Despite his neck pain, he continues to do all activities of daily living, which includes doing laundry in his basement and carrying loads up and down the stairs. He has no chest pain, dyspnea, palpitations, or lightheadedness with this activity or at rest. He has no orthopnea or nocturnal dyspnea. Medical history is notable for a previous non-ST-elevation myocardial infarction with drug-eluting stent placement in his left circumflex artery 3 years ago; an echocardiogram following his myocardial infarction showed normal left ventricular function. He also has type 2 diabetes mellitus, hypertension, and hyperlipidemia. Medications are aspirin, lisinopril, atorvastatin, and metformin.

On physical examination, blood pressure is 138/82 mm Hg, and pulse rate is 62/min. Central venous pressure is 6 cm H_2O. Cardiac and pulmonary examinations are normal. There is trace bilateral pedal edema.

Laboratory studies show a hemoglobin A_{1c} level of 6.3% and a normal serum creatinine level.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Electrocardiography
(B) Noninvasive pharmacologic cardiac stress testing
(C) Resting echocardiography
(D) Treadmill stress echocardiography

Item 164

A 52-year-old man is evaluated for a 3-year history of multiple symptoms, including fatigue, dizziness, headache, upper back pain, shortness of breath, and abdominal pain. He has undergone extensive evaluation of his symptoms with laboratory testing revealing type 2 diabetes mellitus and hyperlipidemia. Radiographic evaluation and consultation with a neurologist, cardiologist, and gastroenterologist have failed to identify a cause of his symptoms. He continues to follow up with his internist monthly; there have been no changes in his symptoms or physical examination findings.

He feels frustrated and dejected because of the lack of a diagnosis and the negative impact of his symptoms on his life. Over the past year, he has withdrawn from family activities, slept excessively during the day, and become relatively hopeless that he will ever regain his health. Recently, he took a leave of absence from work at the request of his boss due to failing productivity. He is anxious that he will be unable to afford college tuition for his son and is having trouble sleeping at night. Medications are ferrous sulfate, vitamin B_{12}, rosuvastatin, and metformin.

On physical examination, vital signs are normal. BMI is 24. The remainder of the physical examination is unremarkable.

Which of the following is the most appropriate treatment?

(A) Alprazolam
(B) Citalopram
(C) Lithium
(D) Methylphenidate

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Item 165

A 20-year-old woman is evaluated for a 3-day history of pain, swelling, and redness of the right eye. She cannot open her eye because of the swelling. One week ago, she developed a fever with sinus congestion and postnasal drainage. Except for a continued subjective fever, these symptoms have resolved. She has no history of eye trauma or surgery. She takes no medications.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 100/62 mm Hg, and pulse rate is 88/min. BMI is 23. Examination of the right eye shows red and edematous upper and lower lids with conjunctival erythema. Pupillary reflex to light is intact. Inspection reveals no foreign bodies. She is unable to move her eye. A limited funduscopic examination is normal. The left eye is normal, and the remainder of the physical examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Blepharitis
(B) Endophthalmitis
(C) Orbital cellulitis
(D) Preseptal cellulitis

Item 166

A 40-year-old woman is evaluated for intermittent heavy vaginal bleeding for the past year. Her menses had been regular until the past 2 years, when they became irregular and would sometimes skip for several months. Her last period was 3 months ago and lasted for almost 3 weeks. Menarche occurred when she was age 12 years. She has never been pregnant and is not currently sexually active. Her most recent cervical cancer screening was 2 years ago. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. BMI is 29. The general medical examination is unremarkable, as is the pelvic examination. A urine pregnancy test is negative.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Endometrial biopsy
(B) Follicle-stimulating hormone level
(C) Serum β-human chorionic gonadotropin level
(D) Transvaginal ultrasonography

Item 167

A 68-year-old woman is evaluated for neck pain of 4 days' duration. The pain developed abruptly and awakened her from sleep. It is located in the posterior neck without radiation down the arms and worsens with neck movement but improves with recumbency. She reports no trauma, fever, muscle weakness, or weight loss. Medical history is significant for ductal carcinoma in situ treated 10 years ago without evidence of recurrence. Her only medication is naproxen for control of pain.

On physical examination, vital signs are normal. Both passive and active range of motion of the neck are severely reduced. Rotation of her head is limited by pain. The cervical paraspinal muscles are tight and tender to palpation. Upper extremity muscle strength and reflexes are normal.

Which of the following is the most appropriate management of this patient?

(A) CT myelography
(B) MRI of the cervical spine
(C) Plain radiography of the cervical spine
(D) Symptomatic care

Item 168

A 52-year-old man is evaluated for colon cancer screening. He feels well with no symptoms. His uncle experienced respiratory arrest with sedation during a screening colonoscopy, and the patient is adamant that he will not undergo colonoscopy. There is no family history of colon cancer or colon polyps.

On physical examination, vital signs are normal. The remainder of the physical examination is normal.

Which of the following is the most appropriate strategy for colon cancer screening in this patient?

(A) CT colonography every 10 years
(B) Fecal immunochemical testing every year
(C) Flexible sigmoidoscopy every 5 years with fecal occult blood testing every year
(D) Stool DNA testing every year

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Answers and Critiques

Item 1 Answer: A

Educational Objective: Screen for osteoporosis in a patient with risk factors.

This patient should be screened for osteoporosis with dual-energy x-ray absorptiometry (DEXA). The U.S. Preventive Services Task Force (USPSTF) recommends screening for osteoporosis by measurement of bone mineral density in women aged 65 years and older and in younger women who have a fracture risk equal to or higher than a 65-year-old white woman (9.3%). The Fracture Risk Assessment Tool (FRAX) (available at www.shef.ac.uk/FRAX/) can be used to determine if the 10-year fracture risk for younger women is greater than or equal to 9.3%. Risk factors that can increase the FRAX score include a first-degree relative with a history of hip fracture, alcohol abuse, smoking, low body mass, and glucocorticoid use. Although this patient is younger than 65 years, her parental history of hip fracture increases her risk of fracture to 13%; therefore, she should be screened for osteoporosis using DEXA.

The USPSTF suggests screening for lipid disorders every 5 years in all men 35 years of age and older and all women 45 years of age and older who are at increased risk of coronary heart disease. This interval should be tailored to individual risk. Since this patient's lipid panel was normal when tested last year, screening in this patient would not be appropriate.

Although the optimal screening interval for diabetes mellitus is unknown, the American Diabetes Association recommends screening for diabetes every 3 years in adults 45 years and older and adults younger than 45 years with a BMI of 25 or higher and one risk factor for diabetes. In 2008, the USPSTF recommended screening for type 2 diabetes only in asymptomatic adults with sustained blood pressure higher than 135/80 mm Hg. An updated draft guideline, issued in October 2014, recommends screening for abnormal blood glucose and type 2 diabetes in adults with risk factors, including age 45 years or older, obesity or overweight, first-degree relative with diabetes, history of gestational diabetes or polycystic ovary syndrome, and certain high-risk ethnic backgrounds (African Americans, American Indians/Alaska Natives, Asian Americans, Hispanics/Latinos, and Native Hawaiians/Pacific Islanders). This patient was screened for diabetes last year, and therefore, she does not need to be screened again now.

A combination of cytology (Pap smear) and human papillomavirus (HPV) testing can be performed every 5 years in women aged 30 to 65 years to screen for cervical cancer. Screening with a Pap smear alone every 3 years is also acceptable. This patient had a normal Pap smear and HPV test 3 years ago.

The USPSTF concludes that there is insufficient evidence to recommend for or against screening for thyroid disease. The American College of Physicians recommends screening women over age 50 years who have at least one symptom that can be attributed to thyroid disease. The American Thyroid Association and the American Association of Clinical Endocrinologists recommend measuring thyroid-stimulating hormone (TSH) level in individuals with risk factors for hypothyroidism (for example, personal history of autoimmune disease, neck radiation, or thyroid surgery) and consideration of TSH testing in adults age 60 years and older. This patient does not have any symptoms of thyroid disease and therefore should not be screened.

KEY POINT

- Women aged 65 years and older and younger women who have a fracture risk of 9.3% or higher should be screened for osteoporosis.

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U.S. Preventive Services Task Force. Screening for osteoporosis: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2011 Mar 1;154(5):356-64. [PMID: 21242341]

Item 2 Answer: D

Educational Objective: Identify the relatively large impact of smoking cessation on improving health.

This patient would most benefit from smoking cessation counseling. Cigarette smoking increases the risk of cancer, heart disease, stroke, and lung disease and is the leading preventable cause of death in the United States. Quitting smoking is the single most important thing that smokers can do to improve their quality and quantity of life. Smoking cessation before age 40 years reduces the risk of death associated with continued tobacco use by approximately 90%. The U.S. Preventive Services Task Force (USPSTF) recommends that clinicians ask all adults about tobacco use and provide tobacco cessation interventions for tobacco users. Behavioral counseling for smoking cessation in primary care settings has been found to improve quit rates and sustained abstinence at 1 year. Even minimal in-office interventions, defined as less than 3 minutes in duration, are effective in improving smoking cessation rates.

A meta-analysis suggested that women who consume an average of two or more alcoholic drinks per day had an increased mortality rate compared with nondrinkers; therefore, this patient may benefit from counseling regarding reducing her alcohol consumption. Nonetheless, the benefit of brief intervention for smoking cessation is still likely to be more impactful in this patient.

Exercising and eating a healthful diet both have a significantly positive impact on health and have been strongly linked with decreased incidence of cardiovascular disease.

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However, the effect of behavioral counseling in promoting healthful diet and physical activity in adults without known cardiovascular disease, hypertension, hyperlipidemia, or diabetes is small. Given small potential effect, time limitations, and opportunity costs, the USPSTF recommends offering dietary and exercise behavioral counseling based only on individual patient circumstances. In this patient, smoking cessation counseling will have a greater benefit than counseling that promotes a healthful diet and physical activity.

Stress reduction and relaxation techniques have the potential to improve this patient's health; however, the health benefits of smoking cessation are likely to be greater.

KEY POINT

- The U.S. Preventive Services Task Force recommends that clinicians ask all adults about tobacco use and provide tobacco cessation interventions for tobacco users.

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Item 3 Answer: B

Educational Objective: Treat a patient with benign paroxysmal positional vertigo.

The Epley maneuver should be performed in this patient presenting with symptoms of benign paroxysmal positional vertigo (BPPV). In patients with vertigo, the Dix-Hallpike maneuver can assist in distinguishing peripheral from central causes. In peripheral vertigo, the maneuver will result in nystagmus that begins after a brief period of latency (2-40 seconds) and lasts less than 1 minute. With repeated trials, the nystagmus may not be further provoked. In vertigo of central origin, the nystagmus is not associated with latency, typically lasts longer than 1 minute, and does not fatigue with repeated trials. BPPV is the most common cause of vertigo and is attributed to debris (canalithiasis), usually in the posterior semicircular canal, perturbing labyrinthine sensory receptors and resulting in the erroneous perception of angular head acceleration. BPPV is characterized by abrupt episodes of vertigo that last less than 1 minute and is provoked by a sudden change in head position. The Epley maneuver, which is performed to reposition otoliths from the semicircular canal into the vestibule, can be curative in patients with BPPV. The maneuver involves sequentially positioning the patient to encourage movement of the otoliths, and modified versions of the procedure allow patients to perform the maneuver themselves for recurrent episodes. A meta-analysis demonstrated that patients with BPPV who were treated with the Epley maneuver had significantly higher rates of improvement in symptoms compared with those who received sham treatment (odds ratio [OR] 4.4; 95% CI, 2.6-7.2).

Pharmacologic therapy for BPPV, including centrally acting antihistamines (such as meclizine), vestibular suppressants (such as diazepam), and antiemetics, may help symptoms transiently but, in general, is ineffective for long-term management or cure.

Vestibular rehabilitation therapy, when delivered by trained physical or occupational therapists, is beneficial in patients with peripheral vertigo, particularly those with recurrent or refractory symptoms; however, the initial management of this patient presenting with BPPV is to perform the Epley maneuver.

KEY POINT

- Benign paroxysmal positional vertigo can be effectively treated with the Epley maneuver, which is performed to reposition otoliths from the semicircular canal into the vestibule of the ear.

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Item 4 Answer: D

Educational Objective: Evaluate pulmonary risk in a preoperative patient.

No further diagnostic studies are needed for this asymptomatic patient scheduled for surgery. For patients with no history of cardiopulmonary disease and no cardiac or respiratory symptoms, preoperative pulmonary diagnostic testing is not beneficial. Moreover, these studies add considerable cost and potential risk (for example, radiation exposure with chest radiography). Although smoking is a risk factor for postoperative pulmonary complications, a history of smoking without other evidence of disease is not an indication for chest radiography, spirometry, or arterial blood gas analysis in the general or preoperative setting. Several studies have demonstrated that these studies do not offer improved prognostic value beyond clinical assessment alone and rarely alter management.

Chest radiography may be considered in patients with known cardiopulmonary disease or symptoms. Spirometry assessment is frequently done prior to cardiothoracic surgery, but its value is limited for other types of surgery. For nonthoracic surgery, spirometry should be performed for the same reasons as in a nonoperative situation (for example, evaluation of dyspnea or hypoxia). Similarly, preoperative arterial blood gas analysis may identify hypercapnia in patients at risk for carbon dioxide retention, but studies have not shown an incremental diagnostic benefit with this testing.

KEY POINT

- For patients with no history of cardiopulmonary disease and no cardiac or respiratory symptoms, preoperative pulmonary diagnostic testing is not beneficial.

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Item 5 Answer: A

Educational Objective: Treat lateral epicondylosis (lateral epicondylitis).

This patient with signs and symptoms consistent with lateral epicondylosis (lateral epicondylitis) should be advised to limit pain-inducing activities. Lateral epicondylosis, also known as tennis elbow, is induced by activities that require repetitive wrist extension, such as prolonged computer use or racquet sports. Pain is located over the lateral elbow but may also radiate to the dorsal forearm. Tenderness over the lateral elbow and pain with resisted wrist extension are characteristic examination findings. Increasing evidence suggests that epicondylosis is a chronic tendinosis with disorganization and neovascularization of the tissues, instead of an acute or chronic inflammatory process as traditionally believed. Because the primary mechanism of injury appears to be mechanical strain, and repetitive use of injured tissues diminishes healing, the primary treatment is avoidance of those activities that cause pain and continued injury to the affected area. Braces may be useful when exacerbating activities cannot be avoided, and counterforce bracing, which alters the mechanical strain on the elbow tendons, may be helpful. With rest, pain usually subsides, although performance of resistance exercises may also be beneficial. The analgesic effect of topical or oral NSAIDs may provide short-term symptomatic relief.

Surgical treatment is indicated only for refractory cases of epicondylosis. Patients should first be treated with appropriate conservative measures, including rest and NSAIDs. The risks of surgical intervention would be warranted in this patient only if she had not responded to all nonsurgical therapy.

Glucocorticoid injections may improve symptoms in the short term, but data are conflicting on long-term benefits. Additionally, there is some evidence that glucocorticoid injections may lead to an increased risk of recurrence. There are associated risks (hyperglycemia in patients with diabetes mellitus, infection) that must also be considered. Glucocorticoid injections cannot be justified in this patient who has not received an adequate trial of conservative therapy.

Imaging, including MRI, is not necessary for diagnosis of lateral epicondylosis if the patient has clinical findings consistent with this disorder. MRI would be indicated if this patient had atypical findings or did not respond to initial treatment.

KEY POINT

- The primary treatment of lateral epicondylosis is avoidance of activities that cause pain.

Bibliography

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Item 6 Answer: B

Educational Objective: Select an appropriate quality improvement method to reduce waiting times.

The Lean model would be the most useful method for reducing waiting times. A number of quality improvement models that apply rigorous processes to identify, measure, and correct areas in need of improvement are in use by health care systems. Understanding the appropriate application of these models is important in achieving optimal quality improvement outcomes. The Lean model is a quality improvement method that focuses on eliminating non–value-added activities, or waste, within a system. Lean uses value stream mapping, a tool that graphically displays the steps of a process and the time required for each step from beginning to end. This allows identification of steps in the process that may be problematic. The Lean model is particularly well suited for analyzing apparent inefficient or redundant processes, such as prolonged waiting times, by identifying where in the system the delays are occurring.

The Define, Measure, Analyze, Improve, Control (DMAIC) process is a five-step approach used within the Six Sigma model, a quality improvement model initially developed to improve industrial manufacturing quality that has since been adapted to optimize health care system function. It tends to focus more on quality control in each step of a process rather than on optimizing the overall efficiency of a system.

Plan, Do, Study, Act (PDSA) cycles are rapid tests of change in which baseline data are collected, an intervention is planned and then implemented on a small scale, the results are analyzed, and an action plan is made. PDSA cycles tend to focus on specific points in a system and are not typically used for studying overall system function and efficiency.

Six Sigma is a quality improvement model that is designed to reduce variation and drive a process toward near perfection. The name Six Sigma is derived from a statistical measure indicating the number of standard deviations from the mean in which no production defects occur. Thus, a Six Sigma measure indicates almost perfect production quality. Several practical methodologies that are oriented toward the quality of each step in a process are used within Six Sigma. As an example, an ICU may have an unacceptably high rate of infections; the Six Sigma model could be used to decrease the defect (infection) rate. Because Six Sigma is highly focused on the quality of each step in a process, it would not be optimal for evaluating factors leading to system inefficiencies, such as patient waiting times.

KEY POINT

- The Lean model is a quality improvement method that focuses on eliminating non–value-added activities, or waste, within a system.

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Item 7 Answer: A

Educational Objective: Treat primary dysmenorrhea.

The most appropriate treatment for this patient is a combined estrogen-progestin contraceptive pill. Her history of cyclic pain and normal findings on pelvic examination are consistent with primary dysmenorrhea, which occurs in up to 50% of menstruating women and causes significant discomfort and disruption of activities. Etiology is thought to be associated with prostaglandin release that induces uterine contractions as a part of menses, resulting in increased uterine basal tone. This increase in tone may decrease uterine microvascular blood flow with relative ischemia and resulting pain. Evidence supports the efficacy of prostaglandin inhibitors (NSAIDs and cyclooxygenase-2 inhibitors) in treating dysmenorrhea; however, because this patient did not tolerate the gastrointestinal adverse effects associated with NSAID use, the next step is a trial of combined estrogen-progestin contraceptive pills, which frequently provide clinical relief.

Depot medroxyprogesterone acetate and progestin-only contraceptive pills are effective forms of contraception that can cause menstrual suppression, although bleeding patterns are very variable. Data for treatment of primary dysmenorrhea with depot medroxyprogesterone acetate or progestin-only contraceptive pills are lacking.

Selective serotonin reuptake inhibitors (SSRIs) may be considered for the treatment of premenstrual syndrome (PMS), in which disruptive physical or behavioral symptoms occur repetitively during the second half of the menstrual cycle, or premenstrual dysphoric disorder (PMDD), which is characterized by severe symptoms of irritability, mood swings, depression, anxiety, sleep disturbance, headache, fatigue, and musculoskeletal pain. Whereas PMS occurs in 30% to 80% of menstruating younger women, PMDD is less prevalent, occurring in 3% to 8% of women of reproductive age. This patient's symptoms are related to her menstrual period and do not support a diagnosis of PMS or PMDD; therefore, initiation of an SSRI is not appropriate.

Tranexamic acid is an antifibrinolytic drug that is used to treat severe menstrual bleeding. It is not an appropriate treatment for dysmenorrhea.

KEY POINT

- NSAIDs and cyclooxygenase-2 inhibitors are an effective treatment for primary dysmenorrhea; however, in patients who cannot tolerate NSAIDs or have incomplete relief of symptoms, use of combined estrogen-progestin hormonal contraceptive therapy is effective.

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Item 8 Answer: C

Educational Objective: Prevent pressure ulcers in an older patient.

A foam mattress overlay is the most appropriate intervention in this patient at risk for a pressure ulcer. Pressure ulcers are a common occurrence in hospitals and long-term care settings, affecting up to 3 million patients and costing nearly $11 billion per year in the United States. It is far less costly to prevent pressure ulcers than to treat them; therefore, physicians need to be proactive in assessing risk for pressure ulcers and instituting evidence-based preventive measures. Risk factors include advanced age, cognitive impairment, reduced mobility, sensory impairment, and comorbid conditions that affect skin integrity (such as low body weight, incontinence, edema, poor microcirculation, and hypoalbuminemia). Intervention is warranted in this patient with multiple risk factors, including older age, advanced dementia, bedbound status, and urinary and fecal incontinence. A clinical practice guideline issued by the American College of Physicians (ACP) recommends the use of advanced static mattresses (a mattress made of foam or gel that does not move when a person lies on it) or an advanced static overlay (a material such as sheepskin or a pad filled with air, water, gel, or foam that is secured to the top of a bed mattress) to prevent pressure ulcers in at-risk individuals. These interventions have been found to lower the risk of pressure ulcers relative to standard hospital mattresses. Advanced static mattresses and overlays work by redistributing pressure and reducing shear that may lead to development of ulcers.

Dynamic support surfaces, such as low-air loss beds or alternating air mattresses or overlays, have no demonstrated benefit in preventing pressure ulcers, and the ACP guideline recommends against their use in pressure ulcer prevention. Additionally, these dynamic systems are very costly and their use for this purpose represents a low-value care intervention. The role of dynamic support surfaces is also unclear in treating patients with established pressure ulcers, as they have not definitively been shown to improve outcomes relative to advanced static support surfaces and frequent repositioning.

Although malnutrition is clearly a risk factor for pressures ulcers, there are minimal data supporting the effectiveness of enteral feeding as an intervention to prevent pressure ulcers. In some studies, the risk of ulcer development appeared higher in patients placed on enteral feedings than in those not receiving enteral nutrition. Additionally, enteral feeding is not without complications and may negatively influence quality of life. Although there is evidence that protein and amino acid supplementation are of benefit in patients with established pressure ulcers, the role of nutritional supplementation, and specifically enteral nutrition, for prevention of pressure ulcers has not been determined.

Frequent repositioning is often performed as a component of multimodal interventions to prevent pressure ulcers.

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H CONT. Such multimodal interventions have been shown to be beneficial; however, there is a paucity of studies of repositioning alone and no good evidence to support repositioning alone as a pressure ulcer prevention tool. Nonetheless, repositioning should always be a part of a multimodal approach to pressure ulcer prevention.

KEY POINT

- Advanced static mattresses or overlays reduce the risk of pressure ulcers in at-risk patients.

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Item 9 Answer: D

Educational Objective: Recognize when to discontinue breast cancer screening.

Recommending discontinuation of breast cancer screening is appropriate in this patient. Clinical trials of screening mammography in women 75 years of age and older are not available; therefore, the survival benefit of screening mammography for breast cancer in these women is not known. Additionally, observational studies suggest a potential benefit of breast cancer screening in women 75 years of age and older only if life expectancy exceeds 10 years. In this older patient with end-stage kidney disease, life expectancy is estimated to be approximately 3 years. There are also considerable potential harms to screening, including false-positive results that lead to overtreatment and psychological distress. Because of these factors, the American Society of Nephrology, through the Choosing Wisely campaign, recommends against performing routine cancer screening in patients on dialysis with limited life expectancies and no signs or symptoms of cancer. Therefore, continuing breast cancer screening with mammography in this patient, either annually or biennially, is likely to cause harm without significant benefit, and recommending discontinuation of screening is appropriate.

Breast MRI in addition to mammography is indicated for screening only in women with a lifetime risk of breast cancer of 20% to 25% or higher as calculated by models largely dependent on family history or other clinical circumstances. The use of breast MRI would not be appropriate in this patient who is not at high risk and without a clear indication for continued screening.

KEY POINT

- Women should have a life expectancy of at least 10 years to benefit from screening mammography.

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Item 10 Answer: D

Educational Objective: Diagnose bulimia nervosa.

The most likely diagnosis is bulimia nervosa. It is important to differentiate between types of eating disorders as the treatment varies depending on the diagnosis. Bulimia nervosa is characterized by frequent episodes (≥1 per week) of binge eating followed by inappropriate compensatory behaviors (self-induced vomiting or misuse of laxatives, diuretics, and enemas) due to fear of weight gain. Physical examination may reveal erosion of dental enamel, parotid gland swelling, xerosis, and Russell sign (scarring or calluses on the dorsum of the hand if used to induce vomiting). This patient meets diagnostic criteria for bulimia nervosa because she has recurrent episodes of binge eating with recurrent purging to try to compensate for the intake of calories.

Anorexia nervosa is characterized by persistent caloric intake restriction leading to significantly low body weight, a distorted body image, and an intense fear of gaining weight or becoming fat. Subtypes include restricting type (no binge eating or purging behaviors) and binge eating/purging type (purging with or without binging). The differentiating factor between bulimia nervosa and the purging subtype of anorexia nervosa is BMI. Because both purging and laxative abuse are ineffective in removing calories (although they may cause loss of water weight), patients with bulimia nervosa tend to be normal weight to slightly overweight, as seen in this patient. Conversely, the diagnostic criteria for anorexia require that the patient be underweight, generally with a BMI less than 18.5. Menstrual irregularities occur in both anorexia nervosa and bulimia nervosa and are present in approximately one half to one third of patients with bulimia. Although amenorrhea previously was a requirement for the diagnosis of anorexia nervosa, it has been removed from the diagnostic criteria in the DSM-5. Many experts consider anorexia nervosa and bulimia nervosa as a continuum, as one condition often develops from the other.

Binge eating disorder is defined as episodes of eating significantly more food in a short period than most people at least once per week over 3 months, while feeling a lack of control, and is often accompanied by feelings of disgust or guilt afterward but without attempted compensatory behaviors for excessive caloric intake.

KEY POINT

- Bulimia nervosa is characterized by frequent episodes (≥1 per week) of binge eating followed by inappropriate compensatory behaviors (self-induced vomiting or misuse of laxatives, diuretics, and enemas) due to fear of weight gain.

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Item 11 Answer: D

Educational Objective: Manage otitis media with effusion.

This patient has otitis media with effusion (OME), and clinical observation is the most appropriate next step in management. OME is defined as fluid in the middle ear but without signs of infection. It is associated with eustachian tube dysfunction, which impairs drainage and causes retention of fluid in the middle ear, and frequently occurs following an upper respiratory tract infection or with exacerbation of seasonal allergies, as in this patient. Patients with OME frequently present with symptoms of aural fullness and hearing loss, and examination shows clear or yellowish fluid present behind a retracted tympanic membrane. Most cases of OME will resolve without treatment over the course of 12 weeks. Although many patients with OME are treated with decongestants, antihistamines, or nasal glucocorticoids, evidence of effectiveness is very limited. However, treatments focused on symptoms associated with underlying conditions that may be contributing to eustachian tube dysfunction and OME, such as the nasal congestion with seasonal allergies in this patient, would be reasonable.

Acute otitis media is characterized by fluid and inflammation in the middle ear accompanied by symptoms of infection. Although evidence to guide treatment of acute otitis media in adults is lacking, oral antibiotics such as amoxicillin, along with analgesics and decongestants, are the mainstays of therapy. This patient has no evidence of infection, and antibiotic therapy is therefore not indicated.

Otitis externa is inflammation of the external ear canal and may present either acutely or chronically. Examination shows inflammation of the external ear canal, and treatment may be with a combined antibiotic and glucocorticoid-containing ototopical agent such as combination neomycin, polymyxin B, and hydrocortisone. In this patient with no evidence of external ear canal inflammation on examination, neomycin, polymyxin B, and hydrocortisone ear drops are not indicated.

Although symptoms of OME will resolve in most patients within 12 weeks, those with persistent symptoms beyond that time period who have not responded to other interventions may be considered for myringotomy with tympanostomy tubes. It would be premature to pursue this treatment at this point in this patient's course.

KEY POINT

- Most cases of otitis media with effusion resolve spontaneously; observation and symptomatic treatment of conditions contributing to eustachian tube dysfunction are appropriate.

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Item 12 Answer: D

Educational Objective: Treat a patient with neuropathic pain.

A lidocaine patch is the most appropriate treatment in this patient with neuropathic pain. Topical lidocaine in the form of either a patch or the less expensive cream has been shown in randomized controlled trials to be very effective in treating postherpetic neuralgia and diabetic peripheral neuropathy. It has also been shown to be better tolerated and to have fewer side effects than systemic therapies. Similarly, topical capsaicin is an effective topical therapy for neuropathic pain. In patients with pain amenable to localized therapy, and particularly in those in whom systemic treatment may be problematic, such as this patient with cognitive impairment and an increased risk for falls, a topical agent that avoids central nervous system toxicity is preferable as first-line therapy.

Fentanyl is a potent opioid that is indicated only in patients who are opioid tolerant due to chronic treatment, and this patient has not been taking opioids regularly. Furthermore, fentanyl carries the same risk of delirium as other opioids and would therefore not be an appropriate choice based on her previous episodes of opioid-associated delirium.

Gabapentin is first-line therapy for systemic neuropathic pain conditions that affect large portions of the body that are difficult to treat topically. However, dizziness and drowsiness are major adverse effects of gabapentin and might increase this patient's risk of falls and worsen her cognitive function. This patient has localized pain, which is better suited to topical therapy; therefore, gabapentin would be considered second-line therapy.

Tramadol binds to opioid receptors in the central nervous system and can cause adverse reactions similar to those of other opioid medications, which this patient does not tolerate. Tramadol also has a wide range of potential drug-drug interactions and a significant side effect profile, making it a poor choice for older patients. It would therefore not be an appropriate choice for treating this patient's pain, which is amenable to topical treatments.

KEY POINT

- Topical lidocaine is effective in the treatment of postherpetic neuralgia.

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Item 13 Answer: D

Educational Objective: Diagnose uveitis.

This patient has uveitis, which is inflammation involving the middle structures of the eye (iris, ciliary body, and choroid).

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It usually presents with unilateral eye pain, redness, and photophobia. The characteristic finding on physical examination is circumferential redness around the border of the sclera and cornea (corneal limbus), termed ciliary flush, which represents dilated conjunctival vessels. Pupillary miosis is also often seen. Slit lamp examination commonly reveals inflammatory ("flare") cells in the anterior chamber. Uveitis can either be idiopathic or occur as part of an underlying systemic condition, such as autoimmune disorders, arthritides associated with HLA-B27 antigen, infection (syphilis, tuberculosis, herpes simplex virus), malignancy, and sarcoidosis. This patient has symptoms suggestive of ankylosing spondylitis, including fatigue and low back pain that awakens her from sleep and improves with activity and NSAID therapy. Ankylosing spondylitis is a systemic condition that may be associated with uveitis.

Corneal ulcers are caused by trauma, contact lens wear, herpes simplex virus infection, bacterial infection, and connective tissue disorders (ankylosing spondylitis). Although corneal ulcers can occur in the setting of ankylosing spondylitis, this patient's ciliary flush is more characteristic of uveitis.

Patients with episcleritis typically present with redness, irritation, and tearing but not significant ocular pain. Additionally, the redness seen in episcleritis is usually more widespread rather than limited to the perilimbic region of the involved eye, making this an unlikely diagnosis in this patient.

Scleritis can be associated with autoimmune disorders; however, it typically presents bilaterally, involves redness across the entire sclera, and does not present with ciliary flush.

KEY POINT

- Uveitis is characterized by unilateral eye pain, photophobia, and ciliary flush; it is commonly associated with autoimmune disorders, arthritides associated with HLA-B27 antigen, infection, malignancy, and sarcoidosis.

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Item 14 Answer: B

Educational Objective: Treat an overweight patient with pharmacologic therapy.

The most appropriate management is to treat this overweight patient with orlistat. Pharmacologic therapy may be used as an adjunct to diet, physical activity, and behavioral treatments in patients with a BMI of 30 or higher or in patients with a BMI of 27 or higher with overweight- or obesity-associated comorbidities. In light of this patient's dieting attempts (including with dietician-monitored diets), physical activity, and behavioral therapy without sustained weight loss, she should be considered for pharmacologic treatment, and the most appropriate pharmacologic agent for this patient is orlistat. Orlistat is an inhibitor of gastric and pancreatic lipases. Taken three times per day (during or up to 1 hour after meals), orlistat results in malabsorption of approximately 30% of ingested fat. Twelve months of orlistat treatment at doses of 120 mg three times per day or 60 mg (available over the counter) three times per day results in a mean weight loss of 3.4 kg or 2.5 kg (7.5 lb or 5.5 lb), respectively, compared with placebo. Orlistat also reduces BMI, waist circumference, blood pressure, blood cholesterol level, and risk for type 2 diabetes mellitus. Loose stool is a common side effect of orlistat; however, this may not be a major concern for this patient given her chronic constipation.

Lorcaserin, a brain serotonin 2C receptor agonist, acts as an appetite suppressant. It should be used with caution in patients taking medications that increase serotonin levels, such as sertraline. Therefore, this patient should not be prescribed lorcaserin.

Combination low-dose phentermine (a sympathomimetic drug) and low-dose topiramate (an antiepileptic drug) has demonstrated efficacy in reducing weight, possibly by suppressing appetite, altering taste, and increasing metabolism. However, phentermine-topiramate is contraindicated in patients with glaucoma; thus, it should not be prescribed in this patient.

Referral for bariatric surgery is indicated in all patients with a BMI of 40 or higher and in patients with a BMI of 35 or higher with obesity-related comorbid conditions. This patient does not meet the criteria for bariatric surgery.

KEY POINT

- Pharmacologic therapy may be used as an adjunct to diet, physical activity, and behavioral treatments in patients with a BMI of 30 or higher or in patients with a BMI of 27 or higher with overweight- or obesity-associated comorbidities.

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Item 15 Answer: B

Educational Objective: Counsel a high-risk older driver.

The patient should be advised to retire from driving. The American Medical Association recommends that physicians assess older patients for physical or mental impairments that might adversely affect driving abilities. Assessing the older driver is complex and relies heavily on physician clinical judgment in addition to evaluation of underlying conditions that pose a risk to safe driving. Risk factors that increase the likelihood of an adverse driving event include cognitive dysfunction, caregiver report of unsafe skills, history of citations or accidents, driving fewer than 60 miles per week, alcohol

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or medications that affect the central nervous system, emotional aggression or impulsivity, impaired mobility (including neck range of motion, range of motion of the extremities, and coordination), visual impairment, and medical disorders that predispose to loss of consciousness. The more risk factors the patient has, the higher the risk of an adverse driving event. This patient has four of these risk factors (cognitive dysfunction, driving fewer than 60 miles per week, caregiver concern, and impaired vision), none of which may be easily reversed. Therefore, given her level of risk, she should be advised to discontinue driving.

Patient self-rating of driving skill has been shown to be unhelpful in assessing driving risk. Caregiver report of driving ability is more reliable. Although this patient is confident in her driving abilities, her daughters' report of "near misses" should be taken into account along with the patient's risk factors for an adverse driving event.

This patient is being seen by an ophthalmologist for her vision loss, which has been stable and meets the minimum limits for the ability to drive. Although her ophthalmologist is able to render an opinion on the status and prognosis of her vision loss, the assessment of the ability to drive safely is complex and multifactorial, of which visual function is only one element. Therefore, the ability of a patient to drive safely should be made by the clinician who has knowledge of these different factors and is able to evaluate them in the overall context of the patient.

Although neuropsychiatric testing may provide greater detail regarding this patient's mild cognitive dysfunction, it is unlikely to change the recommendation to retire from driving considering the multitude of risk factors in addition to her cognitive dysfunction.

KEY POINT

- Older adult patients who have multiple risk factors for an adverse driving event, such as cognitive dysfunction, caregiver report of unsafe skills, history of citations or accidents, impaired mobility, and visual impairment, should be advised to retire from driving.

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Item 16 Answer: C

Educational Objective: Manage medically unexplained symptoms with cognitive-behavioral therapy.

This patient with medically unexplained symptoms (MUS) would benefit most from cognitive-behavioral therapy (CBT). She presents with many of the common symptoms seen in patients with MUS, and her symptoms are significantly affecting her quality of life. She has undergone extensive and costly medical evaluation with normal results, and several medications have been tried without benefit. Although it is tempting for the patient and the physician to think that additional testing or medications will elucidate a previously undiscovered diagnosis, this is rarely the case. This pattern of care often leads to iatrogenic injury, excess health care costs, and patient dissatisfaction. Goals of care should be shifted away from medical diagnosis toward addressing the impact of the patient's symptoms on her life. CBT involves educating the patient so that she understands the plan of care and its purpose, obtaining and reinforcing a commitment from the patient for the chosen plan of care, setting and reviewing mutually chosen patient goals, and negotiating new plans and therapy as needed. CBT has been shown to be effective in patients with MUS. Although CBT is generally performed by trained therapists, the internist can reinforce the basic principles of CBT at each follow-up visit.

Ordering further diagnostic testing, such as a brain MRI, when there is no strong clinical suspicion of disease is inappropriate. Despite this patient's various neurologic symptoms, she has no focal neurologic findings and no indication for brain imaging.

Patients with MUS may have underlying depression; however, this patient reports no depressed mood or affect, anhedonia, or problems with concentration. Additionally, a previous trial of a selective serotonin reuptake inhibitor was unsuccessful. Therefore, treatment with another antidepressant medication is not indicated.

Frequently, the patient with MUS will request referral to a specialist, or the internist will contemplate referral due to frustration or uncertainty. In this patient, referral to another physician risks further fragmentation of care and duplicate or more invasive testing, neither of which is indicated.

Regularly scheduled visits with an internist, accompanied by targeted physical examinations, are essential in the patient with MUS. Randomized trials suggest that this care plan may improve patients' physical functioning. Additionally, recent evidence suggests that telephone contact may be an effective substitute for face-to-face visits. An interval of 6 months between follow-up visits is too long to effectively manage this patient with MUS.

KEY POINT

- Cognitive-behavioral therapy may be beneficial in managing medically unexplained symptoms and should be considered in place of additional testing.

Bibliography

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Item 17 Answer: C

Educational Objective: Evaluate a palpable breast mass in a postmenopausal woman.

This woman should undergo a diagnostic core needle biopsy of the palpable breast mass to obtain a tissue diagnosis.

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Although mammography is indicated with a newly detected breast lump to assist in evaluation, it has false-negative rates of between 10% and 20% even if a standardized reporting system, such as the Breast Imaging Reporting and Data System (BI-RADS), suggests a negative finding as in this patient with a BI-RADS category of 1, indicating that no radiographic masses, architectural disturbances, or suspicious calcifications are present. Therefore, biopsy is required for a palpable breast mass even if a mammogram is negative or nondiagnostic, as in this patient. Fine needle aspiration cytology is also an option, but evidence indicates slightly better sensitivity and specificity with larger bore core biopsy needles.

Breast MRI may further define the characteristics of the mass but would not provide adequate information to obviate the need for a definitive tissue diagnosis.

Conservative management, with re-evaluation at a follow-up visit in 4 weeks or resuming regular mammographic screening, is not appropriate in a postmenopausal woman with a palpable breast mass, which requires further, immediate evaluation.

KEY POINT

- Biopsy is required for a palpable breast mass even if a mammogram is negative or nondiagnostic.

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Item 18 Answer: C

Educational Objective: Evaluate a patient with disequilibrium.

This older patient is experiencing disequilibrium, or unsteadiness with walking or standing, and is likely to benefit from physical therapy. She is lightheaded and dizzy without presyncope, syncope, orthostasis, or vertigo. Disequilibrium frequently presents in frail elderly patients who have multiple sensory deficits (such as impaired visual or auditory acuity and impaired proprioception), motor weakness, joint pain, psychiatric disease, orthostasis, medication side effects, or neuropathic and cerebellar diseases affecting balance and gait. Frequently more than one cause can be identified in a specific patient. Multidisciplinary efforts (physical therapy, visual and auditory screening followed by correction of impairment, and mobility aids that stabilize ambulation) can produce improvement in functional status.

A CT scan of the head is unlikely to be helpful in delineating a cause of dizziness as this patient's neurologic examination is normal and she has no history of falls or head trauma that would put her at risk for a subdural hematoma. CT scans of the head have limited ability to image the posterior fossa and cerebellum, so if a central cause of this patient's symptoms were suspected, MRI of the brain would be the preferred test.

The diagnostic yield of 24- to 48-hour ambulatory electrocardiographic monitoring in uncovering significant cardiac arrhythmias responsible for generalized weakness and dizziness would be low in this patient without a history or symptoms of cardiac disease.

This patient should be evaluated by a physical therapist for the most appropriate gait aid. She currently is unable to use a cane effectively, and she likely will need further evaluation and training in using the best assistive device. A walker should not be provided without additional evaluation.

KEY POINT

- Management of disequilibrium involves physical therapy, visual and auditory screening followed by correction of impairment, and mobility aids that stabilize ambulation; extensive imaging and testing is unnecessary.

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Item 19 Answer: D

Educational Objective: Manage postoperative anemia in a patient with cardiovascular disease.

No transfusion or further diagnostic testing is necessary for this patient with postoperative anemia and cardiovascular disease. He had a considerable decline in hemoglobin level, but this is consistent with the amount of blood loss noted in surgery (1200 mL). Moreover, this degree of blood loss after multilevel spine fusion is not atypical. Multiple studies have demonstrated that a conservative approach to perioperative blood management is as good as or superior to a liberal approach (such as maintaining a hemoglobin level of >10 g/dL [100 g/L]). This approach has been demonstrated even in patients with known cardiac disease or risk factors for cardiac disease. Current guidelines recommend transfusing red blood cells if a patient has symptoms attributable to anemia or a hemoglobin level less than 7 to 8 g/dL (70-80 g/L).

Intravenous iron is typically indicated in patients who are unable to take oral iron or unable to take in adequate amounts of oral iron in the presence of ongoing chronic blood loss, and in patients with kidney failure and anemia. However, this patient with mild anemia and likely normal iron stores may not require iron therapy for postoperative anemia and does not have a clear indication for parenteral iron if therapy were needed.

Transfusion of one unit of packed red blood cells (pRBCs) is not indicated because the patient does not have a clear indication for transfusion. If transfusion were indicated, the number of units administered should be based upon the target hemoglobin level and if active blood loss is present. One unit of pRBCs usually raises the hemoglobin level by 1 g/dL (10 g/L).

A frequent practice of clinicians is to order no less than two units of pRBCs at a time. This is based on the erroneous assumption that "more is better," and that the transfusion

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equina syndrome and is not necessary to establish the diagnosis.

KEY POINT

- Urgent evaluation for surgical decompression is required in all patients with findings of cauda equina syndrome, characterized by acute low back pain, radicular features, saddle anesthesia, urinary retention, absence of reflexes, and decreased anal tone.

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Gitelman A, Hishmeh S, Morelli BN, et al. Cauda equina syndrome: a comprehensive review. Am J Orthop (Belle Mead NJ). 2008 Nov;37(11): 556-62. [PMID: 19104682]

Item 24 Answer: D

Educational Objective: Treat erectile dysfunction in an obese patient.

Lifestyle modification, including weight loss, is the most appropriate next step in the management of this patient who has erectile dysfunction (ED) and is obese. First-line treatments for ED include lifestyle modification (weight loss, exercise, smoking cessation), psychotherapy as needed, and phosphodiesterase type 5 (PDE-5) inhibitors. Randomized controlled trials have shown that obese men who lose weight through dietary changes and exercise experience significant improvement in erectile function compared with obese men who do not lose weight. This patient's sedentary lifestyle has likely contributed to his obesity. He would likely experience improved erectile function as a result of substantial weight loss through healthy diet and exercise. After discussion with the patient, a decision can be made about whether to institute lifestyle changes alone or to combine lifestyle changes with a PDE-5 inhibitor.

Intraurethral alprostadil is more effective than PDE-5 inhibitors at treating ED. However, compliance with intraurethral alprostadil is low, and it is not considered a first-line treatment for ED.

Although it is important to inquire about that status of romantic relationships in patients with sexual dysfunction, this patient reports that his marriage is satisfying; therefore, marriage counseling would not be indicated.

It would be inappropriate to prescribe venlafaxine for depression in this patient who reports that his mood is excellent. Furthermore, venlafaxine is associated with sexual dysfunction.

KEY POINT

- First-line therapy for erectile dysfunction includes lifestyle modification (weight loss, exercise, smoking cessation), psychotherapy as needed, and phosphodiesterase type 5 inhibitors.

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Esposito K, Guigliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA. 2004 Jun 23;291(24):2978-84. [PMID: 15213209]

Item 25 Answer: B

Educational Objective: Treat hyperlipidemia in a patient with atherosclerotic cardiovascular disease and risk factors for statin-associated adverse effects.

The most appropriate treatment for this patient is moderate-intensity statin therapy, such as with rosuvastatin. This patient has peripheral arterial disease, a form of clinical atherosclerotic cardiovascular disease (ASCVD), and therefore meets the criteria for one of four patient groups that have been shown to benefit from the treatment of hyperlipidemia with statin therapy. Patients with clinical ASCVD benefit most from high-intensity statin therapy; however, for those with risk factors for statin-associated adverse effects, moderate-intensity therapy is recommended. This patient is best treated with a moderate-intensity statin because he has three such risk factors: age older than 75 years, chronic kidney disease, and use of a medication known to interact with statins (diltiazem).

The use of high-intensity rosuvastatin in this patient has significant potential to cause adverse effects, including myopathy and liver dysfunction. In this patient, the risks associated with high-dose statin therapy outweigh the potential benefits, especially since moderate-intensity statin therapy can reduce the LDL cholesterol level 30% to 49% and provide secondary prevention of cardiovascular events.

Niacin monotherapy has not been shown to reduce the incidence of cardiovascular events and is not considered first-line therapy for the prevention of ASCVD. Niacin and other nonstatin drugs are only recommended for patients who have severe hypertriglyceridemia, do not respond to statin therapy, or have a history of statin intolerance.

Providing no additional treatment in this patient with ASCVD would be inappropriate. Current American College of Cardiology/American Heart Association guidelines recommend statin therapy for all patients with clinical ASCVD, regardless of LDL cholesterol levels, to reduce the risk of cardiovascular events.

KEY POINT

- In patients with clinical atherosclerotic cardiovascular disease and risk factors for statin-associated adverse effects, moderate-intensity statin therapy is recommended.

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Item 26 Answer: D

Educational Objective: Recognize relative risk as the standard outcome measure for a cohort study.

In this cohort study, the standard outcome measure is relative risk. Cohort studies are a type of observational study that

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examines the outcomes of patients with different exposures or risks. This study investigated the outcomes (erectile function scores) of two groups of men who had received radiation therapy for prostate cancer, one of which was exposed to tadalafil and one of which was not.

Relative risk is the ratio of the probability of developing a specific outcome (in this case, erectile function score) in a group with an exposure or risk factor present (treatment with tadalafil) to the probability of developing the specific outcome in a group without the exposure or risk factor present (no treatment with tadalafil). A relative risk that is greater than or less than 1 indicates a more likely or less likely outcome, respectively, of the measured variable in the exposure or risk factor group compared with the group without the exposure or risk factor present.

Confidence intervals are a method for indicating the range in which a value derived from a study is likely to lie, with 95% being the usual calculated range. Whereas a *P* value is calculated to assess whether a trial result is likely to have occurred simply by chance, confidence intervals provide a range of possible effect size compatible with the data. Confidence intervals may be calculated for most statistical reporting measures but are not themselves used as an outcome measure for evaluating study results.

The number needed to treat (NNT) is an estimate of the number of patients who must receive an intervention to cause one patient to experience the beneficial outcome of interest. The NNT has become a standard reporting measure for randomized controlled trials. It is calculated by taking the inverse of the absolute risk change between study groups. The concept of NNT has been applied to cohort studies to suggest the magnitude of effect of an exposure (sometimes referred to as number needed to be exposed); however, because cohort studies are observational and not experimental trials, the calculation of similar measures for cohort studies is statistically more difficult than in experimental studies. Additionally, the accuracy of these measures for cohort studies is less clear. Therefore, relative risk remains the main outcome measure used for cohort studies.

The odds ratio is conceptually similar to relative risk, but rather than comparing the ratio of rates of occurrence of an event between study groups, the odds ratio compares the odds (the ratio of the probability that the event will happen to the probability that the event will not happen) between study groups. The odds ratio is required for studies using retrospective data, such as case-control studies in which the groups being compared may not have a similar risk for the condition. Case-control studies compare the outcomes of patients with a disease (cases) to those without a disease (controls). Because all of the patients in this study had prostate cancer treated with radiation therapy (a cohort) and a specific subsequent exposure or risk was evaluated, it is not a case-control study and an odds ratio would not be the standard outcome measure.

KEY POINT

- Cohort studies investigate the outcomes of similar patients with different exposures; the standard outcome measure for a cohort study is relative risk.

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Item 27 Answer: C

Educational Objective: Diagnose hearing loss in an older patient.

This older patient should be evaluated for hearing loss with the whispered voice test. Hearing loss is common in older adults, and it results in significant impairment in quality of life and potentially leads to depression and social isolation. Because patients may experience difficulties in understanding and communication, hearing loss is frequently misdiagnosed as cognitive dysfunction. There is some evidence that hearing aids in older patients improve not only hearing but also quality of life; therefore, patients who have cognitive or affective concerns that may be related to hearing should be screened for hearing loss. No one screening test has been shown to be superior to another. Whispered voice test, finger rub test, hearing loss questionnaire, and hand-held audiometry are all reasonable screening tests. Many patients with significant hearing loss deny any hearing deficits and can compensate for their hearing loss in a quiet office environment; therefore, a patient's perception of his or her own hearing or the patient's ability to carry on a normal conversation in the office setting should not be considered as evidence of adequate hearing. Patients who test positive or who report hearing loss should be referred for formal audiologic testing and consideration of amplification with hearing aids.

This patient has stable mild cognitive dysfunction that is not interfering with his executive functioning. His social functioning is impaired, but hearing loss has not been ruled out as the cause of his social impairment. As such, medication for dementia, such as donepezil, is not currently indicated.

Social isolation is a symptom of depression; however, this patient was appropriately screened with the two-question method ("During the past month, have you been bothered by feeling down, depressed, or hopeless?" and "During the past month, have you been bothered by little interest or pleasure in doing things?"), which has a 97% sensitivity for identifying depression in older adults. A more extensive screen for depression, such as the PHQ-9, is not likely to add helpful information in this patient.

A diagnosis of hearing loss and its correction would be missed with clinical observation alone.

KEY POINT

- Older patients who present with symptoms of a mood disorder or cognitive dysfunction should be screened for hearing loss.

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Item 28 Answer: C

Educational Objective: Diagnose sacroiliitis.

This patient most likely has sacroiliitis, or inflammation of the sacroiliac (SI) joints. SI joints are true synovial joints between the sacrum and ilium of the pelvis. The SI joint may be involved as part of a systemic inflammatory syndrome such as spondyloarthritis, particularly ankylosing spondylitis, but may also be involved as an isolated musculoskeletal condition. Biomechanical factors that predispose to SI joint injury include repetitive torsional forces or unidirectional pelvic shear forces, as might occur with stepping off of a curb. Patients with leg length discrepancies or those with other conditions that may alter pelvic mechanics, such as pregnancy, scoliosis, or lumbar fixation, may also be at increased risk. The diagnosis of sacroiliitis is supported by the posterior location of this patient's hip pain and a positive FABER test, in which the hip is Flexed, ABducted, and Externally Rotated and gentle downward pressure is applied to the knee. This test has a high specificity for sacroiliitis and a somewhat lower sensitivity. Therapy for sacroiliitis is similar to that for other joint pain, including rest, anti-inflammatory medications, and possibly physical therapy. A number of additional treatments, including glucocorticoid injections, are used in patients who do not respond to conservative therapy.

Hip joint osteoarthritis causes pain directly in the hip joint that frequently radiates to the groin. Range of motion of the hip is usually limited and reproduces the pain. This patient's pain does not radiate, and his range of motion is normal, making this a less likely diagnosis.

Piriformis syndrome results from compression or limitation of the sciatic nerve by the piriformis muscle. It typically causes symptoms similar to sciatic nerve compression in the lumbosacral spine, with pain, tingling, and numbness that radiate into the leg, findings that are not present in this patient.

Trochanteric bursitis classically causes lateral hip pain over the greater trochanteric bursa, which is located over the greater trochanter lateral to the hip joint. Pain associated with trochanteric bursitis may radiate to the buttock or knee and is often worse when lying on the affected side. It does not affect range of motion. Trochanteric bursitis can be differentiated from hip joint pain based on its characteristic location relative to the pain associated with sacroiliitis.

KEY POINT

- Sacroiliitis is characterized by tenderness to palpation of the sacroiliac joint, pain that is reproduced with the FABER (Flexion, ABduction, External Rotation) test, and no pain with passive range of motion of the hips.

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Byrd JW. Evaluation of the hip: history and physical examination. N Am J Sports Phys Ther. 2007 Nov;2(4):231-40. [PMID: 21509142]

Item 29 Answer: D

Educational Objective: Manage a patient who has undergone direct-to-consumer genetic testing.

In this patient who has no family history of breast or ovarian cancer, no further testing is necessary, despite the results of the direct-to-consumer genetic test. Direct-to-consumer genetic testing, though attractive to patients, is fraught with many potential drawbacks, including the uncertain validity of the tests themselves. This form of testing relies on a case-control–based approach. Single-nucleotide polymorphisms (SNPs) that are disproportionately found in affected individuals with a specific disease are identified, and odds ratios indicating the influence of particular SNPs on the pretest likelihood for the disease are calculated. Unfortunately, most SNPs have very low odds ratios and contribute only a small proportion to total disease burden. This approach also does not capture the complex interaction between genetic influences on development of disease or the effect of other factors, such as environmental exposures, among other potentially confounding issues. Therefore, a positive result with this type of testing frequently does not indicate an increased probability of having the disease but may cause unnecessary patient concern and anxiety.

Additionally, given the lack of pretest counseling, an essential component of proper genetic testing in which the basic concepts of genetic testing and interpretation can be explained, patient misinterpretation of test results is especially likely. It is essential that this patient be educated about the implications of her test results, including the limitations. This patient should be informed that her risk of developing breast cancer is not 52.5% and is instead much lower. Even if the results of this test were found to be valid, her lifetime risk of developing breast cancer would increase from 12.4% (the lifetime risk for women born in the United States who are considered to be at average risk) to approximately 19%.

According to the U.S. Preventive Services Task Force (USPSTF), *BRCA* genetic testing should be limited to patients whose family history indicates a possible familial inheritance as seen by the presence of *BRCA*-related malignancies. There is no such indication of a familial pattern of disease in this patient; therefore, *BRCA* genetic testing would not be indicated.

Breast MRI is a highly sensitive study for detection of breast cancers and other breast pathology. However, its appropriate use as a screening tool is evolving, with variable recommendations existing for use in patients considered at high risk for breast cancer. This patient does not have a clear increased risk based on her history or the results of her direct-to-consumer genetic testing. Therefore, initiating screening MRI in this patient would not be appropriate.

Breast self-examination has not been shown to be a reliable method for detection of breast cancer in average-risk women or in those at increased risk, and the USPSTF advises against its use for screening. It would therefore not be an appropriate management recommendation for this patient.

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KEY POINT

- Direct-to-consumer genetic tests have questionable clinical validity and may lead to patient misinterpretation of test results and unnecessary anxiety.

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Item 30 Answer: D

Educational Objective: Treat dyspnea at the end of life.

The most appropriate treatment of this patient's dyspnea is oral morphine. Dyspnea is common in many chronic progressive diseases near the end of life, and systemic opioids are the standard of care for refractory dyspnea in advanced disease. Although opioids have been shown to be very effective in treating dyspnea, the exact mechanisms underlying this benefit have not been well defined. Potential mechanisms of action that reduce dyspnea include altering central perception of dyspnea or modulating the activity of peripheral receptors in the lung that contribute to the sensation of dyspnea.

Many physicians worry about depressing respiratory drive with opioids in patients with end-stage disease and dyspnea. In fact, numerous studies have shown that opioids, when dosed and titrated appropriately, do not hasten death, do not raise Pco_2, and do not lead to respiratory failure, but do effectively manage the sensation of dyspnea. Accordingly, a consensus statement issued by the American College of Chest Physicians states that systemic opioids, dosed and titrated appropriately, are effective and safe for dyspnea in the setting of advanced disease. The dose is generally titrated to achieve the lowest effective dose needed to adequately treat a patient's dyspnea. This patient's emphysema is already being maximally medically managed without improvement of symptoms; therefore, she should receive oral morphine.

Nebulized lidocaine is sometimes used in suppressing intractable cough, but it has no role in treating dyspnea.

Nebulized morphine is often prescribed for relief of dyspnea. However, a meta-analysis showed that nebulized morphine had no benefit compared with nebulized saline in the treatment of dyspnea, and it should not supplant the use of systemic opioids to treat dyspnea.

Dyspnea often produces anxiety in patients, and benzodiazepines may have a role in the treatment of patients with both dyspnea and anxiety. Additionally, studies show that benzodiazepines can be helpful when added to opioids, but opioids remains first-line treatment for dyspnea. This patient does not have anxiety; therefore, lorazepam is not indicated.

KEY POINT

- Systemic opioids are the standard of care for refractory dyspnea in advanced disease.

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Item 31 Answer: A

Educational Objective: Manage diabetes mellitus medications in the preoperative setting.

The most appropriate management of this patient's insulin prior to surgery is to administer insulin glargine as usual and withhold the scheduled insulin lispro. Preoperative management of diabetes mellitus requires determination of the patient's medical regimen, recent glycemic control, stress/duration of surgery, and anticipated duration of periprocedural fasting. In most cases, long-acting insulins (glargine and detemir) should be continued uninterrupted at the same dose unless a patient has risk factors for hypoglycemia or is undergoing a procedure requiring a prolonged period without enteral nutrition. Conversely, scheduled short-acting insulins such as lispro should be withheld during the fasting state because their purpose is to suppress postprandial hyperglycemia. In this case, the patient does not require a prolonged procedure or extended period of fasting. He also has no risk factors for hypoglycemia, and his average glucose level is higher than goal. Therefore, continuation of long-acting insulin while withholding scheduled short-acting insulin affords the best approach to glycemic control in the immediate perioperative period.

Continuing insulin lispro along with insulin glargine increases the risk for hypoglycemia during the fasting state. Short-acting insulins should be withheld when a patient is not taking anything by mouth unless the patient requires correction doses for significant hyperglycemia (plasma glucose level >200 mg/dL [11.1 mmol/L]).

Continuous insulin infusion is usually reserved for patients with uncontrolled hyperglycemia, with metabolic acidosis, or who are undergoing high-risk procedures (such as cardiac surgery). This patient has an acceptable plasma glucose level and is undergoing intermediate-risk surgery.

No insulin therapy increases the risk of significant hyperglycemia in this patient under physiologic stress. Therefore, treatment is indicated to prevent significant increases in the plasma glucose level.

KEY POINT

- Continuation of long-acting insulin while withholding scheduled short-acting insulin during fasting affords the best approach to glycemic control in the immediate perioperative period.

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Item 32 Answer: C

Educational Objective: Treat bipolar I disorder.

Treatment with the atypical antipsychotic drug quetiapine is appropriate for this patient with bipolar I disorder, which is defined as one or more manic episodes. A manic episode is characterized by at least 7 days of severe, abnormally expansive, euphoric, or irritable mood associated with at least three of the following symptoms (four if irritable mood only): grandiosity or inflated self-esteem, pressured speech, flight of ideas, distractibility, increased goal-directed activity or psychomotor agitation, excessive involvement in pleasurable activities with high potential for adverse consequences (for example, spending sprees or sexual encounters), and lessened need for sleep. Dysfunction is substantial. The episode is not attributable to the physiologic effects of a substance or to another medical condition. Most patients with bipolar I disorder experience depressive episodes and are at an increased risk for suicide. Periods of depression are more frequent than periods of mania or hypomania in patients with bipolar disorder.

In selecting therapy for patients with bipolar disorder, it is paramount to identify the patient's current phase of illness. For the manic or hypomanic phase of illness, there are 10 different treatments, including one typical antipsychotic agent, lithium, two antiepileptic agents, and six atypical antipsychotic agents. Patients presenting in the depressive phase of illness have two treatment options (quetiapine monotherapy or combination olanzapine-fluoxetine). Different treatment options are available for patients in the maintenance phase of illness. Because identifying the patient's phase of illness and determining complex treatment choices are required, it is paramount that psychiatrists are involved in the care of patients with bipolar disorder.

This patient has acute depression. FDA-approved pharmacologic treatments for bipolar depression are quetiapine alone and combination olanzapine-fluoxetine. Patients with bipolar depression treated with quetiapine should be monitored for hypersomnolence, weight gain, tardive dyskinesia, and hyperglycemia. Lamotrigine is FDA approved for maintenance treatment of bipolar I disorder. Lamotrigine can be prescribed for patients taking quetiapine who experience unacceptable side effects or no improvement of depression.

Antidepressant monotherapy is not recommended (nor FDA approved) for depressed patients with bipolar disorder given lack of efficacy and risk for switching affected patients to hypomania or mania. Therefore, this patient should not receive desipramine, paroxetine, or venlafaxine.

KEY POINT

- FDA-approved pharmacologic treatments for bipolar depression are quetiapine monotherapy and combination olanzapine-fluoxetine.

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Frye MA. Clinical practice. Bipolar disorder--a focus on depression. N Engl J Med. 2011 Jan 6;364(1):51-9. [PMID: 21208108]

Item 33 Answer: B

Educational Objective: Manage suspected severe obstructive sleep apnea in the postoperative setting.

This patient should keep the head of his bed elevated at 30 degrees. He is at high risk for obstructive sleep apnea (OSA) as evidenced by his STOP-BANG score of 6 (snoring, observed apneic episodes, hypertension, BMI >35, age >50 years, and male gender). Patients with a STOP-BANG score greater than or equal to 5 have an increased risk for severe OSA and postoperative morbidity. Conservative postoperative measures that may reduce the risk of pulmonary complications from suspected OSA include nonsupine positioning (keeping the head of the bed at 30 degrees), careful use of sedatives and opioids, and continuous pulse oximetry.

Nasogastric intubation is not appropriate in this patient because it is not known to alter risk of complications from possible OSA postoperatively. Nasogastric tubes are associated with an increased risk of aspiration and pneumonia. Good evidence supports the selective use of nasogastric intubation for the same indications as in the nonoperative setting (for example, severe gastric distention and intractable large-volume emesis).

The patient has no wheezing, dyspnea, or other evidence of small airway obstruction. Therefore, he has no indication for the use of albuterol.

Continuous positive airway pressure (CPAP) ventilation is not indicated at this time. The patient is alert, breathing comfortably, and oxygenating well. Furthermore, his pain is well controlled, so he will not require high doses of systemic opioids. The American Society of Anesthesiology recommends only initiating CPAP for patients at risk for OSA who develop hypoxia or apneic episodes. At least one study has suggested that empiric use of CPAP for all patients at risk for OSA did not improve outcomes and increased length of hospital stay.

KEY POINT

- Conservative postoperative measures that may reduce the risk of pulmonary complications from suspected obstructive sleep apnea include nonsupine positioning, careful use of sedatives and opioids, and continuous pulse oximetry.

Bibliography

American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea. Anesthesiology. 2014 Feb;120(2):268-86. [PMID: 24346178]

Item 34 Answer: E

Educational Objective: Manage preoperative evaluation in a patient undergoing low-risk surgery.

This patient is scheduled for cataract extraction, which is a low-risk surgical procedure and requires no specific

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diagnostic studies for preoperative evaluation. For these and other low-risk invasive procedures, including hernia repairs and superficial surgeries, routine preoperative diagnostic testing is very low yield and unlikely to affect perioperative management. In such situations, diagnostic testing should only be ordered if it is otherwise indicated outside of the preoperative context (such as ordering a urinalysis in a patient with dysuria).

Preoperative chest radiography rarely adds useful information in the evaluation of patients at risk for perioperative pulmonary complications. At least four systematic reviews and guidelines recommend against routine preoperative chest radiography in patients without suspicion of intrathoracic disease.

Routine assessment of blood counts or coagulation parameters is not indicated for most surgical procedures, including low-risk eye surgery. Evaluation for adequate hemostasis requires only a thorough history and physical examination except for procedures in which even a small amount of bleeding could be catastrophic (for example, intracranial surgery). A leukocyte count is indicated only if there is a concern for bone marrow abnormalities or infection. Hemoglobin and hematocrit are reasonable to obtain in patients with findings suggestive of anemia or undergoing large blood loss surgery (such as total hip arthroplasty).

Electrocardiography is not routinely indicated for any surgery and should only be obtained prior to low-risk surgery if there is concern for new or evolving cardiac disease. According to the American College of Cardiology/American Heart Association guidelines, patients with coronary artery disease, arrhythmias, or coronary artery disease equivalents should have electrocardiography performed within 30 days of non-low-risk surgery.

Serum electrolytes and creatinine measurements are not necessary before low-risk surgery unless the patient has signs or symptoms suggestive of active disease that would affect these values (such as vomiting or diarrhea). Even for patients with chronic diseases or medications that may affect kidney function or electrolytes, assessment before low-risk procedures is necessary only if there has been a significant change in the patient's status (such as a recent increase in diuretic dose).

KEY POINT

- Routine preoperative diagnostic testing is generally not recommended for healthy patients undergoing low-risk surgery.

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Item 35 Answer: A

Educational Objective: Evaluate a breast mass in a young woman.

The most appropriate management of this woman's breast mass is diagnostic ultrasound. Although up to 90% of breast masses are benign cysts or fibroadenomas, neither the history nor the physical examination can definitively rule in or rule out underlying malignancy with accuracy. Therefore, a palpable mass requires further evaluation with either mammography or ultrasonography; in this 29-year-old woman, a diagnostic ultrasound is the most appropriate next step as it is more sensitive than mammography in younger women. Ultrasonography can effectively determine whether the lesion is solid or cystic, delineate its contours, and can help determine whether additional evaluation with biopsy is indicated.

Mammography, whether digital or film, is less sensitive in women younger than 35 years because of increased breast density. Therefore, ultrasonography is the most appropriate initial imaging choice for this patient.

Aspiration biopsy should not be the next step in this young woman at low risk for breast cancer. She has no family or personal history of breast cancer, has no history of thoracic irradiation, and is not obese. Ultrasonography is the most sensitive and noninvasive way to determine whether or not a biopsy is necessary.

There is no need to stop hormonal contraception in a young woman at risk for pregnancy in the absence of neoplasia or a high risk for neoplasia. One of the therapeutic benefits of combined hormonal contraception is a reduction in prevalence of breast cysts. Given the individualized risk stratification for this young woman, with low risk for breast malignancy, it is reasonable to continue her method of contraception until there is definition of the breast mass.

A palpable breast mass requires further evaluation at any age. The history and physical examination are unlikely to rule out malignancy, and a malignant lesion must be ruled out.

KEY POINT

- A palpable breast mass always requires further evaluation with either mammography or ultrasonography; ultrasonography is a more sensitive test in women younger than 35 years.

Bibliography

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Item 36 Answer: B

Educational Objective: Treat systemic exertion intolerance disease (formerly known as chronic fatigue syndrome) with cognitive-behavioral therapy.

The most appropriate next step in the management of this patient who meets the clinical criteria for systemic exertion intolerance disease (SEID), formerly known as chronic fatigue syndrome, is cognitive-behavioral therapy (CBT). She has severe fatigue that has persisted for more than 6 months, is not due to ongoing exertion, is not relieved by rest, and is interfering with pre-illness daily activities. Additionally,

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the fatigue is accompanied by unrefreshing sleep, difficulty concentrating, myalgia, and arthralgia. The physical examination is normal, and an extensive evaluation for a secondary underlying medical condition, including sleep disorders, was normal. Further diagnostic testing is not indicated, and efforts should now be concentrated on evidence-based management. The two treatment strategies that have been shown to be of greatest benefit in the management of these patients are CBT and graded exercise programs. Improvements in fatigue and physical function have been demonstrated in several randomized controlled trials. CBT, usually performed by trained clinicians, is designed to assist patients in modifying their illness beliefs and supporting behaviors and to incorporate effective coping strategies into daily life.

Approximately 70% of patients with SEID meet criteria for depression, anxiety, or dysthymia. However, this patient does not meet the current DSM-5 criteria for either depression or anxiety. Citalopram, or any other antidepressant, is unlikely to be of major benefit in this patient.

In short-term (4-week) studies, methylphenidate did improve fatigue in 30% of patients with SEID, although long-term effectiveness and potential adverse effects associated with long-term use are unknown. Additionally, in this patient of childbearing age with hypertension, the short- and long-term risks of this medication would be increased. Therefore, methylphenidate would not be the next best step in management.

Although several viruses have been implicated in the development of SEID, no precise cause has been established, and antiviral medications, such as valacyclovir, have not demonstrated any clear benefit.

KEY POINT

- Cognitive-behavioral therapy and graded exercise programs have been shown to improve fatigue and physical functioning in patients with systemic exertion intolerance disease.

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Item 37 Answer: C

Educational Objective: Manage contraception in a young woman with complex migraine.

The most appropriate contraceptive method to recommend to this woman is an intrauterine device (IUD), along with condom use to reduce risk from sexually transmitted infections. Evidence shows that IUDs can be offered to nulliparous or multiparous women across the entire reproductive span, with high rates of continuation and efficacy. There is no evidence of increased risk of pelvic inflammatory disease, infection, or infertility with IUDs. There are two types of IUDs available, one that is hormone free, and one that contains levonorgestrel. The levonorgestrel IUD generally causes significant diminution of menstrual bleeding, although endometrial response is variable. Given that this patient did not tolerate progestin well, the hormone-free IUD is a reasonable choice also.

In choosing contraception, patient preference, acceptability, concurrent medical conditions, and prior response to other methods should be considered. Because of her migraine with visual aura, this patient should not be treated with an estrogen-containing contraceptive. Although the absolute risk of venous thromboembolism or stroke in young women is low, this risk is increased by a history of migraine with visual aura when estrogen-containing preparations are used. Therefore, either an estrogen-progestin oral contraceptive or a vaginal ring is contraindicated.

This patient also indicated that she experienced unpredictable breakthrough bleeding with depot medroxyprogesterone acetate injections, which is a common side effect. Other progestin-only methods, including implantable inserts and pills, although frequently inducing periods of amenorrhea, may all be associated with breakthrough or irregular bleeding and may be less desirable for this patient.

KEY POINT

- Due to increased stroke risk, combined hormonal contraception containing estrogen is contraindicated in women with a history of migraines preceded by visual aura.

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Item 38 Answer: B

Educational Objective: Recognize types of bias that affect screening tests.

Length-time bias is the most likely explanation for the positive outcome of the study. The apparent benefits of early diagnosis and intervention on screen-detected cases compared with cases detected by disease symptoms and signs are almost always more favorable than the true effects seen when the outcomes of an overall screened population are compared with an overall population that is not screened for the disease. This difference is caused by several types of bias that tend to occur when examining the effectiveness of screening studies, one of which is length-time bias. Because indolent disease has a longer latent period than more aggressive forms of disease (which are more likely to be detected with onset of symptoms), indolent disease is more likely to be detected by screening. Length-time bias occurs when there is overrepresentation of indolent (low-grade) disease in the screen-detected cohort and overrepresentation of aggressive disease in the symptom-detected (non-screened) cohort, as was the case in this hypothetical study. This makes

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the screen-detected cohort, with more indolent disease, falsely appear to have a better prognosis than the patients who present with symptoms and signs in the non-screened cohort. A drastic type of length-time bias is termed overdiagnosis and occurs when a disease that is so indolent that it would not otherwise have been clinically significant during a patient's lifespan is detected through screening.

Contamination bias occurs when the control group is unintentionally exposed to the intervention, which biases the estimate toward the null hypothesis. Contamination bias was unlikely in this case as there was little crossover between groups.

Observer bias occurs when knowledge of the hypothesis or intervention received influences data recording, which would not be expected to be an influence in this study in which the researchers were blinded.

Selection bias refers to systematic error in a study resulting from the manner in which the subjects are selected for the study. It can influence the results when the characteristics of the subjects selected for a study differ systematically from those in the target population or when the study and comparison groups are selected from different populations. An example is volunteer bias, in which patients who seek participation in a screening study are often healthier than those who do not undergo screening. Because the patients in this study were randomly selected from the general population, this would not be a likely cause of significant bias.

KEY POINT

- Randomized controlled trials of screening tests may be affected by length-time bias, which occurs when there is overrepresentation of indolent disease in the screen-detected cohort and overrepresentation of aggressive disease in the symptom-detected (non-screened) cohort.

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Item 39 Answer: A

Educational Objective: Manage prepatellar bursitis.

The most appropriate next step in management of this patient is to aspirate the bursal fluid collection for diagnostic and therapeutic purposes. Bursal fluid aspiration and analysis should be performed in all patients who present with prepatellar bursitis. Aspiration is necessary to definitively distinguish the cause of prepatellar bursitis (namely, trauma, gout, and infection). Gram stain and culture of the bursal fluid should be obtained and analyzed for leukocyte count and for the presence of crystals. An extremely elevated leukocyte count (>50,000/μL [50×10^9/L]) should raise suspicion for septic bursitis, although a lower count does not entirely eliminate this possibility.

Compression is indicated only after bursal fluid aspiration has been performed. Dressings should be worn for 24 to 48 hours, and patients should be advised to avoid applying direct pressure to the bursa. Once the compression dressing is removed, patients should be advised to wear a neoprene sleeve.

Glucocorticoid injection into the fluid collection is not indicated for patients presenting with acute prepatellar bursitis. Instead, glucocorticoid injection should be reserved for chronic prepatellar bursitis that has a noninfectious cause or that is postinfectious (negative cultures have been obtained after antibiotic administration).

Imaging, either with plain radiography or ultrasonography, is not usually required for the diagnosis of prepatellar bursitis. Plain radiography may show soft-tissue swelling on lateral views but rarely aids in establishing the correct diagnosis. Ultrasonography will show a fluid collection but will not help identify the cause. Therefore, plain radiography or ultrasonography is not indicated in this patient.

KEY POINT

- Bursal fluid aspiration should be performed for both therapeutic and diagnostic purposes in all patients who present with prepatellar bursitis.

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Item 40 Answer: A

Educational Objective: Manage the risk of perioperative adrenal insufficiency in a patient on chronic glucocorticoid therapy.

The most appropriate management on the morning of surgery is for the patient to take her current morning prednisone dose of 5 mg. For patients on chronic glucocorticoids, appropriate medical management is crucial to prevent complications such as organ transplant rejection and adrenal insufficiency. Evidence to guide decision making is sparse; a recent Cochrane review found the available data insufficient to provide recommendations. Despite this, expert advice provides a fair consensus to inform clinical decision making. For patients taking low doses of prednisone (<10 mg/d), stress dosing of glucocorticoids typically is not required, even before high-risk surgical procedures (such as intrathoracic surgery). Instead, patients should take their usual glucocorticoid dose on the morning of surgery. This patient is scheduled for a low-risk procedure (carpal tunnel release) and is on a low dose of prednisone; therefore, taking the usual dose of prednisone on the morning of surgery is the most appropriate management.

Doubling the patient's usual prednisone dose is not the most appropriate choice because she is undergoing a low-risk procedure with minimal risk of perioperative adrenal

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insufficiency. Increasing her prednisone would only increase her risk of other complications, such as hyperglycemia.

Intravenous hydrocortisone is not necessary for this patient due to her low daily dose of prednisone and the low-risk nature of the procedure. Empiric intravenous hydrocortisone is reasonable for patients with primary adrenal insufficiency or for those on high doses of glucocorticoids (equivalent of prednisone ≥10 mg/d) who are undergoing higher risk surgeries. In those circumstances, intravenous hydrocortisone, 50 to 100 mg, is administered shortly before anesthesia induction and then continued every 8 hours for up to 48 hours after surgery.

Although the patient is on a low dose, withholding prednisone for the procedure is not recommended because interrupting therapy might cause unnecessary fluctuations in her immunosuppression or glucocorticoid levels without a clear benefit to her surgical outcome.

KEY POINT

- For patients taking low doses of glucocorticoids, stress dosing typically is not required; patients should take their usual glucocorticoid dose on the morning of surgery.

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Njoke MJ. Patients with chronic endocrine disease. Med Clin N Am. 2013 Nov;97(6):1123-37. [PMID: 24182723]

Item 41 Answer: C

Educational Objective: Evaluate decision-making capacity in a patient with mild dementia.

This patient has the capacity to make a decision about the proposed procedure; therefore, the physician should proceed with coronary angiography. Informed consent includes a discussion of the information that a reasonable patient would want to know about his or her illness (proposed diagnostic and treatment plans, the risks and benefits of the proposed plans, and any alternatives), an assessment of patient understanding, and the acceptance or refusal of the treatment. The patient must have decision-making capacity and make each decision of his or her own free will for consent to be considered valid. A patient (for example, one with mild dementia) may have the capacity to make some decisions but not other more complex ones. The graver the consequences of the decision, the greater the capacity required. Decision-making capacity exists when a patient demonstrates an ability to understand relevant information, appreciate the situation and its possible consequences, manipulate information rationally, and make a reasoned choice. Despite this patient's mild dementia, he fulfills these standards and therefore has the capacity to make a decision regarding the procedure.

There is no need to wait for the patient's wife to consent to the procedure. Indeed, waiting for his wife to arrive and delaying treatment increases the patient's risk for harm.

A Mini-Mental State Examination is unnecessary. It will likely confirm the diagnosis of mild dementia but will not help in assessing the patient's decision-making capacity. A diagnosis of dementia or a mental illness does not necessarily mean that a patient is incapable of making health care decisions. The clinician must assess whether or not the patient's decision appears consistent with his or her values and goals of care. If it does, it can probably be accepted as valid.

It is unnecessary to obtain a second opinion to assess this patient's decision-making capacity. The core components of decision-making capacity are understanding the situation at hand, understanding the risks and benefits of the decision being made, and the ability to communicate a decision. The patient has demonstrated these core elements.

KEY POINT

- Decision-making capacity exists when a patient demonstrates an ability to understand relevant information, appreciate the situation and its possible consequences, manipulate information rationally, and make a reasoned choice.

Bibliography

Leo RJ. Competency and the capacity to make treatment decisions: a primer for primary care physicians. Prim Care Companion J Clin Psychiatry. 1999 Oct;1(5):131-141. [PMID: 15014674]

Item 42 Answer: A

Educational Objective: Diagnose epididymitis.

The most likely diagnosis in this patient is epididymitis, which causes pain superolateral to the testicle and results from inflammation of the epididymis. Symptom onset in epididymitis is usually subacute, although in some patients the pain may develop relatively acutely or may be more chronic in nature. Examination is remarkable for pain that is relieved by testicular elevation. Epididymitis most commonly has an infectious cause and has a bimodal age distribution of men younger than 35 years and older than 55 years of age. Patients younger than 35 years are more likely to have sexually transmitted etiologies such as chlamydia or gonorrhea, whereas the causes in older patients are usually *Escherichia coli*, Enterobacteriaceae, or *Pseudomonas* species. This patient's presentation includes young age, history of unprotected sexual activity, subacute onset of symptoms, lower urinary tract symptoms, bogginess and pain to palpation over the superior pole of the testis, and pain relief with elevation of the testis, all clinical findings consistent with epididymitis.

Testicular torsion presents acutely along with nausea and vomiting. Unlike in this patient, the testicle would be high riding and transversely oriented, with pain that worsens with manual elevation. Doppler ultrasonography to assess blood flow is sensitive (82%) and specific (100%) in making the diagnosis of testicular torsion.

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H CONT.

Dysuria, frequency, and urgency may accompany epididymitis and suggest the possible presence of a urinary tract infection. However, the presence of testicular bogginess and pain on examination with a lack of significant pyuria on urinalysis does not support the diagnosis of urinary tract infection.

Varicocele does not present with subacute onset, lower urinary tract symptoms, and epididymal swelling and pain. Furthermore, physical examination would reveal a characteristic "bag of worms" consistency with palpation of the scrotal contents that increases with standing and decreases when supine.

KEY POINT

- Epididymitis causes subacute pain in the superolateral testis, is often associated with lower urinary tract symptoms, and is relieved by testicular elevation.

Bibliography

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Item 43 Answer: B

Educational Objective: Treat stress urinary incontinence in a woman.

Pelvic floor muscle training (PFMT) is most appropriate for this patient. The involuntary loss of urine with sneezing, coughing, laughing, or physical exertion is consistent with stress incontinence. Stress incontinence is thought to be related to anatomic changes in which the support structures of the urethra are weakened (through age, pregnancy and childbirth, or repetitive pelvic floor stress), decreasing the ability of the urethra to maintain adequate pressure to prevent incontinence. Treatment for stress incontinence begins with conservative measures. In this patient, the first-line therapeutic option is bladder training using PFMT in conjunction with weight loss counseling. These measures decrease bladder pressure and increase the pressure generated by the urethra and surrounding tissues.

Weight loss in overweight and obese women generally improves urinary control. An 8% decrease in BMI has been shown to reduce incontinence by 50%. PFMT in women involves learning repetitive exercises (Kegel exercises) to strengthen the voluntary urethral sphincter and levator ani muscles. Outcomes are improved when PFMT is combined with biofeedback and when skilled physical therapists direct the training. Adherence remains an issue, as PFMT must be done repetitively and consistently for best results.

Oxybutynin is one of several available anticholinergic agents approved for treating overactive bladder. It is not indicated for treatment of uncomplicated stress incontinence, nor is pharmacotherapy a first-line therapy for this disorder.

Measurement of postvoid residual urine volume is not necessary in this patient whose presentation is consistent with stress incontinence. Clinical evaluation and history, including the patient's report of frequency, severity, precipitants, and impact on quality of life, are adequate for discriminating among types of incontinence and for making nonsurgical treatment decisions. Voiding diaries are useful in defining symptoms.

Prompted voiding and scheduled toileting may help older patients with functional urinary incontinence. Providing assistance and scheduled toileting are effective for patients who have impaired mobility or cognition, neither of which is present in this patient.

Urodynamic studies are not indicated in women with uncomplicated stress urinary incontinence. Compared with diagnosing the patient based on symptom report, evidence-based reviews indicate that urodynamic studies do not better predict response to treatment.

KEY POINT

- Pelvic floor muscle training, along with other conservative measures such as weight loss, is first-line therapy for women with stress urinary incontinence.

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Item 44 Answer: B

Educational Objective: Screen for cervical cancer in a young woman.

This patient should receive a Pap smear in 2 years. According to the U.S. Preventive Services Task Force and the American Congress of Obstetricians and Gynecologists, women aged 21 to 65 years should be screened for cervical cancer every 3 years with cytology (Pap smear). Performing screening more frequently adds little benefit while significantly increasing harms. Harms can include evaluation and treatment of transient lesions as well as false-positive screening results, which may lead to unnecessary colposcopies and emotional distress. Screening for cervical cancer is not recommended in women younger than 21 years, women age 65 years and older who are not at high risk and have had adequate prior Pap smears, and women who have had a hysterectomy with removal of the cervix with no previous history of a precancerous lesion. This patient had a normal Pap smear 1 year ago; therefore, she will be due for her next Pap smear in 2 years.

Owing to poor specificity, screening with human papillomavirus (HPV) DNA testing alone is not recommended. HPV testing is not recommended in women younger than 30 years, as HPV is not only highly prevalent but is also more likely to resolve without treatment in this age group. In women aged 30 to 65 years who want to lengthen the screening interval, a combination of cytology and HPV testing can be performed every 5 years. Women should be informed that there is an increased likelihood of receiving a positive screening result with HPV testing and cytology

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than with cytology alone. A positive HPV test result likely requires additional immediate testing and also involves more frequent surveillance.

All females aged 11 to 26 years should be vaccinated against HPV. HPV vaccination status does not alter recommendations for cervical cancer screening.

KEY POINT

- Women aged 21 to 65 years should be screened for cervical cancer every 3 years with cytology (Pap smear); in women aged 30 to 65 years who want to lengthen the screening interval, a combination of cytology and human papillomavirus testing can be performed every 5 years.

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Moyer VA; U.S. Preventive Services Task Force. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012 Jun 19;156(12):880-91, W312. Erratum in: Ann Intern Med. 2013 Jun 4;158(11):852. [PMID: 22711081]

Item 45 Answer: B

Educational Objective: Treat hyperlipidemia in a patient with diabetes mellitus and elevated cardiovascular risk.

The most appropriate treatment for this patient is high-intensity statin therapy, such as with atorvastatin. Strong evidence indicates that statins are effective in both primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD). According to the American College of Cardiology/American Heart Association guidelines, this patient with diabetes and no clinical ASCVD meets the criteria for one of four patient groups that have been shown to benefit from the treatment of hyperlipidemia with statin therapy. For patients 40 to 75 years of age with diabetes mellitus and an LDL cholesterol level of 70 to 189 mg/dL (1.8-4.90 mmol/L), intensity of statin therapy is dictated by the estimated 10-year risk for ASCVD as determined by the Pooled Cohort Equations. High-intensity statin therapy (for example, atorvastatin, 40-80 mg/d, or rosuvastatin, 20-40 mg/d) is recommended for all patients with a 10-year ASCVD risk of 7.5% or higher, and moderate-intensity therapy is indicated for patients with a risk of less than 7.5%. This patient's 10-year ASCVD risk exceeds 7.5%; therefore, high-intensity therapy is recommended.

Significant reductions in cardiovascular events have not been clearly demonstrated with fibrate monotherapy, rendering gemfibrozil an inferior choice for this patient with elevated risk for clinical ASCVD. Fibrates are indicated for patients with triglyceride levels greater than 500 mg/dL (5.65 mmol/L), patients with hypertriglyceridemia-induced pancreatitis, and patients who have an inadequate response to statin therapy.

Moderate-intensity statin therapy (for example, simvastatin, 20-40 mg/d; atorvastatin, 10-20 mg/d; or rosuvastatin, 5-10 mg/d) is not appropriate for this patient with diabetes, elevated 10-year risk for ASCVD, other cardiovascular risk factors (family history of premature cardiovascular disease), and no contraindications to high-intensity therapy. Moderate-intensity statin therapy is an acceptable alternative to high-intensity therapy in patients who tolerate statins poorly or have risk factors for statin-associated adverse effects (impaired kidney or liver function, history of muscle disorders, use of drugs affecting statin metabolism [calcium channel blockers, fibrates, protease inhibitors, amiodarone, macrolide antibiotics], and age greater than 75 years). Because none of these factors are present in this patient, high-intensity statin therapy would be the optimal therapeutic approach given his risk profile.

Therapeutic lifestyle changes are a cornerstone of treatment for hyperlipidemia and should be encouraged in all patients; however, additional treatment with statins is indicated in this patient with an elevated 10-year risk of ASCVD and diabetes.

KEY POINT

- In adults 40 to 75 years of age with diabetes mellitus, an LDL cholesterol level of 70 to 189 mg/dL (1.8-4.90 mmol/L), and an estimated 10-year atherosclerotic cardiovascular disease risk of 7.5% or higher, high-intensity statin therapy is recommended.

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Item 46 Answer: D

Educational Objective: Manage cardiac testing in an asymptomatic patient with low cardiovascular risk.

This patient needs no further testing. Although he is obese and has a history of hypertension, he is at low risk for cardiovascular disease. Risk assessment for atherosclerotic cardiovascular disease (ASCVD) has traditionally been with the Framingham risk score, although the American College of Cardiology/American Heart Association Pooled Cohort Equations, a new method for assessment that includes additional variables for risk stratification, is increasingly being used. With this method, a 10-year risk of ASCVD of less than 5% is considered low risk, 5% to below 7.5% is considered intermediate risk, and 7.5% and above is designated as high risk. This patient has a calculated 10-year risk of 3.2%, making him at low risk for ASCVD. Therefore, no additional testing is indicated at present.

Patients at low risk for cardiovascular disease, such as this one, do not benefit from aggressive risk factor modification and therefore would not benefit from screening using nontraditional risk factors, such as coronary artery calcium

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scoring. The U.S. Preventive Services Task Force (USPSTF) concludes that there is insufficient evidence to assess the balance of benefits and harms for using nontraditional risk factors to screen asymptomatic, intermediate-risk patients without a history of coronary heart disease. Nontraditional risk factors include ankle-brachial index, CT to assess coronary artery calcification, high-sensitivity C-reactive protein, carotid intima-media thickness, homocysteine, and lipoprotein(a) level. Furthermore, the Society of Cardiovascular Computed Tomography, through the Choosing Wisely campaign, advises against ordering coronary artery calcium scoring for screening purposes in asymptomatic individuals who are at low risk for cardiovascular disease except for those with a family history of premature coronary artery disease.

The USPSTF and the American College of Physicians recommend against resting or exercise electrocardiography (ECG) for cardiovascular disease screening in asymptomatic adults who are at low risk for cardiovascular events. This patient is asymptomatic and is at low risk for cardiovascular disease; therefore, resting and exercise ECG are not indicated. For individuals at intermediate risk for cardiovascular disease, the USPSTF concludes that there is insufficient evidence to assess the balance of benefits and harms for screening with resting or exercise ECG.

KEY POINT

- In asymptomatic patients at low risk for cardiovascular disease, cardiac testing is unnecessary.

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Item 47 Answer: D

Educational Objective: Reduce fall risk in an older patient with vitamin D supplementation.

Vitamin D should be prescribed for this older patient with a high risk for falls. Vitamin D has neuromuscular benefits beyond its role in bone health. Several randomized controlled trials and meta-analyses have shown vitamin D supplementation to significantly decrease the risk for falls in older community-dwelling adults, even in those with normal vitamin D levels. The mechanism of vitamin D supplementation in preventing falls is unclear, although changes in bone mineral density and muscle function have been proposed as contributing factors. With an excellent safety profile, low cost, and a number needed to treat of 15, vitamin D supplementation is an underutilized therapy for fall prevention. The American Geriatrics Society recommends 800 units daily for this purpose.

Compression stockings are used in some patients with orthostatic hypotension to prevent pooling of blood in dependent areas. However, compression stockings are difficult to use, making adherence challenging, and other potential adverse effects such as skin breakdown may occur. Therefore, compression stockings would not be indicated to decrease falls in this patient without evidence of orthostatic hypotension.

Hip protectors are mechanical devices intended to decrease the risk of fractures if falls occur; they do not prevent the falls themselves. Multiple studies have shown that adherence with this intervention is low and there is no compelling evidence that they are effective in preventing hip fractures. Hip protectors would therefore not be indicated in this patient.

Mineralocorticoid supplementation can be helpful in ameliorating orthostasis; however, there is no evidence that this patient's falls are due to orthostatic symptoms. Consequently, there is no indication that mineralocorticoid supplementation would be helpful.

KEY POINT

- Vitamin D supplementation decreases fall risk in older adults, irrespective of vitamin deficiency.

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Item 48 Answer: C

Educational Objective: Diagnose depression in the setting of terminal illness.

This patient's sense of guilt is indicative of pathologic depression. Although anticipatory grief may be common at the end of life, depression is never normal in dying patients. However, it can be very challenging to differentiate normal grief from depression in terminally ill patients. Validated depression screening tools, such as the PHQ-9, rely heavily on the presence of symptoms associated with functions necessary to maintain life (historically termed vegetative symptoms) such as changes in appetite, sleep, and energy level, which are common and expected in patients with advanced illness. This makes these instruments more difficult to interpret when assessing for depression. Many patients with terminal illness, such as this one, verbalize thoughts of death or express a desire for hastened death. Persistent, pervasive thoughts of suicide, which are not seen in this patient, are not normal and should be addressed promptly and aggressively when present. Guilt or self-blame is unique to depression and not seen in normal grief. Other symptoms unique to depression include hopelessness, helplessness, and worthlessness. When differentiating depression from grief, it is important to assess for these symptoms, as depression is highly treatable even in terminally ill patients.

Adjustment disorder with depressed mood occurs in patients who do not meet the criteria for major depression but have a depressed mood. Symptoms begin within

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3 months of a stressful event and do not last longer than 6 months. This patient's guilt is indicative of depression, not an adjustment disorder.

Anticipatory grief occurs in patients and loved ones as they mourn the many losses leading up to an expected death. Such grief is waxing and waning in nature, with periods of sadness interspersed with periods of joy.

Grieving that lasts for more than 12 months (6 months in children); is associated with persistent yearning, sorrow, or preoccupation with the deceased; disrupts normal function or social relationships; and is out of proportion to cultural norms is considered pathologic and is termed persistent complex bereavement disorder, formerly complicated grief disorder. Persistent complex bereavement disorder occurs in loved ones after a death, not in the patient who is dying.

KEY POINT

- In a terminally ill patient, feelings of guilt, hopelessness, helplessness, and worthlessness may distinguish depression from anticipatory grief.

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Item 49 Answer: E

Educational Objective: Evaluate a patient for hypogonadism.

A repeat testosterone level is appropriate for this older patient with fatigue, weakness, and erectile dysfunction (ED). Men with specific signs and symptoms of androgen deficiency should be evaluated by measuring morning total testosterone level as the initial diagnostic test. Men with low or low-normal testosterone levels should have confirmatory testing before initiating testosterone therapy, and further evaluation of the cause of hypogonadism should be pursued before treatment is started, if indicated. If the repeat serum total testosterone level is more equivocal (200-350 ng/dL [6.9-12.1 nmol/L]) or if a sex hormone-binding globulin abnormality is likely in the patient being evaluated, a serum free testosterone level by equilibrium dialysis or a calculated serum free testosterone level can determine whether hypogonadism is truly present.

When hypogonadism is confirmed, the next step is to determine whether the patient has primary or secondary hypogonadism by measuring the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. Primary hypogonadism is indicated by supranormal LH and FSH levels. If secondary hypogonadism is confirmed by inappropriately normal or low LH and FSH levels, measurement of the serum prolactin level to evaluate for hyperprolactinemia and iron saturation level (transferrin saturation and ferritin levels) to exclude hemochromatosis should be performed to assess for the possible cause. In addition, the presence of any additional pituitary hormone deficiencies should be assessed.

An MRI of the pituitary gland should be ordered to exclude hypothalamic or pituitary masses as the cause of decreased gonadotropin production and secretion if any symptoms consistent with mass effect are present, including headaches, visual field changes, a serum total testosterone level less than 150 ng/dL (5.2 nmol/L), an increased prolactin level, or any additional pituitary hormonal deficiencies.

Testosterone replacement in older men should be given only in the setting of hypogonadism that is based on symptoms (such as decreased libido and generalized muscle weakness) and morning serum total testosterone levels lower than 200 ng/dL (6.9 nmol/L) on at least two separate occasions. Therefore, this patient needs confirmation on repeat testing before considering testosterone replacement therapy.

KEY POINT

- Men with low or low-normal testosterone levels should have confirmatory morning serum total testosterone testing before initiating testosterone therapy, and further evaluation of the cause of hypogonadism should be pursued before treatment is started.

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Item 50 Answer: C

Educational Objective: Diagnose plantar fasciitis.

The most likely diagnosis is plantar fasciitis. The pain associated with plantar fasciitis is typically sharp in character and present with the first few steps taken after prolonged inactivity, such as upon awakening in the morning or after sitting for an extended period of time. Plantar fasciitis has a peak incidence between the ages of 40 and 60 years. Risk factors include obesity, pes planus, and a sedentary lifestyle. On examination, there is pain with palpation of the medial calcaneal tubercle where the plantar fascia inserts. Pain is also typically elicited with passive dorsiflexion of the toes (Windlass test).

Achilles tendinopathy is typically associated with posterior heel pain, stiffness, and tenderness approximately 2 to 6 cm proximal to the Achilles tendon insertion. Pain usually develops after there is a rapid increase in exercise level. Pain is generally burning, worsens with activity, and improves with rest.

Heel pad syndrome involves localized inflammation of the soft tissues overlying the heel and is often caused by walking barefoot on hard surfaces. It presents with pain in the middle of the heel that is reproducible on examination, and atrophy of the heel fat pad may occur. Neither of these findings is present in this patient.

Stress fractures typically produce pain in individuals who dramatically increase their physical activity or who exercise repetitively with insufficient rest. The pain associated with a stress fracture of the tarsal navicular bone is usually located on the dorsal midfoot with occasional radiation into the medial arch, which is not present in this patient.

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KEY POINT

- Plantar fasciitis is characterized by pain and tenderness near the medial plantar heel surface that usually occurs with the first few steps taken after prolonged inactivity.

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Item 51 Answer: D

Educational Objective: Treat subacute, nonspecific low back pain.

This patient with subacute low back pain would most likely benefit from a trial of massage therapy. Back pain is classified as acute (lasting <4 weeks), subacute (lasting 4-12 weeks), or chronic (lasting >12 weeks); therefore, this patient's clinical findings are consistent with a subacute process. The overall prognosis for most forms of musculoskeletal back pain without neurologic or systemic findings is excellent, and 90% of patients recover within 6 weeks with self-care (remaining active and application of superficial heat) and pharmacologic therapies (acetaminophen or NSAIDs). Patients who do not improve in that time frame may benefit from additional therapeutic interventions, such as spinal manipulation or massage therapy. Massage therapy has been shown to be an effective intervention in patients with subacute or chronic back pain symptoms and would therefore be an appropriate treatment to recommend to this patient. Patients should also be informed that most low back pain resolves spontaneously without intervention.

Bed rest had been historically recommended as a treatment for back pain but has been shown to decrease functional recovery and increase pain levels in many patients. Based on these data, patients with low back pain, such as this one, should be encouraged to maintain their daily activities, if possible.

Despite their anti-inflammatory effect, systemic glucocorticoids (such as prednisone) have not proved effective in treating low back pain when used either for brief treatment periods or longer courses.

Lumbar support has not been demonstrated to be effective in treating low back pain, even in physically active patients. It would therefore not be an appropriate treatment for this patient.

KEY POINT

- Massage therapy for low back pain is likely to be helpful in patients with subacute or chronic symptoms and no abnormal neurologic findings.

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Furlan AD, Imamura M, Dryden T, Irvin E. Massage for low-back pain. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD001929. [PMID: 18843627]

Item 52 Answer: B

Educational Objective: Continue β-blockers in the perioperative period.

This patient should take his β-blocker, metoprolol, the morning of surgery. He takes three chronic medications, of which two are normally taken in the morning. All medications should be continued uninterrupted throughout surgery unless potential adverse effects from continuation outweigh benefits. Not only is metoprolol important for treatment of his hypertension, but withdrawal of β-blockade in the perioperative setting may cause tachycardia and increased myocardial oxygen demand. The American College of Cardiology (ACC) and the American Heart Association (AHA) provide a level 1 recommendation for the continuation of β-blockers throughout the perioperative period. Thus, metoprolol should be taken the morning of surgery.

Metformin has the potential for causing lactic acidosis and inducing hypoglycemia if taken during fasting. Therefore, it should not be taken on the morning of surgery. Some experts advise withholding this medication for 24 to 48 hours before surgery, although data for the specific withholding timeframe are limited.

The ACC and AHA recommend that for patients currently taking a statin and scheduled for noncardiac surgery, the statin should be continued. This recommendation is based on several systematic reviews that found an association between perioperative statin use and a reduction in postoperative acute coronary syndrome and mortality. This patient should resume his statin therapy in the evening following his operation, maintaining his usual schedule.

KEY POINT

- Perioperative β-blockade should be continued uninterrupted in patients who are already taking a β-blocker.

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Item 53 Answer: A

Educational Objective: Diagnose an anterior cruciate ligament tear.

The most likely diagnosis is an anterior cruciate ligament tear. Anterior cruciate ligament injury usually occurs when a person rapidly decelerates and pivots but may also develop following direct trauma that results in knee hyperextension. A complete tear should be suspected when a popping sound is reported and the patient reports pain and knee instability. The characteristic examination finding is a large effusion with increased laxity seen with both the anterior drawer

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and Lachman tests. In this patient, the sudden onset of knee pain, swelling, and instability; the mechanism of injury (a noncontact injury that occurred with deceleration and pivoting); and the increased laxity observed on examination with both the anterior drawer and Lachman tests all suggest a complete anterior cruciate ligament tear.

Lateral collateral ligament tears result from laterally directed (varus) forces on the knee and are associated with lateral knee pain, swelling, and instability. On examination, there is lateral joint line tenderness and increased laxity with varus-directed forces. Knee effusions are commonly seen. Although this patient has swelling and instability, which could be consistent with a lateral collateral ligament tear, he does not have lateral joint line tenderness and increased laxity with varus-directed forces, which argue against a lateral collateral ligament tear.

Medial collateral ligament tears occur as a result of a contact injury from a medially directed (valgus) force. Patients with medial collateral ligament tears typically present with medial knee pain and joint instability. On examination, there is medial joint line tenderness and increased laxity with valgus stress testing, which are not seen in this patient. A palpable knee effusion is also commonly present.

Patients with meniscal tears are typically able to bear weight immediately after the injury and are often able to continue participating in the activity they were doing before the injury, unlike this patient. Additionally, patients with meniscal tears will frequently report a locking or catching sensation. On examination, abnormal responses may be seen with both the Thessaly and medial-lateral grind tests. Knee effusions may or may not be present.

KEY POINT

- An anterior cruciate ligament tear is characterized by pain and knee instability that occur after a person rapidly decelerates and pivots; examination findings include a large effusion with increased laxity seen with both the anterior drawer and Lachman tests.

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Solomon DH, Simel DL, Bates DW, Katz JN, Schaffer JL. The rational clinical examination. Does this patient have a torn meniscus or ligament of the knee? Value of the physical examination. JAMA. 2001 Oct 3;286(13):1610-20. [PMID: 11585485]

Item 54 Answer: A

Educational Objective: Recognize anchoring as a source of cognitive error.

The care team demonstrated anchoring, a diagnostic cognitive error that results from "locking" onto features of a patient's initial presentation and providing treatment for that diagnosis despite the appearance of new clinical information. In this patient, the care team anchored on the initial history and radiographic findings of constipation and failed to recognize or act upon additional clinical clues, including fever, leukocytosis, and worsening abdominal pain despite treatment, related to the correct diagnosis of cholecystitis.

Confirmation bias involves using or interpreting information (for example, diagnostic studies) in a way that confirms a current hypothesis. This cognitive error results from the tendency to look for evidence that confirms a suspected diagnosis rather than considering evidence that refutes that diagnosis and may lead to another diagnostic option. Because of anchoring to the initial diagnosis, the care team did not seek additional clinical evidence that could be interpreted to support that diagnosis.

Framing bias is a form of cognitive error that occurs when the way clinical information is presented, or "framed," affects decisions based on that information. An example is the perception of increased effectiveness of a specific therapy when the benefit of treatment is reported in relative instead of absolute terms, since relative benefits frequently appear larger than absolute benefits. Similarly, clinical decisions based on cardiovascular risk may differ if the assessed risk is based on an annual event rate compared with a cumulative 10-year risk. Framing bias does not appear to be a significant factor in the outcome of this case.

Triage cueing occurs when the manner in which triage decisions are made influences the evaluation and diagnosis (for example, when a patient with chest pain is admitted to a cardiology service and receives an extensive evaluation for myocardial infarction rather than an evaluation for gastroesophageal reflux). This patient appears to have been appropriately triaged for initial management, but the subsequent changes in his clinical course were not addressed due to anchoring to the initial diagnosis.

KEY POINT

- Anchoring is a diagnostic cognitive error that results from locking onto features of a patient's initial presentation despite the appearance of new clinical information.

Bibliography

Croskerry P. The importance of cognitive errors in diagnosis and strategies to minimize them. Acad Med. 2003 Aug;78(8):775-80. [PMID: 12915363]

Item 55 Answer: D

Educational Objective: Treat acute sinusitis.

This patient, who has acute sinusitis, should be managed with supportive care. Acute sinusitis is most commonly caused by viral infections associated with the common cold, and it has a bacterial etiology in only a small percentage of cases. Acute sinusitis is characterized by symptoms of nasal congestion and obstruction; facial pain, pressure, and fullness that generally worsen when bending forward; headache; purulent nasal discharge; and maxillary tooth pain. When caused by viral infection, fever may be present within the first 24 to 48 hours of symptom onset, often associated with other symptoms such as myalgia and fatigue, but temperature normalizes after this time period. Bacterial sinusitis

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is more likely if there are severe symptoms associated with a high fever for at least 3 or 4 consecutive days following the onset of illness or if symptoms are persistent (lasting more than 10 days). Initial treatment of acute sinusitis is focused on symptom relief with analgesics, decongestants (systemic or topical), antihistamines, intranasal glucocorticoids, and nasal saline irrigation, and these treatment options would be the most appropriate therapy in this patient who does not have findings concerning for a possible bacterial etiology.

Antibiotics are not indicated in this patient at this time. Although more than 90% of cases of acute sinusitis are viral in origin, antibiotics are regularly prescribed for patients presenting with acute sinusitis symptoms. Antibiotics should be reserved for patients with persistent and severe symptoms (such as high fever and marked facial pain), progressively worsening symptoms, or failure to improve after 10 days of supportive care. If antibiotics are indicated, both amoxicillin-clavulanate and doxycycline would be appropriate first-line agents. Although this patient has purulent nasal discharge, the acute nature of the symptoms makes antibiotics inappropriate at this time.

Imaging with plain radiographs or CT is rarely needed in acute sinusitis and does not help in distinguishing a bacterial from viral cause.

KEY POINT

- Intranasal glucocorticoids, antihistamines, and topical decongestants are all appropriate for initial treatment of acute sinusitis; antibiotics should not be used initially.

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Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012 Apr 54(8):e72-e112. [PMID: 22438350]

Item 56 Answer: C

Educational Objective: Treat vasomotor symptoms in a low-risk menopausal woman.

The most appropriate management of this patient is a combination of oral estradiol and progestin. Severe vasomotor symptoms are best treated with systemic hormone therapy. An individualized approach based on personal risk factors (including age, time since menopause, and absence of increased risk for cardiovascular disease, thromboembolism, or breast cancer) suggests that this patient is an appropriate candidate. The absolute risks associated with hormone therapy use in healthy women younger than 60 years are low, as are the risks of adverse cardiovascular events if time since menopause is less than 10 years. Estradiol can be administered orally or transdermally in gel, patch, or spray; progestin is needed to prevent endometrial proliferation in this patient with an intact uterus.

Treatment should begin with the lowest effective dose needed to achieve symptom relief. Systemic hormone therapy treats the symptoms present in this patient, including severe hot flushes, vaginal atrophy, and mood swings. Dose, duration, and route of systemic hormone therapy should be based on symptom response, individualized risk stratification, and patient preference. Because treatment duration greater than 5 years is associated with increased breast cancer risk, the need for treatment should be reassessed annually.

A patient who is amenorrheic for more than 12 months is, by definition, menopausal. Therefore, measuring a serum follicle-stimulating hormone level will not alter management and represents unneeded and low value care.

Measurement of serum estrogen levels in this patient would not be helpful in guiding therapy. The treatment of vasomotor symptoms in a menopausal patient is based on clinical presentation and response to treatment, and laboratory studies are not routinely indicated before starting therapy.

Low-dose selective serotonin reuptake inhibitors (SSRIs) such as paroxetine have been shown to alleviate vasomotor symptoms. However, nonhormonal agents such as SSRIs or gabapentin will not alleviate this patient's symptoms of vaginal atrophy and dyspareunia.

Vaginal estradiol will alleviate symptoms of vaginal atrophy; however, local therapy will not relieve her severe hot flushes and mood changes. Therefore, systemic hormone therapy is a better choice for this patient.

KEY POINT

- The absolute risks for use of hormone therapy in healthy women younger than 60 years are low, as are the risks of adverse cardiovascular events if time since menopause is less than 10 years.

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Item 57 Answer: A

Educational Objective: Use a cause-and-effect (fishbone) diagram to organize results of a root cause analysis.

A cause-and-effect diagram, also known as a fishbone or Ishikawa diagram, should be completed. Root cause analysis is used to discover the factors contributing to an identified problem and involves capturing information from all stakeholders involved, such as by asking each involved individual why he or she believes the problem may be occurring. However, this potentially large amount of information needs to be organized in a logical manner to enable meaningful conclusions to be drawn in order to address the problem. A cause-and-effect diagram is used to organize the root causes of a problem; the problem, or system process, forms the backbone of the diagram, and root causes are branched off (like ribs of a fish). For example, the quality team in this case may complete a root cause analysis to determine why the rate of urinary catheter-associated infections is high

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(the backbone). After interviewing the physicians, nurses, desk staff, and patients, potential root causes are identified and recorded (the ribs). Examining these potential causes, such as the absence of a protocol for discontinuing urinary catheters, relative to the problem helps identify the nature of the contributing factors and their location within the care process. Organizing root cause information in this way may provide a clearer assessment of specific system issues and interventions that may help address the problem and effect system change.

A control chart is used in quality improvement to graphically display variation in a process over time and can help determine if variation is from a predictable or an unpredictable cause. Additionally, control charts can be used to determine if an intervention has resulted in a positive change. For example, the rate of medication errors could be tracked before and after the initiation of a computer physician order system to determine if the system has had an impact on reducing errors.

A Pareto chart is another method for organizing root causes by displaying them on a graph in descending order of frequency. Unlike a fishbone diagram that is used to identify potential causative factors of a problem and the potential relationship between different variables, Pareto charts are more helpful in focusing improvement initiatives on the most common root causes of a problem.

Spaghetti diagrams are used to visually display flow through a system. The flows are drawn as lines on a map and look similar to spaghetti noodles. For example, a spaghetti diagram may be used to follow a medication order through a hospital unit from order generation to administration of the medication. The diagram can help highlight inefficiencies or redundancies in a system.

KEY POINT

- A cause-and-effect diagram, also known as a fishbone or Ishikawa diagram, is a quality improvement tool that is used to organize root causes of a problem.

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Item 58 Answer: D

Educational Objective: Evaluate perioperative cardiac risk in a patient with no significant risk factors for major adverse cardiac events.

No further diagnostic testing is needed for this patient's preoperative cardiovascular risk assessment. This patient is scheduled to undergo surgery (total knee arthroplasty) and has an indeterminate functional capacity, but he does not have coronary artery disease or its equivalents (chronic kidney disease, cerebrovascular disease, heart failure, or diabetes mellitus). Whether a risk calculator (for example, the American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator) or a simplified approach to perioperative cardiac risk assessment (such as the Revised Cardiac Risk Index) is used, this patient's risk for major adverse cardiac events would be low. No further diagnostic testing is therefore indicated.

As outlined by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, noninvasive pharmacologic cardiac stress testing is not appropriate for an asymptomatic patient with low risk of cardiac complications. Such testing is both low yield and prone to false-positive results. Instead, cardiac stress testing may be considered in patients with elevated cardiac risk and poor or indeterminate functional capacity if the results will alter perioperative management.

Resting echocardiography is useful for evaluating structural heart disease (such as valvular disease or cardiomyopathy). It is not an appropriate modality for coronary artery disease assessment. Because this patient has no signs or symptoms of structural heart disease, resting echocardiography is not indicated.

The utility of cardiac biomarkers such as serum troponin in preoperative cardiac risk assessment is still under debate, and ACC/AHA guidelines do not recommend their use in perioperative risk stratification. Even if their use was considered for risk stratification, it would not be appropriate in patients without other cardiac risk factors due to the potential for false-positive results in this population.

KEY POINT

- If a patient has no history, symptoms, or risk factors for coronary artery disease, no preoperative coronary evaluation is necessary.

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Item 59 Answer: B

Educational Objective: Evaluate a patient with syncope.

This patient likely experienced an episode of neurally mediated syncope (reflex syncope) and should undergo electrocardiography. Neurally mediated syncope is the most common cause of syncope and is associated with the vagal prodrome of nausea, warmth, and lightheadedness. In addition to a careful history and physical examination (including orthostatic blood pressure and pulse measurement), the European Society of Cardiology and the National Institute for Health and Care Excellence advocate obtaining a 12-lead electrocardiogram (ECG) in patients with syncope. A normal ECG has a high negative predictive value for serious adverse outcomes. If the ECG is normal in this patient with classic symptoms of vasovagal syncope, no cardiac history, and a normal physical examination, including orthostatic vital

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signs, she can be safely discharged home with outpatient follow-up.

Echocardiography is not recommended as part of the initial evaluation of syncope unless there are historical or clinical findings suggestive of structural heart disease, which are not present in this patient.

Cerebrovascular disease is a rare cause of syncope, and the American College of Physicians does not recommend brain imaging with CT or MRI in any patient with simple syncope and a normal neurologic examination, as is the case in this patient.

Although this patient's clinical history is compatible with neurocardiogenic syncope, a resting electrocardiogram is recommended as part of the evaluation of syncope. Therefore, no additional testing would be inappropriate.

KEY POINT

- In addition to a careful history and physical examination including measurement of orthostatic vital signs, electrocardiography should be performed in all patients with syncope.

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Item 60 Answer: B

Educational Objective: Manage a patient with recent percutaneous coronary intervention who is scheduled for elective noncardiac surgery.

For this patient who underwent percutaneous coronary intervention and stenting with an everolimus-eluting coronary stent 4 months ago, the optimal preoperative management is to delay surgery for at least 8 months. The American College of Cardiology and American Heart Association (ACC/AHA) guideline recommends an optimal delay of elective noncardiac surgery for a minimum of 12 months after placement of a drug-eluting stent (DES) due to the increased risk of cardiovascular complications, regardless of the type of antiplatelet therapy. Although some data suggest 6 months may be sufficient for normalization of risk, the ACC/AHA still advises delaying elective surgery for 12 months after DES placement. The ACC/AHA guideline states that between 6 and 12 months after DES placement, noncardiac surgery can be considered if the benefits outweigh the risks. This requires collaborative decision making with the patient's cardiologist. Patients with percutaneous coronary intervention alone should avoid surgery for 14 days after their intervention, whereas coronary artery bypass grafting and bare metal coronary stenting require a minimum noncardiac surgical delay of 30 days.

Patients with a DES should remain on uninterrupted dual antiplatelet therapy (DAPT) for at least 12 months after their intervention. The only perioperative exception is for urgently required surgery in which the bleeding risks are deemed too high to justify continuation of DAPT (for example, intracranial surgery). For patients who must undergo noncardiac surgery before the minimum duration DAPT, either continuation of both antiplatelet agents or aspirin alone may be considered based on discussions between all members of the perioperative care team. However, in this patient's case, surgery is elective and optimally should be delayed for a minimum of 12 months total after DES placement.

Antiplatelet management in elective surgical patients with a previous history of coronary intervention who have surpassed the minimum duration of DAPT is also controversial. The ACC/AHA recommends consensus decision making between a patient's clinicians to provide an individualized antiplatelet management plan, whereas the American College of Chest Physicians advises that patients on aspirin who are at moderate to high risk for cardiovascular events should remain on aspirin throughout surgery. Those at moderate to high cardiovascular risk include patients with ischemic heart disease, heart failure, diabetes mellitus, prior stroke, kidney disease, or undergoing vascular procedures.

KEY POINT

- Elective noncardiac surgery should optimally be delayed for 1 year after placement of a drug-eluting stent due to the increased risk of cardiovascular complications, regardless of the type of antiplatelet therapy.

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Item 61 Answer: D

Educational Objective: Treat panic disorder.

Treatment with a selective serotonin reuptake inhibitor (SSRI) such as sertraline is appropriate for this patient who meets the diagnostic criteria for panic disorder. Panic disorder is characterized by recurrent, unexpected, and abrupt surges of extreme anxiety that peaks within minutes and is accompanied by four or more of the following symptoms: palpitations, sweating, trembling, dyspnea, choking sensation, chest pain, nausea or abdominal pain, lightheadedness, chills or heat sensations, numbness or tingling, feeling detached from oneself, and fear of losing control or dying. Diagnosis requires that an attack be followed by at least 1 month of worry by the patient that he or she will experience a recurrent attack. Recommended treatment of panic disorder is a combination of cognitive-behavioral therapy and medication because this has been shown to be more effective than either treatment alone. Various forms of

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pharmacologic treatment for panic disorder are available: SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, tricyclic antidepressants, and monoamine oxidase inhibitors. SSRIs, SNRIs, benzodiazepines, and tricyclic antidepressants are equally effective in treating anxiety and reducing frequency of panic attacks. However, SSRIs are the mainstay of pharmacologic treatment for panic disorder because of side effects associated with the other drug classes. The initial SSRI dose should be low and gradually titrated upward, with the goal of elimination of panic attacks. If response is inadequate, then switching to another SSRI or another class of drug is recommended.

Benzodiazepines, such as alprazolam, are not recommended as the first treatment choice for panic disorder because of their side effects, including potential for dependency and withdrawal syndrome. However, benzodiazepines (such as clonazepam) may have a short-term role in combination with an SSRI for initial treatment of panic disorder. Such short-term (but not long-term) combinations result in more rapid resolution of symptoms and elimination of attacks than SSRI treatment alone.

Buspirone is effective in treating generalized anxiety disorder, but not panic disorder.

β-Blockers such as propranolol can reduce situation-specific anxiety symptoms (for example, public speaking) but are not effective as monotherapy for panic disorder.

KEY POINT

- Selective serotonin reuptake inhibitors are the mainstay of pharmacologic treatment for panic disorder.

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Item 62 Answer: D

Educational Objective: Evaluate a patient prior to prescribing hormonal contraception.

This woman may be prescribed a combined hormonal oral contraceptive after a negative screening pregnancy test is obtained. A pregnancy test should be obtained prior to initiating contraception if more than 1 week has passed since the last menstrual period, as in this patient.

In healthy women without chronic conditions, few tests are needed before initiation of combined hormonal contraceptives, and this patient has no history of smoking, thromboembolism, or migraine that could influence the choice of contraceptive method. Blood pressure should be measured before initiation of combined hormonal contraceptives. Baseline weight and BMI are useful for monitoring contraceptive users over time. In this patient, no other screening tests are indicated.

Newer-generation oral contraceptives that contain lower dosages and less androgenic hormones have minimized their effect on different lipid parameters. Because lipid changes seen with hormonal contraception are mild, usually transient, and not clearly associated with increased cardiovascular risk, testing lipid parameters prior to starting treatment is not indicated.

Breast cancer screening with mammography is also not recommended prior to initiation of hormonal contraception. Breast cancer screening should be performed according to recommended guidelines.

In healthy women of reproductive age, a screening pelvic examination or cervical cancer screening is not required prior to initiation of combined hormonal contraceptives in the absence of symptoms or other clinical findings. Cervical cancer screening should follow recommended guidelines, and this patient is up to date with her age-appropriate screening.

Combined hormonal contraceptives, which include pills, transdermal patches, and vaginal rings, can be initiated at any time in the menstrual cycle. Because these are contraceptive methods that depend on consistent and correct use, patient education and engagement are essential. The provision of information about common side effects such as unscheduled bleeding, especially during the first 3 to 6 months of use, has been shown to increase continuation rates. Bleeding irregularities are generally not harmful and usually improve with continued use. The patient should also be counseled regarding the continued need for condom use to reduce risk of sexually transmitted infections and HIV infection.

KEY POINT

- A pregnancy test should be obtained in all women prior to prescribing hormonal contraception if more than 1 week has passed since the last menstrual period.

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Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention (CDC). U.S. Selected Practice Recommendations for Contraceptive Use, 2013: adapted from the World Health Organization selected practice recommendations for contraceptive use. 2nd edition. MMWR Recomm Rep. 2013 Jun 21;62(RR-05):1-60. [PMID: 23784109]

Item 63 Answer: B

Educational Objective: Treat upper respiratory tract infection.

This patient should be treated with a combination antihistamine and decongestant, such as chlorpheniramine-pseudoephedrine. This otherwise healthy nonsmoker has acute cough most likely caused by viral upper respiratory tract infection. His examination findings do not implicate lower respiratory tract infection, and there is no evidence of reactive airways disease. The treatment of acute viral upper respiratory tract infections is based on symptoms. First-generation antihistamine and decongestant preparations (such as chlorpheniramine-pseudoephedrine), inhaled ipratropium, and cromolyn sodium may be used to decrease sneezing and rhinorrhea.

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Routine antibiotic treatment of uncomplicated viral upper respiratory tract infections in immunocompetent patients is ineffective, associated with many adverse effects, contributes to antibiotic resistance, and represents low value care; it is therefore not recommended. The purulent nature of this patient's sputum does not reliably differentiate between bacterial and viral causes of infection, and he should not be prescribed an antibiotic.

Codeine is less useful as a cough suppressant in acute cough, as in this patient. Studies suggest, however, that opioids may decrease cough frequency and severity in patients with chronic cough.

This patient has no wheezing or history of reactive airways disease; therefore, inhaled β_2-agonists, such as albuterol, are not indicated.

KEY POINT

- The treatment of acute cough associated with upper respiratory tract infection is symptomatic; routine antibiotic treatment is not recommended.

Bibliography

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Item 64 Answer: B

Educational Objective: Diagnose a suspected full-thickness rotator cuff tear.

The most appropriate next step in management of this patient is to obtain an MRI of the right shoulder. This patient likely has an acute full-thickness tear of the right supraspinatus tendon, as suggested by her inability to abduct her right shoulder beyond 90 degrees, to lower her arm from 90 degrees of abduction (drop-arm test), and to maintain full external rotation when the arm is passively externally rotated at 20 degrees of abduction (external rotation lag test). To confirm the diagnosis in this patient, the most appropriate management would be to obtain a shoulder MRI, as it is a highly accurate and widely available modality for diagnosing full-thickness tears. Musculoskeletal ultrasonography is also highly sensitive for rotator cuff tears and may be used as a diagnostic study for suspected rotator cuff injuries. In the case of an acute full-thickness tear, immediate surgery is indicated.

Although glucocorticoid injection can lead to short-term pain improvement, the evidence for its use in rotator cuff tears is limited. Such injections may have a negative impact on healthy shoulder tendons, leading to worse surgical outcomes, and should therefore be avoided in patients who are potential surgical candidates.

Physical therapy alone would not be appropriate in this patient with a suspected complete rotator cuff tear who is a surgical candidate, as delayed orthopedic referral (>6 weeks) can lead to suboptimal surgical outcomes.

Although this patient has weakness on examination, she lacks other findings, such as paresthesias or pain in a dermatomal distribution, that suggest a nerve injury and might make a nerve conduction study helpful in diagnosis.

KEY POINT

- MRI is the preferred imaging modality for diagnosing full-thickness rotator cuff tears.

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Item 65 Answer: B

Educational Objective: Manage depression that does not respond to full-dose antidepressant monotherapy.

Discontinuation of citalopram and initiation of a different antidepressant such as bupropion is the most appropriate next step in the management of this patient. About 40% of patients with depression do not respond to antidepressant monotherapy. However, patients who do not respond to full-dose antidepressant monotherapy for 6 weeks may respond to switching to a different antidepressant drug, either from the same or a different class, or the addition of a second antidepressant drug.

Available evidence is not convincing regarding the efficacy of liothyronine in combination with, or augmenting, selective serotonin reuptake inhibitor treatment of depression.

Patients who do not respond to full-dose antidepressant monotherapy for 6 weeks may respond to the addition of an antipsychotic drug. The FDA has approved the following combinations of antidepressant and antipsychotic drugs for the treatment of depression: aripiprazole or quetiapine extended-release added to any antidepressant, and olanzapine added to fluoxetine. However, olanzapine monotherapy is not an appropriate treatment for this patient.

Electroconvulsive therapy may be appropriate for patients with depression refractory to multiple antidepressant drugs (or intolerance of such drugs), with or without psychotherapy, and patients with severe life-threatening depression (for example, suicidal ideation and catatonia).

Most patients with depression are treated with either antidepressant drugs or psychotherapy; a minority receive combined therapy. However, in a recent meta-analysis, pharmacotherapy combined with psychotherapy was more effective than pharmacotherapy alone in the treatment of depression. In addition to switching to a different antidepressant or adding a second antidepressant or an antipsychotic agent, clinicians should consider psychotherapy for depressed patients who do not respond to antidepressant drug monotherapy.

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KEY POINT

- Patients refractory to full-dose antidepressant monotherapy within 6 weeks may respond to a change in therapy, which may include replacement with another antidepressant, either from the same or a different class, or the addition of a second antidepressant.

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Item 66 Answer: A

Educational Objective: Recognize unprofessional physician conduct on social media.

The physician should meet with the colleague to advise that she remove the inappropriate content. The use of social media has grown dramatically in recent years and has changed how people communicate and interact with each other. Although social media can be useful for improving patient care and advocacy, its use creates challenges for professionalism. Physicians should manifest online activity that reflects standards of professional behavior, and they should strive to keep their social and professional online presences separate and conduct themselves professionally in both spheres. Furthermore, physicians should be aware that all posted content is generally public and permanent, and they must assume that patients will be able to view social media postings. In this case, the physician should meet with the colleague to express concerns about the social media postings and why the postings do not reflect standards of professionalism; may diminish patients' trust in the doctor, her group, and the profession; and should be removed if possible.

At this stage, it is unnecessary to report the concern to the head physician of the practice; the colleague will likely respond favorably to discreet feedback. If she does not, escalation to involve the practice leadership would be indicated.

Commenting on the colleague's social media page about the unprofessional content is an inappropriate means of providing feedback.

The physician should not disregard the inappropriate social media posts, even if none of the content can be linked to individual patients.

KEY POINT

- Physicians should keep their social and professional online presences separate and conduct themselves professionally in both spheres.

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Item 67 Answer: D

Educational Objective: Manage chronic cough due to gastroesophageal reflux disease.

The most appropriate management of this patient with chronic cough is an empiric trial of a proton pump inhibitor. In general, an algorithmic approach to chronic cough (cough of greater than 8 weeks' duration) leads to successful outcomes in more than 90% of patients. Patients with chronic cough, especially smokers, should undergo chest radiography. If the chest radiograph does not reveal a potential cause of cough, the physician should consider upper airway cough syndrome, asthma, nonasthmatic eosinophilic bronchitis, and gastroesophageal reflux disease (GERD) and begin a stepwise approach for evaluation and treatment. The definitive diagnosis may be suggested by history and physical examination findings and confirmed by successful empiric treatment. This obese patient with a 15-pack-year history has chronic cough and symptoms typical of GERD (heartburn, cough that is worsened after a large meal). Additionally, his tobacco use, alcohol use, and caffeine intake are risk factors for GERD. Initiating a proton pump inhibitor such as omeprazole is the next most appropriate step and can be started without 24-hour esophageal pH monitoring. All patients with chronic cough who smoke should also receive tobacco cessation counseling.

A combination antihistamine and decongestant is helpful in patients with cough due to upper airway cough syndrome; however, this patient does not present with symptoms or signs of upper airway cough syndrome (allergic symptoms or postnasal drip).

In the presence of a normal chest radiograph, bronchoscopy is unlikely to be of benefit and should be reserved for second-line testing if the patient's symptoms fail to improve after several months of optimized therapy with a proton pump inhibitor.

Echocardiography is helpful in evaluating left ventricular function or valvular heart disease as a cause of cough; however, in the absence of symptoms (shortness of breath, paroxysmal nocturnal dyspnea) or physical examination findings (crackles, S_3, edema, murmur), an echocardiogram is unnecessary and represents low value care.

KEY POINT

- Proton pump inhibitor therapy can be initiated without 24-hour esophageal pH monitoring in patients with chronic cough who have a normal chest radiograph and symptoms suggestive of gastroesophageal reflux disease.

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Item 68 Answer: C

Educational Objective: Screen for atrial fibrillation during the physical examination.

Palpating the pulse to screen for atrial fibrillation should be included in this patient's physical examination. Palpating the pulse has been shown to increase atrial fibrillation case finding among adults age 65 years and older. A cluster-randomized trial of more than 14,000 patients found that detection of new cases of atrial fibrillation was 1.64% per year in patients randomized to receive opportunistic screening (pulse taking and invitation for electrocardiography if the pulse was irregular) compared with 1.04% in patients randomized to receive no active screening.

Abdominal palpation for the detection of abdominal aortic aneurysm (AAA) has been shown to have poor reliability. Ultrasonography is the preferred screening test for detection of AAA because it is noninvasive, easy to implement, and has excellent sensitivity and specificity. The U.S. Preventive Services Task Force (USPSTF) recommends one-time screening for AAA with abdominal ultrasonography in all men aged 65 to 75 years who have smoked at least 100 cigarettes in their lifetime and selective screening in men in this age group who have never smoked.

Carotid artery auscultation of bruits for detection of carotid stenosis has also been shown to have poor accuracy. Although ultrasonography has higher sensitivity and specificity than auscultation, the USPSTF recommends against screening for carotid stenosis in adults, as the harms of screening outweigh the benefits.

The USPSTF recommends against routine testicular examination for the purposes of cancer screening, primarily due to the low incidence and high survival rate of patients with testicular cancer, even when it is clinically detected. Harms associated with testicular cancer screening include false-positive results and unnecessary anxiety.

KEY POINT

- Palpating the pulse has been shown to increase the detection rate of atrial fibrillation among adults age 65 years and older.

Bibliography

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Item 69 Answer: D

Educational Objective: Treat trichomoniasis.

The most appropriate additional intervention in this patient is to treat her partner. This patient has the characteristic features of frothy yellow discharge, burning, and dyspareunia associated with infection by *Trichomonas vaginalis* organisms, which are seen on microscopy. Trichomoniasis is the most common curable sexually transmitted infection (STI) worldwide and is evenly distributed among women of all age groups, unlike other STIs that predominate in younger people. It is caused by motile flagellated protozoa that infect the urogenital tract, causing inflammatory vaginitis and urethritis. Treatment with a single 2-g dose of metronidazole is associated with a high rate of cure and should be offered to all symptomatic women. It is important that sexual partners also be treated, even if asymptomatic, because of a high rate of reinfection; documentation of infection is not required before treatment in any partners. Once trichomoniasis is identified, testing for other STIs should be considered in both individuals.

Trichomoniasis has been traditionally associated with a vaginal pH of greater than 4.5 and diagnosed by direct visualization of trichomonads on saline microscopy. However, the specificity of a high vaginal pH and the sensitivity of saline microscopy findings are low. Therefore, point-of-care vaginal swab rapid immunoassays and nucleic acid amplification tests (NAATs) for detection of *T. vaginalis* are increasingly considered to be the gold standard for diagnosis, and particularly when microscopy is not available. NAATs can be performed on a vaginal (or endocervical) swab, urine sample, or liquid-based Pap test specimens. In this patient in whom trichomonads are seen on microscopy, confirmatory testing with another assay is not necessary.

Trichomoniasis causes an inflammatory vaginitis, and cervical contact bleeding may occur due to inflammation from the infection. This inflammation resolves with treatment of the infection, and a follow-up Pap smear to detect cervical pathology would not be required in the absence of additional symptoms or findings.

Treatment of trichomoniasis with single-dose metronidazole is highly effective; therefore, testing for cure is not required in patients whose symptoms have resolved with therapy.

KEY POINT

- Trichomoniasis is characterized by copious, malodorous, pale yellow or gray frothy discharge with vulvar itching, burning, and postcoital bleeding; it is effectively treated with a single dose of metronidazole.

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Item 70 Answer: A

Educational Objective: Reduce cardiovascular risk in a patient with metabolic syndrome.

Aspirin is the most appropriate treatment to reduce cardiovascular risk in this patient with metabolic syndrome. According to the International Diabetes Federation and the American Heart Association (AHA), diagnosis of metabolic syndrome is made by the presence of three or more of the

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following five criteria: (1) increased waist circumference; (2) serum triglyceride level of 150 mg/dL (1.70 mmol/L) or higher (or taking medications for hypertriglyceridemia); (3) HDL cholesterol level lower than 40 mg/dL (1.04 mmol/L) in men and lower than 50 mg/dL (1.30 mmol/L) in women (or taking medication specifically for low HDL cholesterol); (4) blood pressure of 130/85 mm Hg or higher (or taking antihypertensive medications); and (5) fasting plasma glucose level of 100 mg/dL (5.6 mmol/L) or higher (or taking medications for hyperglycemia). The patient meets at least three criteria (elevated triglyceride level, decreased HDL cholesterol level, antihypertensive treatment). Management of patients with metabolic syndrome should focus on optimizing general health and targeting the individual components of the metabolic syndrome. Lifestyle changes include education on the importance of following a heart-healthy diet, implementing a weight loss plan, and exercising for 30 minutes daily at least 5 days per week. Patients with hypertension should be treated aggressively to achieve the blood pressure goals outlined by the Eighth Joint National Committee. Similarly, dyslipidemia should be treated according to American College of Cardiology (ACC) and AHA cholesterol treatment guideline, and hyperglycemia should be managed per guidelines from the American Diabetes Association. Additionally, the AHA recommends low-dose aspirin for patients with metabolic syndrome with a 10-year cardiovascular risk of 10% or higher. This patient's hypertension and hyperlipidemia are being managed; however, he should also be prescribed aspirin based on his increased risk, provided that his risk for bleeding is not increased.

Diltiazem will not provide additional cardiovascular risk reduction in this patient. Moreover, intensification of his hypertension therapy is not indicated, since the blood pressure goal for patients younger than 60 years is a systolic pressure of less than 140 mm Hg and a diastolic pressure of less than 90 mm Hg. The patient's pressures are within this range.

Fenofibrate increases the potential for drug-induced side effects and has uncertain additive cardiovascular risk reduction when used with statins, which are clearly indicated in this patient based on ACC/AHA guidelines. Fibrate therapy is reserved for patients with hyperlipidemia who do not tolerate or do not respond to statin monotherapy, patients who have triglyceride levels higher than 500 mg/dL (5.65 mmol/L), or patients with hypertriglyceridemia-induced pancreatitis.

The role of metformin in the metabolic syndrome has not been clearly defined. It may reduce the incidence of metabolic syndrome in at-risk patients, but healthy lifestyle modifications are equally effective or superior to metformin in reducing cardiovascular risk. Metformin has also not been shown to reduce cardiovascular events in patients without diabetes. Metformin would be a reasonable choice for both treatment of hyperglycemia and improvement of metabolic parameters if this patient did have impaired fasting glucose or impaired glucose tolerance, and it would be the initial drug of choice if the patient develops diabetes.

KEY POINT

- Patients with metabolic syndrome who have a 10-year cardiovascular risk of 10% or higher should be treated with low-dose aspirin for primary prevention of cardiovascular disease.

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Item 71 Answer: C

Educational Objective: Treat severe menopausal vasomotor symptoms in a woman whose uterus has been removed.

Transdermal estradiol without a progestin is the most appropriate choice for this patient with severe vasomotor symptoms of menopause that are refractory to conservative treatment and are affecting her quality of life. Systemic estrogen improves both hot flushes and genitourinary symptoms. She has had a hysterectomy and therefore does not require the use of a progestin to oppose the proliferative effects of estrogen on the endometrium, making therapy with estrogen alone an appropriate treatment option.

The use of hormones to treat menopausal symptoms requires balancing potential benefits and risks, and an individualized risk profile must be considered. This patient is recently menopausal, younger than 60 years, and does not have a history of thromboembolism or cardiac disease or have an increased risk for breast cancer. Treatment with systemic estrogen would be a reasonable choice and can be administered orally or transdermally by patch, gel, or spray. There is some evidence that transdermal estrogen may be associated with less thromboembolic risk than oral estrogen by avoiding the hepatic first-pass effect. All formulations are equally effective for treating vasomotor symptoms.

Current evidence does not support the use of progestin alone to treat vasomotor symptoms. Although progestins may improve vasomotor symptoms, safety data for progestin alone are lacking. Also, in the Women's Health Initiative, the risk of breast cancer was increased in the estrogen and medroxprogesterone acetate arm, but not in the estrogen-alone arm, raising concern that the risk of breast cancer may be related to progestin use. Therefore, a progestin alone is not the most appropriate choice for the management of vasomotor symptoms.

Vaginal estradiol therapy is useful in treating menopausal genitourinary symptoms, including dryness, itching, dysuria, and dyspareunia. However, local topical treatment does not alleviate vasomotor or other systemic menopausal symptoms. In this patient who has both vaginal symptoms and severe vasomotor symptoms, vaginal treatment alone would not be adequate.

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KEY POINT

- In women without a uterus taking systemic estrogen therapy for management of menopausal symptoms, concurrent progestin is not indicated.

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ACOG Practice Bulletin No. 141: management of menopausal symptoms. Obstet Gynecol. 2014 Jan;123(1):202-16. [PMID: 24463691]

Item 72 Answer: A

Educational Objective: Adjust medications in a woman who may become pregnant.

Discontinuation of atorvastatin is indicated in this patient who is planning pregnancy. Statin medications should be avoided in pregnancy due to the potential risk for congenital abnormalities. In patients actively planning pregnancy, dyslipidemia is best managed with diet and lifestyle modification for the duration of the pregnancy. Because the effects of statin use during breastfeeding are not known, their use during nursing should be discouraged.

ACE inhibitors and angiotensin receptor blockers are also contraindicated due to potential risk of teratogenicity and should be discontinued in women who are planning pregnancy, as was done in this patient. Her hypertension should be followed and treated, if needed, with another agent known to be safe in pregnancy, such as β-blockers, calcium channel blockers, or methyldopa.

Oral antidiabetic agents should be continued in women contemplating pregnancy to maintain control of diabetes mellitus. Metformin is an FDA pregnancy category B medication (no definitive studies in pregnant women but no animal studies showing risk to the fetus) and is a reasonable option for controlling this patient's hyperglycemia before pregnancy. Evidence suggests that metformin and sulfonylureas are acceptable during pregnancy; however, further management decisions are best made through co-management of medical and obstetric issues with a high-risk obstetrician.

In the treatment of depression, medication discontinuation may not be appropriate in women with a history of major or recurrent depression. Some selective serotonin reuptake inhibitors (SSRIs), including sertraline and fluoxetine, are FDA pregnancy category C (no definitive studies in pregnant women but evidence of potential harm in animal reproduction studies, although potential benefits may warrant use despite potential risks), and their use must be determined on an individual basis. Such agents may be continued if needed, but the risks and benefits of treatment, taking into account severity of depressive symptoms, stage of gestation, and associated circumstances, should be evaluated by a psychiatrist or high-risk obstetrician. SSRIs should not be stopped precipitously.

Because this patient is on a known medication classified as FDA pregnancy category X (atorvastatin), continued treatment with this agent would be inappropriate.

KEY POINT

- Statins, ACE inhibitors, and angiotensin receptor blockers are teratogenic and should be discontinued in women planning pregnancy.

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Item 73 Answer: A

Educational Objective: Treat an overweight patient with behavioral therapy.

The most appropriate additional treatment for this patient is behavioral therapy. With a BMI of 29, this patient is overweight, and her waist circumference of 92 cm (36 in) is independently associated with increased cardiovascular risk. According to the American College of Cardiology, American Heart Association, and The Obesity Society, all overweight and obese patients should be offered a comprehensive lifestyle intervention (comprised of diet, physical activity, and behavioral treatments) for weight loss. Behavioral therapy includes providing patients with strategies to facilitate a shift from personal maladaptive eating patterns toward healthful eating and exercise, particularly in this patient who acknowledges eating to reduce stress and suboptimal dietary choices. Such strategies are associated with weight loss and reduced risk for developing diabetes mellitus and hypertension. Although best conducted by a trained therapist, behavioral therapy can be initiated by internists. Specifically, internists can emphasize the behavioral therapy components of self-monitoring, stimulus control, goal setting, and social support. Given this patient's eating patterns and previous dieting attempts, she should be offered behavioral therapy.

Bariatric surgery, such as laparoscopic adjustable gastric banding, should be considered in all patients with a BMI of 40 or higher and in patients with a BMI of 35 or higher with obesity-related comorbid conditions; it is therefore not indicated in this patient.

Pharmacologic agents, such as orlistat or phentermine, are used along with diet, physical activity, and behavioral treatments in patients with a BMI of 30 or higher or in patients with a BMI of 27 or higher with overweight- or obesity-associated comorbidities. This patient does not currently meet the criteria for pharmacologic therapy.

KEY POINT

- All overweight and obese patients should be offered a comprehensive lifestyle intervention for weight loss including diet, physical activity, and behavioral therapy.

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Item 74 Answer: D

Educational Objective: Diagnose somatic symptom disorder.

The patient meets the diagnostic criteria for somatic symptom disorder. These criteria include having at least one somatic symptom causing distress or interference with daily life; excessive thoughts, feelings, and behaviors related to the somatic symptoms; and persistence of somatic symptoms for at least 6 months. Furthermore, potential medical causes must be excluded. She has two somatic symptoms (chest and abdominal pain), which have been present for well over 6 months and have no identifiable organic source despite thorough diagnostic testing. Her missed time from work demonstrates interference with daily functioning, and her frequent utilization of health care resources and daily research of Internet resources are indicative of excessive concern over her symptoms.

Conversion disorder involves one or more symptoms of abnormal sensation or motor function that are not explained by a medical condition and are inconsistent with physical examination findings. This patient's symptoms are somatic rather than neurologic, thus eliminating the possibility of conversion disorder.

Patients with factitious disorder deliberately falsify symptoms or inflict injury upon themselves or another. Although patients with factitious disorder may have no apparent external benefit for their fabricated illness, this patient has no evidence (such as tenderness on abdominal examination) that she is falsifying her symptoms.

Illness anxiety disorder (formerly known as hypochondriasis) is characterized by excessive concern over general health and is associated with undue focus on health-related activities. However, unlike this patient with debilitating somatic symptoms, patients with illness anxiety disorder have minimal or no somatic symptoms.

KEY POINT

- Diagnostic criteria for somatic symptom disorder include having at least one somatic symptom causing distress or interference with daily life; excessive thoughts, feelings, and behaviors related to the somatic symptoms; and persistence of somatic symptoms for at least 6 months.

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Dimsdale JE, Creed F, Escobar J, et al. Somatic symptom disorder: an important change in DSM. J Psychosom Res. 2013 Sep;75(3):223-8. [PMID: 23972410]

Item 75 Answer: A

Educational Objective: Treat chronic pain with cognitive-behavioral therapy.

Cognitive-behavioral interventions are some of the most useful tools in helping to manage chronic pain and are consistently recommended in pain management guidelines. There are many different types of cognitive-behavioral interventions, such as cognitive restructuring, relaxation techniques, and mindfulness-based stress reduction, all of which replace maladaptive coping patterns (such as catastrophizing, fear avoidance, and overgeneralizing) with more constructive coping skills. How cognitive-behavioral techniques are incorporated into an individual patient's multimodal management strategy depends on local resources and patient preference; however, numerous studies show that primary care physicians can implement some cognitive-behavioral techniques effectively in the office setting.

The lidocaine patch is an effective topical agent for localized neuropathic pain; however, it would not be an effective option to treat widespread central pain, such as that in this patient with fibromyalgia.

NSAID therapy can be considered for intermittent flares of pain, but it is generally ineffective when used on a scheduled basis for central pain.

There is little evidence supporting the use of opioids in patients with chronic noncancer pain and ample evidence of potential harms of chronic opioid therapy in such patients. Furthermore, there is some weak evidence that opioids may in fact worsen central pain. Therefore, opioids should only be considered as a last resort in certain low-risk patients after all other modalities have failed.

KEY POINT

- Cognitive-behavioral therapy, in which maladaptive coping patterns are replaced with more constructive coping skills, is recommended in the management of chronic pain.

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Item 76 Answer: A

Educational Objective: Manage a patient's request for genetic testing.

The most appropriate management of this patient is to obtain a comprehensive three-generation family history that specifically assesses for the presence of breast, ovarian, and other cancers. According to the U.S. Preventive Services Task Force (USPSTF), the decision of whether or not to perform *BRCA* genetic testing should be based on a woman's family history of breast cancer. Family history attributes that suggest an increased likelihood of the presence of a *BRCA* gene

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mutation include multiple family members with breast cancer, the presence of both breast and ovarian cancer, breast cancer diagnosis before the age of 50 years, breast cancer in one or more male family members, bilateral breast cancer, and Ashkenazi Jewish heritage. Women who are found to be at increased risk for carrying the *BRCA1* and *BRCA2* gene mutations should be offered genetic counseling and, if appropriate after counseling, *BRCA* genetic testing. The USPSTF recommends against routine testing for *BRCA1* and *BRCA2* gene mutations in women who lack a family history suggestive of such mutations.

Ordering screening mammography for this 32-year-old woman is also not appropriate because of her young age. The USPSTF currently recommends biennial screening mammography for women aged 50 to 74 years. Additionally, the USPSTF recommends individualized screening decisions for women younger than 50 years based on patient context and values regarding specific benefits and harms.

According to the USPSTF, performing genetic testing for *BRCA1* and *BRCA2* gene mutations would not be appropriate before obtaining a comprehensive family history.

Referral for genetic counseling would also be inappropriate at this stage. Referral for genetic counseling should occur if, after obtaining a three-generation family history, *BRCA* genetic testing is indicated. Genetic counseling should always occur before any genetic test is performed.

KEY POINT

- Genetic testing for *BRCA* gene mutations should only be performed in patients with a family history that is suggestive of an increased genetic risk.

Bibliography

Moyer VA; U.S. Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014 Feb 18;160(4):271-81. [PMID: 24366376]

Item 77 Answer: D

Educational Objective: Prevent falls in a cognitively impaired patient.

There is no specific intervention that would be beneficial in this older patient with cognitive impairment; therefore, continuing this patient's current care is appropriate. In older adults, falls are a source of morbidity, mortality, decreased functionality, and premature institutionalization. Risk factors for falling are myriad and include lower extremity weakness, history of falls, gait or balance deficits, polypharmacy, low vitamin D level, visual impairments, and cognitive impairment. Many risk factors are amenable to remediation; however, there is insufficient evidence to support any specific interventions to reduce fall risk in the cognitively impaired beyond those risk factors that can be treated. This patient is under close supervision and well cared for by her family, and she has no clearly reversible risk factors. Therefore, it is reasonable to continue her current care provided by her family.

Although individualized exercise programs to decrease falls have been shown to be effective in cognitively intact, community dwelling adults, such exercise programs have not been shown to benefit cognitively impaired individuals. The lack of benefit is speculated to be caused by the cognitively impaired patient's inability to retain and incorporate instructions over time.

Antipsychotic medications, such as risperidone, have not been shown to reduce falls in patients with cognitive deficits. Furthermore, risperidone may induce orthostatic hypotension, which may actually increase this patient's risk of falling.

Although many patients are placed in skilled nursing facilities due to falls, there is no evidence that care in a skilled nursing facility is more likely to reduce falls than conscientious care in the home. This is particularly true in this case in which the patient's daughter is clearly meticulous in the care she provides.

KEY POINT

- No specific interventions have been shown to be beneficial in reducing fall risk in the cognitively impaired patient beyond treating reversible risk factors.

Bibliography

Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society. Summary of the updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc. 2011 Jan;59(1):148-57. [PMID: 21226685]

Item 78 Answer: A

Educational Objective: Administer the seasonal influenza vaccine to a patient with a history of egg allergy.

This patient with a history of egg allergy should receive inactivated influenza vaccine (IIV). Although IIV is prepared using chicken eggs and contains a very small amount of egg protein, it has been shown to be safe in patients who have only experienced hives upon exposure to eggs, according to recommendations released by the Advisory Committee on Immunization Practices (ACIP). As a precaution, however, IIV should be administered in these patients by a health care professional who is trained to recognize the manifestations of egg allergy, and the patient should be observed for 30 minutes or longer for any signs of an adverse reaction. Since this patient has only experienced hives, not anaphylaxis, upon egg exposure, he may receive IIV.

Live attenuated influenza vaccine (LAIV) also contains only a small amount of egg protein; however, it is only approved to be administered to immunocompetent adults aged 49 years and younger without a history of any egg allergies, as it has not been extensively studied in patients with this allergy. Therefore, use of LAIV in this patient would not be appropriate.

Skin testing (either prick or intradermal) with influenza vaccine before vaccine administration is not recommended for patients with egg allergy because the presence of a

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positive skin test is not predictive of a subsequent systemic reaction. Skin testing with the vaccine may be appropriate for evaluation of patients with possible allergy to the vaccine itself, but not specifically egg allergy.

Influenza vaccination is recommended for all persons aged 6 months and older unless specifically contraindicated. As inactivated influenza vaccine can be safely administered to patients with a history of hives after exposure to egg, it is inappropriate to avoid vaccinating this patient against influenza.

Recombinant influenza vaccine (RIV) is produced using recombinant DNA technology, does not contain egg proteins, and can be used in patients with severe egg allergy (such as those who experience anaphylaxis). However, it would not be necessary in this patient who is a candidate for routine IIV administration.

KEY POINT

- Inactivated influenza vaccine can be safely administered to patients with an egg allergy who have only experienced hives upon exposure to eggs.

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Item 79 Answer: D

Educational Objective: Recommend appropriate pharmacologic treatment for smoking cessation.

Varenicline will most likely give this patient the greatest chance of success in quitting smoking. A recent Cochrane meta-analysis showed that varenicline increased the odds of quitting smoking compared with placebo (OR, 2.88; 95% CI, 2.40-3.47). Although concerns have been raised regarding varenicline use and an increase in cardiovascular events, the FDA noted that the benefits outweigh potential risks in terms of cardiovascular risk.

Varenicline is more effective than bupropion (OR, 1.59; 95% CI, 1.29-1.96). Additionally, there is also concern that bupropion can lower seizure threshold and thus would not be the best option for this patient who has a history of seizures. Both varenicline and bupropion also have FDA warnings highlighting the risk of serious neuropsychiatric symptoms in patients using these medications.

Electronic cigarettes (E-cigarettes) may not be effective in reducing smoking cessation rates. In a recent randomized controlled superiority trial, adult smokers were randomly assigned to nicotine E-cigarettes, nicotine patches, or placebo E-cigarettes (no nicotine), with low intensity behavioral support. At 6 months, the risk difference for nicotine E-cigarettes versus nicotine patches was 1.51 (95% CI, 2.49-5.51); for nicotine E-cigarettes versus placebo E-cigarettes, 3.16 (95% CI, -2.29-8.61). There was insufficient statistical power to conclude superiority of nicotine E-cigarettes to patches or to placebo E-cigarettes. Currently, the role of E-cigarettes in smoking cessation is uncertain.

Varenicline was also found to be more effective than the nicotine patch (OR, 1.51; 95% CI, 1.22-1.87) and nicotine gum (OR, 1.72; 95% CI, 1.38-2.13), and the nicotine inhaler, spray, tablets, or lozenges (OR, 1.42; 95% CI, 1.12-1.79) all used as single agents. Varenicline was not more effective than combination nicotine replacement therapy (OR, 1.06; 95% CI, 0.75-1.48) such as the combination of a rapid-onset nicotine replacement product (for example, nicotine spray or inhaler) with a long-duration nicotine replacement product (for example, a nicotine patch).

KEY POINT

- Varenicline is more effective in achieving smoking cessation than bupropion or single-agent nicotine replacement therapy but not more effective than combination nicotine replacement therapy.

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Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013 May 31;5:CD009329. [PMID: 23728690]

Item 80 Answer: D

Educational Objective: Diagnose brainstem stroke in a patient with vertigo.

This patient has acute vestibular syndrome (AVS), which may be caused by brainstem infarction or hemorrhage, and he should undergo MRI of the brain. AVS is characterized by prolonged vertigo of acute onset, spontaneous nystagmus, postural instability, and autonomic symptoms. The symptoms of AVS may mimic vestibular neuronitis; however, in this older patient with vascular disease, diplopia, gait instability, and immediate nystagmus with the Dix-Hallpike maneuver, a central cause of vertigo must first be ruled out. MRI is the initial test of choice in the patient presenting with a suspected central cause of vertigo. Diffusion-weighted MRI of the brain is recommended over CT scanning in evaluation of the posterior fossa as bone-related artifacts lead to inadequate imaging by CT.

This patient does not demonstrate neurologic signs or symptoms in the carotid artery distribution (monocular visual loss, hemisensory or hemimotor findings, apraxia, or problems with speech); therefore, carotid Doppler ultrasonography is not indicated.

A CT scan of the head and lumbar puncture are the tests of choice for the evaluation of subarachnoid hemorrhage, which is usually accompanied by severe headache and does not present with vertigo. In this patient, CT scan would not effectively image the posterior fossa.

KEY POINT

- Central vertigo is suggested by accompanying symptoms of dysarthria, dysphagia, diplopia, weakness, numbness, or ataxia.

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Item 81 Answer: C

Educational Objective: Manage a patient with a family history suggestive of an inherited disorder.

This patient should be referred for genetic counseling. Huntington disease, a neurodegenerative disorder, is transmitted as an autosomal dominant condition and is caused by cytosine-adenine-guanine trinucleotide repeat expansion in the *HD* gene (also known as the huntingtin or *HTT* gene). This patient has family members in multiple generations who have been diagnosed with Huntington disease, and he has a 50% chance of inheriting the gene from his father. Obtaining presymptomatic genetic testing in this patient would be appropriate; however, testing should only be performed after the patient undergoes genetic counseling. Key components of genetic counseling include informing the patient of the purpose of the test, implications of the test results, alternative testing options (including the option of foregoing testing), and possible risks and benefits of testing.

Although the choreiform movements that are seen in patients with symptomatic Huntington disease can be captured on electromyography, electromyography is not typically used in diagnosing Huntington disease and has no role in presymptomatic testing. Therefore, obtaining an electromyogram in this patient would not be appropriate.

Performing genetic testing without first providing adequate genetic counseling is not an appropriate intervention. It is essential that patients understand all of the ramifications of testing before testing is performed in order to make an educated decision.

It is inappropriate to tell this patient that genetic testing is unnecessary. Genetic testing is clearly warranted if the patient desires it.

KEY POINT

- Patients with a family history suggestive of an inherited disorder should receive genetic counseling before undergoing genetic testing.

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Bordelon YM. Clinical neurogenetics: Huntington disease. Neurol Clin. 2013 Nov;31(4):1085-94. [PMID: 24176425]

Item 82 Answer: C

Educational Objective: Facilitate decision-making for a patient who lacks decision-making capacity.

The most appropriate course of action is to ask this patient's surrogates, his children, to relate what decisions the patient would make if he were capable. In the case of a patient who lacks decision-making capacity, a surrogate must guide decision making. If such a patient has an advance directive, the person named in that advance directive is the most appropriate (and legal) surrogate. If the patient's advance directive does not name a surrogate, or if the patient does not have an advance directive, the best surrogate is the person who best knows the patient's health care values, goals, and preferences; however, many U.S. states stipulate a hierarchy of surrogate decision makers in the absence of an advance directive (for example, the patient's spouse, followed by an adult child, and so forth). Surrogate decision making in the absence of an advance directive is common, as only about 20% of U.S. adults have advance directives in place. In the case of this patient, the two surviving adult children are the most appropriate surrogates. They have ethical and legal obligations to make decisions based on their father's health care–related values, goals, and preferences (that is, substituted judgment). The physician should ask what decision their father would make about his care if he were able.

Many surrogates are often aware of patients' values, goals, and preferences; however, if these values, goals, and preferences are unknown, a surrogate should make decisions in the patient's best interests.

A surrogate should not make decisions based on his or her own values, preferences, or what he or she feels is the correct course of action, as these views may differ from those of the patient.

Because nonmedical personnel may not be able to accurately convey specific medical details that might influence decision making, physicians should not defer these discussions to others (for example, social workers). Additionally, engaging in therapeutic decision making is an inherent professional responsibility of the attending physician.

Court-appointed guardians are selected for patients who lack decision-making capacity; whose health care–related values, goals, and preferences are unknown; and for whom no obvious surrogate decision maker exists. In the case of this patient, surrogates are available.

KEY POINT

- When a patient lacks decision-making capacity and does not have an advance directive, a surrogate who best knows the patient's health care values, goals, and preferences must make decisions.

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Item 83 Answer: B

Educational Objective: Screen for breast cancer in a patient with high breast density.

This patient with high breast density should receive routine digital screening mammography. High breast density, categorized as either heterogeneously dense breast tissue or extremely dense breast tissue (using the Breast Imaging

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Reporting and Data System [BI-RADS] breast density categories) on mammography, imparts an increased risk of breast cancer (relative risk [RR] of 1.2 for heterogeneously dense breast tissue, RR of 2.1 for extremely dense breast tissue). Approximately 50% of women have high breast density, and some states mandate that increased breast density on mammography is directly reported to patients to inform them of this increased risk. High breast density also decreases the sensitivity of mammography to detect small lesions. Although high breast density alone does not necessitate additional or more frequent breast imaging other than routine screening mammography, there is evidence that digital mammography has an increased sensitivity for detecting small lesions in dense breasts compared with film mammography; it is therefore the preferred modality for routine screening, if available.

MRI is not recommended for either primary screening or as a supplemental test for women with increased breast density due to a lack of documented effectiveness and a high false-positive rate leading to unnecessary biopsies.

Breast ultrasonography is recommended by some organizations as supplemental testing in addition to mammography in women with dense breasts. However, no prospective trials of breast ultrasonography as a primary screening modality currently exist, and its role as a supplemental test to mammography has not been clearly defined. It is therefore not recommended as a replacement to digital mammography.

KEY POINT

- Women with high breast density, categorized as either heterogeneously dense breast tissue or extremely dense breast tissue with the Breast Imaging Reporting and Data System (BI-RADS) breast density categories, should undergo routine digital screening mammography.

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Wang AT, Vachon CM, Brandt KR, Ghosh K. Breast density and breast cancer risk: a practical review. Mayo Clin Proc. 2014 Apr;89(4):548-57. [PMID: 24684876]

Item 84 Answer: D

Educational Objective: Evaluate lower extremity edema due to chronic venous insufficiency.

No additional testing is indicated in this patient. The patient's isolated bilateral lower extremity edema is most likely due to chronic venous insufficiency, as supported by the otherwise normal examination findings and lack of abnormal laboratory test results, and no further diagnostic studies are indicated. The edema associated with chronic venous insufficiency typically is insidious in onset. It worsens with prolonged standing and is improved with elevating the legs and with walking. Leg discomfort is also often gradual in onset and is described as a tired or heavy sensation in the legs. Other symptoms can include pruritus, skin discoloration, and ulceration. Compression stockings are considered first-line therapy for patients with lower extremity edema due to chronic venous disease. The patient should be instructed to put on these stockings in the morning before edema is present and to wear the stockings as much as possible when he is in a standing position. The stockings can be removed at night.

Obtaining an abdominal/pelvic CT scan in this patient would not be appropriate, as he lacks signs and symptoms that would suggest abdominal or pelvic pathology.

Lower extremity venous duplex ultrasonography is not necessary in this patient who lacks risk factors for deep venous thrombosis (prolonged immobility, known cancer history, or use of predisposing medications) and does not have a clinical picture consistent with bilateral deep venous thrombosis.

In the absence of symptoms and examination findings that suggest heart failure (such as orthopnea, dyspnea, paroxysmal nocturnal dyspnea, elevated central venous pressure, crackles in the lower lung fields, and S_3 and/or S_4 heart sounds), the diagnostic utility of a transthoracic echocardiogram is likely low and therefore not appropriate in this patient.

KEY POINT

- The diagnosis of lower extremity edema due to chronic venous insufficiency usually may be made based on a consistent clinical presentation and minimal laboratory testing.

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Item 85 Answer: C

Educational Objective: Manage functional incontinence in a frail older woman.

Behavioral therapy utilizing prompted voiding is the most appropriate management of this patient. This patient's incontinence may be due to multiple factors, including structural and functional causes complicated by her cognitive impairment and decreased mobility. Prompted voiding involves regularly asking the patient to report on incontinence, asking the patient if he or she needs to void, providing assistance with access to the bathroom, and praising the patient for continence. This technique has been shown to reduce urinary incontinence in older patients who have caregivers capable of working with them, such as this one, as well as those residing in assisted-care facilities. This intervention is also usually timed so that prompted voiding occurs before accumulation of a large volume of urine in the bladder, reducing the likelihood that incontinence will occur. With active and consistent caregiver involvement, timed and prompted voiding can help achieve improved bladder control.

Antimuscarinic agents are used to decrease urgency, frequency, or incontinence in overactive bladder with urge incontinence. Adverse effects are common, however, including constipation, dry mouth, dizziness, and confusion, and older patients are at greatest risk for adverse consequences. Therefore, an antimuscarinic agent would not be an

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appropriate therapeutic choice in this older patient with cognitive impairment.

Pelvic floor muscle training is effective in reducing incontinence but requires active participation by the patient. Although training is implemented by physical therapists or advanced practice nurses, both pelvic floor muscle and bladder training require intact cognition and the ability to self-manage and self-sustain a training regimen and are therefore unlikely to be effective in this patient with dementia.

Systemic estrogen therapy has not been shown to alleviate urinary incontinence and may worsen symptoms. It is also associated with increased cardiovascular risks when initiated in women more than 10 years post-menopause.

Attention to skin care and use of absorptive products with frequent changes are extremely important in preventing skin breakdown in older patients with incontinence. A review of modifiable factors is also helpful, including medication use, mobility issues, weight reduction, and caffeine reduction.

KEY POINT

- Behavioral therapy utilizing prompted voiding has been shown to reduce urinary incontinence in older patients with dementia.

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Markland AD, Vaughan CP, Johnson TM 2nd, Burgio KL, Goode PS. Incontinence. Med Clin North Am. 2011 May;95(3):539-54. [PMID: 21549877]

Item 86 Answer: D

Educational Objective: Treat an unstageable pressure ulcer in an older patient.

This patient has a sacral decubitus pressure ulcer that is unstageable, and the most appropriate treatment is surgical debridement. Unstageable pressure ulcers are characterized by full-thickness tissue loss in which the base of the ulcer is covered by slough or eschar. The black eschar at the base of the wound prevents adequate evaluation of wound depth and further impairs wound healing. Therefore, this patient should undergo debridement of the eschar to expose healthy, viable tissue in order to assess the depth of the wound, allow for wound staging, and promote healing. Debridement can be accomplished either surgically or with specialized dressings, such as saline wet-to-dry dressings or autolytic dressings.

Lymphomatous invasion of the skin is highly unlikely in this patient without other evidence of active disease following recent treatment; therefore, biopsy is not indicated.

Antibiotics would be indicated in the case of an infected pressure ulcer; however, there is no evidence that this patient's wound is infected at this time. There is no visible drainage or pus, and there is no surrounding erythema to suggest cellulitis. Additionally, he has no systemic signs or symptoms of infection.

The goal environment for ideal wound healing is a moist wound bed that controls excess exudate. The wound bed should be neither too moist (macerated) nor too dry. Leaving a wound open to air to dry is rarely, if ever, appropriate management.

KEY POINT

- Debridement of eschar is necessary in patients with unstageable pressure ulcers to assess the depth of the wound and promote wound healing.

Bibliography

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Item 87 Answer: B

Educational Objective: Treat extrapyramidal symptoms in a patient who has schizophrenia.

The most appropriate treatment for this patient with schizophrenia is to switch his chlorpromazine to clozapine. His history and physical examination findings are suggestive of extrapyramidal symptoms, and tardive dyskinesia in particular. Extrapyramidal symptoms are drug-induced disorders of movement that usually occur with agents that block dopamine receptors. Although a number of different drugs may be associated with extrapyramidal symptoms, they are most frequently caused by first-generation antipsychotic medications (such as chlorpromazine) that antagonize D_2 dopamine receptors. Extrapyramidal symptoms typically include akathisia (a sense of motor restlessness with a compelling urge to move that makes it difficult to sit still), dystonia (continuous, involuntary spasms and contractions of major muscle groups), and parkinsonism (tremor, rigidity, and bradykinesia). Tardive dyskinesia is a specific form of extrapyramidal movement disorder that occurs with longer-term use (typically >1 month) of dopamine-blocking agents with variable findings of orofacial dyskinesia, facial grimacing, athetotic (slow, writhing) movements, and tics. Extrapyramidal symptoms are more common with first-generation antipsychotic agents compared with second-generation antipsychotic medications. Thus, switching to the second-generation antipsychotic clozapine would be the best option in this patient. A recent meta-analysis showed that clozapine was not only the least likely to cause extrapyramidal symptoms among antipsychotic agents, but was also the most effective drug. This patient also exhibits a significant amount of negative symptoms (flat affect, monotone speech, social withdrawal), which may respond better to a second-generation antipsychotic medication.

Continuing chlorpromazine would be inappropriate in this patient because tardive dyskinesia is a serious manifestation of extrapyramidal symptoms and may become untreatable if prolonged. Thus, the offending agent should be stopped as soon as possible.

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Haloperidol has been shown to be significantly more likely to cause extrapyramidal symptoms than any other first-generation or second-generation antipsychotic medication; therefore, switching to haloperidol in this patient would not be appropriate.

Similarly, switching to another first-generation antipsychotic agent, thioridazine, would also likely not address his extrapyramidal side effects associated with therapy.

KEY POINT

- The second-generation antipsychotic agent clozapine is the most appropriate treatment option for patients with schizophrenia who exhibit extrapyramidal symptoms.

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Item 88 Answer: A

Educational Objective: Treat menopausal genitourinary symptoms.

Estradiol vaginal tablets are the most appropriate treatment for this patient with genitourinary syndrome of menopause, indicated by her history of vaginal dryness, dyspareunia, and by pale mucosa with decreased rugae on physical examination, as well as the vaginal pH greater than 4.5. In menopausal women, low estrogen levels result in physiologic changes in the urogenital tissues that may result in genitourinary symptoms. The abnormal vaginal discharge is consistent with atrophic tissue friability.

Menopausal genitourinary symptoms that do not respond to vaginal lubricants are best treated with topical low-dose vaginal estradiol, which is available as vaginal tablets or a cream. Low-dose vaginal formulations are not absorbed systemically to a significant degree, and therefore, oral progestin is not needed when administering these topical agents. Estrogen-containing pliable polymer vaginal rings are also available, but only the low-dose ring is appropriate for treatment of menopausal genitourinary symptoms.

Bacterial vaginosis is commonly characterized by a malodorous thin gray discharge, with a positive whiff test and clue cells on saline microscopy. The absence of these findings argues against this diagnosis, and treatment for bacterial vaginosis with metronidazole vaginal gel would not be appropriate.

Miconazole vaginal cream is the treatment for vulvovaginal candidiasis. This patient did not have the white discharge and pruritus that are associated with a yeast infection, and the wet mount was negative for hyphae. Therefore, this would not be an appropriate treatment for this patient.

When genitourinary symptoms are the primary concern in a menopausal woman, low-dose vaginal estradiol is the therapeutic standard. Systemic hormone therapy can be used selectively to treat moderate to severe systemic vasomotor symptoms, but for this patient, systemic hormone therapy is not indicated.

KEY POINT

- Menopausal genitourinary symptoms that do not respond to vaginal lubricants are best treated with topical low-dose vaginal estradiol.

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Item 89 Answer: B

Educational Objective: Treat acute pain in a patient at the end of life.

This patient with acute severe pain should be treated with hydromorphone. The opioid analgesic hydromorphone is a very effective pain medication. It is preferred over morphine in the setting of kidney failure because it is metabolized primarily by the liver and is less likely to lead to the accumulation of potentially toxic metabolites. When a parenteral route of medication administration is indicated, such as when titrating medication for acute pain, either intravenous or subcutaneous routes are acceptable. The intravenous route results in a faster onset of action, although the medication wears off faster; the subcutaneous route has only a slightly slower onset of action, but the effect may last longer. Absorption and effect are very reliable with both routes of administration. Although the intravenous route tends to be more commonly used, subcutaneous administration is a reasonable alternative in hospitalized patients who may not be good candidates for intravenous medications or may not wish intravenous access, as may occur in patients receiving comfort care measures.

Fentanyl transdermal patches should only be used in patients who already have some degree of opioid tolerance, and this patient is opioid naïve. Additionally, the onset of action for a fentanyl patch is 12 to 18 hours, far too long for a patient with acute severe pain.

Morphine is contraindicated in the setting of significant kidney failure (estimated glomerular filtration rate <30 mL/min/1.73 m^2), even at the end of life, due to the accumulation of toxic metabolites that may cause neurotoxicity with symptoms of delirium, myoclonus, and seizure.

This patient has no bowel sounds on examination, and it is unclear whether she would absorb oral medication, such as tramadol. Additionally, oral medications have a longer onset of action than either intravenous or subcutaneous routes. In the setting of acute severe pain, a parenteral route with more reliable absorption and shorter onset of action is more appropriate.

KEY POINT

- Morphine should be avoided in the setting of kidney failure.

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Item 90 Answer: B

Educational Objective: Report an impaired colleague to the appropriate authorities.

The physician should report his colleague's behavior to the colleague's supervisor. Physicians may be reluctant to report colleagues suspected of impairment because of discomfort associated with "speaking up," fears of retaliation, and desire to protect colleagues. However, physicians have a duty to speak up, as an impaired and disruptive colleague's behaviors may harm patients, negatively affect team morale, and impede learning. This physician's colleague manifests multiple behaviors suggestive of impairment, including frequent absences, altered mood, lapses in judgment, and changes in clinical performance. Since the physician has already directly confronted his colleague and his concerns were dismissed, he should report the impaired colleague to the appropriate supervisor.

Asking other physicians if they have made similar observations delays the reporting process and does not relieve the observing physician of his responsibility of reporting the suspected impaired colleague.

Physicians should not review the medical records of patients who are not under their care; therefore, the observing physician should not review the colleague's patient care notes for evidence of negligent care. Conducting such record reviews delays and does not relieve the observing physician of his responsibility of reporting the suspected impaired colleague. Additionally, assuming the observing physician is not the colleague's personal physician, it would be unethical and illegal (breach of confidentiality) for the observing physician to review the colleague's medical record to determine if there might be a medical or psychiatric reason for his behavior, even under circumstances of possible impairment.

The observing physician has a professional and ethical responsibility to report the impaired colleague. Taking no further action may result in patient harm.

KEY POINT

- Physicians have a duty to "speak up" about impaired and disruptive colleagues in order to protect patient welfare.

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Item 91 Answer: D

Educational Objective: Evaluate syncope with appropriate use of tilt-table testing.

The most appropriate diagnostic study is tilt-table testing. Tilt-table testing may be helpful in patients with reflex syncope triggered by standing, patients in high-risk settings (for example, construction workers, surgeons) with unexplained episodes of syncope, patients with recurrent syncopal episodes in the absence of organic heart disease, or patients with recurrent episodes in the presence of heart disease when cardiac causes of syncope are excluded. Given that this patient's syncope is triggered by prolonged standing in the operating room, occurs in a high-risk setting (posing a significant occupational hazard), and occurs in the absence of organic heart disease, she should undergo tilt-table testing. Although the sensitivity, specificity, and reproducibility of the tilt-table test are low, in this setting it may be helpful in elucidating the diagnosis and in differentiating orthostatic hypotension from neurocardiogenic syncope.

The American College of Physicians and other groups do not recommend brain imaging, either with CT or MRI, in the setting of witnessed syncope without seizure activity or other neurologic symptoms because the likelihood of a central nervous system cause of the syncope is extremely low and patient outcomes are not improved with further neurologic testing. This patient did not exhibit seizure activity, and her neurologic examination is normal; therefore, brain MRI is not indicated.

Echocardiography is recommended in the evaluation of syncope if structural heart disease is suspected. However, a cardiac cause of syncope is extremely low in this patient who has no history of structural or ischemic heart disease, no symptoms suggesting heart disease, no murmur on examination, and a normal 12-lead electrocardiogram.

The diagnostic yield of 24- to 48-hour electrocardiographic monitoring is very low (1%-2%) unless there are frequent syncopal episodes over a short period of time. Because this patient has already undergone 24-hour ambulatory electrocardiographic monitoring with normal results and her episodes occur every few months, it is unlikely that 48-hour ambulatory electrocardiographic monitoring will be diagnostically helpful. If arrhythmias were strongly suspected, an implantable loop recorder would be a more appropriate diagnostic option for this patient.

Since this patient has had three separate episodes of syncope that occur in high-risk situations, further diagnostic evaluation to determine the cause of the syncope and guide therapy should be pursued.

KEY POINT

- Tilt-table testing is helpful in evaluating reflex syncope triggered by standing, unexplained episodes of syncope in a high-risk setting, recurrent episodes of syncope in the absence of organic heart disease, or recurrent episodes of syncope in the presence of heart disease when cardiac causes are excluded.

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Item 92 Answer: B

Educational Objective: Diagnose generalized anxiety disorder.

The most likely diagnosis is generalized anxiety disorder (GAD). The DSM-5 diagnostic criteria for GAD are as

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follows: 1) excessive anxiety or worry about a number of events or activities (for example, school or work) occurring more days than not for at least 6 months; 2) the patient recognizes it is difficult to control the worry; 3) the anxiety or worry is associated with at least three of the following symptoms: restlessness, easy fatigability, difficulty concentrating, irritability, muscle tension, and sleep disturbance; 4) the anxiety, worry, or symptoms cause impairment at school, work, or other settings and cannot be attributable to medical or other psychiatric conditions, medications, or substance use. A useful tool for identifying and assessing the severity of GAD is the Generalized Anxiety Disorder 7 (GAD-7) assessment tool that rates seven items on a scale of 0 to 3 based on increasing severity. A score of 5 to 9 indicates mild anxiety, 10 to 14 moderate anxiety, and 15 to 21 severe anxiety. This patient meets the DSM-5 criteria, and his GAD-7 score of 13 is consistent with this diagnosis. Treatment options include psychotherapy and medications. Cognitive-behavioral therapy is the most effective psychotherapy for GAD and in trials has been shown to be as effective as medications.

Symptoms of GAD overlap with those of attention-deficit/hyperactivity disorder. However, the main symptoms that this patient is experiencing are worry and anxiety with associated physical symptoms.

Patients with GAD may manifest symptoms of depression; indeed, patients with anxiety disorders may also experience depression. However, the main symptoms that this patient is experiencing are not related to mood, but rather to worry and anxiety.

This patient is not manifesting symptoms of obsessive-compulsive disorder (such as recurrent and persistent thoughts or impulses), making this diagnosis unlikely.

KEY POINT

- Generalized anxiety disorder is characterized by excessive anxiety and worry about various events or activities occurring most days for at least 6 months, with difficulty controlling worrying.

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Item 93 Answer: A

Educational Objective: Manage hepatitis B virus vaccination in a patient with an interrupted vaccine series.

This patient should receive a third dose of the hepatitis B virus (HBV) vaccine to complete the vaccine series. HBV vaccination is indicated in this patient who is traveling to China, an area with a hepatitis B surface antigen (HBsAg) prevalence of 5% to 7%. Typically, the vaccine series is administered as a three-dose regimen over a 6-month time period, with doses administered at 0, 1, and 6 months. Administration of the entire series in accordance with the recommended schedule leads to seroconversion and adequate immunity in more than 95% of persons. This patient has only received two doses over a period of 9 months; consequently, the series is considered to be interrupted. When a vaccine series is interrupted, the most appropriate approach is to resume rather than restart the series, as development of immunity is progressive and giving doses at longer-than-recommended intervals does not usually decrease the final immunologic response. Therefore, the third dose of the HBV vaccine should be administered to this patient now.

Serologic testing to determine this patient's immunity against hepatitis B is unnecessary, because this patient has yet to complete the primary HBV vaccine series, and routine postvaccination testing is not recommended by the Centers for Disease Control and Prevention. Postvaccination serologic testing is indicated only in patients whose subsequent management depends on their immunity status. These individuals may include health care and public safety workers, HIV-positive individuals, persons who are receiving chronic hemodialysis, sexual partners of HBsAg-positive individuals, and injection drug users.

Administering only two of the three recommended doses of HBV vaccine decreases the likelihood of seroconversion. Therefore, discontinuing the vaccine series following only two doses would not be appropriate.

KEY POINT

- When a vaccine series is interrupted, the most appropriate approach is to resume rather than restart the series.

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Item 94 Answer: B

Educational Objective: Treat a patient with olecranon bursitis.

The most appropriate treatment for this patient is NSAID therapy. The patient is experiencing olecranon bursitis, most likely from the low-level repetitive trauma of rubbing his elbow against the car armrest. The olecranon bursa is a subcutaneous synovial-lined sac overlying the olecranon process at the proximal aspect of the ulna. It cushions the olecranon and reduces friction between the olecranon and the skin during movement. Because of its superficial location, it is particularly susceptible to inflammation with acute or chronic trauma. Although most cases of olecranon bursitis are noninfectious, they may be caused by bacterial infection, particularly if there is an overlying abrasion or cellulitis. Less commonly, olecranon bursitis may be due to a crystalline process, such as gout. Aspiration is indicated in patients with suspected infectious or crystalline bursitis,

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or if the swelling is extensive and impairs activity, even if likely benign. Protection of the bursa from further trauma or irritation is the cornerstone of therapy, and treatment with an agent that inhibits inflammation and provides pain relief is usually helpful in decreasing fluid accumulation and providing symptom relief. NSAIDs have both analgesic and anti-inflammatory effects, which is ideal for this purpose. Given the patient's otherwise good health, a short course of NSAID therapy at an anti-inflammatory dose will provide maximal benefit with relatively little risk.

Intrabursal glucocorticoid injections may reduce swelling in bursitis. However, there is not strong evidence of effectiveness when used in superficial areas such as the olecranon bursa, and there is significant risk of side effects, including skin atrophy, development of a draining sinus tract, and infection. Additionally, glucocorticoids provide no analgesia. They are therefore used only in severe or refractory cases of olecranon bursitis.

Topical lidocaine and tramadol are analgesic agents and do not have anti-inflammatory effects. They will provide some pain relief but will not reduce the swelling of the bursitis. Topical analgesics may have value in minimizing systemic drug exposure; however, this would not be a major issue for this patient.

KEY POINT

- Physical protection of the bursa and NSAID therapy are effective treatments for noninfectious olecranon bursitis.

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Item 95 Answer: D

Educational Objective: Evaluate a patient with medically unexplained symptoms.

This patient with medically unexplained symptoms (MUS) should not undergo repeated or additional testing. Repeated physical examinations and appropriate laboratory and ancillary testing by internists and specialists over an extended period of time have been unrevealing of significant disease. Without significant change in the clinical picture, no further testing is indicated. The physician should instead focus on establishing and strengthening a therapeutic alliance with the patient using patient-centered methods. Cognitive-behavioral therapy that consists of 1) educating the patient so he or she understands the symptoms, 2) obtaining a commitment from the patient to assume responsibility for his or her improvement, 3) facilitating realistic goals, and 4) negotiating a treatment plan can be helpful in the office setting. A systematic review of 34 randomized controlled trials demonstrated that, in most studies, cognitive-behavioral therapy was effective in treating patients with MUS.

Although this patient may have intolerance to certain foods and believes that dietary manipulation improves her symptoms, she does not have evidence of significant food allergy, which may be manifested as an IgE-mediated allergic reaction or more chronic symptoms isolated to the gastrointestinal tract. She has also been evaluated by an allergist who did not pursue food allergy testing. Therefore, food allergy testing would likely be of low yield in this patient.

Although this patient has chronic low back pain, she is without concerning symptoms or physical examination findings that would warrant further imaging of her lumbosacral spine, and MRI would not be beneficial.

Repeat Lyme disease serologic testing is unwarranted in this patient. Although systemic symptoms and chronic fatigue are often attributed to Lyme infection, this is a very uncommon occurrence and would be extremely unlikely in this patient with no clinical findings and negative serology.

KEY POINT

- Patients with medically unexplained symptoms should not undergo repeated or additional testing if there is no change in the clinical presentation.

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Item 96 Answer: A

Educational Objective: Diagnose syncope due to orthostatic hypotension.

The most likely cause of syncope in this patient is orthostatic hypotension. Syncope is nontraumatic, complete transient loss of consciousness and loss of postural tone. Onset is abrupt and recovery is spontaneous, rapid, and complete. Orthostatic syncope is associated with a decline of 20 mm Hg or more in systolic blood pressure (or ≥10 mm Hg drop in diastolic blood pressure) within 3 minutes of standing. Orthostatic syncope may occur as a result of primary autonomic failure, secondary autonomic failure (due to diabetes mellitus, amyloidosis, spinal cord injuries, or Parkinson disease), hypovolemia, medications (vasodilators, diuretics), or age-associated changes in blood pressure regulation. On examination, this patient has significant orthostasis by blood pressure and pulse measurements. These orthostatic changes may be due to volume contraction secondary to chronically elevated blood glucose levels resulting in an osmotic diuresis, autonomic insufficiency as a consequence of long-standing diabetes, and treatment with a vasodilating blood pressure medication. The initial treatment is hydration with isotonic saline, and further evaluation of his diabetic control and medication regimen is indicated.

The absence of aura, rhythmic involuntary movement, postictal confusion, and tongue biting make seizure an unlikely cause of this patient's syncope.

Although patients with diabetes are at risk for cardiac ischemia, this patient has no cardiac symptoms and has an

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electrocardiogram without acute changes or evidence of prior myocardial infarction, suggesting against a subclinical ischemic cardiac cause.

Cardiac syncope due to arrhythmia is abrupt in onset and may be accompanied by palpitations, which this patient did not have. Additionally, orthostatic changes or other evidence of volume depletion, as is present in this patient, would not be expected with arrhythmia, ischemia, or seizure.

KEY POINT

- Orthostatic syncope is characterized by a decline of 20 mm Hg or more in systolic blood pressure (or ≥10 mm Hg drop in diastolic blood pressure) within 3 minutes of standing and occurs as a result of autonomic failure, hypovolemia, medication use, or age-associated changes in blood pressure regulation.

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Item 97 Answer: C

Educational Objective: Screen for HIV infection.

This patient should be screened for HIV infection. The U.S. Preventive Services Task Force (USPSTF) recommends one-time HIV screening for all adults aged 15 to 65 years. Screening in adolescents younger than 15 years and adults older than 65 years may be indicated depending on individual risk factors. The currently recommended method for initial testing is a combination immunoassay that detects both HIV antibody and p24 antigen, a viral capsid protein that is elevated early in infection. This test replaces the previously used highly sensitive enzyme-linked irnmunosorbent assay (ELISA) for antibodies directed toward HIV. It is estimated that approximately 25% of persons with HIV infection are unaware of their diagnosis. Initiating antiretroviral therapy in asymptomatic patients compared with those who present clinically is associated with reduced risk for AIDS-related death.

The USPSTF strongly recommends lipid screening in women aged 45 years and older who have risk factors for coronary heart disease (diabetes mellitus, personal history of coronary heart disease or noncoronary atherosclerosis, family history of cardiovascular disease before age 50 years in male relatives or age 60 years in female relatives, tobacco use, hypertension, obesity [BMI ≥30]). Although the optimal screening interval is undetermined, it is reasonable to rescreen every 5 years, or at a shorter interval if the patient's lipid levels are approaching those that would indicate therapy. The 2013 American College of Cardiology/American Heart Association cardiovascular risk guideline indicates that it is reasonable to assess traditional risk factors (including total and HDL cholesterol levels) every 4 to 6 years in adults between the ages of 20 and 79 years who are free from atherosclerotic cardiovascular disease. This patient's lipid levels were normal last year and she is otherwise at low risk for cardiovascular disease; therefore, she would not benefit from repeat lipid screening.

The USPSTF currently recommends screening for type 2 diabetes mellitus only in asymptomatic adults with sustained blood pressure higher than 135/80 mm Hg; however, a USPSTF draft guideline from 2014 recommends screening for abnormal blood glucose level and type 2 diabetes in adults with risk factors, including age 45 years or older, obesity or overweight, first-degree relative with diabetes, history of gestational diabetes or polycystic ovary syndrome, and certain high-risk ethnic backgrounds (African Americans, American Indians/Alaska Natives, Asian Americans, Hispanics/Latinos, and Native Hawaiians/Pacific Islanders). The American Diabetes Association recommends screening for diabetes in all adults aged 45 years and older and adults younger than 45 years with a BMI of 25 or higher and one risk factor for diabetes. The optimal screening interval is unknown, although the American Diabetes Association recommends screening every 3 years. Because a fasting plasma glucose level was obtained in this patient last year, repeat testing is not necessary at this time.

In women aged 30 to 65 years in whom cytology (Pap smear) and human papillomavirus (HPV) testing are negative, repeat testing is recommended in 5 years. Because a Pap smear and HPV testing were performed in this patient 3 years ago, she should be screened again for cervical cancer in 2 years.

KEY POINT

- HIV screening is recommended for all adults aged 15 to 65 years.

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Item 98 Answer: C

Educational Objective: Manage an older patient with visual impairment.

This older adult patient with vision difficulties should be referred to an eye professional. Vision impairment is common in older adults, and unlike in younger patients, older patients are more likely to have conditions such as glaucoma, macular degeneration, or diseases of the vitreous body or retina. An undilated ophthalmoscopic examination in the primary care setting is insufficient to diagnose these eye disorders. Evaluation for glaucoma involves measurement of intraocular pressure (tonometry), which is not available in most clinicians' offices, and other conditions involving the vitreous body or retina require eye dilation and examination with a slit lamp to allow for full evaluation. Additionally, the relatively rapid change in this patient's otherwise stable vision is suggestive of an acute or rapidly progressive process. Therefore, timely referral to an eye professional is the

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most appropriate next step in managing this patient's vision symptoms.

Obtaining an erythrocyte sedimentation rate is necessary in patients with suspected giant cell arteritis; however, this patient does not present with symptoms of headache, muscle aches, or jaw claudication, making the pretest probability of giant cell arteritis very low. Therefore, obtaining an erythrocyte sedimentation rate is not indicated at this time.

Visual screening tests, such as the Snellen eye chart or the pinhole test, are used primarily to assess for presbyopia. Although these tests may be abnormal in this patient, they would not sufficiently evaluate other potentially serious visual conditions that may be present.

KEY POINT

- Visual acuity screening alone is insufficient to adequately assess for eye disorders in older patients.

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Item 99 Answer: B

Educational Objective: Diagnose patellofemoral pain syndrome.

This patient has patellofemoral pain syndrome. Patellofemoral pain syndrome is of unclear etiology but is likely due to several different factors that affect the load distribution underneath the patella, such as deconditioning and patellofemoral malalignment. It is characterized by anterior knee pain that is slow in onset and typically made worse with running, climbing stairs, and prolonged sitting. On examination, there is frequently increased patellar laxity with medial and lateral displacement. Additionally, pain may be reproduced when posteriorly directed pressure is applied to the patella. Treatment is often challenging but generally consists of addressing any identified underlying causes (such as deconditioning), activity modification, and physical therapy.

Iliotibial band syndrome can occur from overuse or from alterations in anatomic alignment or biomechanical function. It typically causes lateral knee pain that is worsened by walking down an incline. On examination, there is frequently tenderness to palpation of the lateral femoral epicondyle, which is approximately 2 to 3 cm proximal to the lateral joint line, accompanied by weakness of the hip abductor muscles and the knee extender and flexor muscles. Pain is reproduced when the examiner repeatedly flexes and extends the supine patient's knee while the examiner's thumb is on the lateral femoral epicondyle (positive Noble test).

Pes anserine bursitis is caused by inflammation of the pes anserine bursa, located at the proximal anteromedial tibia. Bursitis usually develops as the result of overuse or constant friction and stress on the bursa. Pes anserine bursitis is common in athletes, particularly runners. Tenderness on the anteromedial aspect of the knee about 4 to 5 cm below the joint line is reproduced by palpation.

Prepatellar bursitis is caused by inflammation of the prepatellar bursa, which overlies the anterior surface of the patella. Patients with prepatellar bursitis present with anterior knee pain and swelling. Possible causes include direct trauma, gout, and infection. On examination, a palpable fluid collection is often present.

KEY POINT

- Patellofemoral pain syndrome is characterized by anterior knee pain that is slow in onset and typically made worse with running, climbing stairs, and prolonged sitting.

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Item 100 Answer: D

Educational Objective: Manage cachexia in a patient with cancer.

The patient's current care should be continued. Anorexia, weight loss, and cachexia reflect a final common pathway during the terminal phase of most disease processes. Assuming potentially reversible conditions (nausea, altered taste, medication side effects, bowel obstruction, dysphagia, psychological comorbidities) have been ruled out, disease-related cachexia is caused by an altered neurohormonal, inflammatory milieu that results in profound alterations in metabolism. These changes lead to a decreased appetite and increased catabolism, leading to progressive weight loss. Educating this patient and her family on the etiology and pathophysiology of cachexia is the primary intervention and may help them to better understand and accept the expected course of the disease.

Only 20% to 30% of patients who take pharmacologic agents, such as dronabinol and megestrol, for cachexia of advanced disease gain any weight at all. For those who do gain weight, there is no improvement in mortality, and the majority of studies of their use in cachexia associated with cancer show no improvement in the quality of life. The role of other agents for treatment of cachexia in advanced disease, including anabolic steroids, medical marijuana and its derivatives, melatonin, and NSAIDs, remains to be defined.

Cachexia cannot be significantly reversed by more aggressive or invasive methods of nutritional support, including enteral (or parenteral) nutrition, and these interventions in the context of cachexia of advanced disease do not improve morbidity or mortality. Additionally, interventions to provide artificial nutrition, such as use of a nasogastric or nasojejunal tube or placement of a percutaneous endoscopic gastrostomy tube, have some associated risk and a potential negative effect on the patient's quality of life.

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KEY POINT

- Artificial nutrition and pharmacologic agents do not improve morbidity and mortality or quality of life in cancer patients with cachexia.

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Item 101 Answer: A

Educational Objective: Diagnose a central pain syndrome.

This patient has fibromyalgia, one type of central pain syndrome. Central pain results from dysregulation of sensory processing pathways within the nervous system. This dysregulation amplifies sensory input, resulting in the increased perception of pain. Central pain can be classically neuropathic, such as poststroke pain or post-spinal cord injury pain, or it can be more indistinct, such as in fibromyalgia. The pain is usually constant, with bursts of more severe pain, often exacerbated by cough, temperature changes, movement, or emotions. Central pain syndromes can also evolve out of unrelenting chronic pain when persistent stimulation of peripheral pain receptors results in the upregulation of central pain modulators. It is important to recognize patients who have pain as a result of central mechanisms, as these conditions respond particularly well to multimodal pain management, and neuromodulating medications are more effective for this type of pain than opioids.

The hallmarks of neuropathic pain are stinging, burning, or tingling sensations, none of which are present in this patient. Furthermore, neuropathic pain follows the distribution of the nerves affected. This patient describes widespread pain all over her body that is not compatible with an anatomic nerve distribution.

Nociceptive pain is dull, aching, or throbbing pain caused by tissue injury. It is localized to the site of the injury. This patient has no evidence of tissue injury, and her pain is not localized.

Although psychological conditions can impact how patients experience their pain or can perpetuate pain, they are not thought to be a mechanism of pain generation in and of themselves. Additionally, this patient has no evidence of psychological comorbidity.

KEY POINT

- Central pain varies widely in character and may affect a specific area of the body or occur more diffusely; pain is usually constant, with bursts of more severe pain, often exacerbated by cough, temperature changes, movement, or emotions.

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Item 102 Answer: B

Educational Objective: Vaccinate a patient with anatomic asplenia against pneumococcal disease.

This patient who will be undergoing splenectomy should receive the pneumococcal conjugate vaccine (PCV13) now, followed by the pneumococcal polysaccharide vaccine (PPSV23) in 8 weeks. Persons with functional or anatomic asplenia are at risk for infection with encapsulated organisms and therefore should be vaccinated against pneumococcus. There are two pneumococcal vaccines: a polysaccharide vaccine composed of capsular material from 23 pneumococcal subtypes (PPSV23) and a conjugate vaccine containing capsular material from 13 pneumococcal subtypes conjugated to a nontoxic protein (PCV13), which increases its immunogenicity. Both pneumococcal vaccines are recommended in these patients; however, when PCV13 is indicated, it should be given before PPSV23. Therefore, administration of PCV13 would be appropriate now, followed by a single dose of PPSV23 8 weeks later. Administration of a second dose of PPSV23 is recommended 5 years after administration of the first PPSV23 dose for patients aged 19 to 64 years who have functional or anatomic asplenia. Furthermore, individuals who receive PPSV23 before age 65 years should receive an additional dose of PPSV23 at age 65 years provided that at least 5 years have passed since the most recent PPSV23 administration. Therefore, this patient should receive a second dose of PPSV23 at age 40 years and a third dose of PPSV23 once he is 65 years of age, provided that he remains on schedule. No additional doses of PCV13 are required.

According to the Advisory Committee on Immunization Practices, PCV13 and PPSV23 should not be administered together. The minimum acceptable interval between administration of PCV13 and PPSV23 is 8 weeks.

PPSV23 should not be the only pneumococcal vaccine administered in patients with asplenia, as it is significantly less immunogenic than PCV13. PPSV23 is only 60% to 70% effective in preventing invasive pneumococcal disease; however, PCV13 is more than 90% effective.

Several large randomized, multicenter trials have shown a decreased serologic response in patients who received PCV13 after PPSV23 compared with those who received PCV13 first; therefore, administration of PPSV23 now and PCV13 in 8 weeks is not recommended.

KEY POINT

- Patients with functional or anatomic asplenia should receive a dose of pneumococcal conjugate vaccine (PCV13), followed by a dose of pneumococcal polysaccharide vaccine (PPSV23) 8 weeks later.

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Item 103 Answer: D

Educational Objective: Treat social anxiety disorder.

The most appropriate pharmacologic treatment for this patient with social anxiety disorder is a selective serotonin reuptake inhibitor (SSRI), such as sertraline. Social anxiety disorder is characterized by severe, persistent anxiety or fear of social or performance situations (public speaking, meeting unfamiliar people) lasting at least 6 months. In these situations, affected patients experience anxiety and physical symptoms such as palpitations, dyspnea, and flushing. Patients recognize their anxiety is excessive but nonetheless avoid trigger situations (or endure them with extreme anxiety), resulting in impairments at home, work, and other settings. SSRIs and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine are first-line therapy for social anxiety disorder. In addition, cognitive-behavioral therapy (CBT) is very effective for social anxiety disorder.

Limited evidence suggests that benzodiazepines, such as clonazepam and diazepam, may be useful in patients with social anxiety disorder and are commonly used in patients with social anxiety disorder who cannot tolerate or do not adequately respond to SSRIs or SNRIs. However, benzodiazepines are not first-line drugs for social anxiety disorder because of their side effects, including potential for dependency and withdrawal syndrome and potential for impairment when mental clarity is important (for example, during a speech).

β-Blockers are useful on an as-needed basis for performance anxiety (for example, propranolol, 10-20 mg, taken orally 60 minutes before a performance or speech). However, this patient's anxiety surrounding social interaction impairs her ability to function effectively in her workplace. Therefore, episodic therapy for performance anxiety would not be appropriate for this patient with an indication for treatment of a more extensive anxiety disorder.

CBT, which seeks to address maladaptive beliefs, anxious feelings, and avoidance behaviors, has been shown to be of benefit and is an alternative approach to pharmacologic therapy. There is limited evidence that combining pharmacologic therapy and CBT is superior to either treatment alone.

KEY POINT

- Selective serotonin reuptake inhibitors and the serotonin-norepinephrine reuptake inhibitor venlafaxine are first-line therapy for patients with social anxiety disorder.

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Schneier FR. Clinical practice. Social anxiety disorder. N Engl J Med. 2006 Sep 7;355(10):1029-36. [PMID: 16957148]

Item 104 Answer: C

Educational Objective: Evaluate a patient with asymptomatic severe aortic stenosis undergoing elective noncardiac surgery.

The most appropriate management is to proceed to surgery with anesthesiology consultation. This patient has asymptomatic severe aortic stenosis, a condition that previously had been associated with a high risk of adverse cardiac events. However, advances in anesthetic and surgical techniques have led to a significant decrease in perioperative complications, and newer data indicate only a twofold increase in risk of postoperative myocardial infarction and 30-day mortality. The American College of Cardiology/American Heart Association (ACC/AHA) and American College of Chest Physicians (ACCP) guidelines recommend that elective noncardiac surgery is reasonable to perform in patients with asymptomatic severe aortic stenosis with appropriate intraoperative and postoperative hemodynamic monitoring (as can be determined by anesthesiology consultation). The risks of surgical delay must be weighed against the risks of the procedure. In this patient who meets no criteria for aortic valve replacement and is losing the ability to perform activities of daily living, performance of elective shoulder arthroscopy offers the best balance of risks.

Delaying or foregoing surgery would avoid potential perioperative risks but would also leave the patient with significant disability that could endanger her ability to remain independent in the community.

Dobutamine stress echocardiography is not indicated because the patient underwent an appropriate stress test less than 1 year ago and had no evidence of ischemia or symptoms after achievement of target heart rate and 4 metabolic equivalents (METs).

Repeat echocardiography would provide little additional value because this patient's cardiac structure and function are highly unlikely to have changed in less than 1 year. The ACC/AHA guideline recommends preoperative echocardiography for patients with moderate or worse valvular disease if it has been more than 1 year since the last study or the patient has had a change in clinical status.

KEY POINT

- Elective noncardiac surgery is reasonable to perform in patients with asymptomatic severe aortic stenosis with appropriate intraoperative and postoperative hemodynamic monitoring.

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Fleisher LA, Fleischmann KE, Auerbach AD, et al; American College of Cardiology; American Heart Association. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014 Dec 9;64(22):e77-137. [PMID: 25091544]

Item 105 Answer: C

Educational Objective: Treat drug-induced lower extremity edema.

The most appropriate next step in management is to switch amlodipine to lisinopril. Based on the normal physical examination findings and laboratory test results, this patient most likely has drug-induced edema caused by the calcium

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channel blocker amlodipine. Peripheral edema is a common side effect of calcium channel blockers, occurring in up to 25% of patients who take these medications. The risk of developing edema appears to be both dose and treatment duration dependent, with high doses and long treatment times associated with an increased incidence. Drug-induced edema typically resolves after withdrawal of the offending drug. Therefore, the first step in the management of this patient is to discontinue amlodipine and switch to an alternative antihypertensive agent, such as lisinopril.

Compression stockings may help to reduce this patient's edema; however, compression stockings may not be needed if his edema is due to his medication and an acceptable agent could be substituted for amlodipine in his antihypertensive therapy. Additionally, compliance with wearing compression stockings is often low due to the difficulty that patients experience in donning and removing the stockings.

Lower extremity venous duplex ultrasonography may be used in evaluating for the presence of venous thrombosis; however, this patient's clinical presentation and lack of calf tenderness are not consistent with a deep venous thrombosis. Therefore, venous duplex ultrasonography is not necessary or cost effective in this patient.

Diuretics are often used to treat generalized edema caused by cirrhosis or heart failure, as these conditions are associated with total body volume overload. However, the mechanism of lower extremity edema in this patient is associated with the vasodilatory properties of the medication and not volume overload. Therefore, diuretics are only minimally helpful in treating edema caused by calcium channel blockers. Additionally, diuretics may lead to electrolyte abnormalities and kidney dysfunction.

KEY POINT

- Treatment of drug-induced lower extremity edema is discontinuation of the offending agent.

Bibliography

Makani H, Bangalore S, Romero J, et al. Peripheral edema associated with calcium channel blockers: incidence and withdrawal rate–a meta-analysis of randomized trials. J Hypertens. 2011 Jul;29(7):1270-80. [PMID: 21558959]

Item 106 Answer: E

Educational Objective: Manage cyclic mastalgia.

The most appropriate management for this patient's breast pain is use of a support bra. Breast pain is common among women and is categorized primarily as cyclic and noncyclic. This patient has cyclic mastalgia, which is bilateral and worsens in the days before menses and then abates. A well-fitting support bra has been shown to alleviate discomfort for many women. Reassurance and education are important, and women are often greatly relieved to hear that breast pain is rarely a symptom of malignancy.

In the absence of palpable abnormalities, skin changes, or other pathologic findings, diagnostic imaging is not indicated. There is no role for ultrasound in the management of cyclic mastalgia.

There is no clear evidence that the exclusion of methylxanthines present in tea, coffee, cola and chocolate improves symptoms. Similarly, placebo-controlled trials have failed to support the efficacy of vitamins A, B, and E for treating breast pain.

Combined hormonal contraception is not effective in treating cyclic mastalgia and may even be associated with increased breast tenderness.

Medical treatment for cyclic mastalgia is generally reserved for women with severe and persistent pain that has not responded to conservative measures and interferes with quality of life. Danazol is FDA approved for the treatment of cyclic mastalgia, but side effects are frequent and limit its use. Danazol would not be appropriate for this patient before conservative measures are tried.

KEY POINT

- Cyclic mastalgia is initially treated conservatively; measures include education, reassurance, and use of a well-fitting support bra.

Bibliography

Onstad M, Stuckey A. Benign breast disorders. Obstet Gynecol Clin North Am. 2013 Sep;40(3):459-73. [PMID: 24021252]

Item 107 Answer: C

Educational Objective: Manage cardiac syncope with appropriate inpatient cardiac monitoring in a high-risk patient.

This patient should undergo inpatient cardiac monitoring because of his clinical history and presentation consistent with cardiogenic syncope. His loss of consciousness was abrupt, without prodrome except for palpitations, and occurred while seated, all of which are characteristics consistent with the presentation of cardiogenic syncope. Additionally, he is at high risk for ischemic cardiac disease based on his risk factors, including hypertension, hyperlipidemia, diabetes mellitus, tobacco use, and left bundle branch block noted on electrocardiogram. Cardiac syncope is associated with a high mortality rate (1-year mortality rate of 18%-33%), whereas the risk for negative outcomes with most other causes of syncope is markedly lower. Therefore, patients with syncope of possible cardiac etiology, such as this one, should be admitted to the hospital for further monitoring and evaluation.

Several risk stratification tools are available to assist in making admission decisions in patients with syncope. The Risk Stratification of Syncope in the Emergency Department (ROSE) index is a validated tool that identifies specific independent predictors for severe outcomes at 1 month (myocardial infarction, life-threatening arrhythmia, pulmonary embolism, stroke, intracranial or subarachnoid hemorrhage, or pacemaker insertion). These predictors are elevated B-type natriuretic peptide concentration (≥300 pg/mL),

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H CONT. bradycardia (≤50 beats/minute), fecal occult blood in patients with suspected gastrointestinal bleeding, anemia (hemoglobin level ≤9 g/dL [90 g/L]), chest pain, electrocardiogram with Q waves (not in lead III), and oxygen saturation less than 94% on ambient air. Other high risk factors include age greater than 65 years; abnormal ECG; history of heart failure, ischemic heart disease, or ventricular arrhythmias; or lack of warning signs or symptoms. In patients with these clinical findings, many of which are present in this patient, inpatient monitoring and evaluation are recommended.

As this patient with a history suggestive of cardiac syncope is at high risk for adverse events, outpatient evaluation with event monitoring would not be appropriate.

Implantable loop recorders are best reserved for patients with unexplained recurrent syncope, which is not present in this patient. Inpatient monitoring and further cardiac evaluation for ischemia are the most appropriate next steps in management.

Criteria for pacemaker insertion in a patient with syncope include symptomatic bradycardia or asystolic pauses. This patient currently only has mild bradycardia, which would not be the cause of his syncope, and a pacemaker is not indicated at this time. He should be monitored for further decline in heart rate and symptoms or for the development of advanced-degree block and other symptomatic arrhythmias. This should initially take place in the inpatient setting.

KEY POINT

- Patients with syncope who have identified clinical risk factors for adverse outcomes should undergo inpatient monitoring and evaluation.

Bibliography

Ebell MH. Risk stratification of patients presenting with syncope. Am Fam Physician. 2012 Jun 1;85(11):1047-52. [PMID: 22962874]

Item 108 Answer: A

Educational Objective: Manage a patient with rotator cuff tendinitis.

This patient most likely has rotator cuff tendinitis (specifically, supraspinatus tendinitis). He has pain with overhead activities, a painful arc, and pain with active abduction on examination, all of which are consistent with this diagnosis. Additionally, he works as a painter, a profession that frequently involves overhead activities that predispose patients to developing rotator cuff tendinitis. Given the patient's presentation and examination findings, it is appropriate to diagnose the patient without further testing. Initial therapy typically includes rest, avoidance of aggravating activities, NSAIDs, and physical therapy that strengthens the rotator cuff muscles and improves flexibility.

When the diagnosis is unclear or if concern exists for a rotator cuff tear, imaging of the shoulder should be obtained. MRI is the preferred imaging modality (>90% sensitivity), although ultrasonography, in experienced hands, is also an option. This patient has no evidence of a rotator cuff tear, as his strength is preserved and he has negative drop-arm, external rotation lag, external rotation resistance, and internal rotation lag tests, all of which argue against a full-thickness tear. Therefore, MRI of the left shoulder is unnecessary in this patient.

Referral for orthopedic surgery would be premature prior to a trial of conservative measures for 6 to 9 months.

In the absence of trauma and tenderness to palpation of bony structures, obtaining shoulder radiographs is likely to be of limited value and is unnecessary in this patient.

KEY POINT

- Imaging of the shoulder is typically not needed to diagnose rotator cuff tendinitis but should be considered if a full-thickness rotator cuff tear is suspected or if there is diagnostic uncertainty.

Bibliography

Hermans J, Luime JJ, Meuffels DE, Reijman M, Simel DL, Bierma-Zeinstra SM. Does this patient with shoulder pain have rotator cuff disease?: The Rational Clinical Examination systematic review. JAMA. 2013 Aug 28;310(8):837-47. [PMID: 23982370]

Item 109 Answer: D

Educational Objective: Evaluate acute, nonspecific low back pain.

This patient with nonspecific low back pain does not require additional testing. In patients presenting with low back pain, the history and physical examination should focus on determining the likelihood of a specific underlying condition causing the back pain and identifying any neurologic involvement that may be present. In patients in whom low back pain cannot be attributed to a specific disease or spinal abnormality (defined as nonspecific low back pain), the American College of Physicians and other organizations recommend against imaging or obtaining other diagnostic studies routinely. Such testing should be reserved for patients in whom a serious underlying condition is suspected, those with severe or progressive neurologic deficits, or patients who do not have symptom improvement after 4 to 6 weeks of conservative management. As this patient's pain meets the definition of nonspecific low back pain, no additional imaging or testing is indicated before initiating therapy.

An erythrocyte sedimentation rate is a marker of inflammation and is indicated only if a systemic inflammatory process or infectious cause of low back pain is suspected, neither of which is suggested in this patient.

Ankylosing spondylitis is a spondyloarthritis with systemic features that typically presents with low back pain, morning stiffness, and sacroiliitis; extra-articular manifestations may include uveitis. HLA-B27 testing can be useful in the appropriate clinical scenario to support the diagnosis of ankylosing spondylitis; however, HLA-B27 can be positive in other disease processes as well. This patient has no additional symptoms associated with his back pain and no

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suggestive findings on examination, making the diagnosis of ankylosing spondylitis unlikely.

Radiography of the lumbar spine is indicated only if fracture, degenerative arthritis, or an inflammatory process such as ankylosing spondylitis is suspected, none of which are likely diagnostic considerations in this patient.

KEY POINT

- Imaging or other diagnostic tests should not be routinely obtained in patients with nonspecific low back pain.

Bibliography

Chou R, Qaseem A, Snow A, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007 Oct 2;147(7): 478-91. [PMID: 17909209]

Item 110 Answer: D

Educational Objective: Treat mild lower urinary tract symptoms caused by benign prostatic hyperplasia.

This patient with mild lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH) should be conservatively managed with observation. The main purpose of treating LUTS from presumed BPH is to reduce bothersome symptoms. The American Urological Association Symptom Index (AUA-SI) score is a validated questionnaire used to determine the severity of and to monitor LUTS. The questionnaire assesses frequency, nocturia, weak stream, hesitancy, intermittency, incomplete emptying, and urgency, with each question graded on a 5-point scale from 0 (not present) to 5 (almost always present). The total score is interpreted as follows: 1-7 (mild), 8-19 (moderate), and 20-35 (severe). This patient's AUA-SI score of 4 indicates mild symptoms. The AUA currently suggests a treatment approach that is based on AUA-SI score severity. Mild LUTS from BPH can be addressed by observation. Conservative measures that may help patients with mild symptoms include reducing fluid intake, timed voiding (every 3 hours while awake), limiting caffeine and alcohol, modifying medications, improving mobility, and avoiding bladder irritants.

Urinalysis is the only test indicated for all patients with LUTS that is believed to be secondary to BPH. However, this patient's urinalysis, which shows only 2 leukocytes/hpf, does not clearly indicate the presence of a urinary tract infection, and his clinical presentation is not suggestive of chronic prostatitis. Therefore, antibiotic therapy with ciprofloxacin is not indicated.

5-α Reductase inhibitors, such as finasteride, are indicated in patients with large prostates (40 mL), elevated prostate-specific antigen levels, and/or severe symptoms of BPH. Finasteride is not indicated in this patient with mild symptoms.

α-Blockers, such as tamsulosin, are first-line therapy for treating BPH. However, observation without medical therapy would be the most appropriate first-line approach in this patient with mild BPH.

KEY POINT

- In patients with mild lower urinary tract symptoms caused by benign prostatic hyperplasia, observation with conservative therapy measures is appropriate.

Bibliography

Beckman TJ, Mynderse LA. Evaluation and medical management of benign prostatic hyperplasia. Mayo Clin Proc. 2005 Oct;80(10):1356-62. [PMID: 16212149]

Item 111 Answer: B

Educational Objective: Identify mood disorder as a cause of erectile dysfunction.

This patient has erectile dysfunction (ED) secondary to a mood disorder, most likely major depressive disorder. Characteristic features of inorganic (psychological) ED are sudden onset of symptoms and persistence of nocturnal or morning erections, which indicates that the anatomic and physiologic mechanisms for erection are intact. This patient has guilt, low energy, and decreased interest, all of which are symptoms of depression. Patients with inorganic ED can be reassured that their condition is likely to resolve with time and effective treatment of their mood disorder.

This middle-aged man is not likely to have hypogonadism. His testicles are of normal volume, and he reports continued sexual desires. One of the earliest symptoms of hypogonadism is substantial reduction or absence of sexual thoughts.

This patient has poor sleep; however, he is not overweight and reports no snoring, gasping, apnea, or daytime somnolence. Depression is the most likely cause for this patient's fatigue, given his guilt, anhedonia, and inorganic ED.

Although an early sign of prolactinoma is ED, the persistence of nocturnal and morning erections in this patient makes an organic cause unlikely. Additionally, he lacks other symptoms of prolactinoma, such as headache, visual changes, or decreased body and facial hair.

KEY POINT

- Characteristic features of inorganic erectile dysfunction are sudden onset of symptoms and persistence of nocturnal or morning erections.

Bibliography

Beckman TJ, Abu-Lebdeh HS, Mynderse LA. Evaluation and medical management of erectile dysfunction. Mayo Clin Proc. 2006 Mar;81(3): 385-90. [PMID: 16529142]

Item 112 Answer: C

Educational Objective: Recognize threats to the validity of a study.

The validity of this study could be improved by measuring the outcomes of both study groups concurrently.

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Validity, or the trustworthiness of a study's results, can be threatened by many factors, including errors in sampling, measurement, and data analysis. Systematic error results from bias that influences the study findings in a certain direction. Systematic error must be addressed by eliminating sources of bias, and doing so is a primary goal of study design. Seasonal variation in asthma symptoms is widely recognized, and in this study, the separation of study groups into summer and winter months is a systematic error that could account for the different peak-flow rates and quality-of-life scores between groups. This represents a potentially significant bias that could threaten the validity of the study outcomes. Therefore, this study could be improved by measuring outcomes for both study groups at the same time of year in order to eliminate this potential source of bias.

Including patients with COPD in the study would not improve the study's validity regarding the impact of meditation on the outcomes of patients with asthma.

Increasing the sample size and precision of measures would be effective in reducing the impact of random errors, but not systematic errors.

KEY POINT

- Systematic error threatens the validity of a study and must be addressed by eliminating bias.

Bibliography

Guyatt GH, Haynes RB, Jaeschke RZ, et al. Users' Guides to the Medical Literature: XXV. Evidence-based medicine: principles for applying the Users' Guides to patient care. Evidence-Based Medicine Working Group. JAMA. 2000 Sep 13;284(10):1290-6. [PMID: 10979117]

Item 113 Answer: D

Educational Objective: Diagnose vestibular neuronitis.

This patient has vestibular neuronitis, which is manifested by acute, severe, and persistent nonpositional peripheral vertigo. Vestibular neuronitis may follow a viral upper respiratory tract infection and is thought to be caused by postviral inflammation of the vestibular portion of cranial nerve VIII. Symptoms may be severe and prolonged. Nausea and vomiting are common. When the Dix-Hallpike maneuver is performed on this patient, the results are consistent with peripheral vertigo, with nystagmus that is provoked after a brief latency period and is relatively severe and short in duration (<1 minute).

Benign paroxysmal positional vertigo (BPPV), the most common cause of vertigo, is classically precipitated by head movement and is caused by otoliths that perturb the labyrinthian sensory receptors. In a patient with BPPV, episodes of vertigo generally last less than 1 minute.

Brainstem infarction or hemorrhage as well as cerebellar infarction or hemorrhage cause vertigo of central origin. In central vertigo, there is no latency in the occurrence of nystagmus with the Dix-Hallpike maneuver. Compared with the findings in a patient with peripheral vertigo, the nystagmus generally lasts longer than 1 minute and symptoms are less severe. Based on the history and physical examination, this patient's presentation is inconsistent with brainstem infarction.

Labyrinthitis is similar to vestibular neuronitis in etiology and presentation except that in labyrinthitis patients exhibit hearing loss. Hearing is preserved in this patient, making labyrinthitis an unlikely diagnosis.

KEY POINT

- Vestibular neuronitis is characterized by acute, severe, and persistent nonpositional peripheral vertigo.

Bibliography

Huh YE, Kim JS. Bedside evaluation of dizzy patients. J Clin Neurol. 2013 Oct;9(4):203-13. [PMID: 24285961]

Item 114 Answer: D

Educational Objective: Manage risk for cardiovascular disease and cancer in a healthy patient.

No vitamin supplementation is indicated to reduce the risk for cardiovascular disease and cancer in this patient. Although one third of U.S. adults use supplemental vitamins, the U.S. Preventive Services Task Force (USPSTF) has concluded that there is insufficient evidence to assess the balance of benefits and harms of vitamin use, including use of vitamin A, vitamin C, and antioxidant combinations, in the prevention of cardiovascular disease and cancer. This recommendation applies to multivitamin preparations and to single- or paired-vitamin preparations, with the exception of vitamin E and β-carotene. Because of potential adverse effects associated with their use, the USPSTF specifically recommends against the use of vitamin E and β-carotene for these purposes. This patient should be advised that taking supplemental vitamins or minerals will not lower his risk for cardiovascular disease and cancer. Instead, he should continue to consume a balanced diet that includes fruits and vegetables and to exercise regularly.

Vitamin supplementation should be used in treating known deficiencies or in clinical situations in which it has been shown to be effective, such as vitamin D supplementation in patients with osteoporosis.

KEY POINT

- Vitamin supplementation, either with a multivitamin or with a single- or paired-vitamin preparation, has not been shown to reduce the risk for cardiovascular disease or cancer.

Bibliography

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Item 115 Answer: C

Educational Objective: Diagnose scleritis.

This patient most likely has scleritis. Scleritis is inflammation of the fibrous layers of the eye underlying the episclera and conjunctiva and overlying the choroid. Patients may present with severe, continuous, boring ocular pain that radiates to the surrounding facial areas, redness, photophobia, and tearing. It most commonly affects both eyes and is frequently worse at night, and because of traction of the extraocular muscles on the sclera, pain is often worse with eye movement. Vision may be normal, but impairment may result from inflammatory involvement of adjacent ocular structures or loss of globe integrity. Roughly 50% of patients with scleritis have an underlying systemic disease, such as an inflammatory connective tissue disorder (rheumatoid arthritis) or infection (tuberculosis). Because scleritis can be a sight-threatening condition, it requires urgent referral to an ophthalmologist for further evaluation and treatment.

The episclera is a vascular fibroelastic structure superior to the sclera. Inflammation of the episclera, or episcleritis, is less commonly associated with pain or photophobia, as seen in this patient, but more commonly with redness, irritation, and tearing. This history is usually most helpful in differentiating scleritis from episcleritis, as they may be difficult to distinguish by physical examination alone. Episcleritis is also uncommonly associated with risk for visual impairment.

Keratoconjunctivitis sicca (dry eye) includes symptoms of dryness, irritation, and burning. This patient does not have a presentation consistent with dry eye.

Patients with subconjunctival hemorrhage present with blotchy redness (from extravascular blood) that is typically confined to one area of the conjunctiva. Subconjunctival hemorrhage is painless, occurs spontaneously, and resolves within several weeks. This patient's severe eye pain, diffuse redness, and persistence of symptoms argue against the diagnosis of subconjunctival hemorrhage.

KEY POINT

- Scleritis, painful inflammation of the fibrous layers of the eye underlying the episclera and conjunctiva, is often associated with systemic diseases including inflammatory connective tissue disorders and infections.

Bibliography

Bal SK, Hollingworth GR. Red eye. BMJ. 2005 Aug 20;331(7514):438. [PMID: 16110072]

Item 116 Answer: B

Educational Objective: Diagnose borderline personality disorder.

This patient has borderline personality disorder (BPD). Features of BPD include interpersonal hypersensitivity (for example, intense and unstable relationships and intense efforts to avoid abandonment), difficulty controlling emotions such as anger, impulsive or destructive behavior (for example, spending money or promiscuous sex), recurrent suicidal gestures, and unstable self-image. BPD can be misdiagnosed as depression or bipolar disorder. About 6% of primary care patients have BPD. The mainstay of treatment for BPD is psychotherapy. Pharmacologic treatment of BPD is adjunctive to psychotherapy. There are no FDA-approved medications for personality disorders; medications are used to relieve symptoms (for example, mood stabilizers for mood swings and impulsivity).

Patients with bipolar disorder report different neurovegetative symptoms than patients with BPD, such as a decreased need for sleep and waking with increased energy; they report an increase in activities but may move from one thing to another without completing tasks and may become more social or hypersexual but without indication of interpersonal loss. The patient's speech is often loud and full of jokes and puns, and he or she may be distractible, responding to irrelevant stimuli. Patients with BPD tend to behave angrily, impulsively, or self-destructively in the context of real or perceived interpersonal loss, whereas no such pattern is apparent in those with bipolar disorder.

Depressed mood, anhedonia, lack of motivation, lack of energy or mood reactivity, overeating, and oversleeping are typical characteristics of a depressive disorder. BPD depressions are often characterized by feelings of emptiness; patients' mood often improves after being reunited with a "lost" partner or finding a new loved one.

Generalized anxiety disorder (GAD) is characterized by excessive anxiety and worry about various events or activities on most days for at least 6 months, with difficulty controlling worrying. Associated symptoms include fatigue, irritability, restlessness, insomnia, and difficulty concentrating. Such patients often have comorbid anxiety disorders, depression, or substance abuse. Patients with GAD often have somatoform symptoms, which can make them high utilizers of health care resources. This patient does not exhibit any of these symptoms, making this diagnosis unlikely.

KEY POINT

- Features of borderline personality disorder include interpersonal hypersensitivity, difficulty controlling emotions such as anger, impulsive and destructive behavior, recurrent suicidal gestures, and unstable self-image.

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Gunderson JG. Clinical practice. Borderline personality disorder. N Engl J Med. 2011 May 26;364(21):2037-42. [PMID: 21612472]

Item 117 Answer: B

Educational Objective: Evaluate cardiovascular risk in a patient with erectile dysfunction before initiating therapy.

The most appropriate next step in management is a cardiac stress test for this patient with erectile dysfunction (ED) and symptoms indicative of cardiovascular disease.

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First-line therapy for ED includes lifestyle modification (smoking cessation, exercise, and weight loss) and phosphodiesterase type 5 (PDE-5) inhibitor therapy. ED and cardiovascular disease share many risk factors (diabetes mellitus, hyperlipidemia, and hypertension), and ED is itself a cardiac risk factor that independently predicts mortality and confers a risk similar to that of moderate smoking. Therefore, it is important to assess cardiovascular risk and safety for sexual activity before initiating a PDE-5 inhibitor. This can generally be accomplished using guidelines established by the Third Princeton Consensus Conference. This patient has new-onset exertional dyspnea and fatigue that resolve with rest, raising the possibility of ischemic heart disease. Consequently, this patient should undergo cardiac stress testing, especially before considering medical therapy for ED.

Patients with symptoms of ischemic heart disease should undergo exercise stress testing before initiating a PDE-5 inhibitor such as tadalafil. If stress testing demonstrates that the patient can achieve 5 to 6 metabolic equivalents without ischemia, the patient is at low risk for cardiovascular events with PDE-5 inhibitor therapy and sexual activity. Also, this patient is already taking the α-blocker tamsulosin and has a low-normal blood pressure. PDE-5 medications and α-blockers should be combined with caution due to the risk of profound hypotension.

This patient does not require a psychiatric evaluation because he has no obvious symptoms of mood disorder. Features of his sexual history that point against mood disorder are intact interpersonal relationships, strong libido, gradual onset of erectile dysfunction, and loss of nocturnal erections.

Nearly one third of obese men will have improvement in ED symptoms simply by exercising regularly and losing weight. Attempts should therefore be made to lower the BMI below 30. However, weight loss is not the most appropriate next step in management in this mildly overweight patient who may have untreated coronary artery disease.

KEY POINT

- Because erectile dysfunction shares many risk factors with atherosclerotic cardiovascular disease and itself is an independent risk factor, an assessment of the patient's cardiovascular risk should be made before prescribing a phosphodiesterase type 5 inhibitor for treatment of erectile dysfunction.

Bibliography

Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012 Aug;87(8):766-78. [PMID: 22862865]

Item 118 Answer: B

Educational Objective: Recognize autism spectrum disorder.

This patient meets criteria for autism spectrum disorder (ASD). ASD encompasses a group of heterogeneous conditions characterized by (1) persistent deficits in communication and social interaction associated with impairment in function and (2) repetitive behaviors that are inflexible and nonfunctional and interests that are often restricted. This patient's persistent problems with social communication and interaction, including difficulty with relationships and reading body language, adherence to routines, and repetitive behaviors, are consistent with this diagnosis. The DSM-5 has eliminated the subclassifications of autism (including Asperger syndrome) and merged all related entities into ASD.

Antisocial personality disorder is characterized by lack of remorse and disregard for others. Patients with this disorder usually have no regard for right and wrong. Although this patient has difficulty with social relationships, his symptoms are not consistent with antisocial personality disorder.

Although this patient's insistence on turning the light off and on three times and lining up his shoelaces nightly may be classified as obsessions, his difficulty with social relationships and communication make his clinical findings more consistent with autism than obsessive-compulsive disorder.

Social anxiety disorder is characterized by severe and persistent anxiety regarding social situations, including public speaking and meeting new people. Patients with this disorder may also have difficulty with social relationships accompanied by significant, often debilitating, anxiety. However, patients with social anxiety disorder do not have the restricted or repetitive behaviors that are associated with autism, as seen in this patient.

KEY POINT

- Autism spectrum disorder encompasses a group of heterogeneous conditions characterized by restrictive, repetitive behaviors and interests and persistent deficits in communication and social interaction associated with impairment in function.

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Item 119 Answer: B

Educational Objective: Prevent recurrent vulvovaginal candidiasis.

The most appropriate recommendation for this patient is extended-course antifungal treatment to decrease the risk of recurrent vulvovaginal candidiasis (VVC). Although VVC is common, complicated VVC is recurrent (defined as four or more episodes in 1 year), characterized by more severe symptoms, or may be due to non-albicans candida such as *Candida glabrata*. Complicated infection may develop in women who are pregnant, have uncontrolled diabetes mellitus, or are immunosuppressed but may also occur in patients without associated medical issues, such as this one. In women with complicated VVC, more sustained treatment

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of a recurrent infection may be needed to achieve symptom relief and cure. Extended-course antifungal therapy appears to decrease the risk of recurrence, and there is minimal evidence suggesting that more prolonged treatment increases the level of fungal resistance to antimicrobial agents. However, the optimal antifungal regimen and time frame have not been defined.

The role of sexual activity in recurrent VVC is unclear, and there is equivocal evidence that treatment of a sexual partner for *Candida* is of benefit in decreasing the risk of recurrent infection. Therefore, treating this patient's partner in the absence of symptoms is not recommended.

The probiotic *Lactobacillus* is sometimes taken by patients, either orally or intravaginally, in an attempt to decrease the colonization of the vagina with *Candida*, thereby reducing the risk of recurrent VVC. However, there are few data suggesting that women with VVC are deficient in lactobacilli or that attempting to reduce vaginal *Candida* colonization by this method is effective in decreasing recurrent VVC. It is therefore not recommended as a method of preventing recurrent infection.

Although indwelling contraceptive methods (such as vaginal sponges, diaphragms, and intrauterine devices) have been inconsistently associated with *Candida* colonization, switching to an alternative contraceptive method would not be expected to be of benefit in reducing infections in this patient.

KEY POINT

- Extended-course antifungal agents may be helpful for decreasing the risk of recurrent vulvovaginal candidiasis.

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Item 120 Answer: D

Educational Objective: Diagnose retinal detachment.

This patient most likely has retinal detachment. Retinal detachment, which occurs mainly in patients with myopia, results when the neurosensory layer of the retina separates from the retinal pigment epithelial layer and choroid. The characteristic features of retinal detachment are floaters, flashes of light (photopsias), and squiggly lines, followed by a sudden, peripheral visual field defect that resembles a black curtain and progresses across the entire visual field. The most common type of retinal detachment is posterior vitreous detachment (PVD), which typically occurs in persons aged 50 to 75 years. Symptoms usually progress over a period of 1 week to 3 months and can lead to blindness. Patients with retinal detachment should be urgently evaluated by an ophthalmologist.

Age-related macular degeneration (AMD) is a leading cause of blindness in older patients. In dry AMD, extracellular material (drusen) is deposited in the macular region of one or both eyes. Patients often report a gradual loss of vision. In wet AMD, patients with pre-existing dry AMD will progress to develop new vessel growth under the retina. Bleeding and exudation from these vessels result in sudden (or rapid onset over weeks), painless blurring or warping of central vision. Wet AMD results in severe vision loss. This patient's peripheral vision loss and the presence of floaters and photopsias are not consistent with AMD.

Patients with branch retinal vein occlusion, which is caused by arterial compression of the retinal vein, are typically asymptomatic. Funduscopic examination may reveal an afferent pupillary defect, congested retinal veins, scattered retinal hemorrhages, and cotton wool spots in the region of occlusion, which are not present in this patient.

Central retinal artery occlusion (CRAO) is caused by vasospasm or emboli. Patients with CRAO are usually elderly and present with profound and sudden vision loss. Findings on funduscopic examination include afferent pupillary defect and cherry red fovea that is accentuated by a pale retinal background, both of which are absent in this patient.

KEY POINT

- Retinal detachment, which occurs mainly in patients with myopia, is characterized by floaters, photopsias, and squiggly lines, followed by a sudden, peripheral visual field defect that resembles a black curtain and progresses across the peripheral field of vision.

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Item 121 Answer: D

Educational Objective: Diagnose spinal stenosis.

Spinal stenosis is the most likely cause of this patient's symptoms. Spinal stenosis results from narrowing of the spinal canal, usually due to degenerative arthritis of the spine that causes mechanical compression and ischemia of the lumbosacral spine nerve roots. Clinical manifestations of spinal stenosis are progressively worsening low back discomfort and severe leg pain that tends to be minimized when the low back is flexed (leading patients to lean forward) and worsened with spinal extension (such as when standing and walking up steps). Plain radiographs may reveal degenerative changes or alterations in the mechanical structure of the lumbosacral spine; however, CT may be more helpful in defining bony changes, and MRI is the study of choice for evaluating the neural structures in the low back. It is important to note that spinal stenosis may be incidentally detected in a substantial number of asymptomatic patients who have imaging for other reasons, and the degree of stenosis does not predict development of symptoms. Therefore, this finding alone does not require further evaluation in the absence of symptoms or possibly associated clinical findings.

Compression fractures may cause low back pain and, if severe, may cause nerve compression and radiculopathy.

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However, this patient does not have clear risk factors for compression fracture (such as trauma, glucocorticoid use, or osteoporosis), and the symptoms associated with compression fracture tend to be of acute onset (and not progressive, as in this patient) with significant point tenderness over the spine at the level of the fracture. Additionally, the symptoms associated with compression fracture tend to be less positional than those seen in spinal stenosis.

Hip osteoarthritis may be worsened with walking, and pain may radiate posteriorly toward the low back and groin region. However, it would not explain this patient's lower extremity symptoms and other positional findings.

Symptoms associated with spinal stenosis are sometimes termed pseudoclaudication because they worsen with ambulation and improve with rest, similar to claudication due to peripheral arterial disease. However, these conditions are usually distinguished by the fact that vascular claudication symptoms do not tend to worsen with standing or spinal extension. Additionally, this patient has no clear risk factors for peripheral arterial disease.

KEY POINT

- Spinal stenosis is characterized by pseudoclaudication and severe leg pain that is absent when seated and may be relieved when leaning forward.

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Item 122 Answer: D

Educational Objective: Manage a patient with medically unexplained symptoms.

The most appropriate management of this patient who has had extensive evaluation of multiple nonspecific symptoms and has been appropriately diagnosed with medically unexplained symptoms (MUS) is regular visits with her internist. Consistent, regularly scheduled follow-up visits with brief focused history and physical examination, rather than ad hoc, unscheduled visits for crisis management, are the cornerstone of management. Regular visits allow for growth of the physician-patient relationship and the ability to discuss the diagnosis and specific symptoms with the patient and anticipate potential problems and issues. This patient's symptoms are persistent but not progressive, and there are no accompanying pathologic findings on examination or with previous diagnostic testing. Additionally, her symptoms have adversely affected her quality of life, and previous trials of antidepressant medication have been unsuccessful. Although co-management with a psychiatrist can be beneficial in the care plan of some patients with MUS, the internist assumes the central role, and this would be the most appropriate approach to managing this patient.

Long-acting benzodiazepines are not recommended in patients with MUS because they have not been proved beneficial in treating symptoms, and the sedative effects and risk for dependence outweigh any potential benefits.

Neuropsychological testing is generally performed to further evaluate cognitive dysfunction and is unnecessary in this patient who has clinically normal cognitive function.

Physical therapy may be beneficial in the patient with prominent musculoskeletal symptoms. However, these symptoms are absent in this patient, and physical therapy should not supplant the central role of regularly scheduled visits with the internist.

KEY POINT

- Consistent, regularly scheduled follow-up visits with brief focused history and physical examination are the cornerstone of management of patients with medically unexplained symptoms.

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Item 123 Answer: C

Educational Objective: Treat a patient with alcohol withdrawal.

Lorazepam is the most appropriate treatment for this patient with alcohol withdrawal and chronic liver disease. Alcohol withdrawal symptoms can start within 4 hours to several days after the last drink. Alcohol activates the same receptor as γ-aminobutyric acid, which is the major inhibitory neurotransmitter in the brain, causing central nervous system depression. If ethanol has been present frequently enough in a heavy drinker to develop tolerance and dependence, sudden withdrawal creates a state of central nervous system hyperactivity, which can be life threatening. Early symptoms include agitation, tremulousness, headache, and symptoms of autonomic hyperactivity (fever, diaphoresis, tachycardia, and hypertension). As withdrawal becomes more severe, patients may experience seizures and/or hallucinations, usually within 12 to 24 hours of abstinence. Delirium tremens is a systemic syndrome characterized by hypertension, tachycardia, diaphoresis, fever, disorientation, and hallucinations. Onset is usually 48 to 96 hours after the last drink and sometimes persists for many days. Benzodiazepines are the treatment of choice for alcohol withdrawal. Thiamine, glucose, and folate are supplemented routinely, and nutrition should be instituted early.

All benzodiazepines appear similarly efficacious in reducing signs and symptoms of alcohol withdrawal. Longer-acting agents, such as chlordiazepoxide, may be more effective in preventing seizures but can pose a risk for excess sedation in older adults and patients with marked liver disease, such as this patient. Short-acting benzodiazepines, such as lorazepam, are preferred to long-acting benzodiazepines in patients with liver disease because short-acting benzodiazepines cause less metabolite buildup in the liver. In this patient, benzodiazepines will not only help to control

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CONT.

his current symptoms but will also help to prevent him from progressing to severe alcohol withdrawal.

Clonidine and β-blockers such as propranolol have been used as an adjunctive therapy in alcohol withdrawal because they reduce withdrawal symptoms related to autonomic hyperactivity. However, there is little evidence that either of these medications reduce or prevent seizures and delirium.

KEY POINT

- Benzodiazepines are the treatment of choice for alcohol withdrawal.

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Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. N Engl J Med. 2003 May 1;348(18):1786-95. [PMID: 12724485]

Item 124 Answer: D

Educational Objective: Evaluate an obese patient.

The most appropriate cardiovascular risk stratification strategy for this obese patient is to measure waist circumference. The American Heart Association, American College of Cardiology, and The Obesity Society (AHA/ACC/TOS) guideline for the management of overweight and obesity recommends screening for overweight and obesity by calculating BMI at annual visits or more frequently. Additionally, the guideline recommends measuring waist circumference at the level of the iliac crest in overweight and obese patients. (Measuring waist circumference in patients with a BMI >35 is unnecessary, as the waist circumference will likely be elevated.) Central adiposity (waist circumference >102 cm [40 in] in men and >88 cm [35 in] in women) is associated with an increased risk for hypertension, type 2 diabetes mellitus, and coronary heart disease, independent of BMI. Together, BMI and waist circumference can be used to risk stratify patients.

Exercise stress testing is typically indicated for evaluation of chest pain in symptomatic individuals. This patient is asymptomatic and likely at low risk for coronary heart disease. Therefore, there are no indications for stress testing.

Although the patient reports occasional snoring, he does not report nonrestorative sleep or daytime hypersomnolence, which would be suggestive of obstructive sleep apnea. Therefore, overnight oximetry or polysomnography is not indicated.

Screening resting electrocardiography should not be performed in this patient. The American College of Physicians specifically recommends against screening asymptomatic low-risk adults for ischemic heart disease with resting or stress electrocardiography, stress echocardiography, or stress myocardial perfusion imaging. Instead, clinicians should address modifiable cardiovascular risk factors, such as obesity, smoking, hypertension, hyperlipidemia, and diabetes, and encourage healthy diet and levels of exercise.

Along with a history and physical examination, the AHA/ACC/TOS obesity guideline recommends performing clinical and laboratory assessments, including measuring blood pressure, fasting plasma glucose level, and fasting lipid levels, in overweight and obese patients to assess for cardiovascular risk factors and obesity-associated comorbidities.

KEY POINT

- Central adiposity increases risk for hypertension, type 2 diabetes mellitus, and coronary heart disease; in obese and overweight patients, measuring waist circumference is a cost-effective way to risk stratify patients.

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Item 125 Answer: C

Educational Objective: Monitor statin therapy in an asymptomatic patient with hyperlipidemia.

A fasting lipid panel is the most appropriate laboratory test for this patient. He has a history of atherosclerotic cardiovascular disease and is being treated with high-intensity statin therapy in accordance with the American College of Cardiology/American Heart Association cholesterol treatment guideline. Before initiating statin therapy, a fasting lipid panel, including total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol levels, should be obtained. Although therapy is not adjusted to achieve specific LDL cholesterol targets, a repeat fasting lipid panel is appropriate 1 to 3 months after initiation of statin therapy to determine medication adherence and effectiveness of treatment, which is defined as a reduction in the LDL cholesterol level of 50% or more from the pretreatment baseline. Further monitoring of statin therapy should be individualized, but in patients on a stable dose, the guidelines recommend retesting at 3- to 12-month intervals.

Alanine aminotransferase level should be measured before initiating therapy to rule out undiagnosed liver disease; however, based on the low risk of hepatotoxicity, the FDA no longer suggests measurement of hepatic enzymes during statin therapy. If the patient experiences symptoms suggestive of liver dysfunction, including fatigue, anorexia, jaundice, nausea, or abdominal pain, assessment of hepatic aminotransferases would be appropriate.

Baseline assessment of creatine kinase level is useful in patients with a family history of myopathy or risk factors for statin-induced myopathy (for example, concomitant therapy with medications that alter statin metabolism). Routine creatine kinase assessment is low yield and cost ineffective, as the incidence of myopathy is relatively rare. For this patient without symptoms or risk factors for myopathy, neither initial creatine kinase measurement nor testing during statin therapy is indicated.

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Elevated high-sensitivity C-reactive protein level is a risk factor for cardiovascular disease and may be useful in patients for whom the best therapeutic approach for hyperlipidemia is uncertain. However, this patient has a clear indication for high-intensity statin therapy based on his clinical atherosclerotic cardiovascular disease. Therefore, high-sensitivity C-reactive protein testing is not indicated.

KEY POINT

- A repeat fasting lipid panel should be obtained 1 to 3 months after initiation of statin therapy to determine medication adherence and effectiveness of treatment.

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Item 126 Answer: D

Educational Objective: Manage cervical cancer screening in an older woman.

Cervical cancer screening, including Pap smears and human papillomavirus (HPV) testing, should be discontinued in this patient. Screening for cervical cancer can be stopped in women age 65 years and older who have had adequate prior screening, which consists of three consecutive negative Pap smears or two consecutive negative Pap smears plus HPV tests within the last 10 years. The most recent testing should be within the last 5 years. This patient meets these criteria with consistently negative Pap smear screenings, with the latest being 2 years ago. The American Cancer Society recommends that screening not continue in women over age 65 years, even in those who have a new sexual partner. Women who have had a hysterectomy with removal of the cervix for benign reasons (no history of high-grade precancerous lesions or cervical cancer) should not be screened regardless of age. This includes women who have had a hysterectomy with removal of the cervix during surgery for ovarian or endometrial cancer, as they are not considered to be at high risk for cervical cancer.

In women age 65 years and older who are at high risk for cervical cancer, including immunocompromised women (such as those with HIV infection), women with in utero exposure to diethylstilbestrol (DES), and women who have had previous treatment of a high-grade precancerous lesion, screening should continue.

KEY POINT

- Screening for cervical cancer can be stopped in women age 65 years and older who have had three consecutive negative Pap smears or two consecutive negative Pap smears plus human papillomavirus test results within the last 10 years, with the most recent test performed within 5 years.

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Moyer VA; U.S. Preventive Services Task Force. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012 Jun 19;156(12):880-91, W312. Erratum in: Ann Intern Med. 2013 Jun 4;158(11):852. [PMID: 22711081]

Item 127 Answer: D

Educational Objective: Treat chronic neurogenic neck pain.

This patient should be treated with gabapentin. Her history and physical examination findings are consistent with chronic neurogenic neck pain. Features that support this diagnosis are the quality of the pain (burning and tingling), radiation to the arms, limited range of motion of the neck, and reproduction of pain with compression of the spinal nerves via the Spurling test. The findings of normal upper extremity muscle strength, the absence of upper extremity hyperreflexia and spasticity, and her imaging results make spinal cord involvement unlikely, as does the lack of evidence of a systemic process such as malignancy. Patients with chronic neurogenic neck pain frequently do not respond to analgesics, such as acetaminophen, or anti-inflammatory medications, such as NSAIDs. However, they may respond to agents such as gabapentin and tricyclic antidepressants.

Muscle relaxants such as cyclobenzaprine are sometimes used in patients with neck and back pain, particularly if muscle spasm is present. However, muscle relaxants tend to be more effective for acute than chronic pain and have considerable side effects, such as sedation. Additionally, although benzodiazepines such as diazepam have muscle relaxant properties, they have not been shown to be superior to nonbenzodiazepine muscle relaxants and also have greater potential for abuse. Therefore, they are often reserved for use in patients with muscle spasm in whom other muscle relaxants have failed. Muscle relaxant therapy, particularly with a benzodiazepine, would not be indicated in this patient without evidence of significant muscle spasm associated with her neck pain.

Data supporting the effectiveness of epidural glucocorticoid injections for chronic neurogenic neck pain are limited and inconsistent. Although they are occasionally used in patients with chronic pain refractory to other therapies, the FDA has issued a drug safety communication about epidural injection of glucocorticoids due to the potential for rare but serious adverse effects. Therefore, this would not be an appropriate intervention in this patient who has not been treated with other interventions for her pain.

Laboratory tests, such as erythrocyte sedimentation rate, are also not indicated in the absence of clinical evidence of a systemic disorder that might be the cause of neck pain. This patient is otherwise healthy, and there is no clear need for laboratory testing as part of the evaluation of her neck pain.

KEY POINT

- Patients with chronic neurogenic neck pain may respond to agents such as gabapentin and tricyclic antidepressants.

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Item 128 Answer: A

Educational Objective: Manage surrogate decision making in a patient without decision-making capacity.

The surrogate decision maker's understanding of this patient's medical condition and previously expressed health care wishes and values should be evaluated. For the patient who lacks decision-making capacity, the surrogate decision maker should not make decisions based on his or her own values and preferences. Rather, the surrogate has ethical and legal obligations to make decisions that are based on the patient's health care values, goals, and preferences (the concept of substituted judgment). If these values, goals, and preferences are unknown, the surrogate should make decisions based on what he or she considers to be the best interests of the patient. In this case, the patient's daughter may think that the patient's prognosis is poor and may be acting based on that misconception. The patient's daughter should be engaged in a discussion to evaluate her understanding of the patient's condition and to clarify the patient's health care preferences in order to ensure that the decision is consistent with the patient's previously expressed wishes.

Obtaining a court-appointed guardian is not indicated in this case in which the patient clearly stated her views in her advance directive and subsequent care decisions will be made by a duly appointed surrogate based on the patient's wishes. The most appropriate approach is to explore the daughter's understanding of her mother's medical condition as well as her understanding of her mother's previously expressed health care wishes and values.

The patient's daughter's refusal of further treatment should not be summarily accepted. Rather, the physician should determine the daughter's understanding of the proposed treatment plan and suggest a treatment recommendation that does not conflict with the patient's previously expressed wishes. If the surrogate's decisions seem inconsistent with the patient's values or previous directives, the clinician should proceed with extreme caution. Ethics consultations are helpful in reconciling these conflicts.

KEY POINT

- A surrogate decision maker has ethical and legal obligations to make decisions that are based on the patient's health care values, goals, and preferences.

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Item 129 Answer: A

Educational Objective: Evaluate a study using absolute risk reduction.

According to this study, the absolute risk reduction (ARR) in mortality from a myocardial infarction (MI) after taking a statin medication for 5 years is 4%.

The effectiveness of different therapeutic interventions is frequently reported as relative or absolute risk differences between study groups. Relative comparisons compare the rates of events, such as death or complications, in two study groups, and the differences between groups is usually reported as relative risk (RR), odds ratio, or hazard ratio. Absolute comparisons, however, represent the absolute (that is, total) difference in outcomes between the experimental and control groups. Absolute measures may also be used to calculate the number needed to treat (NNT), an estimate of the number of patients needing to be exposed to an intervention to expect the studied outcome to occur. To perform calculations for diagnostic tests and medical therapeutics, it is useful to create a table (shown):

	Disease	
	Yes	**No**
Exposed	a	b
Not exposed	c	d

The data extracted from this study are shown:

	Death from Myocardial Infarction	
	Yes	**No**
Statin	53	1000
Placebo	93	1000

ARR can then be calculated as follows:

$$\text{Control event rate (CER)} = c/(c+d) = 93/(93+1000) = 0.085$$

$$\text{Experimental event rate (EER)} = a/(a+b) = 53/(53+1000) = 0.050$$

$$\text{ARR} = \text{CER} - \text{EER} = 0.085 - 0.050 = 0.035$$

$$\text{NNT} = 1/0.035 = 29$$

Relative risk reduction (RRR) can be calculated as follows:

$$\text{RR} = \text{EER}/\text{CER} = 0.050/0.085 = 0.59$$

$$\text{RRR} = 1 - \text{RR} = 1 - 0.59 = 0.41$$

A disadvantage of relative comparisons is the potential for exaggerated outcomes, especially if the outcomes are uncommon. For example, although statin medications were associated with a 41% RRR in mortality from MI, the ARR was only 4%.

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KEY POINT

- A disadvantage of relative comparisons is the potential for exaggerated outcomes, especially if the outcomes are uncommon; absolute risk reduction can provide a more realistic estimate of risk than relative risk reduction.

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Item 130 Answer: C

Educational Objective: Diagnose sexual interest/arousal disorder.

This woman most likely has sexual interest/arousal disorder. She reports persistent lack of interest and decreased receptiveness to sexual activity over the past 2 years, and these issues have caused her personal distress. Sexual dysfunction comprises various sexual problems with overlapping biologic, psychological, and interpersonal components. Rather than discrete diagnostic categories, the DSM-5 categorizes female sexual dysfunction into broad domains that allow for increased complexity within a diagnosis. Sexual interest/arousal disorder is characterized by the presence of at least three of the following symptoms: lack of sexual interest, lack of sexual thoughts or fantasies, decreased initiation of sexual activity or decreased responsiveness to partner's initiation attempts, reduced excitement or pleasure during sexual activity, decreased response to sexual cues, or decreased sensations during sexual activity; the presence of associated personal distress is required for diagnosis. Furthermore, a diagnosis of sexual dysfunction requires a duration of at least 6 months to distinguish transient sexual difficulties from more persistent dysfunction.

Genitopelvic pain/penetration disorder is characterized by persistent urogenital pain associated with intercourse that is not related exclusively to inadequate lubrication or vaginismus. Physiologic conditions that may cause dyspareunia and pelvic pain include interstitial cystitis, pelvic adhesions, infection, and endometriosis. This patient's absence of sexual pain and lack of other associated symptoms and signs make this disorder unlikely.

Orgasmic disorder is the persistent or recurrent delay or absence of orgasm following a normal excitement phase. In this patient, the distress is associated with a lack of interest and decreased libido, rather than lack of orgasm, so this is a less likely diagnosis.

Vulvodynia is a syndrome of persistent vulvar or vestibular discomfort or burning pain, generally occurring in the absence of clinically identifiable findings. The pain is marked and chronic, but variable in terms of severity, constancy, and provocative features. Its etiology is unknown. In this patient, pain is not a symptom, so this is not a correct diagnosis.

KEY POINT

- Sexual interest/arousal disorder is characterized by a lack of sexual interest or arousal; symptoms must be present for at least 6 months and must cause the patient personal distress.

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Item 131 Answer: D

Educational Objective: Exclude hypertrophic cardiomyopathy in a high school athlete.

No further testing is required in this patient. For persons undergoing a preparticipation sports evaluation, current American Heart Association guidelines consist of a 12-step clinical history and physical examination focused on cardiovascular screening. The elements of this examination include obtaining a family history for evidence of heart disease or premature death, evaluating the patient for cardiac-related symptoms (such as unexplained near-syncope/syncope or exertional dyspnea or fatigue), and performing a physical examination. Physical examination findings in patients with hypertrophic cardiomyopathy (HCM) usually include a systolic crescendo-decrescendo murmur frequently heard best at the left lower sternal border, which is due to left ventricular outflow tract obstruction. The murmur of HCM is augmented by maneuvers that decrease venous return (Valsalva) and is diminished by those that increase preload (leg elevation, hand-grip). Additional testing, with either cardiovascular imaging or electrocardiography, is not indicated in the absence of suspicious symptoms, physical findings, or family history. Therefore, no further testing is indicated in this patient with normal findings on physical examination and no suspicious symptoms or historical findings.

Because HCM is the most common cause of sudden cardiac death in persons younger than age 35 years, especially during athletic training and competition, evaluating for this diagnosis is often the focus of a preparticipation sports evaluation. However, the routine use of electrocardiography, echocardiography, or electrocardiographic stress testing to exclude HCM in the United States is probably impractical, lacks proven cost-effectiveness, and would require considerable infrastructure that currently does not exist. Additionally, such screening also could potentially cause harm to many young athletes because of false-positive results that would lead to unnecessary further evaluation, anxiety, and possibly unwarranted disqualification from sports. These guidelines differ from recommendations in Europe, where a 12-lead electrocardiogram is often incorporated into preparticipation sports evaluations. Focused screening is indicated only for first-degree relatives of patients with HCM, with the timing of screening intervals based on age, aerobic activity, family history, and clinical suspicion. Screening in these

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individuals includes electrocardiography and an imaging study in addition to a comprehensive history and physical examination.

KEY POINT

- In the absence of suspicious symptoms, physical examination findings, or family history in a patient undergoing a preparticipation sports evaluation, additional testing with either cardiovascular imaging or electrocardiography to exclude hypertrophic cardiomyopathy is not indicated.

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Item 132 Answer: D

Educational Objective: Monitor a patient with chronic noncancer pain on opioid therapy.

This patient's long-term opioid therapy should be monitored with surveillance of a prescription monitoring program, if available. Prescription monitoring programs are state-run systems that gather information on controlled substance prescriptions from pharmacies and prescribers, allowing prescribers to view a patient's controlled substance history and to monitor controlled substance use. This information is helpful in documenting adherence and for early detection of possible abuse.

Although there is little to no evidence supporting the use of long-term opioid therapy for chronic noncancer pain, there are substantial documented risks, even in patients who are compliant and whose medication is prescribed within recommended guidelines. As such, the decision to treat patients with long-term opioid therapy should be made with great care. Although the evidence that shows improved outcomes with various risk mitigation strategies is weak, most guidelines strongly recommend employing a risk assessment tool (such as the DIRE [Diagnosis, Intractability, Risk, and Efficacy] score), baseline urine drug screening, and written treatment agreements. Guidelines also agree that adherence monitoring in the form of regular surveillance of prescription monitoring programs should be performed to reduce prescription drug abuse. With continuous adherence monitoring, opioid therapy can be maintained in appropriate populations with improvement in physical functional status and minimal adverse effects.

Documentation of opioid side effects (cognitive impairment, sedation, constipation, falls), absence of aberrant opioid behavior (lost prescriptions, early refill requests, multiple concurrent opioid providers or "doctor shopping," consistently missed appointments, or erratic follow-up), and the patient's enduring functional improvement is recommended at every visit in order to justify the ongoing benefit of continued opioid therapy.

Experts recommend frequent and regularly scheduled office visits indefinitely as long as the patient remains on opioid therapy. Follow-up functional assessment twice yearly in a patient being started on long-term opioid therapy would not be adequate to monitor medication adherence, appropriateness of dosing, or potential side effects. Converting to as-needed follow-up after 3 months also would not be appropriate.

Guidelines recommend baseline and periodic urine drug testing to assess adherence, but there is no recommendation that it be performed at every visit.

KEY POINT

- In patients on long-term opioid therapy for chronic noncancer pain, adherence monitoring in the form of regular surveillance of prescription monitoring programs should be performed to reduce prescription drug abuse.

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Item 133 Answer: E

Educational Objective: Treat hyperlipidemia in a patient with low risk for atherosclerotic cardiovascular disease.

Therapeutic lifestyle modification is the most appropriate therapy for this patient. Lifestyle modification is an essential element of treatment for all patients with elevated lipid parameters but is the primary therapy in those with hyperlipidemia without clinical atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus, elevation of LDL cholesterol greater than 190 mg/dL (4.92 mmol/L), or elevated 10-year risk for developing ASCVD. The 2013 American Heart Association/American College of Cardiology lifestyle management guideline strongly recommends that adults who would benefit from LDL cholesterol lowering (1) consume a diet that emphasizes vegetables, fruits, and whole grains, and limits intake of sweets and red meats; (2) aim for a dietary intake of 5% to 6% of calories from saturated fat; and (3) reduce the percentage of calories from saturated fat and *trans* fat. Moderate-strength recommendations include performing aerobic physical activity (three to four sessions per week, with an average of 40 minutes per session, and involving moderate- to vigorous-intensity physical activity) to lower LDL cholesterol level, non-HDL cholesterol level, and blood pressure.

Ezetimibe is not recommended as first-line therapy for hyperlipidemia in patients with an indication for treatment, as there are insufficient data on the efficacy of ezetimibe in

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reducing ASCVD risk. There is also no indication for its use in patients at low risk.

In patients without clinical ASCVD or diabetes, statin therapy is typically reserved for those with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher or an estimated 10-year risk of ASCVD of 7.5% or higher. The benefits of statin therapy in healthy patients with an LDL cholesterol level lower than 190 mg/dL (4.92 mmol/L) are not established. In this patient, treatment with neither high-intensity statin therapy nor moderate-intensity statin therapy would be appropriate.

Although niacin has several favorable effects on lipids, it is less effective than statin drugs in preventing ASCVD and is also not recommended as first-line therapy for patients with an indication for treatment. It would also not be appropriate treatment for this patient who does not have a clear indication for pharmacologic lipid-lowering therapy.

KEY POINT

- In patients with hyperlipidemia but without clinical atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus, an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher, or elevated 10-year risk for developing ASCVD, therapeutic lifestyle modification is the primary intervention for prevention of ASCVD.

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Item 134 Answer: D

Educational Objective: Manage disclosure of a medical error to an affected patient.

The attending physician's colleague should be informed of the medical error, and steps should be taken to prevent future errors. Physicians are ethically and legally obligated to disclose medical errors to patients. Medical errors do not necessarily represent unethical behavior, negligence, or malpractice; however, failure to disclose errors may. Nondisclosure, if discovered, damages trust, engenders patient and family anger, and increases the likelihood of legal action. In contrast, full disclosure facilitates informed decision making about future care. Patients who are informed of medical errors and receive authentic apologies are more likely to be forgiving and work with involved caregivers. In this case, the colleague who erred in prescribing trimethoprim-sulfamethoxazole should be held accountable for the error. However, informing the colleague of the error is not the patient's responsibility. Instead, the attending physician has this responsibility and should hold the colleague accountable (for example, by taking steps to prevent future errors).

Although the pharmacy shares responsibility for the error, assigning blame at this stage (before an investigation is held) is inappropriate.

The attending physician should not offer to transfer the patient's care to a physician at another hospital unless a trusting and therapeutic relationship with the patient no longer exists or the patient desires the transfer.

KEY POINT

- Physicians are ethically and legally obligated to disclose medical errors to patients.

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Snyder L; American College of Physicians Ethics, Professionalism, and Human Rights Committee. American College of Physicians Ethics Manual: sixth edition. Ann Intern Med. 2012 Jan 3;156(1 Pt 2):73-104. [PMID: 22213573]

Item 135 Answer: D

Educational Objective: Manage perioperative anticoagulation in a patient on chronic warfarin therapy who has a low annual risk of thromboembolism.

This patient should stop warfarin 5 days before his umbilical hernia repair surgery but requires no bridging anticoagulation. He is scheduled for an invasive procedure with a moderate or high risk of bleeding and therefore requires discontinuation of warfarin for surgery. Cessation of warfarin 5 days before surgery is typically sufficient to assure a normalized INR for the procedure. For patients requiring stoppage of chronic anticoagulation, the necessity of bridging anticoagulation must then be determined based on the patient's thromboembolic risk. Contemporary mechanical aortic valve prostheses have a low (<5%) annual risk of thromboembolism, and guidelines recommend no anticoagulation bridging for patients with these prostheses if they are in sinus rhythm and have no additional risk factors for arterial thromboembolism. Perioperative aspirin continuation in a patient whose only indication for antiplatelet therapy is a mechanical valve prosthesis is a matter of debate. The American College of Chest Physicians and the American College of Cardiology/American Heart Association both suggest that aspirin be continued throughout surgery in any patient in whom the antithrombotic benefits outweigh the bleeding risks. If aspirin is continued, the additional bleeding risk it confers should be factored into the decision making regarding bridging anticoagulation.

Both intravenous unfractionated heparin and therapeutic-dose subcutaneous enoxaparin are not appropriate in this patient. Either is an acceptable form of bridging anticoagulation for patients at intermediate or high risk of thromboembolism, but for patients with low thromboembolism risk, the potential bleeding complications of bridging outweigh the possible thromboembolism prevention. For bridging-eligible patients, low-molecular-weight heparin (LMWH) is often preferred because it can be administered

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in the outpatient setting and does not require laboratory monitoring; however, no evidence suggests any difference in outcomes with LMWH or unfractionated heparin.

Prophylactic-dose subcutaneous enoxaparin is only an acceptable choice for perioperative anticoagulation bridging in intermediate-risk (5%-10% annual rate of thromboembolism) patients on warfarin for a history of venous thromboembolism. For other chronic anticoagulation indications (atrial fibrillation and mechanical heart valves), no data are available to suggest a benefit from prophylactic-dose LMWH.

KEY POINT

- Bridging anticoagulation is not indicated for patients who stop chronic warfarin therapy before surgery and have a low annual risk of thromboembolism.

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Item 136 Answer: D

Educational Objective: Treat upper airway cough syndrome due to allergic rhinitis.

The most appropriate treatment for this patient is an intranasal glucocorticoid. This patient has chronic cough (cough of more than 8 weeks' duration) due to upper airway cough syndrome (UACS) associated with allergic rhinitis. UACS is associated with conditions that cause excessive mucus production in the upper airways and postnasal drip, triggering cough. Allergic rhinitis is a frequent cause of UACS and is likely in this patient with evidence of seasonal allergies (clear nasal drainage, postnasal drip) and symptoms that are worse in high allergy seasons (fall and spring). Patients with UACS due to allergic rhinitis respond well to intranasal glucocorticoids, and these agents are considered first-line therapy.

Antibiotics are not indicated in this patient who has no clinical evidence of acute or chronic bacterial sinusitis.

First-generation antihistamine and decongestant therapy is recommended for patients with UACS due to nonallergic rhinitis. Since this patient's presentation is typical of seasonal allergies, intranasal glucocorticoids are a better option. Additionally, the systemic side effects associated with oral medications do not occur with intranasal administration.

Although cough can be a manifestation of asthma, this patient had no reports of wheezing, even with exercise, and physical examination did not reveal the presence of wheeze or airflow limitation. Therefore, inhaled bronchodilators are not indicated.

KEY POINT

- Intranasal glucocorticoids are first-line therapy for patients with upper airway cough syndrome due to allergic rhinitis; antibiotics should not be used without clear evidence of bacterial infection.

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Item 137 Answer: D

Educational Objective: Treat obesity with lifestyle modification.

This patient should be advised to reduce his caloric intake to maintain a deficit of 500 kcal/d. With a BMI of 36, this patient meets the criterion for obesity (BMI greater than or equal to 30). Furthermore, his waist circumference is higher than 102 cm (40 in), which is independently associated with increased cardiovascular risk. Treatment of overweight and obese patients should begin with establishing a weight loss goal and individualized treatment plan. A reasonable goal is weight loss of 0.5 to 1.0 kg (1.1-2.2 lb) per week to achieve a total weight loss of 10%. The mainstay of obesity treatment is lifestyle modification that includes diet for weight loss, increased physical activity, and behavioral therapy. In addition to increasing physical activity and behavioral therapy (aimed at avoiding fast food and inappropriate snacking), this patient should be prescribed a diet that maintains a 500-kcal/d deficit. Maintaining a continuous negative energy balance of 500 kcal/d results in a weight loss of about 0.5 kg (1.1 lb) per week. Involving dieticians, exercise therapists, and behavioral therapists increases the chances of success.

Bariatric surgery, such as laparoscopic adjustable gastric banding or sleeve gastrectomy, should be considered in all patients with a BMI of 40 or higher and in patients with a BMI of 35 or higher with obesity-related comorbid conditions. This patient does not meet the criteria for bariatric surgery at this time.

Pharmacologic treatment is preferably used as an adjunctive therapy in patients with a BMI of 30 or higher or in patients with a BMI of 27 or higher with overweight- or obesity-associated comorbidities who have not achieved significant weight loss with comprehensive lifestyle interventions. Orlistat is an inhibitor of gastric and pancreatic lipases that leads to malabsorption of approximately 30% of ingested fat. It is available both over the counter and by prescription. If lifestyle interventions are ineffective in obesity treatment, a pharmacologic agent such as orlistat can be added to, not substituted for, those lifestyle interventions.

Lorcaserin is another effective weight loss agent that acts as an appetite suppressant by stimulating serotonin 2C receptors in the brain. However, it would not be a preferable next step in management prior to initiation of comprehensive lifestyle interventions.

KEY POINT

- The mainstay of obesity treatment is lifestyle modification that includes diet for weight loss, increased physical activity, and behavioral therapy.

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Item 138 Answer: C

Educational Objective: Evaluate a patient with benign prostatic hyperplasia.

Obtaining a urinalysis is the most appropriate next step in the management of this patient with benign prostatic hyperplasia (BPH), a common cause of lower urinary tract symptoms (LUTS). Most men age 60 years and older have LUTS of varying degree associated with prostate enlargement. Symptoms may be mild and include decreased urinary stream, incomplete bladder emptying, urinary frequency, and nocturia. Severe symptoms may include urinary retention, urgency, and incontinence. Diagnosis of BPH in most cases is by history and physical examination, with exclusion of other potential causes of LUTS, which may include malignancy (prostate, bladder), infection (prostatitis, sexually transmitted infections), neurologic causes (spinal cord injury, stroke, Parkinson disease), medical conditions (poorly controlled diabetes mellitus, hypercalcemia), and behavior (alcohol or caffeine intake, excessive water consumption). When these other causes are not highly suspected, only a urinalysis is recommended to exclude infection (bacteria and pyuria), malignancy (hematuria), or postobstructive nephropathy (active urine sediment). Prostate-specific antigen testing is not routinely indicated for diagnosis or following the course of BPH because it may be inconsistently elevated due to prostate hypertrophy, and increased levels of prostate-specific antigen associated with BPH do not reliably correlate with LUTS.

An increased postvoid residual urine volume, determined by catheterization or ultrasonography, is supportive of the presence of BPH but is not required for diagnosis. It has also been used as an indicator of significant obstruction to inform decisions regarding the need for surgical intervention in BPH, although there is not significant evidence that the postvoid residual volume is a reliable predictor of surgical outcomes. Because this patient has no evidence of significant urinary retention, measurement of postvoid residual volume is not indicated.

Prostate ultrasonography is an effective method for measuring prostate volume or evaluating other prostate abnormalities such as nodules. However, volume measurement by ultrasonography is not required for diagnosis of BPH, and this patient has no other indication for prostate imaging.

Urine flow studies are an accurate means of determining bladder outlet obstruction. However, this study is usually reserved for patients with atypical symptoms in whom the diagnosis of BPH is unclear or if there is concern for other urinary tract flow problems in addition to BPH. Because this patient has mild, typical symptoms consistent with BPH, urine flow studies are not indicated.

KEY POINT

- In patients with usual symptoms of benign prostatic hyperplasia (BPH), a careful history and physical examination can usually render the diagnosis; a urinalysis is also indicated in evaluating BPH to exclude infection, malignancy, or postobstructive nephropathy.

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Item 139 Answer: B

Educational Objective: Treat a patient with chronic insomnia.

This patient with chronic insomnia should undergo counseling regarding sleep hygiene. Insomnia is defined as the inability to initiate or maintain adequate sleep and is a common disorder. It can lead to daytime somnolence, work absenteeism, motor vehicle accidents, poor general health, functional impairment, and impaired quality of life. The initial management of insomnia focuses on implementing good sleep hygiene, which refers to the optimization of the environmental and behavioral factors associated with sleep. Patients should be advised to establish a regular relaxing bedtime routine; associate the bed and bedroom with sleep; avoid increasingly common disruptors of sleep such as cell phone, television, or computer use in the bedroom; adhere to a stable bed time and arising time; and keep the room quiet and dark.

Alcohol disrupts continuous sleep; however, this patient's modest alcohol use is unlikely to be contributing to his chronic and progressive insomnia.

Antidepressant therapy may improve sleep difficulties in the depressed patient. In addition, some antidepressants, including trazodone, doxepin, and mirtazapine, have sedative side effects, which can be used to advantage in a depressed patient with significant insomnia. Doxepin, in doses lower than needed for an antidepressant effect, is the only antidepressant agent approved for the treatment of insomnia. This patient does not manifest other symptoms of depression, and treating insomnia in the absence of depression with antidepressant agents other than doxepin is not indicated.

Zolpidem is a short-acting nonbenzodiazapine that is used in the treatment of insomnia. Because of potential adverse effects, the use of pharmacologic agents such as zolpidem should be considered only after attempts at behavioral therapy and other nonpharmacologic interventions have failed.

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KEY POINT

- The initial treatment of insomnia focuses on implementing good sleep hygiene, which refers to the optimization of the environmental and behavioral factors associated with sleep.

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Item 140 Answer: D

Educational Objective: Manage cerumen impaction.

Clinical observation is the most appropriate management of this patient. Cerumen, or ear wax, is secreted in the lateral third aspect of the external auditory canal and serves as a protective lining against water damage and infection. Cerumen is normally progressively removed from the ear by epithelial migration and movement of the soft tissues of the lateral ear canal by normal motions such as chewing. Cerumen may accumulate if there is excessive production or interference with this normal removal process. Cerumen impaction is an accumulation of cerumen that causes symptoms or blocks visualization of the tympanic membrane. Guidelines suggest that treatment of cerumen impaction is indicated only in symptomatic patients or if the tympanic membrane needs to be visualized. Since this patient's impacted cerumen was found incidentally and he has no hearing loss, tinnitus, or ear pain, clinical observation is all that is needed at this time.

Ceruminolytic agents, manual removal, and irrigation are all effective means to remove cerumen in symptomatic patients. No ceruminolytic agent has been shown to be superior to any other. Manual removal does not subject the ear canal to moisture, so it may be associated with lower rates of infection. However, manual removal requires operator skill and a cooperative patient, with the potential for mechanical injury to the ear canal and tympanic membranes. Vacuum devices that extract cerumen with suction are available and avoid many of the complications of irrigation or manual cerumen removal.

KEY POINT

- Treatment of cerumen impaction is indicated only in symptomatic patients or if the tympanic membrane needs to be visualized.

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Item 141 Answer: D

Educational Objective: Manage the gastrointestinal side effects of opioid therapy.

The most appropriate management of this patient is to add a scheduled stimulant laxative, such as senna. Opioid-induced constipation is nearly universal in patients on regularly scheduled opioid therapy. Unlike other side effects of opioid medications such as nausea or somnolence, tolerance to constipation does not develop over time. Therefore, all patients on scheduled opioids should be prescribed a scheduled stimulant laxative, such as senna or bisacodyl. If this therapy does not adequately control opioid-associated constipation, osmotic agents (polyethylene glycol powder, sorbitol, lactulose) can be added.

Stool softeners, such as docusate, are inadequate to manage opioid-induced constipation when given alone. However, stool softeners may be given along with a stimulant laxative to further aid in preventing constipation in patients on chronic opioid therapy. Similarly, fiber supplements or other bulking agents are ineffective in managing opioid-induced constipation.

Methylnaltrexone, an injectable peripheral opioid antagonist, is very effective in treating opioid-induced constipation without adversely affecting analgesia. However, it is reserved for opioid-induced constipation that has failed to respond to an aggressive laxative regimen, and as such, it is considered second-line therapy. This patient has not had a trial of aggressive laxative therapy; therefore, methylnaltrexone is not yet indicated.

KEY POINT

- All patients on scheduled opioid therapy should be prescribed a scheduled stimulant laxative.

Bibliography

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Item 142 Answer: C

Educational Objective: Manage postoperative venous thromboembolism prophylaxis in a patient with abdominal cancer.

Prophylactic-dose enoxaparin for up to 28 days after surgery is the most appropriate management for venous thromboembolism (VTE) prophylaxis for this patient. He just underwent major abdominal surgery to resect a malignancy. The VTE risk in patients following abdominal cancer surgery is particularly high due to the prothrombotic state caused by a neoplasm and the immobility caused by major abdominal surgery. Unless bleeding risk is considered prohibitive, these patients should receive pharmacologic VTE prophylaxis. Current American College of Chest Physicians (ACCP) guidelines recommend the use of prophylactic-dose low-molecular-weight heparins for up to 28 days after surgery. This patient had relatively low blood loss with only a small decline in his hemoglobin level and has no other known risk factors for severe bleeding. Therefore, his bleeding risk is not high. Because of this, use of prophylactic-dose enoxaparin for 1 month after surgery is the most appropriate management.

Intermittent pneumatic compression devices do not provide sufficient VTE prophylaxis in patients who have undergone abdominal surgery and have other risk factors

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such as cancer. They are appropriate to use if a patient has an elevated bleeding risk, but this patient has no evidence of bleeding or risk factors for bleeding (for example, concomitant antiplatelet therapy).

Aspirin is not an acceptable choice for VTE prophylaxis following abdominal surgery. ACCP guidelines only recommend aspirin as an option after hip or knee arthroplasty, and in that situation, it should be continued for 35 days after surgery. Data on the most effective dose of aspirin for major orthopedic surgery VTE prophylaxis are sparse.

Prophylactic-dose enoxaparin limited to the duration of hospitalization is not considered to be a sufficient duration of therapy.

Similar to aspirin, therapeutic warfarin is a VTE prophylaxis option recommended only for major orthopedic surgery (hip or knee replacement or hip fracture repair).

KEY POINT

- The most appropriate venous thromboembolism prophylaxis in patients who have undergone cancer surgery is prophylactic-dose low-molecular-weight heparin for up to 28 days after surgery.

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Item 143 Answer: D

Educational Objective: Initiate palliative care in an appropriate patient.

Palliative care should be initiated now in this patient with serious, life-limiting illness. Palliative care focuses on achieving individualized goals of therapy and coordinating management of care to achieve those goals. Historically, palliative care was equated only with end-of-life care or considered appropriate only when other, potentially curative therapies had failed. However, contrary to this view, palliative care may be provided concurrently with life-prolonging therapies or with therapies with curative intent. It may be appropriately accessed at any time during a patient's illness, from diagnosis to death. Ideally, palliative care is initiated early and integrated throughout the disease trajectory to help optimize the focus of care on the patient's values and goals of treatment, an important aspect of managing complex and serious disease. Provision of early palliative care has been shown to result in prolonged life of higher quality. For example, patients with metastatic non-small cell lung cancer randomized to early palliative care had improved quality of life, less aggressive care at the end of life, and lived on average 2.7 months longer than those patients randomized to standard care (median survival 11.6 months versus 8.9 months). This is a survival benefit comparable to first-line chemotherapy in patients with non-small cell lung cancer. It is a common and unfortunate misconception that palliative care decreases life expectancy.

Hospice is a specialized type of palliative care that is reserved for patients in the terminal phase of their disease, arbitrarily defined as the last 6 months of life. Since this patient is interested in pursuing life-prolonging treatment, initiation of hospice care would not be appropriate.

Although one of the main goals of palliative care is aggressive symptom management, uncontrolled symptoms are not a requirement for palliative care involvement. Palliative care has much to offer patients outside of the domain of symptom management, including care coordination, help in establishing goals of care and navigating complex decision making, and assistance with coping. Therefore, there is no need to wait until the patient has pain or completes active treatment before accessing palliative care.

KEY POINT

- Palliative care that is initiated early and integrated throughout the disease trajectory results in prolonged life of higher quality in patients with serious illness when compared with patients who do not receive palliative care.

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Item 144 Answer: C

Educational Objective: Manage transition of care in an older patient who requires posthospital rehabilitation.

The most appropriate management of this patient is short-term rehabilitation at a skilled nursing facility (SNF). The purpose of rehabilitation is to maximize functional recovery and independence. Older patients such as this one often require posthospital rehabilitation due to deconditioning associated with acute medical or surgical illness. Rehabilitation can be provided in many different settings, and the optimal type and location of rehabilitation depends on the medical needs of the patient and his or her ability to participate in rehabilitation activities. This patient requires the assistance of another person for safety in accomplishing basic activities of daily living, such as transfers and toileting, and although her family is supportive, they would not be able to provide the level of care needed. Additionally, this patient is actively participating in therapy and making progress; however, she is unable to tolerate intensive rehabilitation services (usually defined as 3 hours per day, 5 days per week) at this time. For these reasons, this patient would be better suited to lower-intensity rehabilitation at a SNF, most of which are able to provide these services.

Rehabilitation services can be provided on an outpatient basis, either in the patient's own home if the patient is homebound or at an outpatient rehabilitation clinic in

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patients who are more functional. However, because this patient's family is not able to provide adequately extensive care in the home, rehabilitation services in this setting are not appropriate.

Long-term acute care hospitals (LTACHs) are designed to accommodate complex, high-intensity care needs for patients who require frequent physician input but no longer require standard hospitalization. Patients who require care at an LTACH include those with ongoing mechanical ventilation weaning, complex wound care needs, or multiple intravenous therapies. Although LTACHs may provide rehabilitation services, this is not their primary function. This patient does not require the level of medical care provided in an LTACH, and the focus of her care should be on rehabilitation.

Free-standing rehabilitation hospitals or units provide specialized, high-intensity rehabilitation under the direction of physiatrists. They have specific admission criteria, one of which is usually the ability to participate in 3 hours of therapy per day during the week, which this patient would not tolerate.

KEY POINT

- In older patients who require posthospital rehabilitation but cannot tolerate active, intensive therapy (3 hours per day, 5 days per week), rehabilitation services may be performed in a skilled nursing facility.

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Kane RL. Finding the right level of posthospital care: "We didn't realize there was any other option for him". JAMA. 2011 Jan 19;305(3):284-93. [PMID: 21245184]

Item 145 Answer: A

Educational Objective: Treat moderate dry age-related macular degeneration with high-dose antioxidants to prevent progression to advanced disease.

This patient with moderate dry age-related macular degeneration (AMD) should be treated with antioxidant vitamins and zinc, using the Age-related Eye Disease Study 2 (AREDS2) formulation. AMD is a degenerative disease of the macula that results in loss of central vision. Dry AMD is typically seen as subretinal deposits of yellowish or white extracellular material (drusen) and atrophy of the retinal pigment epithelium. Wet AMD is characterized by growth of abnormal blood vessels (neovascularization) into the subretinal space. Although dry AMD is more common, wet AMD is associated with a greater risk of vision loss. The Age-related Eye Disease Study (AREDS) found that daily high doses of vitamins C and E, β-carotene, and the minerals zinc and copper (the AREDS formulation) slowed the progression of moderate dry AMD (defined as extensive intermediate size drusen or at least one large lesion, or significant retinal pigment epithelium atrophy in one or both eyes) to advanced AMD. A second randomized trial, AREDS2, focused on whether the AREDS formulation could be improved with the addition of omega-3 fatty acids and/or certain antioxidants (lutein and zeaxanthin) and the subtraction of β-carotene. Although omega-3 fatty acids did not provide any additional benefit, lutein and zeaxanthin were found to be an appropriate substitute for β-carotene. Since β-carotene has been associated with an increased risk of lung cancer, particularly in smokers and former smokers, the AREDS2 formulation is a more appropriate choice for this patient with a significant smoking history; the AREDS formulation would be an appropriate choice for nonsmokers.

Laser therapy has not been shown to be beneficial in patients with dry AMD and may be detrimental by increasing rates of neovascularization. Laser therapy may have a very limited role in treating selected patients with wet AMD, but it would not be an appropriate therapy in this patient.

Vascular endothelial growth factor inhibitors are an established therapy for wet AMD due to their inhibitory effect on neovascularization, but they do not have a role in treating dry AMD.

Clinical observation without treatment with antioxidant vitamins would not be appropriate in this patient with moderate dry AMD given the established benefit of antioxidants in reducing the risk of developing more advanced and potentially sight-threatening disease.

KEY POINT

- High-dose antioxidant vitamins are indicated to prevent the progression of moderate dry age-related macular degeneration (AMD) to advanced AMD.

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Aronow ME, Chew EY. Age-related Eye Disease Study 2: perspectives, recommendations, and unanswered questions. Curr Opin Ophthalmol. 2014 May;25(3):186-90. [PMID: 24614146]

Item 146 Answer: D

Educational Objective: Manage a patient's refusal of life-prolonging treatment.

Hemodialysis should be withheld in this patient who has refused treatment. Patients have the right to refuse any treatment, including those that are life prolonging. A patient's decision to refuse life-prolonging treatments is not necessarily irrational; rather, it is often based on the patient's health care values, goals, and preferences in the context of the perceived benefits and burdens of the proposed treatment. In these cases, the physician's duty is to understand the rationale for the decision and ensure that it is informed. This patient has provided informed refusal for hemodialysis, and her decision should be respected.

A psychiatric evaluation is not necessary in this case because the patient has demonstrated all three elements of decision-making capacity: understanding of her current situation, understanding of the risks and benefits of her decision, and the ability to communicate her decision. In addition, her decision appears well aligned with her

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underlying beliefs. Psychiatrists may be helpful in determining decision-making capacity in situations in which there is a question about the patient's ability to make decisions or apparent misalignment between the decision and underlying beliefs. Additionally, a psychiatrist cannot determine if a patient is competent, as this is a legal decision made by the courts.

If a physician begins or continues a treatment that a patient has refused, the physician, regardless of his or her intent, is committing battery. Overriding this patient's refusal of hemodialysis is unethical and illegal.

There is no evidence that this patient lacks decision-making capacity; therefore, there is no need to refer to the patient's advance directive and ask the son to make a decision regarding his mother's hemodialysis.

KEY POINT

- In the case of a patient who refuses life-prolonging treatment, the physician's duty is to understand the rationale for the decision and ensure that it is informed; provided that the decision meets these criteria, the physician must honor it.

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Item 147 Answer: A

Educational Objective: Diagnose Achilles tendinopathy.

This patient most likely has Achilles tendinopathy, which classically presents with burning heel pain and stiffness that worsen with activity and improve with rest. As there is no inflammation seen on histopathologic examination, use of the term tendinopathy is preferred to tendinitis. On examination, there is frequently tenderness to palpation approximately 2 to 6 cm proximal to the Achilles tendon insertion on the calcaneus. Symptoms typically begin after an individual increases his or her level of physical activity, as is the case with this patient.

This patient has no evidence of Achilles tendon rupture, which usually but not always presents with the sudden onset of heel pain while the patient is participating in a strenuous activity. Patients may also report hearing a popping sound. On examination, a palpable Achilles tendon defect may be present, and there is usually a positive Thompson test.

High ankle sprains typically result from excessive dorsiflexion or eversion that causes injury to the tibiofibular syndesmotic ligaments connecting the distal tibia and fibula. Unlike in this patient, pain is typically elicited by medial-lateral compression of the leg at the mid-calf level (squeeze test) or by having the patient cross his legs with the mid-calf of the painful leg resting on the other knee (crossed-leg test).

Tarsal tunnel syndrome is caused by compression of the posterior tibial nerve as it passes within the tarsal tunnel below the medial malleolus. It is characterized by pain and paresthesias in the medial ankle that extend into the midfoot. Symptoms commonly worsen with standing, walking, and running. On examination, pain can be elicited by tapping on the posterior tibial nerve along its course.

KEY POINT

- Achilles tendinopathy classically presents with burning heel pain and stiffness that worsen with activity and improve with rest.

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Item 148 Answer: D

Educational Objective: Treat genitourinary syndrome of menopause.

The most appropriate management of this woman with dyspareunia due to genitourinary syndrome of menopause is topical vaginal estradiol. Symptoms of atrophic vaginitis affect 10% to 40% of postmenopausal women and include vaginal dryness, dyspareunia, vulvovaginal irritation, and itch. The associated dyspareunia may lead to avoidance of sexual activity due to discomfort. Treatment for genitourinary syndrome of menopause may include hormone-free vaginal moisturizers, which may control symptoms in some women. If symptoms persist with lubricant use, topical estradiol is useful in alleviating vaginal symptoms. A low-dose tablet containing 25 μg of 17-β estradiol is available; it is generally inserted nightly for 2 weeks and then twice weekly on nonconsecutive nights to restore vaginal epithelium. Concurrent progestin is generally not indicated for women with an intact uterus who use low-dose vaginal estrogen alone, as systemic absorption is minimal.

Several classes of medication may exacerbate vaginal dryness, including antiestrogens (tamoxifen, aromatase inhibitors), progestins, antihistamines, and anticholinergics. However, ACE inhibitors, such as benazepril, are not associated with vaginal dryness.

Systemic estrogen therapy with a patch, gel, or tablet may be used in conjunction with vaginal estrogen to treat vasomotor symptoms or for other indications, along with concurrent progestin treatment in patients with an intact uterus. Moderate to severe vasomotor symptoms can be treated with systemic hormone therapy in the appropriate risk-stratified patient; however, this patient's hot flush symptoms are tolerable and do not warrant systemic hormone therapy.

This patient's decreased interest in sexual intercourse is likely related to her dyspareunia and not decreased libido. Additionally, topical or systemic testosterone is not currently FDA approved for treatment of decreased libido in women, and its use for this purpose is discouraged by the Endocrine Society until long-term safety data can be established.

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KEY POINT

- Vaginal estrogen therapy is effective in treating women who have moderate to severe symptoms of genitourinary syndrome of menopause that have not responded to lubricants.

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Item 149 Answer: D

Educational Objective: Diagnose the cause of tinnitus.

This patient has sensorineural hearing loss, which is the most common cause of continuous, high-pitched tinnitus. Sensorineural hearing loss results from decreased sound perception due to disorders of the cochlea or acoustic nerve. Risk factors include age (presbycusis), exposure to loud noise, and ototoxic medications. Given this patient's age, chronic and bilateral symptoms, past sound exposure, and difficulty hearing when background noise is present, sensorineural hearing loss is the most likely cause of his tinnitus. Evaluation for hearing loss in the office may be accomplished by the whispered voice test, in which the examiner stands at arm's length behind the patient and the patient occludes the untested ear canal. The examiner then whispers six sets of three letter or number combinations to the patient; failure to repeat at least three of the six sets correctly constitutes a positive result.

Acoustic neuroma (or vestibular schwannoma) is a Schwann cell-derived tumor that arises from the vestibular portion of cranial nerve VIII and may cause sensorineural hearing loss and tinnitus. However, acoustic neuromas are rarely bilateral or cause symmetric hearing loss, such as that seen in this patient, making this an unlikely diagnosis.

Meniere disease is typically characterized by the triad of sensorineural hearing loss, tinnitus, and vertigo. Although this patient has evidence of sensorineural hearing loss and tinnitus, which frequently accompany one another, he does not have vertigo. Therefore, Meniere disease is much less likely.

Otosclerosis is a cause of conductive hearing loss resulting from bony changes in the middle ear. Although usually also of progressive onset, otosclerosis results in loss of ability to hear low-pitched sounds without tinnitus. Conductive hearing loss can be distinguished in the office from sensorineural hearing loss by using the Weber and Rinne tests.

KEY POINT

- Sensorineural hearing loss is the most common cause of continuous, high-pitched tinnitus; risk factors include age, exposure to loud noise, and ototoxic medications.

Bibliography

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Item 150 Answer: D

Educational Objective: Diagnose primary open angle glaucoma.

This patient has primary open angle glaucoma (POAG). Patients with POAG present with bilateral peripheral visual loss that occurs gradually and painlessly. Findings on examination are increased cup:disc ratio, vertical extension of the central cup, and disc hemorrhages. Testing shows an elevation of intraocular pressure (generally considered >22 mm Hg) and loss of peripheral visual field depth. The primary treatment for POAG is lowering the intraocular pressure with medications. β-Blockers have traditionally been used as first-line therapy, although prostaglandins are increasingly being used for this purpose. Other medication options include α-adrenergic agonists, cholinergic agents, and topical carbonic anhydrase inhibitors, and although effective, they are associated with more ocular side effects than β-blockers or prostaglandins. Other interventions include laser therapy and surgical therapy, such as iridectomy or trabeculectomy.

Ophthalmic or posterior ciliary artery occlusion (sometimes referred to as arteritic anterior ischemic optic neuropathy) is the most common cause of permanent vision loss in patients with giant cell arteritis, as the ophthalmic artery and the posterior ciliary artery (a branch of the ophthalmic artery from the internal carotid artery) serve as the main arterial supply to the optic nerve. Giant cell arteritis is unlikely in this patient due to his younger age, chronic symptoms, bilateral involvement, and the absence of systemic symptoms such as fatigue, fever, or weight loss.

Optic neuritis is an inflammatory, demyelinating condition, most commonly occurring in the setting of multiple sclerosis, which typically presents with rapid onset (hours to days) of eye pain (particularly with movement) and monocular visual loss. This diagnosis is not supported by this patient's clinical setting or presentation.

Papilledema, or swelling of the optic disc, results from increased intracranial pressure. Papilledema may be seen with any entity that causes increased intracranial pressure, including intracranial mass lesions, cerebral edema, and cerebrospinal fluid production or resorption abnormalities. Findings on funduscopic examination include venous engorgement, blurring of the optic margins, and elevation of the optic disc, none of which are seen in this patient.

KEY POINT

- Findings of primary open angle glaucoma include increased cup:disc ratio, vertical extension of the central cup, disc hemorrhages, and increased intraocular pressure.

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Item 151 Answer: C

Educational Objective: Treat insomnia in a patient in whom sleep hygiene techniques are ineffective.

The most appropriate next step in the management of this patient is to recommend sleep restriction counseling. Insomnia is the inability to initiate or maintain adequate sleep, and it may be acute or chronic. This patient's symptoms have been persistent. The initial step in the evaluation of a patient with insomnia is a thorough history and physical examination. When there is no evidence of stimulant use, sleep-disordered breathing, restless legs syndrome, hypothyroidism, depression, or other chronic medical problems that might impair sleep (COPD, heart failure, osteoarthritis), initial treatment should focus on sleep hygiene and, if unsuccessful, a trial of sleep restriction. Sleep restriction limits and then gradually increases the time in bed for sleep. It utilizes the concept of sleep efficiency (total sleep time divided by total time in bed). The patient calculates the average total sleep time per night, and then he or she spends that amount of time in bed, keeping the arising time constant. For example, if a patient determines that his total time asleep is 6 hours per night and he sets his waking time as 6:00 AM, his bedtime would be 12:00 AM, even if he is feels tired before that time. The time in bed gradually increases by 15 minutes as long as the sleep efficiency is greater than 85%. This patient has implemented good sleep hygiene techniques (avoiding daytime napping, limiting caffeine and alcohol, keeping the bedroom quiet and dark, and avoiding the use of electronic devices in bed) without achieving significant benefit. Sleep restriction should be initiated next in this patient.

Diphenhydramine, an over-the-counter sedating antihistamine, is commonly used to treat insomnia. It induces sedation; however, its resultant anticholinergic side effects, daytime somnolence, and cognitive impairment limit its overall safety and benefit. In most patients, nonpharmacologic interventions are preferred for treatment of insomnia, particularly chronic insomnia. If pharmacologic therapy is needed, diphenhydramine is not generally recommended due to its significant side effect profile.

In general, a regular exercise regimen can help improve sleep. However, vigorous exercise before bedtime should be avoided because it may impair the ability to fall asleep.

Zolpidem, a short-acting nonbenzodiazepine selective γ-aminobutyric acid (GABA) agonist, is prescribed for the treatment of short-term or situational insomnia. It may have fewer side effects than older prescription sleep aids, but cognitive impairment, rebound insomnia, dependency, sedation, and, rarely, sleep driving, eating, and walking have been reported. In this patient, sleep restriction should be tried before pharmacologic therapy.

KEY POINT

- In patients with insomnia in whom sleep hygiene techniques are ineffective, sleep restriction may be beneficial; sleep restriction limits and then gradually increases the time in bed for sleep.

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Masters PA. In the clinic. Insomnia. Ann Intern Med. 2014 Oct 7;161:ITC1-15. [PMID: 25285559]

Item 152 Answer: A

Educational Objective: Diagnose allergic conjunctivitis.

This patient most likely has allergic conjunctivitis, which typically presents with eye redness, itching, and tearing, often in conjunction with allergy symptoms following allergen exposure. Eye findings are typically bilateral, and chemosis (conjunctival edema) and a watery, nonpurulent discharge are often seen on examination. Treatment of allergic conjunctivitis includes allergen avoidance and other nonpharmacologic interventions, such as cool topical compresses and artificial tears. Discontinuing contact lens use is also usually recommended for symptomatic patients. Pharmacologic treatment may include over-the-counter antihistamine/vasoconstrictor eye drops, oral antihistamines, or topical antihistamines (olopatadine ophthalmic 0.1%, ketotifen ophthalmic).

Bacterial conjunctivitis tends to be an acute process, commonly occurring in one eye. Patients frequently report redness, itching, and a mucopurulent discharge that causes crusting in the morning but also persists during the day. Bacterial conjunctivitis is commonly caused by infection with *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*. It tends to be very contagious, and treatment is topical antibiotics. This patient's watery eye discharge is not consistent with bacterial conjunctivitis.

Blepharitis is a diffuse inflammation of the sebaceous glands or lash follicles of the eyelids. Common causes are *S. aureus* infection, rosacea, and seborrheic dermatitis. This patient does not have evidence of seborrheic dermatitis, which, if present, would predispose her to blepharitis.

Viral conjunctivitis is usually an acute process associated with antecedent upper respiratory tract infection. It is commonly caused by one of several types of adenovirus and is often seen following exposure to infected persons. One eye is frequently involved, although the other eye may become involved following the first. Symptoms include itching, foreign body sensation, and a watery or mucoid discharge with crusting of the eyelids following sleep. Treatment is supportive, including cold compresses and artificial tears. This patient's symptoms and clinical course make viral conjunctivitis less likely.

KEY POINT

- Allergic conjunctivitis, which occurs following exposure to an allergen, is characterized by bilateral eye redness, chemosis, itching, and tearing.

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Item 153 Answer: A

Educational Objective: Prevent stroke with statin therapy following a transient ischemic attack.

High-intensity statin therapy (atorvastatin, 40-80 mg/d; rosuvastatin, 20-40 mg/d) is appropriate in this patient who experienced a transient ischemic attack, a clinical manifestation of atherosclerotic cardiovascular disease (ASCVD). In addition to aspirin and treatment of other cardiovascular risk factors (hypertension, diabetes mellitus, smoking), statin therapy should be initiated for its well-established benefits in treating blood cholesterol levels to reduce future cardiovascular events. Even with concomitant hypertriglyceridemia, high-intensity statin therapy is still the primary treatment for patients with clinical ASCVD, unless patients have risk factors for statin-related adverse effects.

Moderate-intensity statin therapy (atorvastatin, 10-20 mg/d; simvastatin, 20-40 mg/d; fluvastatin, 40 mg twice daily; lovastatin, 40 mg/d; pitavastatin, 2-4 mg/d; pravastatin, 40-80 mg/d; rosuvastatin, 5-10 mg/d) is not the first choice for patients with clinical ASCVD due to the superior benefits of high-intensity statin therapy in this population. If the patient had risk factors for statin-related adverse effects, such as age older than 75 years or kidney or hepatic dysfunction, moderate-intensity statin therapy is an appropriate second-line treatment.

Fibrates are effective in treating hypertriglyceridemia; however, fibrate monotherapy, such as with fenofibrate, is not an acceptable initial choice for secondary prevention in patients with clinical ASCVD. Although treatment of hyperlipidemia no longer focuses on a specific LDL cholesterol target, the primary goal of treatment remains lowering LDL cholesterol, and statins have been shown to be effective at reducing LDL cholesterol levels and recurrent cardiovascular events. Only if triglyceride levels exceed 500 mg/dL (5.65 mmol/L) or the patient has a history of hypertriglyceridemia-induced pancreatitis should fibrate therapy be considered.

Studies have demonstrated that there is no additional ASCVD risk reduction with the use of combination therapy (statin plus nonstatin drugs). Nonstatin medications also have significant potential to cause adverse effects. Therefore, combination therapy is reserved for those with inadequate response or poor tolerance to statin therapy.

KEY POINT

- High-intensity statin therapy is indicated for secondary prevention in patients with clinical atherosclerotic cardiovascular disease.

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Item 154 Answer: A

Educational Objective: Treat a patient at high risk for group A streptococcal pharyngitis.

This patient is at high risk for group A streptococcal (GAS) pharyngitis and should be treated with penicillin. Pharyngitis most frequently has viral causes (up to 80% of cases). However, GAS pharyngitis, which accounts for approximately 15% of cases, should be detected to prevent potentially serious complications, such as acute rheumatic fever. Diagnosis and treatment of patients with GAS pharyngitis is aided by the four-point Centor criteria: (1) fever, (2) absence of cough, (3) tonsillar exudates, and (4) tender anterior cervical lymphadenopathy. Patients who meet the four criteria, such as this one, are at highest risk and can be treated empirically with antibiotics. Penicillin is the first-line agent; a macrolide antibiotic is indicated for penicillin-allergic patients.

Rapid streptococcal antigen test or GAS throat culture is indicated to confirm the diagnosis in patients who meet two or three Centor criteria. Rapid antigen detection testing for GAS has a specificity of greater than 95% and a sensitivity of 85% to 95%. Antibiotics should be initiated only if either test is positive.

If one Centor criterion is present, reassurance and symptomatic treatment is recommended.

KEY POINT

- A patient at high risk for group A streptococcal pharyngitis based on the Centor criteria should be treated with empiric antibiotics.

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Weber R. Pharyngitis. Prim Care. 2014 Mar:41:91-8. [PMID: 24439883]

Item 155 Answer: B

Educational Objective: Manage a patient's request to withdraw life-prolonging treatment.

This patient's request for implantable cardioverter-defibrillator (ICD) deactivation should be carried out. Patients have the right to refuse or request the withdrawal of any treatment, even those that are life prolonging (that is, death inevitably follows withdrawal of the treatment). In these circumstances, the physician's duty is to understand the reasons for the request and to ensure that the request is informed. Patients who have ICDs may experience uncomfortable shocks during the dying process, and in order to avoid shocks, some patients request ICD deactivation. This patient understands the consequences of ICD deactivation, and her request should be fulfilled. In caring for a patient at the end of life, withdrawing a treatment that is perceived by the patient as burdensome or may cause discomfort (in this case, ICD shocks) is consistent with comfort care.

No treatment has unique moral status; that is, there is no treatment that must always be administered or must be

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CONT.

continued once started. Because this patient has demonstrated clear and consistent decision-making capacity, it is unethical to refuse to comply with her wishes and continue the ICD.

It is ethically and legally permissible for physicians to withhold or withdraw treatments from patients who no longer want them without need for a psychiatric evaluation, provided the patient demonstrates clear and consistent decision-making capacity. In addition, a psychiatric evaluation cannot determine a patient's competence, as that is a legal determination made in a court of law.

It is illegal to invoke this patient's power of attorney and advance directive, as these only go into effect at a time when the patient herself is unable to make her own decisions. As long as the patient is awake and demonstrates decision-making capacity, her decisions override those of her power of attorney and those outlined in her advanced directive.

KEY POINT

- Patients with intact decision-making capacity have the right to request the withdrawal of any treatment, even those that are life prolonging.

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Item 156 Answer: B

Educational Objective: Administer the tetanus, diphtheria, and acellular pertussis vaccine during pregnancy.

This pregnant patient should receive the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine now. To decrease the burden of pertussis in infants (who are at the greatest risk for the disease), the Advisory Committee on Immunization Practices (ACIP) recommends that pregnant women receive a single dose of the Tdap vaccine during each pregnancy, regardless of when they last received either the tetanus and diphtheria (Td) or Tdap vaccine. Because maternal immunity wanes over time, administering the Tdap vaccine between 27 and 36 weeks' gestation is thought to provide optimal protection against pertussis for the infant throughout the newborn period, during which time the child is solely dependent upon maternal antibodies for protection, by boosting the mother's antibody levels. The Td and Tdap vaccines do not contain live elements and are considered safe to administer to pregnant women, as there is no evidence to suggest an increased rate of adverse events in this population.

Although the Tdap vaccine can be given at any point during a woman's pregnancy, administering the vaccine between 27 and 36 weeks' gestation is thought to confer maximal antibody protection to newborn infants. It is not advisable to wait until after 36 weeks of pregnancy.

The Td vaccine does not provide protection against pertussis and therefore should not be given either now or after 36 weeks' gestation.

Withholding vaccination against tetanus, diphtheria, and acellular pertussis during pregnancy is inappropriate. Although this patient received the Tdap vaccine during her first pregnancy, that vaccination is unlikely to provide sufficient protection for her second child at the time of delivery, as antibody levels wane significantly during the first year after vaccination.

KEY POINT

- Pregnant women should receive a single dose of the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine between 27 and 36 weeks' gestation during each pregnancy, regardless of when they last received either the tetanus and diphtheria (Td) or Tdap vaccine.

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Item 157 Answer: D

Educational Objective: Evaluate a patient with systemic exertion intolerance disease (formerly known as chronic fatigue syndrome).

No further testing is indicated in this patient who meets the clinical criteria for systemic exertion intolerance disease (SEID), previously termed chronic fatigue syndrome. He has fatigue that has persisted for more than 6 months that is not due to exertion and is not relieved by adequate sleep. He also experiences unrefreshing sleep, muscle pain, joint pain without synovitis, headaches, and recurring sore throat.

There is no specific objective laboratory test to diagnose SEID, and since the presenting symptoms are nonspecific, it remains a diagnosis of exclusion. Recommended value-based screening tests include complete blood count, glucose levels, and thyroid function tests. If indicated by the history and physical examination, electrolytes, calcium level, serum creatinine level, hepatic enzyme levels, liver chemistry tests, and antinuclear antibody test may be performed. This patient has undergone evaluation for underlying medical conditions in which fatigue is a common symptom, and all test results were normal. At present, no further testing is indicated, and attention should be directed to management with either graded exercise or cognitive-behavioral therapy.

Although Lyme disease and Epstein-Barr virus have been implicated in the development of SEID, no single infectious cause has been definitively linked. An Epstein-Barr virus titer

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would not be indicated, as this test is nondiagnostic and not value based. Additionally, antiviral treatment has been shown to be ineffective. Lyme disease testing is also unwarranted because this patient's nonspecific symptoms are not consistent with Lyme disease. Additionally, the pretest probability of Lyme disease is low, and testing for Lyme antibodies is not recommended by the American College of Rheumatology.

Repeat HIV testing in this patient would be low value care. He had a recent negative HIV test and has not had high-risk exposure since that time.

KEY POINT

- There is no specific objective laboratory test to diagnose systemic exertion intolerance disease (formerly known as chronic fatigue syndrome); recommended value-based tests to rule out this disease include complete blood count, glucose level, and thyroid function tests.

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Item 158 Answer: C

Educational Objective: Diagnose otosclerosis as a cause of conductive hearing loss.

This patient most likely has otosclerosis, a form of conductive hearing loss. Otosclerosis is caused by abnormal bone hardening and growth in the middle ear that disrupts sound transmission from the middle ear to the inner ear. Diagnostic clues in this patient include gradual onset, difficulty hearing low-pitched sounds, and no history of exposure to loud noises. When the Weber test is performed on this patient, the tuning fork is heard more loudly on the left, indicative of conductive hearing loss in the left ear. Treatment of otosclerosis is amplification or surgical stapedectomy, in which a portion of the stapes is removed and replaced with a prosthesis to improve conductive hearing.

Drug-induced hearing loss, a form of sensorineural hearing loss, can be caused by ototoxic medications, including aminoglycosides, chemotherapeutic agents, aspirin, antimalarial agents, and loop diuretics. The dose of aspirin this patient is taking would not be high enough to cause ototoxicity.

Meniere disease is classically a triad of sensorineural hearing loss, tinnitus, and vertigo. This patient does not have either tinnitus or vertigo.

Presbycusis, another form of sensorineural hearing loss, is age-related hearing loss and is typically symmetric and affecting high frequencies. Although this patient is older, his hearing loss is asymmetric and low frequency, which is less consistent with presbycusis.

KEY POINT

- Otosclerosis is a form of conductive hearing loss characterized by gradual onset, difficulty hearing low-pitched sounds, and no history of exposure to loud noises.

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Walling AD, Dickson GM. Hearing loss in older adults. Am Fam Physician. 2012 Jun 15;85(12):1150-6. [PMID: 22962895]

Item 159 Answer: A

Educational Objective: Treat a patient with medically complicated obesity.

This patient with medically complicated obesity should be referred for bariatric surgery. He has multiple obesity-associated comorbidities including hypertension, inadequately controlled type 2 diabetes mellitus, obstructive sleep apnea, and bilateral knee osteoarthritis. In light of his previously unsuccessful weight loss attempts with diet and pharmacologic agents, he should be referred for bariatric surgery. Referral for bariatric surgery should be considered in all patients with a BMI of 40 or higher and in patients with a BMI of 35 or higher with obesity-related comorbid conditions, such as this patient. The goal of bariatric surgery is weight loss that prevents and treats obesity-associated complications. Candidates should be evaluated by a multidisciplinary team with medical, surgical, nutritional, and psychiatric expertise.

The evidence for the use of hypnosis for weight loss in obese patients is unclear.

Lorcaserin, a brain serotonin 2C receptor agonist, acts as an appetite suppressant. It should be used with caution in patients taking medications that increase serotonin levels, such as paroxetine. Therefore, lorcaserin should be avoided in this patient. Additionally, he has already tried a different pharmacologic agent (orlistat) without sustained weight loss.

Diet for weight loss is one of the key components of obesity treatment. There are many diets available, from high-protein, high-fat diets to very-low-fat diets. They differ in their palatability and ability to suppress appetite in individual patients; however, when effective, these diets achieve the same outcome: calorie deficits that result in weight loss. However, given this patient's failure to achieve sustained weight loss in the past with multiple dietary interventions, another dieting attempt in this patient will likely be unsuccessful. He should continue dietary, lifestyle (physical activity), and behavioral therapy measures following bariatric surgery.

KEY POINT

- Referral for bariatric surgery should be considered in all patients with a BMI of 40 or higher and in patients with a BMI of 35 or higher with obesity-related comorbid conditions.

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63(25 Pt B):2985-3023. Erratum in: J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):3029-3030. [PMID: 24239920]

Item 160 Answer: B

Educational Objective: Manage polypharmacy in an older patient.

This older patient's clinical findings are most likely the result of adverse medication effects related to polypharmacy, and her drug regimen requires adjustment. She has significant medical comorbidities and is taking numerous drugs. Administration of multiple medications increases the risk for inappropriate use, drug-drug interactions, adverse reactions, poor adherence, and medication errors. This patient is taking two anticholinergic agents (oxybutynin for urinary incontinence and the over-the-counter antihistamine loratadine). The American Geriatrics Society Beers Criteria recommend against the use of anticholinergic agents in older patients because they can cause confusion, urinary retention, constipation, and dry mouth. She is also on the proton pump inhibitor omeprazole without an apparent indication for treatment. In addition, the risk-to-benefit ratio of using a lipid-lowering agent to confer long-term benefits must be reassessed in very elderly adults. Prescriptions for statins are frequently carried over from previous years, but statin use results in additional cost, extra pills, and increased risk for drug-drug interactions. Lastly, parameters for blood pressure control are less stringent in older adults, and, in this patient, antihypertensive agents should be reassessed, as her hypertension is overtreated. Ongoing review of the indications, risks, benefits, and dosing of all drugs in older patients is recommended.

This patient has a history of mild chronic kidney disease; however, with normal volume status, normal electrolytes, and a minimal change in her serum creatinine level, she does not have evidence of significant worsening of her kidney function. This would make acute kidney injury an unlikely cause of her current clinical findings.

Infections are a frequent cause of systemic symptoms, including weakness, dizziness, anorexia, and altered mental status in older patients, with pneumonia and urinary tract infection being the most common types. However, this patient has no clinical findings consistent with pneumonia given her normal oxygenation, leukocyte count, and chest radiograph, or suggestion of urinary tract infection with a normal urinalysis. Therefore, the absence of evidence of infection makes this an unlikely cause of her current clinical findings.

KEY POINT

- Administration of multiple medications, especially in older patients, increases the risk for inappropriate use, drug-drug interactions, adverse reactions, and medication errors.

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Item 161 Answer: B

Educational Objective: Manage sexual side effects in a patient taking a selective serotonin reuptake inhibitor.

The norepinephrine and dopamine reuptake inhibitor bupropion is the most appropriate alternative treatment recommendation for this patient with depression. The most widely prescribed antidepressant drugs are selective serotonin reuptake inhibitors (SSRIs), which have excellent safety profiles compared with tricyclic antidepressant drugs. She has responded well to treatment with the SSRI citalopram, with improved clinical symptoms and objective scoring on the PHQ-9. However, sexual side effects are common with SSRIs. Bupropion is an appropriate alternative agent for an overweight patient experiencing sexual side effects with an SSRI because it is an effective antidepressant, has a low rate of sexual side effects, and is not associated with weight gain.

Tricyclic antidepressants are also effective antidepressant agents but are associated with both sexual side effects and weight gain; therefore, amitriptyline would not be a good alternative treatment choice for this patient.

Buspirone is approved for the treatment of anxiety disorders, but not depression. Although there is some evidence suggesting that buspirone, when added to SSRI treatment for depression, may augment the antidepressant effect and counter sexual side effects caused by SSRIs, it would not be an appropriate substitution as a single agent in this patient.

Although mirtazapine is associated with a low rate of sexual side effects, this agent stimulates appetite and is associated with weight gain. Mirtazapine is an appropriate antidepressant for patients with anorexia and weight loss due to depression.

KEY POINT

- The norepinephrine and dopamine reuptake inhibitor bupropion is an appropriate alternative antidepressant for patients who experience sexual side effects from selective serotonin reuptake inhibitor therapy.

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Item 162 Answer: D

Educational Objective: Evaluate a study using number needed to treat.

The number needed to treat (NNT) is 10. Numbers needed are estimates of the number of patients who must receive an intervention to cause one patient to experience the outcome being studied; if beneficial, it is termed the NNT, and if detrimental, the number needed to harm (NNH). Numbers needed are useful indicators of the clinical impact of an intervention because they provide a sense of magnitude

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expected from the intervention. If available, NNT and NNH for the same intervention provide a convenient method for evaluating the benefits and harms of an intervention, which is immensely valuable for high value care decision making.

The NNT is calculated by taking the reciprocal of the absolute risk reduction (ARR). In this study, the risk of developing prostate cancer in the control (placebo) group can be calculated as:

$$\text{Absolute risk (AR)} = (\text{patients with event in group})/(\text{total patients in group})$$
$$\text{AR} = 300/(300 + 700) = 300/1000 = 0.30$$

The risk of developing prostate cancer in the group treated with finasteride can be calculated as:

$$\text{AR} = 200/(200 + 800) = 200/1000 = 0.20$$

The ARR is the difference in rates of events between the treatment group and control group, which is 0.10 for this study. The NNT is therefore 1/0.10, or 10. This indicates that 10 patients would need to be treated with finasteride for 7 years to prevent one case of prostate cancer.

KEY POINT

- The number needed to treat, which is the number of patients required to receive an intervention in order for one patient to benefit from it, is the reciprocal of the absolute risk reduction.

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Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ. 1995;310(6977):452-4. Erratum in: BMJ 1995;310(6986):1056. [PMID: 7873954]

Item 163 Answer: A

Educational Objective: Evaluate perioperative cardiovascular risk in a patient with cardiac risk factors but good functional capacity.

For this patient with known coronary artery disease (CAD) but normal cardiac function scheduled for intermediate-risk surgery (defined as a risk of cardiac death or nonfatal myocardial infarction of 1%-5%), electrocardiography is indicated according to the current American College of Cardiology/American Heart Association (ACC/AHA) guideline. Due to the patient's CAD, the baseline electrocardiogram may be abnormal but probably would not alter preoperative management. Instead, the electrocardiogram guides postoperative medication management by identifying conduction disturbances (such as QT-interval prolongation) and is useful as a comparison should the patient develop postoperative cardiac symptoms.

The ACC/AHA guideline does not support noninvasive coronary evaluation (either pharmacologic or exercise stress testing) in this patient. Regardless of cardiac risk factors, no further coronary evaluation is advised for patients with an exercise capacity greater than or equal to 4 metabolic equivalents (METs), and climbing a flight of stairs meets that criterion. In patients with an exercise capacity less than 4 METs, coronary evaluation is indicated if the estimated risk of perioperative major adverse cardiac events is greater than or equal to 1%. Due to its superior prognostic value, exercise testing is preferred to pharmacologic stress testing unless contraindicated by patient factors.

A resting echocardiogram only provides diagnostic information about structural heart disease and is not an appropriate form of noninvasive coronary evaluation. Therefore, preoperative echocardiography is not indicated in this patient without evidence of significant structural heart disease.

KEY POINT

- In patients with cardiac risk factors undergoing elevated-risk procedures, preoperative coronary evaluation is not required if the patient has a good functional capacity (≥4 metabolic equivalents).

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Fleisher LA, Fleischmann KE, Auerbach AD, et al; American College of Cardiology; American Heart Association. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014 Dec 9;64(22):e77-137. [PMID: 25091544]

Item 164 Answer: B

Educational Objective: Treat underlying depression in a patient with medically unexplained symptoms.

The most appropriate treatment for this patient with medically unexplained symptoms (MUS) is citalopram. This patient has a 3-year history of multiple nonspecific symptoms with an extensive negative evaluation, consistent with the presentation of MUS. Patients with MUS frequently have primary or secondary underlying depression, which may be overlooked during the unsuccessful quest for a unifying or previously undiagnosed organic illness. This patient meets the criteria for depression; he has depressed mood and affect for more than 6 months accompanied by hypersomnia and hopelessness. Antidepressant therapy, such as with the selective serotonin reuptake inhibitor (SSRI) citalopram, is the most appropriate treatment at this time. A systematic review of 94 randomized controlled trials found improvement in symptoms in patients with MUS who were treated with antidepressants.

Although the patient experiences anxiety at night and is unable to sleep well, alprazolam, a benzodiazepine, is a poor choice for chronic management of his anxiety. Alprazolam is associated with sedation, impaired cognition, and a high risk of dependence. This patient's primary symptoms of depression and anxiety will most likely respond to an SSRI.

Lithium would be appropriate if the patient had symptoms consistent with bipolar disorder. This patient has no history of bipolar disorder, and he is not manifesting any symptoms of mania.

Methylphenidate is a central nervous system stimulant that is used in the treatment of attention-deficit/hyperactivity

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disorder and narcolepsy. It may be used off label for the treatment of depression in adults who are terminally ill or receiving palliative care. First-line treatment of this patient with underlying depression is an SSRI.

KEY POINT

- Antidepressant therapy has been found to improve symptoms in patients with medically unexplained symptoms and primary or secondary underlying depression.

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Item 165 Answer: C

Educational Objective: Diagnose orbital cellulitis.

This patient has orbital cellulitis, which is inflammation of the structures of the orbit, including the extraocular muscles and orbital fat. Orbital cellulitis often results from a contiguous dental or sinus infection, as was likely present in this patient. Clinical characteristics of orbital cellulitis include eyelid swelling, ophthalmoplegia, pain with eye movement, and occasionally proptosis. Because it is a deep infection and involves critical structures, rapid diagnosis and treatment are necessary to preserve vision and prevent extension to central nervous system structures. CT is used to evaluate the extent of infection and to exclude abscess, which may need surgical drainage. This patient requires hospitalization and intravenous antibiotics.

Blepharitis is inflammation of the sebaceous glands or lash follicles of the eyelid, which can progress to conjunctivitis or keratitis. It usually presents with findings limited to the eyelid, although patients may complain of a gritty, burning sensation in the eye. Blepharitis is not associated with the key findings of orbital cellulitis.

Endophthalmitis is inflammation of the aqueous and vitreous humors. Symptoms may include visual loss, photophobia, and ocular pain and discharge. It is usually caused by bacterial or fungal infection following surgery, especially for cataracts. Other causes are globe trauma and foreign bodies.

Preseptal cellulitis is inflammation that is limited to the areas of the eyelids and facial tissues that are anterior to the orbital septum. It is more common than orbital cellulitis in adults and can usually be differentiated from orbital cellulitis by pain localized to the anterior tissues without ophthalmoplegia, pain with eye movement, or proptosis, which this patient has. Therefore, it is a less likely diagnosis in this patient.

KEY POINT

- Orbital cellulitis often occurs in the setting of recent dental or sinus infection; characteristic findings include eyelid swelling, ophthalmoplegia, pain with eye movement, and occasionally proptosis.

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Item 166 Answer: A

Educational Objective: Evaluate anovulatory bleeding in a premenopausal woman.

The most appropriate next step for this woman with intermittent heavy vaginal bleeding is referral for endometrial biopsy. Her bleeding is characteristic of an anovulatory pattern based on the unpredictable occurrence of bleeding of variable flow and duration. In women with prolonged anovulation, there is loss of normal hormonal flux with exposure to unopposed estrogen without the normal endometrial protective effect of progesterone. This increases the risk for endometrial hyperplasia and endometrial malignancy. Additional risk factors for endometrial cancer in premenopausal women include obesity, nulliparity, age 35 years or older, diabetes mellitus, family history of colon cancer, infertility, and treatment with tamoxifen. In women younger than 35 years of age with anovulatory bleeding and no other risk factors for endometrial cancer, hormonal therapy for anovulation is appropriate. However, in women younger than 35 years of age with risk factors, or any patient with anovulatory bleeding 35 years of age or older, endometrial biopsy should be performed to exclude significant endometrial pathology. Because this patient is 40 years of age and has an additional risk factor for endometrial cancer (nulliparity), endometrial biopsy is the most appropriate next step in management.

A follicle-stimulating hormone (FSH) level can be used to evaluate ovarian dysfunction, but levels vary depending on menstrual phase, age, medications, and hormonal disorders. FSH level can be used to confirm menopausal status if a woman has been amenorrheic for longer than 12 months. However, a single FSH level can be misleading during perimenopause because levels may vary. In this patient, who is premenopausal, measurement of the FSH level is of limited use.

In a woman of reproductive age with abnormal vaginal bleeding, the first test to be performed is always a urine pregnancy test, which is a sensitive qualitative measure of β-human chorionic gonadotropin level and was already obtained in this patient. There is no further gain from obtaining a serum β-human chorionic gonadotropin level, which is a quantitative measure but adds no further value in this diagnostic evaluation.

Transvaginal ultrasonography may have a role in evaluation of postmenopausal bleeding to assess for endometrial thickness, but it is not useful in assessing bleeding in premenopausal women due to significant variations in endometrial thickness caused by hormonal fluctuation. It is therefore not used routinely for evaluation of premenopausal bleeding unless a structural uterine abnormality that may be contributing to bleeding is suspected.

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KEY POINT

- In women with anovulatory bleeding with risk factors for endometrial cancer, endometrial biopsy should be performed to exclude significant endometrial pathology.

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Item 167 Answer: D

Educational Objective: Recognize the indications for imaging studies in the diagnosis of neck pain.

Symptomatic care is indicated in this patient. Most patients with neck pain do not require diagnostic imaging. Imaging is indicated for neck pain following trauma or if a structural abnormality, such as a compression fracture, is suspected. Imaging may also be indicated in patients who have weakness or clinical evidence of spinal cord involvement as a cause of neck pain. Additionally, imaging may be useful in those with a clinical presentation suggestive of malignancy or infection as a cause of neck pain. This patient has no history of trauma, weakness, or findings suggestive of a spinal cause of her pain. Despite her history of breast neoplasm, she has not had evidence of recurrence and has no other symptoms or findings suggestive of metastatic disease (such as point tenderness to palpation over the spine). Her otherwise normal presentation does not support a systemic process such as infection. Therefore, imaging in this patient would not be expected to be of benefit. Instead, the focus should be on symptomatic treatment of her neck pain using usual therapeutic modalities including mobilization, exercise, and analgesic agents.

CT myelography involves injection of nonionic water-soluble contrast agents into the spinal canal followed by a CT scan. Because of the effectiveness of other imaging modalities, myelography is usually limited to specific situations in which it may provide more helpful information than other studies, such as multilevel disk abnormalities or radiculopathies, fragmented disks, and patients who have had spinal surgery. This patient has no clear indication for this form of imaging.

MRI of the cervical spine best delineates the spinal cord and nerve roots, intervertebral disks, surrounding soft tissue, ligamentous structures, and vertebral arteries, but it is not indicated in this patient who has no neurologic signs or findings suggestive of abnormalities of these structures.

Plain radiography of the cervical spine is useful in evaluating the bony structures of the spine and is therefore helpful in excluding fracture in patients with trauma or who are suspected of having other bony abnormalities, such as compression fractures, metastatic disease, or infection affecting the spine. However, this patient has no history suggestive of an abnormality likely to be detected with plain radiography.

KEY POINT

- Most patients with neck pain do not require diagnostic imaging.

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Item 168 Answer: B

Educational Objective: Manage colorectal cancer screening in an average-risk patient.

The most appropriate screening strategy for this patient is yearly fecal immunochemical testing (FIT). Annual stool testing for occult blood using either high-sensitivity guaiac fecal occult blood testing (gFOBT) or FIT is an acceptable colon cancer screening strategy in average-risk patients. Randomized controlled trials have shown statistically significant reductions in colorectal cancer incidence (17%-20%) and mortality (15%-33%) with regular gFOBT screening. Limitations of gFOBT screening include low sensitivity for advanced adenomas (11%-41%), diet and medication interactions that may produce false-positive or false-negative results, and the need for appropriate diagnostic follow-up (that is, colonoscopy) if test results are positive to achieve maximum benefit. FIT uses specific antibodies to detect globin in the stool and is generally considered to be a more sensitive study than guaiac-based testing. In cross-sectional studies, FIT sensitivity has ranged from 60% to 85% for colorectal cancer and 25% to 50% for advanced adenomas. Pretest dietary restrictions are not necessary. As with gFOBT, FIT requires appropriate diagnostic follow-up for positive results.

The U.S. Preventive Services Task Force (USPSTF) recommends screening all adults aged 50 to 75 years for colorectal cancer with one of several different methods: high-sensitivity fecal occult blood testing (gFOBT or FIT) every year, flexible sigmoidoscopy every 5 years, combined flexible sigmoidoscopy every 5 years with high-sensitivity fecal occult blood testing every 3 years, or colonoscopy every 10 years. The American Cancer Society (ACS), U.S. Multi-Society Task Force on Colorectal Cancer, and American College of Radiology (ACR) colorectal cancer screening guideline includes additional screening options: CT colonography (every 5 years) and stool DNA testing (interval unknown). Since publication of the guideline, the ACS has recommended that stool DNA testing occur every 3 years. As these are newer tests with many areas of uncertainty, they are not currently recommended by the USPSTF. The ACS/U.S. Multi-Society Task Force/ACR guideline also recommends preference to cancer prevention tests

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(colonoscopy, flexible sigmoidoscopy, double contrast barium enema, or CT colonography) over cancer detection tests (gFOBT or FIT) when resources are available.

The USPSTF recommends flexible sigmoidoscopy every 5 years with gFOBT or FIT every 3 years, not yearly. Randomized controlled trials have consistently demonstrated a mortality benefit for distal, but not proximal, colorectal cancer of 30% to 50% with flexible sigmoidoscopy.

In patients at average risk, colonoscopy can be performed every 10 years. Observational studies have shown that colonoscopy provides significant mortality benefit for both distal and proximal colorectal cancer. Colonoscopy is the preferred test of the American College of Gastroenterology.

KEY POINT

- All adults aged 50 to 75 years should be screened for colorectal cancer using high-sensitivity fecal occult blood testing every year, flexible sigmoidoscopy every 5 years, combined flexible sigmoidoscopy every 5 years with high-sensitivity fecal occult blood testing every 3 years, or colonoscopy every 10 years.

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Welcome to the Hematology and Oncology Section of MKSAP 17!

In these pages, you will find updated information on hematopoietic stem cell disorders, multiple myeloma, bleeding disorders, hematologic issues in pregnancy, and other hematologic topics. Also addressed are issues in oncology; breast, ovarian, and cervical cancers; gastroenterological malignancies; lung cancer; lymphoid malignancies; cancer of unknown primary site; melanoma; and other topics in oncology. The effects of cancer therapy and survivorship are discussed, as well. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of hematology and oncology.

The publication of the 17th edition of Medical Knowledge Self-Assessment Program (MKSAP) represents nearly a half-century of serving as the gold-standard resource for internal medicine education. It also marks its evolution into an innovative learning system to better meet the changing educational needs and learning styles of all internists.

The core content of MKSAP has been developed as in previous editions—newly generated, essential information in 11 topic areas of internal medicine created by dozens of leading generalists and subspecialists and guided by certification and recertification requirements, emerging knowledge in the field, and user feedback. MKSAP 17 also contains 1200 all-new, psychometrically validated, and peer-reviewed multiple-choice questions (MCQs) for self-assessment and study, including 149 in Hematology and Oncology. MKSAP 17 continues to include *High Value Care* (HVC) recommendations, based on the concept of balancing clinical benefit with costs and harms, with links to MCQs that illustrate these principles. In addition, HVC Key Points are highlighted in the text. Also highlighted, with blue text, are *Hospitalist*-focused content and MCQs that directly address the learning needs of internists who work in the hospital setting.

MKSAP 17 Digital provides access to additional tools allowing you to customize your learning experience, including regular text updates with practice-changing, new information and 200 new self-assessment questions; a board-style pretest to help direct your learning; and enhanced custom-quiz options. And, with MKSAP Complete, learners can access 1200 electronic flashcards for quick review of important concepts or review the updated and enhanced version of Virtual Dx, an image-based self-assessment tool.

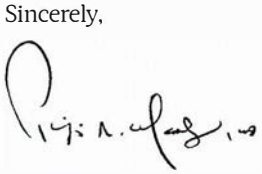
As before, MKSAP 17 is optimized for use on your mobile devices, with iOS- and Android-based apps allowing you to sync your work between your apps and online account and submit for CME credits and MOC points online.

Please visit us at the MKSAP Resource Site (mksap.acponline.org) to find out how we can help you study, earn CME credit and MOC points, and stay up to date.

Whether you prefer to use the traditional print version or take advantage of the features available through the digital version, we hope you enjoy MKSAP 17 and that it meets and exceeds your personal learning needs.

On behalf of the many internists who have offered their time and expertise to create the content for MKSAP 17 and the editorial staff who work to bring this material to you in the best possible way, we are honored that you have chosen to use MKSAP 17 and appreciate any feedback about the program you may have. Please feel free to send us any comments to mksap_editors@acponline.org.

Sincerely,



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The MKSAP Resource Site (mksap.acponline.org) is a continually updated site that provides links to MKSAP 17 online answer sheets for print subscribers; the latest details on Continuing Medical Education (CME) and Maintenance of Certification (MOC) in the United States, Canada, and Australia; errata; and other new information.

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Hematology and Oncology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 17 in several important ways. MKSAP 17 now includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Hematology and Oncology section of MKSAP 17.

- Management of aplastic anemia with hematopoietic growth factors is ineffective.
- Myelodysplastic syndrome should be managed based on risk stratification, with patients with low-risk disease requiring no treatment (see Item 72).
- Observation alone is safe for patients with essential thrombocythemia at low risk for thromboembolic complications, whereas platelet-lowering therapy is indicated for patients at high risk.
- Patients with a clear cause of secondary erythrocytosis such as hypoxemia should be managed with treatment of the underlying problem and do not require bone marrow biopsy, *JAK2 V617F* testing, or phlebotomy (see Item 18).
- Serum and urine protein electrophoresis for plasma cell dyscrasias (PCDs) should be restricted to situations in which a symptomatic PCD requiring intervention or an asymptomatic PCD at high risk of progression to a clinically symptomatic condition is suspected
- Measurement of erythropoietin levels is not useful in diagnosing the anemia of kidney disease.
- Inflammatory anemia typically requires no treatment other than for the underlying condition (see Item 45).
- α-Thalassemia trait (or α-thalassemia minor), which is associated with mild anemia, microcytosis, hypochromia, target cells on the peripheral blood smear, and, in adults, normal hemoglobin electrophoresis results, requires no treatment (see Item 61).
- Methylmalonic acid and total homocysteine levels are helpful in differentiating cobalamin deficiency (both levels are elevated) from folate deficiency (elevated homocysteine but normal methylmalonic acid level); bone marrow biopsy is not necessary and can be confusing.
- In patients with sickle cell disease, including pregnant patients, transfusion is not indicated for uncomplicated pregnancy, routine painful episodes, minor surgery not requiring anesthesia, or asymptomatic anemia (see Item 34).
- Expert opinion recommends that pregnant patients should receive the same treatment for acute vaso-occlusive crisis as nonpregnant patients with sickle cell disease (see Item 65).
- An elevated transferrin saturation remains the most sensitive and cost-effective initial screening test for hemochromatosis.
- Universal screening for hereditary hemochromatosis is not recommended and should be reserved for first-degree relatives of patients with classic *HFE*-related hemochromatosis, those with active liver disease, and patients with abnormal iron study results.
- No diagnostic test can identify immune-mediated thrombocytopenia, and antiplatelet antibody testing is not recommended because of its low sensitivity and specificity.
- Patients with immune thrombocytopenic purpura without evidence of bleeding and platelet counts greater than 30,000 to 40,000/μL ($30\text{-}40 \times 10^9$/L) have less than a 15% chance of developing more severe thrombocytopenia requiring treatment and can be managed with careful observation (see Item 23).
- Assessing the pretest probability of heparin-induced thrombocytopenia by using a risk scoring system, such as the 4T score, is helpful in guiding therapy in patients at low risk for it (see Item 39).
- In hospitalized patients without symptoms or end-organ damage, a restrictive treatment strategy for hemoglobin levels less than 7 g/dL (70 g/L) and targeting 7 to 9 g/dL (70-90 g/L) is appropriate (see Item 40).

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- Patients with mild coagulopathy requiring central venous catheter insertion do not need to receive fresh frozen plasma or other transfusions before the procedure (see Item 41).
- Fresh frozen plasma is ineffective for treating mild coagulopathies characterized by an INR of 1.85 or less.
- Platelet clumping signifies pseudothrombocytopenia, which will resolve if blood is redrawn using a citrated or heparinized tube (see Item 42).
- Clinically stable patients with chemotherapy-induced thrombocytopenia who are not bleeding do not benefit from platelet transfusion when the platelet count is 10,000/μL (10×10^9/L) or greater (see Item 20).
- Routine extensive screening for underlying cancer in all patients with unprovoked venous thromboembolism is not recommended.
- A low-probability Wells score with a negative D-dimer blood test rules out venous thromboembolism.
- A blood D-dimer test using a moderately or highly sensitive assay should be the first step in the diagnosis of deep venous thrombosis in a patient with low pretest probability (see Item 52).
- The preferred initial diagnostic test to perform in a pregnant patient with possible pulmonary embolism is lower extremity venous duplex ultrasonography to assess for the presence of deep venous thrombosis, which, if present, would obviate the need for radiation and contrast exposure associated with other diagnostic studies (see Item 14).
- Outpatient anticoagulation management is possible for patients with pulmonary embolism, unless they require supplemental oxygen, intravenous pain medications, or management of comorbid conditions that may contribute to rapid clinical deterioration or if home circumstances make outpatient therapy unfeasible (see Item 63).
- Thrombophilia testing is not indicated in patients who develop a venous thromboembolism in the setting of a major transient risk factor (major surgery or trauma or prolonged immobility), because results would not influence duration or intensity of anticoagulation therapy (see Item 12).
- Routine testing for factor V Leiden (FVL) mutation in offspring of a patient with FVL is not indicated (see Item 30).
- The only clear indication for an inferior vena cava filter is in patients with acute pelvic or proximal leg DVT who cannot be anticoagulated because of active bleeding or a very high risk for bleeding
- Although prophylactic transfusions during pregnancy can reduce pain crises in patients with sickle cell disease, neither transfusion nor exchange transfusion has been shown to reduce pregnancy-related morbidity or mortality, and increased risk for alloantibody production in this population must be considered.
- During staging of patients with cancer, tests with a very low yield should not be ordered in the absence of specific directing symptoms.
- Less toxic regimens or no chemotherapy may be warranted in patients with cancer and a poor performance status and for whom supportive, comfort-oriented care may be most appropriate.
- Supportive, comfort-oriented care is appropriate for a frail patient with metastatic cancer, significant medical comorbidities, and a poor performance status (see Item 81).
- The goal of personalized medicine is to direct therapeutic approaches that are optimally beneficial to an individual patient through a better understanding of the molecular makeup of the individual and the tumor.
- Imaging studies to identify occult metastatic disease are not needed in patients with stage I and II breast cancer unless worrisome symptoms or the following poor prognostic features are present: hormone receptor–negative cancer, *HER2* overexpression, large tumor size, high tumor grade, positive lymph nodes, and the presence of extensive lymphovascular invasion.
- After completion of treatment, follow-up monitoring in patients with early-stage breast cancer should occur every 3 to 6 months for 2 years, every 6 months during years 2 through 5, and then annually, with annual mammography for all survivors, and MRI of the breast reserved for those at high risk for recurrence.
- In asymptomatic patients with a history of early breast cancer, routine imaging studies (excluding annual mammography) or blood tests, including tumor marker studies, are not beneficial (see Item 126).
- Women at average risk for ovarian cancer should not receive ovarian cancer screening; the predictive value of serum CA-125 testing and ultrasonography are each less than 3% and lead to a high rate of false-positive results and unnecessary surgeries (see Item 114).
- Follow-up for patients who have completed treatment for ovarian cancer includes a periodic history, physical examination, and pelvic examination for 5 years after treatment; routine monitoring of CA-125 levels, other laboratory testing, and imaging studies does not improve survival and should be reserved for addressing specific clinical concerns.
- The human papillomavirus vaccine, given before infection develops, is 90% effective at preventing infection and 97% to 100% effective at preventing cervical intraepithelial neoplasia and invasive cervical cancer.
- PET scans have not been demonstrated to improve preoperative staging in patients with colorectal cancer and should not be routinely used.
- Treatment of small-volume, widely metastatic, but asymptomatic, disease discovered on surveillance has not been associated with improved outcomes and may subject patients to significant treatment toxicity.
- PET scanning should not be used for routine surveillance of patients with colorectal cancer but may be used to further evaluate an equivocal finding on CT scans in some patients.

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- Because well-differentiated neuroendocrine tumors are so indolent, patients often can be effectively managed with expectant observation and serial imaging using triple-phase contrast-enhanced CT scanning or MRI with gadolinium.
- Appropriate management for a patient with an incidental finding of a metastatic low-grade carcinoid tumor that is asymptomatic and hormonally nonfunctional consists of expectant observation and repeat imaging studies several times each year to determine whether the disease is progressing (see Item 135).
- Metastatic non–small cell lung cancer (stage IV) is not curable and treatment is palliative; the benefit of systemic therapy in this patient population is confined to those with adequate performance status.
- Patients with metastatic non–small cell lung cancer and adequate performance status should be treated with systemic therapy selected based on the pattern of metastatic spread and the results of histologic and molecular assessment.
- Patients with lung cancer and poor performance status do not benefit from chemotherapy and should undergo a palliative care assessment (see Item 138).
- Early palliative care has shown to improve symptom control and survival in patients with non–small cell lung cancer and associated poor performance status (see Item 149).
- In patients with prostate cancer, imaging studies to assess for possible metastatic disease or regional lymph node involvement are only indicated for men with poor-risk features (typically men with intermediate, high, or very high–risk cancer).
- Imaging studies are not indicated for men with newly diagnosed early-stage prostate cancer in the absence of symptoms or other high-risk features (see Item 107).
- Active surveillance, with the use of serum prostate-specific antigen measurement, digital rectal examination, and repeat prostate biopsy, is appropriate only for men with very low–risk or low-risk prostate cancer who have a life expectancy of at least 10 years.
- Observation is the appropriate management for an elderly man with newly diagnosed, low-risk prostate cancer and medical comorbidities that significantly limit life expectancy (see Item 132).
- Patients with small, soft, freely moveable lymph nodes that are limited to one or two adjacent sites and who have no other significant history or physical examination findings can be followed with serial examinations and require no laboratory studies or imaging.
- Patients with asymptomatic grade 1 and 2 follicular lymphoma should be observed and only treated when they become symptomatic; treatment is not curative and does not improve survival (see Item 102).
- The initial treatment of a patient with gastric mucosa-associated lymphoid tissue (MALT) lymphoma associated with *Helicobacter pylori* infection is antimicrobial therapy plus a proton pump inhibitor (see Item 121).
- Asymptomatic patients with low-stage chronic lymphocytic leukemia (stage 0 to II) can be observed without therapy for decades.
- The clinical evaluation in patients with cancer of unknown primary site should not involve an exhaustive search for a primary tumor because finding an asymptomatic and occult primary site does not improve outcome.
- In patients with cancer of unknown primary site, measurement of serum tumor marker levels, such as carcinoembryonic antigen, CA-19-9, CA-15-3, and CA-125, is rarely helpful and virtually never diagnostic.
- Although PET scans may sometimes suggest the location of a primary tumor, these findings are rarely definitive and do not improve long-term outcome in patients with cancer of unknown primary site.
- In the follow-up care of patients with melanoma, routine blood tests are not recommended, and the value of screening chest radiography, CT scanning, or PET/CT scanning is questionable.
- Hematopoietic growth factors, including granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, can decrease the severity and duration of neutropenia but due to expense and only modest effect on outcomes, they should be reserved for patients at high risk for neutropenia-associated infection.
- Platelet growth factors such as thrombopoietin are not considered standard therapeutic practice for patients with chemotherapy-induced thrombocytopenia and are reserved for those with immune-mediated thrombocytopenia.
- Close observation is the standard of care for patients following surgical resection for nonmetastatic renal cell carcinoma, as no studies to date have identified an adjuvant therapy that improves survival in these patients (see Item 115).
- Active surveillance is the recommended management strategy for patients with stage I seminoma diagnosed after radical inguinal orchiectomy; other options are adjuvant single-agent carboplatin or para-aortic lymph node irradiation (see Item 123).

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Hematology and Oncology

Hematopoietic Stem Cells and Their Disorders

Overview

Hematopoiesis is the orderly formation of all recognizable blood elements from a pluripotent stem cell in the bone marrow. Hematopoietic stem cells (HSCs) can self-renew and differentiate (**Figure 1**) but can also transdifferentiate into mesenchymal tissues. Hematopoietic growth factors, bone marrow stroma, and adequate nutrients are all key ingredients in normal blood production. Disorders of the blood may occur at the HSC level or with any of the more differentiated descendants such as the myeloid, lymphoid, or erythroid progenitors.

Pure red cell aplasia (PRCA) and isolated neutropenia often reflect the response of the blood to autoimmunity or viral infection. Similarly, isolated thrombocytopenia is rarely caused by bone marrow failure. Its mechanism usually involves peripheral consumption and immune-mediated causes. Pancytopenia, in contrast, indicates failure of the bone marrow or severe peripheral sequestration, most often associated with cirrhosis and hypersplenism.

Aplastic anemia and myelodysplastic syndrome (MDS) are contrasting marrow-failure disorders presenting with pancytopenia and very different findings within the bone marrow. The myeloproliferative neoplasms (MPNs) are clonal myeloid conditions in which blood production is deregulated and independent of hematopoietic growth factors.

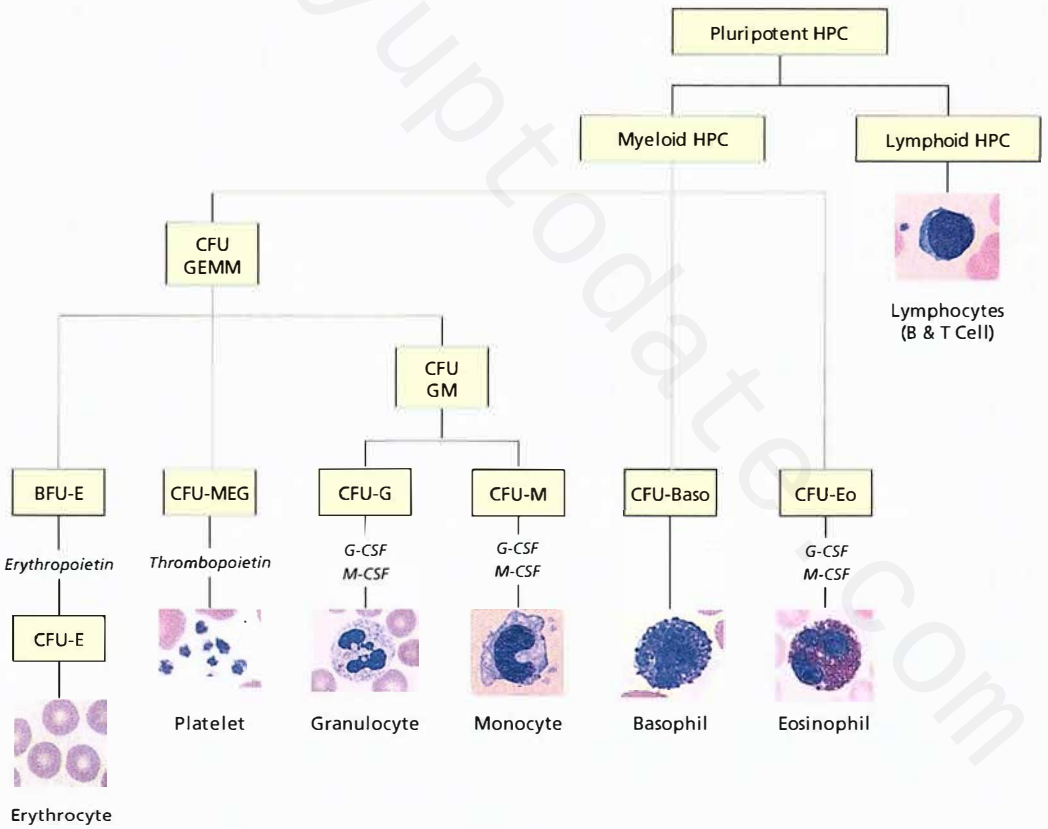

FIGURE 1. Regulation of hematopoiesis. The process of hematopoiesis is regulated by lineage-specific cytokines. These cytokines stimulate the proliferation and/or differentiation of pluripotent stem cells to committed mature peripheral blood cells. The pluripotent HPC is also known as an HSC.

BFU-E = burst-forming unit-erythrocyte; CFU-Baso = colony-forming unit-basophil; CFU-E = colony-forming unit-erythrocyte; CFU-Eo = colony-forming unit-eosinophil; CFU-G = colony-forming unit-granulocyte; CFU GEMM = colony-forming unit-granulocyte, erythrocyte, megakaryocyte, monocyte; CFU GM = colony-forming unit-granulocyte, monocyte; CFU-M = colony-forming unit-monocyte; CFU-MEG = colony-forming unit-megakaryocyte; G-CSF = granulocyte colony-stimulating factor; HPC = hematopoietic progenitor cell; M-CSF = macrophage colony-stimulating factor.

Cell images courtesy of Deepty Bhansali, MD; Baylor Scott & White Health.

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Acute leukemias of myeloblastic (AML) or lymphoblastic (ALL) origin can arise de novo or from a pre-existing MDS or MPN. They are often initially managed emergently. The clinical use of hematopoietic growth factors and HSC transplantation (HSCT) can be very helpful in the management of these diseases.

Bone Marrow Failure Syndromes

Aplastic Anemia

The normal adult bone marrow contains blood-making elements and fat in a ratio inversely related to age. Aplastic (without formation) anemia (AA) is a condition characterized by pancytopenia, with associated neutropenia, anemia, and thrombocytopenia, and a severely hypocellular bone marrow (<10%). Isolated cytopenias are uncommon despite the designation of anemia. The severity of the condition is defined by the degree of neutropenia, thrombocytopenia, or reticulocytopenia and has important implications for treatment and prognosis (**Table 1**). AA is usually acquired and is caused by toxic, viral, or autoimmune mechanisms.

Although many medications may cause dose-related suppression of the bone marrow, true AA is rare. Marrow suppression caused by NSAIDs, β-lactam antibiotics, antiepileptic drugs, and psychotropic medications will usually resolve with discontinuation of the medication. Finding a definitive medication or viral association with AA, however, is uncommon. Autoimmunity is the dominant cause of adult AA. Autoreactive T cells attack pluripotent HSCs and cause aplasia. Therefore, immunosuppression with cyclosporine and antithymocyte globulin is first-line therapy and leads to disease control in 70% of adult patients. Allogeneic HSCT is a potentially curative therapy and should be considered for those younger than 50 years who have compatible donors. Treatment with hematopoietic growth factors is ineffective.

AA, paroxysmal nocturnal hemoglobinuria (PNH), and MDS are all acquired defects of the HSC, so clinical overlap is considerable. PNH is an acquired disorder in which erythrocytes lack membrane proteins CD55 and CD59 required to stabilize complement, leading to episodic intravascular hemolysis (see Erythrocyte Disorders). Screening patients with AA reveals that up to 50% have erythrocytes lacking CD55 and CD59; however, this is usually without evidence of overt hemolysis or thrombosis. A hypoplastic variant of MDS exists that can be difficult to distinguish from AA. Clues indicating the former can include cytogenetic abnormalities or dysplastic hematopoietic cells in the marrow. Up to 10% of patients with AA will develop typical MDS or AML within 10 years.

KEY POINTS

- Immunosuppression with cyclosporine and antithymocyte globulin leads to disease control in 70% of adult patients with aplastic anemia.
- Allogeneic hematopoietic stem cell transplantation is a potentially curative therapy for aplastic anemia and should be considered for patients younger than 50 years who have compatible donors.
- Management of aplastic anemia with hematopoietic growth factors is ineffective. HVC

Pure Red Cell Aplasia

The cardinal clinical feature in PRCA is isolated, severe anemia without an adequate reticulocyte response. Examination of the bone marrow shows an absence of erythrocyte precursors. Known causes and associations of PRCA are listed in **Table 2**. Similar to AA, the mechanism of action is predominantly T cell autoimmunity (pregnancy, thymoma, malignancy) or direct toxicity to erythrocyte precursors (viral, medications).

In patients with chronic, compensated hemolytic anemia such as sickle cell anemia, parvovirus B19 infection can cause PRCA and a severe anemic crisis. Such patients rely on high levels of reticulocytosis and can lose all reserve with infection. Intravenous immune globulin (IVIG) may hasten viral clearance by providing adopted immunity to parvovirus and can be helpful in immunocompromised patients. Immunocompetent patients and those without chronic hemolytic anemia are less vulnerable to PRCA from this infection and may recover without IVIG.

Bone marrow examination is required to diagnose PRCA and is useful for excluding secondary causes such as chronic lymphocytic leukemia or other indolent non-Hodgkin

TABLE 1. Classification of Aplastic Anemia

Classification	Characteristics
Very severe aplastic anemia	ANC <200/μL (0.2×10^9/L)
Severe aplastic anemia	Two or more of the following: ANC 200-500/μL ($0.2\text{-}0.5 \times 10^9$/L) Platelet count <20,000/μL (20×10^9/L) Absolute reticulocyte count <40,000/μL (40×10^9/L)

ANC = absolute neutrophil count.

TABLE 2. Causes of Acquired Pure Red Cell Aplasia

Parvovirus B19 infection
Thymoma
Autoimmune disease
Lymphoid leukemias and lymphomas
Solid tumors
Drugs (phenytoin, isoniazid)
Pregnancy
Anti-EPO antibodies in patients receiving EPO

EPO = erythropoietin.

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CONT. lymphomas. Leukemias and lymphomas cause PRCA by immune-mediated mechanisms rather than direct ablation of erythrocyte precursors. A particular T-cell lymphoproliferative disorder, large granular lymphocytosis, can be associated with PRCA and is associated with rheumatoid arthritis in one third of patients. It is diagnosed by peripheral blood smear and lymphocyte CD57 positivity on flow cytometry. It can be treated with methotrexate and has clinical overlap with Felty syndrome, which is the clinical triad of rheumatoid arthritis, splenomegaly, and neutropenia. Thymoma is excluded by CT scan of the chest for patients in whom infectious or marrow-based causes are not apparent.

Idiopathic cases of PRCA are presumed to have an autoimmune cause and are treated primarily with immunosuppression. Prednisone, either administered alone or with cyclosporine or cyclophosphamide, can lead to improvement within 1 to 3 months.

KEY POINTS

- Diagnosis of pure red cell aplasia requires bone marrow examination, which can also exclude secondary causes such as lymphoproliferative disorders.
- Treatment of patients with idiopathic pure red cell aplasia primarily consists of immunosuppression, with prednisone as monotherapy or in combination with cyclosporine or cyclophosphamide, leading to improvement in 1 to 3 months.

Neutropenia

Isolated neutropenia usually has a hereditary, toxic, or immune cause. Patients of African and Middle Eastern heritage often have lower neutrophil counts with no clinical consequence. A large U.S. population-based study demonstrated that mild neutropenia (1000-1500/μL [1-1.5 × 10^9/L]) was present in about 4% of healthy black persons. Neutropenia of greater severity (500-1000/μL [0.5-1 × 10^9/L]) was seen in 1% of healthy persons. An absolute neutrophil count less than 500/μL (0.5 × 10^9/L) is less likely to be a normal variant and more likely to be associated with increased risk for bacterial and fungal infections.

Toxicity to neutrophil precursors can be caused by viral or bacterial infections or by medications. Acute HIV, cytomegalovirus, and Epstein-Barr virus infection may all lead to isolated neutropenia. Rickettsial infection or overwhelming bacterial infection can similarly manifest with isolated leukopenia as opposed to leukocytosis. Neutropenia is an expected toxicity of many cytotoxic chemotherapies. More common medications associated with neutropenia are NSAIDs, carbamazepine, phenytoin, propylthiouracil, cephalosporins, trimethoprim-sulfamethoxazole, and psychotropic drugs. Reactions to these agents tend to be idiosyncratic rather than dose dependent. Drug-induced neutropenia usually resolves with removal of the offending medication alone and is diagnosed by history, appropriate timing, and exclusion of other causes.

Immune-mediated neutropenia is frequently associated with connective tissue diseases such as systemic lupus erythematosus and rheumatoid arthritis. Treatment with antirheumatic drugs often alleviates neutropenia. Similar to PRCA, populations of large granular lymphocytes may be identified in clinically diagnosed Felty syndrome.

Neutropenia can be a presenting sign of nutritional deficiencies such as vitamin B_{12} or folate deficiency. Likewise, MDS may present with neutropenia in isolation, although both are much more likely to be associated with other cytopenias, especially anemia.

Therapy for neutropenia attempts first to correct the underlying cause. An offending drug can be removed and growth factor support with granulocyte colony-stimulating factor (G-CSF) can shorten the duration of neutropenia associated with chemotherapy. Viral infections are usually treated supportively. Immune-associated neutropenia related to frequent infections is treated with immunosuppressive therapy.

KEY POINT

- Drug-induced neutropenia, diagnosed by history, appropriate timing, and exclusion of other causes, usually resolves with removal of the offending medication.

The Myelodysplastic Syndromes

In distinction to AA, the dysplastic (difficult formation) marrow of MDS is most commonly hypercellular. A full bone marrow yields low blood counts because the cells are ineffectively formed and have limited survival. MDS can be associated with past radiation or chemotherapy exposure, but is more commonly a primary process. MDS ranges in severity from an asymptomatic disease characterized by mild normocytic or macrocytic anemia to a transfusion-dependent anemia heralding conversion to AML. The World Health Organization (WHO) classification of MDS and the frequency of each subtype are presented in **Table 3**.

The incidence of MDS increases with age. The diagnosis should be suspected in patients with macrocytic anemia or pancytopenia in whom vitamin B_{12} and folate deficiency have been excluded. Abnormal erythrocyte forms with basophilic stippling or Howell-Jolly bodies and dysplastic neutrophils with decreased nuclear segmentation and granulation may be present. Increased myeloblasts can be seen in more advanced disease. Diagnosis and prognosis require bone marrow biopsy and aspiration with cytogenetic studies. Many older adult patients have mild stable macrocytic anemia that probably represents mild MDS. These patients do not generally require consultation. The revised International Prognostic Scoring System (IPSS-R) presented in **Table 4** weighs percentage of marrow blasts, cytogenetics of the marrow, and peripheral blood cytopenias to assign prognosis and inform therapy.

Treatment has two goals. The first is to relieve transfusion dependence. Many patients with low-risk MDS require no treatment at all or infrequent transfusions. In 25% of

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TABLE 3. World Health Organization Classification of MDS

Category	Frequency	Marrow Blasts	Other Features
Refractory cytopenia with unilineage dysplasia	20%	<5%	Single cell line dysplasia (usually erythrocytes)
Refractory cytopenia with multilineage dysplasia	30%	<5%	Dysplasia in ≥2 lineages
MDS associated with isolated 5q−	Uncommon	<5%	Increased hypolobated megakaryocytes
Refractory anemia with ring sideroblasts	10%	<5%	Erythroid dysplasia, ≥15% ring sideroblasts
RAEB-1	40%	5%-9%	Unilineage or multilineage dysplasia
RAEB-2	40%	10%-19%	Unilineage or multilineage dysplasia
MDS, unclassified	Uncommon	<5%	Does not fit other categories

MDS = myelodysplastic syndrome; RAEB-1/2 = refractory anemia with excess blasts, type 1 or 2.

TABLE 4. International Prognostic Scoring System-Revised (IPSS-R) for Myelodysplastic Syndromes

Variable	Points						
	0	0.5	1	1.5	2	3	4
Bone marrow blasts (%)	<2		>2 to <5		5-10	>10	
Cytogenetics[a]	Very good		Good		Intermediate	Poor	Very poor
Hemoglobin (g/dL [g/L])	>10 (100)		8-10 (80-100)	<8 (80)			
Platelet count (cells/μL [x 10^9/L])	>100,000 (100)	50,000-100,000 (50-100)	<50,000 (50)				
ANC (cells/μL [x 10^9/L])	>800 (0.8)	<800 (0.8)					

Risk Group	IPSS-R Score	Median Survival (yrs)
Very low	≤1.5	8.8
Low	>1.5-3	5.3
Intermediate	>3-4.5	3
High	>4.5-6	1.6
Very high	>6	0.8

ANC = absolute neutrophil count.

[a]Cytogenetics: Very good: -Y, del 11q. Good: Normal, del(5q), del(12p), del(20q) Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones. Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities. Very poor: Complex: >3 abnormalities.

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CONT.

patients needing more frequent transfusions, erythropoiesis-stimulating agents (ESAs) can decrease transfusion burden. The second goal of therapy is to prevent transformation to AML, a complication that is uniformly resistant to treatment and associated with short survival. In reviewing the IPSS-R, it is apparent that a patient with complex cytogenetics and a marrow blast count of greater than 10% has a median time to AML progression and death of less than 1 year. Patients considered high or very high risk by IPSS-R criteria require treatment at diagnosis. Therapies include allogeneic HSCT in fit younger patients with a compatible donor or hypomethylating chemotherapy such as azacytidine and decitabine. Both agents can reduce transfusion requirements and delay transformation to AML. However, both also worsen blood counts initially and may take up to 6 months to show an effect. Transfusion support and antibiotics for infection are required until an effect or lack thereof is apparent.

KEY POINTS

- Diagnosis and prognosis of myelodysplastic syndrome require bone marrow biopsy and aspiration with cytogenetic studies.
- Many patients with low-risk myelodysplastic syndrome require no treatment at all or infrequent transfusions.

HVC

Myeloproliferative Neoplasms

The MPNs are caused by acquired genetic defects in myeloid stem cells and are characterized by deregulated production of leukocytes, erythrocytes, or platelets. Although each disorder

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is named according to the dominant cell line affected, all can cause an elevation in several cell lines. The MPNs may present with unusual thromboses, massive splenomegaly, or constitutional symptoms such as fever, chills, weight loss, and drenching night sweats. Each has a chronic phase that may progress at varying frequency to AML. For this reason, MPNs are considered myeloid neoplasms, albeit with widely varying prognoses. Long-standing MPNs can also cause secondary fibrosis of the bone marrow, likely as a result of fibroblasts responding to activated HSC growth factors.

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) remains the classic MPN with regard to pathophysiology, diagnosis, and targeted therapy. CML may be diagnosed incidentally on a complete blood count (CBC) obtained for another reason or based on the constitutional symptoms and splenomegaly shared by other MPNs. Granulocytic leukocytosis is present on CBC, and earlier myeloid forms such as metamyelocytes, myelocytes, and less than 5% blasts are present on peripheral blood smear review (**Figure 2**). Eosinophilia or basophilia may also be present. The main indicator for extreme granulocytic leukocytosis (leukocyte count >50,000/μL [50 × 10^9/L]) is the leukemoid reaction. When sepsis occurs, the bone marrow responds by releasing early cells into circulation, and a leukemoid reaction may be difficult to distinguish from CML in an acutely ill patient. However, very few patients with typical sepsis, even gram-negative bacillary bacteremia, develop such counts. *Clostridium difficile* is the most common hospital-based cause. Blasts and basophils are much less likely with a leukemoid reaction.

CML is caused by the Philadelphia chromosome, an acquired translocation of chromosomes 9 and 22 [t(9;22)] in an HSC, that leads to development of a fusion gene called *BCR-ABL*. The *BCR-ABL* gene encodes a mutant, activated tyrosine kinase that leads to constant downstream proliferative signaling. Discovery of the Philadelphia chromosome in 1960 was the first example of a cancer having a defining molecular event. The t(9;22) is both necessary and sufficient for diagnosing CML. The presence of *BCR-ABL* and t(9;22) may be verified in less than 24 hours with reverse transcriptase polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH), respectively, performed on peripheral blood. Standard cytogenetic studies by karyotype take several days to complete but are able to reveal more complex cytogenetic abnormalities that may influence prognosis.

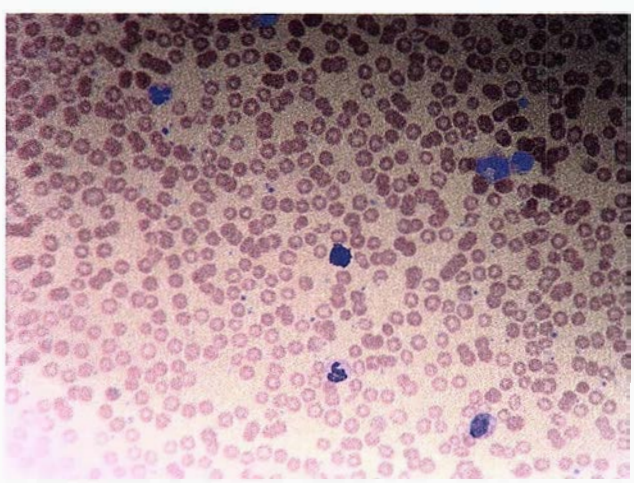

FIGURE 2. Chronic myeloid leukemia is characterized by a preponderance of mature granulocytes (*upper left*) as well as less mature myeloid cells such as myelocytes (*bottom right*) and metamyelocytes (*top right*). Basophils (*center*) are helpful in differentiating the myeloproliferative neoplasms from reactive processes.

Figure courtesy of Deepty Bhansali, MD; Baylor Scott & White Health.

CML is usually diagnosed in the chronic phase. Therapy is required at diagnosis, as opposed to management of essential thrombocytosis (ET) and primary myelofibrosis (PMF) in which observation for patients with minimal symptoms may be appropriate. CML can enter a transitional accelerated phase or progress to an overt blast crisis, which is a secondary form of acute leukemia. Of the acute leukemias arising from CML, 80% are myeloid (AML) and 20% are lymphoid (ALL). Both types harbor the *BCR-ABL* mutation. Effective therapy has made accelerated phase and blast crisis transformation of CML less common.

Tyrosine kinase inhibitors (TKIs) target the protein product of the *BCR-ABL* gene, decreasing tumor cell proliferation; imatinib was the first-in-class drug of this type. TKI therapy revolutionized CML treatment, but also heralded a host of specific inhibitors to come in the next decade, many as a result of the Human Genome Project. Before 2000, the 8-year overall survival for CML diagnosed in the chronic phase was approximately 50%. Since 2001, this number has increased to 87%. Allogeneic HSCT for CML is now rare.

Either imatinib or second-generation TKIs such as nilotinib or dasatinib may be used as first-line therapy. Although second-generation agents lead to quicker molecular remission, they have not been demonstrated to improve overall survival. All TKIs can prolong the QT interval, and careful attention to drug interactions and periodic electrocardiographic monitoring are recommended. Dasatinib has a unique association with pericardial and pleural effusions and has been more recently associated with pulmonary arterial hypertension. No TKI is considered safe in pregnancy. Therapeutic options include close observation without therapy or interferon alfa.

Progression of CML is usually a result of medication nonadherence or mutation of the BCR-ABL tyrosine kinase that causes resistance to TKI therapy. A new TKI, ponatinib, which overcomes some resistance to previous TKIs, was recently FDA approved. However, ponatinib has been associated with severe thromboembolic complications and requires strict safety measures mandated by the FDA in its approval.

All commercially available TKIs for the treatment of CML cost approximately $100,000/year. Multidisciplinary support, including social work, is required to help patients obtain the treatment. The benefit of these medications is that a uniformly

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fatal disease has been transformed into a chronic illness with modest toxicity.

KEY POINTS

- Chronic myeloid leukemia may be diagnosed by detection of the (9;22) gene translocation using reverse transcriptase polymerase chain reaction or fluorescence in situ hybridization performed on peripheral blood.
- Initial and subsequent therapy for chronic myeloid leukemia centers on tyrosine kinase inhibitors that target the BCR-ABL protein.
- All tyrosine kinase inhibitors can prolong the QT interval, and careful attention to drug interactions and periodic electrocardiographic monitoring are recommended.

Polycythemia Vera

Polycythemia vera (PV) is a disorder of the myeloid/erythroid stem cell that causes erythropoietin-independent proliferation of erythrocytes. Analogous to the Philadelphia chromosome in CML, an activating mutation of *JAK2* (*JAK2 V617F*) is present in 97% of PV. PV is suspected with a hemoglobin level greater than 18.5 g/dL (185 g/L) in men or greater than 16.5 g/dL (165 g/L) in women after secondary causes are excluded. Activation of *JAK2* has been implicated in the thrombotic risk of PV, but the mechanism is not completely understood. Erythrocyte elevations secondary to other causes must be excluded to implicate PV. Most causes of secondary erythrocytosis share the mechanism of an elevated erythropoietin level. Most commonly, this is driven by hypoxemia, but can be due to ectopic production of growth factor. **Table 5** compares and contrasts the primary and secondary causes of erythrocytosis with regard to symptoms and examination and laboratory findings.

The clinical features that help differentiate secondary erythrocytosis from the MPNs include pruritus after a warm bath or shower; intermittent heat, redness, and pain of the palms and soles (erythromelalgia); hepatosplenomegaly; a concomitant elevation of the leukocyte and platelet counts; and a propensity for unusual thromboses. Basophilia is a strong predictor of PV instead of a reactive state. Elevated serum vitamin B_{12} levels, caused by increased levels of transcobalamin III produced in proliferating leukocytes, and hyperuricemia as a consequence of DNA turnover in the marrow are classic for PV. A rational evaluation begins with a consideration of the clinical features of secondary erythrocytosis. Pulse oximetry should be conducted with ambient air as well as palpation of the abdomen to detect splenomegaly. Review of the peripheral blood smear is required to evaluate the presence of basophils or immature myeloid forms. Determination of serum erythropoietin level and JAK2 will

TABLE 5. Causes of Secondary Erythrocytosis

Disorders	Symptoms	Physical Examination	Laboratory Studies
Polycythemia vera (primary)	Pruritus after a warm shower Erythromelalgia Transient ischemic attack Deep venous thrombosis/pulmonary embolism	Splenomegaly Plethora	Low erythropoietin Basophilia Leukocytosis Thrombocytosis *JAK2* positive
Mediated by hypoxemia COPD Sleep apnea Congenital heart disease Intrapulmonary shunting Elevated altitude Renal artery stenosis	Thrombosis Transient ischemic attack Erythromelalgia unlikely Pruritus unlikely	Plethora No splenomegaly	High erythropoietin No basophilia No leukocytosis *JAK2* negative
Mediated by ectopic or excessive erythropoietin Renal cell carcinoma Hepatocellular carcinoma Uterine fibroids	Thrombosis possible Transient ischemic attack unlikely Erythromelalgia unlikely Pruritus unlikely	Plethora No splenomegaly	High erythropoietin Microscopic hematuria No basophilia Leukocytosis possible *JAK2* negative
Unusual causes High oxygen affinity hemoglobin	Thrombosis Transient ischemic attack Erythromelalgia unlikely Pruritus unlikely	Plethora No splenomegaly	High erythropoietin No basophilia No leukocytosis *JAK2* negative

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complete the evaluation and lead to a diagnosis in most patients. A patient with no apparent cause for secondary erythrocytosis and a low or undetectable erythropoietin level likely has PV. The *JAK2* mutation confirms the diagnosis.

PV may be diagnosed in the latent phase, proliferative phase, or, more rarely, the spent phase that mimics PMF. The latent phase may present with symptoms of erythrocytosis but does not pose the same thrombotic risks as the proliferative phase. Unusual clots, especially portal or splanchnic clots, are classic for MPNs in general and PV specifically. Diagnosis of hepatic vein thrombosis (the Budd-Chiari syndrome) or portal vein thrombosis should prompt consideration of PV. Interestingly, in approximately 50% of young women taking oral contraceptive pills who develop Budd-Chiari syndrome, the *JAK2* mutation is present without other features of MPN.

As with CML, therapy for PV is required at diagnosis. Low-dose aspirin (<100 mg/d) decreases arterial and venous clot risk in PV and should be initiated unless strong contraindications exist. Phlebotomy is the mainstay of therapy and may be safely applied in addition to aspirin in patients younger than 60 years without a previous thromboembolic event. The goal of phlebotomy is to attain a hematocrit level of less than 45%. This may be achieved by weekly phlebotomy and may be maintained with intermittent treatments. Hydroxyurea, an antimetabolite chemotherapeutic agent, can be used in conjunction with phlebotomy in patients older than 60 years or those with previous thromboembolic events. Use of hydroxyurea decreases thrombotic risk independently of its effect on lowering hemoglobin.

PV may remain stable with therapy (70%), enter a spent or burned out phase (20%), or evolve into secondary AML (10%). In the spent phase, secondary fibrosis occurs in the bone marrow and extramedullary hematopoiesis leads to progressive splenic and hepatic enlargement. A patient with decreasing phlebotomy or hydroxyurea requirements and increasing splenomegaly may be entering this fibrotic stage. A leukoerythroblastic blood smear (teardrop cells, nucleated erythrocytes, and immature myeloid forms) similar to that seen with PMF and other myelophthisic processes that displace normal marrow elements will result (**Figure 3**).

KEY POINTS

- The evaluation of erythrocytosis includes pulse oximetry, examination of the peripheral blood smear, measurement of the serum erythropoietin level, and evaluation for *JAK2* mutation.
- Low-dose aspirin and phlebotomy comprise initial therapy for most patients with polycythemia vera; hydroxyurea can be combined with phlebotomy for patients older than 60 years or those with a higher risk of thromboembolism.

Essential Thrombocythemia

Essential thrombocythemia (ET) is suspected when a platelet count of greater than 600,000/μL (600×10^9/L) is detected on two occasions at least 1 month apart in the absence of secondary causes. Iron deficiency anemia is the most common cause of secondary thrombocytosis followed by reactive states due to infection or inflammation. The *JAK2* mutation is present in 50% of patients with ET, so a negative test does not exclude the diagnosis. The Philadelphia chromosome must also be excluded, because CML may present with thrombocytosis alone.

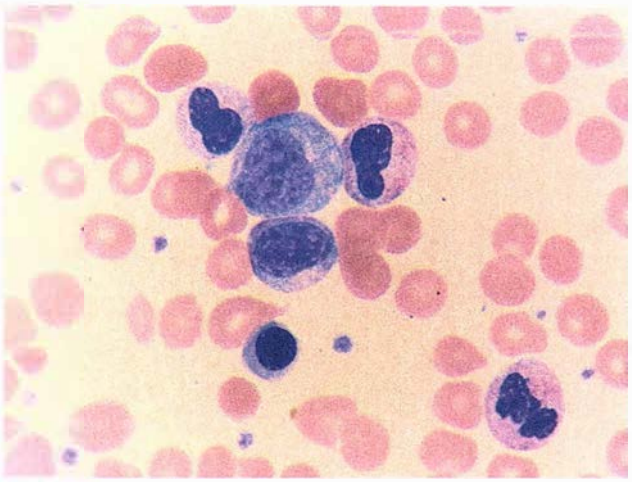

FIGURE 3. Leukoerythroblastic blood smear. Left-shifted granulopoiesis and nucleated and teardrop-shaped erythrocytes define a crowded myelophthisic marrow such as is seen in primary myelofibrosis or other secondary processes such as metastatic carcinoma.

Most patients will be asymptomatic, but symptoms from digital ischemia, erythromelalgia, transient ischemic attack, visual disturbances, venous thromboembolism, or bleeding (due to dysfunctional platelets) may be present. In contrast to CML and PV, many patients with ET may be observed. By using the International Prognostic Score for ET (**Table 6**) and other observations from large series, patients at low risk may be defined as meeting all these criteria: younger than 60 years, no previous thrombosis, and leukocyte count less than 11,000/μL (11×10^9/L). Such patients may be safely observed without platelet-lowering therapy. Low-dose aspirin does not increase bleeding risk in such patients and does reduce erythromelalgia.

Platelet-lowering therapy is indicated for any patient at high risk. Hydroxyurea was compared with anagrelide, an agent that inhibits megakaryocyte budding, and was found to be superior in preventing thrombosis and bleeding regardless of platelet count achieved. Anagrelide may cause fluid retention and exacerbation of chronic heart failure. By contrast, hydroxyurea is well tolerated in older adult patients and is considered first-line therapy for nonpregnant patients. Interferon alfa is the only platelet-lowering agent safe in pregnancy. Plateletpheresis may be employed emergently to temporarily decrease platelet counts in symptomatic patients with extreme thrombocytosis (generally greater than 1,000,000/μL [1000×10^9/L]).

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TABLE 6. International Prognostic Score for Essential Thrombocytosis

Factor	Points
Age ≥60 years	2
Leukocyte count >11,000/μL (11×10^9/L)	1
History of thrombosis	1

Applying Score to Prognosis

Score	Median Overall Survival	10-Year Thrombosis-free Survival
0 — Low Risk	Not reached	89%
1 or 2 — Intermediate Risk	24.5 years	84%
3 or 4 — High Risk	13.8 years	69%

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ET is the least likely MPN to progress to AML or secondary fibrosis, and the least likely to present with symptomatic splenomegaly or constitutional symptoms.

KEY POINT

HVC
- Observation alone is safe for patients with essential thrombocythemia at low risk for thromboembolic complications, whereas platelet-lowering therapy is indicated for patients at high risk.

Primary Myelofibrosis

PMF is an MPN that does not present with a dominant blood count elevation. Rather, it is a clonal myeloid disorder characterized by abnormal, proliferating megakaryocytes that produce excess fibroblast growth factor. This causes marrow fibrosis and leads to extramedullary hematopoiesis. The classic leukoerythroblastic peripheral blood smear of PMF is not distinguishable from fibrosis of secondary cause or myelophthisic processes of different origin (see Figure 3). An attempt at bone marrow aspiration in PMF is often described as a "dry tap." Markers of increased cell turnover such as lactate dehydrogenase and uric acid are frequently elevated. The *JAK2* mutation is present in 50% of patients.

Sites of extramedullary hematopoiesis, caused as HSCs seek refuge from a fibrotic marrow, include the spine or lymph nodes. Cytokine-mediated symptoms such as fever, chills, night sweats, and malaise may predominate in PMF. Early satiety, weight loss, and abdominal discomfort from splenomegaly are also common, because the splenomegaly may be massive, with the spleen descending to the pelvic brim.

Although the presentation of PMF may be dramatic, it can also be indolent. Initial and sometimes prolonged observation is possible. Treatment is required for symptomatic splenomegaly, worsening cytopenias, and constitutional symptoms. With the exception of allogeneic HSCT, which can be applied in younger patients, treatment is palliative. Splenectomy in PMF is a perilous procedure with a higher risk of complication and death than expected from other indications.

Hydroxyurea may be used to alleviate splenomegaly and constitutional symptoms. The first JAK2 inhibitor, ruxolitinib, has demonstrated an ability to relieve symptoms in PMF. Risk of thrombosis and AML conversion are not affected. Interestingly, palliative benefit is independent of *JAK2* mutation. It is most effective in patients with severe symptoms and may yield relief of constitutional symptoms and a 33% reduction in spleen volume. Ruxolitinib has not been found effective in the treatment of PV or ET.

KEY POINT

- With the exception of allogeneic hematopoietic stem cell transplantation, which can be applied in younger patients, treatment for primary myelofibrosis is palliative.

Eosinophilia and Hypereosinophilic Syndromes

The general differential diagnosis of eosinophilia has long been described by the mnemonic CHINA (**Table 7**). A careful history, including current and past medications, and a physical examination, including dermatologic and lymphatic assessment, are critical for evaluation of atopy, asthma, and malignancy. Helminthic infections are common causes of eosinophilia around the world; they are less common within the United States, but coccidioidomycosis is endemic in much of the country. *Strongyloides* is well described in the evaluation of chronic diarrhea associated with eosinophilia.

Hypereosinophilic syndromes (HESs) are diseases characterized by eosinophilia with a count greater than 1500/μL (1.5×10^9/L) and eosinophilic infiltrates of the tissues (skin, lungs, heart, liver, spleen, lymph nodes) resulting in organ damage in addition to systemic symptoms such as fever, chills, night sweats, and weight loss. HES may be primary or have a reactive cause. Primary, or neoplastic, HES is characterized as an MPN with molecular activation of platelet-derived growth factor receptor (PDGFR) α or β or without a known stimulating factor. Reactive, or secondary, HES results from polyclonal expansion in response to an identified stimulus such as a parasitic infection.

TABLE 7. Causes of Eosinophilia

C	Collagen vascular disease (eosinophilic granulomatosis with polyangiitis [formerly known as Churg-Strauss syndrome])
H	Helminthic (parasitic worm) infection (*Strongyloides*)
I	Idiopathic hypereosinophilic syndrome (cause unknown after extensive evaluation)
N	Neoplasia (lymphomas most common)
A	Allergy, atopy, asthma (also drug induced: carbamazepine, sulfonamides)

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Glucocorticoids have a dramatic lytic effect on peripheral and tissue eosinophils, but long-term use in patients with HES is problematic. Likewise, steroid-refractory HESs are common; for those with activating mutations of PDGFR α or β, imatinib leads to durable and dramatic responses.

KEY POINT

- Glucocorticoids have a dramatic lytic effect on peripheral and tissue eosinophils, and imatinib leads to durable and dramatic responses in steroid-refractory primary hypereosinophilic syndrome with activation mutations of platelet-derived growth factor receptors α or β.

Acute Leukemias

Acute Myeloid Leukemia

AML is an acquired, malignant HSC disorder that may manifest de novo or arise from preceding MDS or MPN. Age is the greatest risk factor, with a mean age at presentation of 67 years. Leukemic blasts divide on an hourly basis, and the typical patient becomes ill over days to weeks. Diagnosis requires 20% or more myeloblasts in either the peripheral blood or the marrow. Symptoms of anemia, thrombocytopenia, and neutropenia prevail. In adults, 90% of acute leukemia is myeloblastic and 10% is lymphoblastic. The incidence reverses for children and adolescents. Within the first 24 hours of a suspected acute leukemia, a few key decisions must be made (**Table 8**). In practice, urgent consultation with a hematologist and pathologist is required when acute leukemia is suspected. For patients with greater than 50,000 circulating myeloid blasts, a hyperleukocytosis syndrome including hypoxemia and mental status changes can be caused by stasis of the immature cells in small capillary networks. Removal of the cells by leukapheresis is a life-saving, but temporizing, measure until specific chemotherapy is administered.

Especially in older patients, leukemia may present with pancytopenia rather than with leukocytosis and circulating blasts. Bone marrow examination will demonstrate a hypercellular marrow with 20% or more blasts. Underlying dysplasia may be assessed in other cell lines as a clue to the primary or secondary nature of the process. The greatest influence on survival in AML is the genetic profile of the leukemic cells. Traditional risk factors and the modifications provided by newer molecular markers are presented in **Table 9**.

A type of AML, acute promyelocytic leukemia (APL), must be quickly recognized and promptly treated. Disseminated intravascular coagulation is the defining clinical clue to this subtype of AML characterized by t(15;17). All-*trans* retinoic acid (ATRA) allows prompt resolution of disseminated intravascular coagulation and is the backbone of specific therapy. Recently, ATRA in combination with arsenic trioxide (ATO) was found to be equivalent to ATRA plus chemotherapy in low- to intermediate-risk APL. This non–chemotherapy-containing regimen may be safely administered to older patients with the intention of cure. ATRA and ATO can cause a differentiation syndrome characterized by hypoxemia, pulmonary infiltrates, and fever. Prompt initiation of glucocorticoids and brief interruption of the medications are effective in treatment. Monitoring for QT prolongation and careful attention to drug interactions are required with ATO usage.

TABLE 8. Acute Leukemia Decisions

Task	Method
Suspected Acute Leukemia: Early Decisions[a]	
Confirm acute leukemia	Exclude leukemoid reaction, atypical monocytosis, and chronic leukemias: peripheral blood smear review, flow cytometry
AML vs. ALL	Auer rod on blood smear suggests AML, confirmed with flow cytometry; different treatment paths
Exclude APL	Clinically suspected with DIC, classically with promyelocytes and prominent Auer rods, microgranular variant evaluated by flow cytometry (within 24 hours is ideal, but not possible at all institutions), FISH for t(15;17). Administer ATRA if suspected; do not await confirmation.
AML — not APL	Begin induction therapy with cytosine arabinoside and an anthracycline
ALL	Philadelphia chromosome positivity or negativity (determination within 24 hours is ideal, but not possible at all institutions) decides TKI therapy during induction; adolescents/young adults benefit from more intensive pediatric regimens
Acute Leukemia: Later Decisions	
Allogeneic HSC consolidation	Based on fitness of patient and risk of leukemia, predominantly determined by cytogenetic and molecular risk profile
Chemotherapy consolidation	Lower risk leukemia, older or less fit patient

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; APL = acute promyelocytic leukemia; ATRA = all-*trans* retinoic acid; DIC = disseminated intravascular coagulation; FISH = fluorescence in situ hybridization; HSC = hematopoietic stem cell; TKI = tyrosine kinase inhibitor.

[a]Consultation with an experienced hematologist is recommended in early determinations of suspected acute leukemia.

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TABLE 9. Acute Myeloid Leukemia Genetic Risk Profile and Effect on 5-Year Survival

Cytogenetic Category	Age ≤55 Years	Age >55 Years
Favorable t(8;21), inv(16), t(15;17)	65%	34%
Intermediate neither favorable nor high	41%	13%
High complex (≥5 abnormalities), -5,-7,del(5q), 3q abnormal	14%	2%

Molecular modifications to traditional risk profile: Favorable: *c-kit* mutation worsens prognosis of t(8;21) and inv(16); Intermediate: *Flt3* internal tandem duplication mutation worsens prognosis; Intermediate: *NPM1* mutation improves prognosis.

Non-APL AML is treated with a 7-day course of cytarabine and a 3-day course of an anthracycline in fit patients. Patients older than 70 years or ill younger adults do not tolerate this therapy well. A less toxic alternative for older patients is a hypomethylating agent such as azacitidine or decitabine administered on an outpatient basis with transfusion support. Less fit older patients are best served by palliative care.

KEY POINT

- Disseminated intravascular coagulation is the defining clinical clue to promyelocytic leukemia characterized by t(15;17), and all-*trans* retinoic acid allows prompt resolution of disseminated intravascular coagulation.

Acute Lymphoblastic Leukemia

ALL is less common in adult patients. The clinical presentation is similar to AML, although in contrast, frequent involvement of the central nervous system requires staging by cerebrospinal fluid analysis and prophylaxis with intrathecal chemotherapy. The presence of 25% lymphoblasts in the blood or bone marrow defines the diagnosis. Lymphoid blasts are usually terminal deoxynucleotidyl transferase positive and myeloperoxidase negative. Like AML, risk stratification in ALL relies on clinical and cytogenetic factors. Predictors of poor outcome include advanced age, B-cell versus T-cell disease, more than 30,000 blasts at diagnosis, and poor-risk cytogenetics. *MLL* gene rearrangement and hypodiploidy are adverse risk factors. The Philadelphia chromosome, t(9;22), also portends a poor prognosis, but now offers an attractive target to the TKI dasatinib. This is especially true in older patients in whom traditional chemotherapy is more toxic and less effective.

Young adults, up to the age of 30 years, have better results if they are treated with intensive pediatric regimens containing asparaginase. Therapy for ALL involves induction, intensification, and up to 2 years of maintenance therapy. Alternatively, for fit patients with high-risk disease, allogeneic HSCT can be used to consolidate remission. Overall prognosis for adults with ALL is poor, with 30% to 40% of patients cured by chemotherapy-based approaches.

KEY POINTS

- Otherwise healthy patients with high-risk acute lymphoblastic leukemia can be treated with allogeneic hematopoietic stem cell transplantation to consolidate remission.
- Patients with Philadelphia chromosome–positive acute lymphoblastic leukemia can be treated with the tyrosine kinase inhibitor, dasatinib.

Hematopoietic Growth Factors

At each stage of hematopoietic development, cytokine growth factors stimulate production of mature blood cells. Two recombinant growth factors are in common clinical use. G-CSF is used to stimulate production of neutrophils in autoimmune neutropenia, to hasten neutrophil recovery after cytotoxic chemotherapy, and for HSC mobilization. In the more common chemotherapy regimen, it is usually administered in a pegylated formulation that has activity for several weeks.

Recombinant erythropoietin, an ESA, is indicated for treatment of anemia of chronic kidney disease in the dialysis or predialysis population if iron, vitamin B_{12}, and folate levels are replete. Targets before treatment include transferrin saturation greater than 20% and serum ferritin level greater than 100 ng/mL (100 µg/L). Erythropoietin can lead to arterial and venous thrombosis when normal hemoglobin levels are reached. Current guidelines for use in anemia of chronic kidney disease target a hemoglobin level of no more than 11 g/dL (110 g/L).

Another indication for erythropoietin is to hasten recovery in chemotherapy-associated anemia. In several clinical trials using erythropoietin during potentially curative chemotherapy, overall mortality worsened as higher hemoglobin levels were obtained. Current guidelines allow initiation of erythropoietin for chemotherapy-associated anemia for symptomatic anemia with an initial hemoglobin level less than 10 g/dL (100 g/L) only in noncurative regimens. In practice, judicious transfusion may be preferable. Erythropoietin is also used in MDS to reduce transfusion requirements.

KEY POINTS

- Granulocyte colony-stimulating factor is used to stimulate production of neutrophils in autoimmune neutropenia and to hasten neutrophil recovery after cytotoxic chemotherapy.
- Recombinant erythropoietin is indicated for treatment of anemia of chronic kidney disease if iron, vitamin B_{12}, and folate levels are replete and to hasten recovery in chemotherapy-associated anemia.

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Hematopoietic Stem Cell Transplantation

In theory, allogeneic HSCT can cure any benign or malignant bone marrow failure syndrome. On the level of case series, this is true. In practice, allogeneic HSCT is most helpful in treating AA, high-risk MDS, and acute leukemias. In an allogeneic HSCT, an HLA-matched sibling or matched unrelated donor undergoes HSC collection by apheresis after G-CSF mobilization.

Patients undergoing allogeneic HSCT are immunosuppressed to allow donor HSCs to engraft. Unlike solid organ transplants, this immunosuppression can be tapered over 3 months to 1 year. Chemotherapy preceding modern allogeneic HSCT is generally less intense (reduced intensity conditioning), which has led to decreased short-term morbidity and mortality. HSCs from the donor (graft) are infused by peripheral blood and begin to proliferate in the patient (host). Cure of many bone marrow disorders is possible with this therapy because the blood and immune system of the donor replace that of the patient. Donor immune cells recognize the patient's cancer cells as foreign and mount a T-cell/NK-cell–mediated attack. This is referred to as a graft-versus-leukemia effect and is the goal of HSCT.

Opportunistic infection and graft-versus-host disease (GVHD) are major risks to allogeneic transplantation. Common bacterial infections, viral infections with cytomegalovirus or varicella-zoster virus, and invasive fungal disease such as aspergillosis are common. Infectious morbidity has decreased with improved methods to detect and treat such infections. Acute GVHD occurs when graft T cells recognize the patient's normal gut, skin, and liver sinusoids as foreign. Severe GVHD is life threatening and is treated with high-dose glucocorticoids. Varying second-line immunosuppressants are used for steroid-refractory disease but none have emerged as superior. Therapy for GVHD can be tapered as the disease burns out, generally after 1 year of treatment. With improved supportive care, outcomes with unrelated donor transplants have approached those of sibling transplants. Despite risks of infection and GVHD, the primary cause of mortality after HSCT for malignant disease is relapse of the original disease.

KEY POINTS

- Allogeneic hematopoietic stem cell transplantation is most helpful in treating aplastic anemia, high-risk myelodysplastic syndrome, and acute leukemias.
- Life-threatening acute graft-versus-host disease occurs when graft T cells recognize the patient's normal gut, skin, and liver sinusoids as foreign; treatment is high-dose glucocorticoids.

Multiple Myeloma and Related Disorders

Overview

Plasma cell dyscrasias (PCDs) are clonal plasma or lymphoplasmacytic cell disorders characterized by the production of monoclonal antibody (M protein) detectable in the serum or urine (**Table 10**). PCDs produce an M protein consisting of a heavy chain (IgG, IgA, IgD, or IgM) complexed with a κ or λ light chain or of κ or λ free light chains (FLCs) without a heavy chain component. These disorders may be asymptomatic. Alternatively, pathogenic antibodies or proliferation of the abnormal clone may produce clinical manifestations that require treatment.

Evaluation for Monoclonal Gammopathies

Monoclonal gammopathy of undetermined significance (MGUS) is common and usually does not evolve into a condition requiring treatment. Therefore, testing should be restricted to situations in which a symptomatic PCD requiring intervention or an asymptomatic PCD at high risk of progression to a clinically symptomatic condition is suspected. PCDs are more common with advancing age, and other common diseases may share similar clinical features. **Table 11** outlines appropriate clinical scenarios for testing.

TABLE 10. Disorders Associated with Monoclonal Gammopathies

Plasma Cell Disorders
Monoclonal gammopathy of undetermined significance[a]
Multiple myeloma
Immunoglobulin light-chain (AL) amyloidosis
Monoclonal immunoglobulin deposition disease
Proximal tubulopathy (with or without Fanconi syndrome)
Solitary plasmacytoma
Solitary plasmacytoma of bone
Solitary extramedullary plasmacytoma
POEMS syndrome[b]/Osteosclerotic myeloma
B-cell Disorders
Waldenström macroglobulinemia/lymphoplasmacytic lymphoma
Marginal zone lymphoma
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Heavy chain disease

[a]Many diseases may be associated with monoclonocal gammopathy of undetermined significance, including but not limited to connective tissue diseases, hepatitis C, HIV, cryoglobulinemia, and cold agglutinin disease.

[b]Polyneuropathy, Organomegaly, Endocrinopathy, presence of M protein, and Skin changes.

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TABLE 11. Common Clinical Scenarios for Consideration of Plasma Cell Dyscrasia Testing[a]

Clinical Scenario	Disease Considerations	Disease Characteristics	Associated PCDs/ Lymphoproliferative Disorders	Additional Investigative Evaluation[b]
Lytic bone lesions or hypercalcemia	MM	Osteolytic bone lesions, PTH-independent hypercalcemia	MM	Standard investigative evaluation
Age-inappropriate bone loss[c]	MGUS, MM	Osteopenia or osteoporosis with or without associated fractures	MGUS, MM	Standard investigative evaluation
Peripheral neuropathy	AL amyloidosis	Sensorimotor axonal polyneuropathy	MGUS, MM, WM (rare)	Tissue aspirate/biopsy for amyloid
	POEMS syndrome	Sensorimotor inflammatory demyelinating polyneuropathy, hepatosplenomegaly, endocrinopathies (hypogonadism, adrenal insufficiency), hyperpigmentation, hypertrichosis, multicentric Castleman disease, osteosclerotic bone lesions	MGUS, MM, solitary plasmacytoma of bone	VEGF, endocrine evaluation (e.g., testosterone level)
	Anti-MAG neuropathy	Sensory demyelinating polyneuropathy	IgM MGUS, WM	Anti-MAG antibodies
	Cryoglobulinemic vasculitis	Sensory or sensorimotor polyneuropathy, mononeuropathy multiplex	MGUS, MM, B-cell non-Hodgkin lymphoma (e.g., WM)	Cryoglobulins, complement levels
Kidney disease	Cast nephropathy	Acute kidney injury, nonalbumin proteinuria (monoclonal FLCs), bland urine sediment	MM	Kidney biopsy
	AL amyloidosis	Nephrotic syndrome	MGUS, MM	Tissue aspirate/biopsy for amyloid
	MIDD	Proteinuria (sometimes nephrotic range), acute kidney impairment, hepatomegaly/impairment (rare), cardiomyopathy (rare)	MGUS, MM	Kidney biopsy
	Proximal tubulopathy +/– Fanconi syndrome	Normal anion gap, hyperchloremic metabolic acidosis, hypophosphatemia, hypouricemia, renal glucosuria, amino aciduria	MGUS, MM	Kidney biopsy, serum phosphorus and uric acid, urinalysis
	Cryoglobulinemic vasculitis	Membranoproliferative glomerulonephritis with proteinuria and active urinary sediment	IgM MGUS, B-cell non-Hodgkin lymphoma (e.g., WM)	Cryoglobulins, complement levels
Anemia	Cold agglutinin disease	Normocytic anemia, jaundice, dark urine, acrocyanosis	IgM MGUS, B-cell non-Hodgkin lymphoma (e.g., WM)	Reticulocyte count, lactate dehydrogenase, total bilirubin, direct antiglobulin (Coombs) test, cold agglutinin titer
	MM	Normocytic (occasionally macrocytic) anemia	MM	Standard investigative evaluation

AL amyloidosis = immunoglobulin light-chain amyloidosis; FLC = free light chain; MAG = myelin-associated glycoprotein; MGUS = monoclonal gammopathy of undetermined significance; MIDD = monoclonal immunoglobulin deposition disease; MM = multiple myeloma; POEMS = Polyneuropathy, Organomegaly, Endocrinopathy, M protein, and Skin changes; PTH = parathyroid hormone; VEGF = vascular endothelial growth factor; WM = Waldenström macroglobulinemia.

[a]This is not an all-inclusive list; other less common conditions can be associated with plasma cell dyscrasias.

[b]Evaluation beyond the standard evaluation for a monoclonal gammopathy.

[c]Premenopausal women or men <65 years of age with no additional risk factors for bone loss.

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Available tests for detection of PCDs include serum or urine protein electrophoresis (SPEP and UPEP), serum or urine immunofixation, and serum FLC testing (**Figure 4**). SPEP and UPEP detect the presence of and quantify M proteins but do not determine their isotype. UPEP is more sensitive at detecting monoclonal FLCs than SPEP. Serum and urine immunofixation assays identify the isotype of an M protein and are more sensitive than SPEP and UPEP. The serum FLC test is an antibody-based assay that measures the amount of free κ and λ light chains not complexed to heavy chains and is the most sensitive test for detecting monoclonal FLC gammopathies. FLCs are usually reported as the ratio of κ to λ FLCs. An increased amount of either κ or λ FLCs, with the increased component termed the "involved" light chain, will skew the ratio of κ to λ light chains outside of the normal range and indicates the presence of a PCD. With advancing kidney impairment, the basal levels of serum FLCs increase, κ more than λ, leading to an increased serum κ to λ FLC ratio. As such, a corrected normal reference range has been proposed for those with advanced kidney dysfunction. Generally, a combination of SPEP and serum FLCs detects most PCDs. A serum immunofixation and 24-hour UPEP and urine immunofixation may also be needed if SPEP and serum FLC testing are negative and suspicion of a clinically significant PCD persists. The specificity and cost effectiveness of these approaches in different clinical scenarios have not been rigorously assessed.

Many PCDs cause clinical disease, not all of which are associated with multiple myeloma or B-cell lymphomas. As such, an investigative evaluation of a confirmed monoclonal gammopathy requires not only an assessment of possible multiple myeloma or lymphoma but of the other PCDs (see Table 10). Tests that should be considered in all patients with a confirmed monoclonal gammopathy include a complete blood count (CBC); serum chemistries, including creatinine, calcium, and albumin; urinalysis; SPEP, 24-hour UPEP, serum and urine immunofixation, and serum FLC tests (if not already done); and quantitative immunoglobulins (serum IgG, IgA, and IgM). Other laboratory testing is dictated by the suspected disease entity and should be guided by a thorough history and physical examination (see Table 11). For non-IgM gammopathies, a skeletal survey (plain radiographs of the skeleton) is performed to assess for the presence of lytic bone lesions or osteopenia that might be seen with multiple myeloma. IgM gammopathies are more likely associated with B-cell lymphomas, and CT scans of the chest, abdomen, and pelvis should be performed in patients with appropriate signs and symptoms (unexplained fever or weight loss, drenching sweats, lymphadenopathy, or hepatosplenomegaly). A bone marrow biopsy is performed in many cases, but patients with an IgG

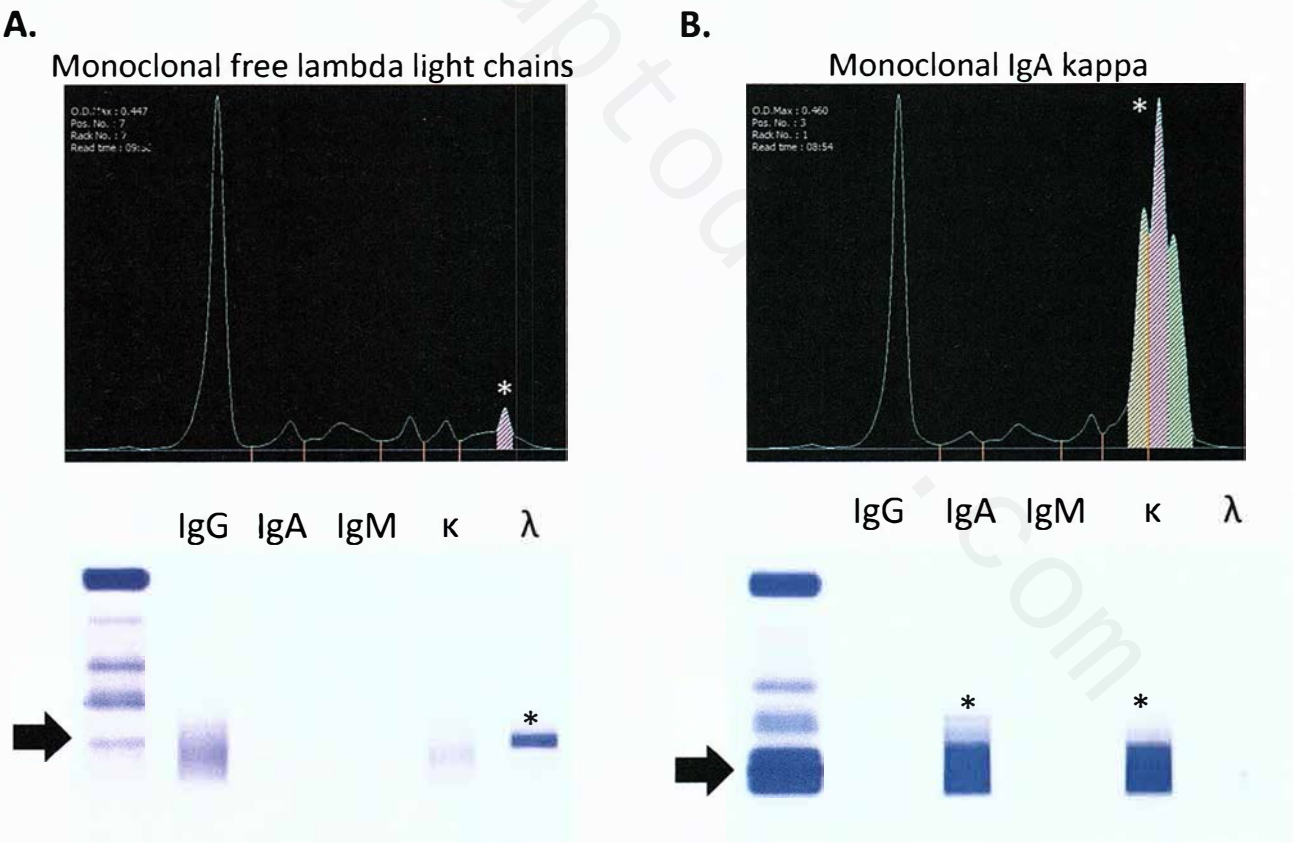

FIGURE 4. Serum protein electrophoresis (SPEP, *top panels*) and immunofixation testing (*bottom panels*) in a patient with free λ light chain (*A*) and IgA κ (*B*) multiple myeloma. The top panels represent serum protein fractions separated by capillary gel electrophoresis. The *white asterisks* denote the monoclonal protein. The bottom panels show patient sera run on multiple lanes of a gel, with each lane stained using anti-IgG, -IgA, -IgM, -κ or -λ antibodies. The first lanes are the SPEP results for that patient. The *black arrows* denote the monoclonal protein band identified by SPEP and the *black asterisks* the isotype specificity of the monoclonal protein by immunofixation testing.

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gammopathy measuring less than 1.5 g/dL, a normal serum FLC ratio, and no evidence of disease-specific end-organ damage can safely defer testing.

KEY POINTS

- Serum and urine protein electrophoresis for plasma cell dyscrasias (PCDs) should be restricted to situations in which a symptomatic PCD requiring intervention or an asymptomatic PCD at high risk of progression to a clinically symptomatic condition is suspected
- The serum free light chain (FLC) assay can detect monoclonal FLCs before they are detectable by urine protein electrophoresis and is the most sensitive test for detecting monoclonal FLC gammopathies.

(Continued)

KEY POINTS *(continued)*

- A combination of serum protein electrophoresis, serum immunofixation, and serum free light chain testing detects almost all plasma cell dyscrasias.

Monoclonal Gammopathy of Undetermined Significance

MGUS is defined as an M protein level less than 3 g/dL (or less than 500 mg/24 hr of urinary monoclonal FLCs), clonal plasma cells comprising less than 10% of the bone marrow cellularity, and the absence of PCD-related signs or symptoms (**Table 12**). MGUS is common, with a prevalence of 5.3% for persons aged 70 years or older.

TABLE 12. Diagnostic Criteria for the Plasma and Lymphoplasmacytic Cell Dyscrasias

Diagnosis	M Protein	Bone Marrow Clonal Plasma Cells or Lymphoid Cells	Disease-specific Signs/Symptoms
MGUS			
Non-IgM (IgG, IgA)	<3 g/dL	<10%	No
IgM	<3 g/dL	<10%	No
Light chain[a]	Affected serum FLC increased and serum FLC ratio increased Urinary M protein <500 mg/24 hr	<10%	No
Smoldering myeloma[b]	IgG or IgA ≥3 g/dL or κ or λ urinary FLC M protein ≥500 mg/24 hr	10%-59%	No
Smoldering WM[b]	IgM ≥3 g/dL	≥10%	No
Multiple myeloma requiring therapy	Present (absent in nonsecretory disease)	≥10% or biopsy evidence of a bony or extramedullary plasmacytoma	Yes
WM requiring therapy	Present	≥10%	Yes
CRAB Criteria for Myeloma-related Signs and Symptoms			
Hypercalcemia. Serum calcium >11 mg/dL (2.8 mmol/L) or >1 mg/dL (0.3 mmol/L) higher than the upper limit of normal			
Renal failure. Serum creatinine >2 mg/dL (177 μmol/L) or creatinine clearance <40 mL/min			
Anemia. Hemoglobin <10 g/dL (100 g/L) or 2 g/dL (20 g/L) below the lower limit of normal			
Bone disease. ≥1 lytic bone lesions on imaging studies			
Myeloma-defining Biomarkers for Myeloma-related Signs and Symptoms			
≥60% clonal plasma cells on bone marrow examination			
Involved: uninvolved serum FLC ratio ≥100			
≥1 focal lesion on MRI			
WM-related Signs and Symptoms			
Systemic symptoms: Fatigue, B symptoms (fevers, night sweats, weight loss), neuropathy, hyperviscosity			
Physical examination findings: Symptomatic lymphadenopathy or hepatosplenomegaly			
Laboratory findings: Cytopenias (anemia, thrombocytopenia)			

AL amyloidosis = immunoglobulin light-chain amyloidosis; FLC = free light chain; MGUS = monoclonal gammopathy of undetermined significance; WM = Waldenström macroglobulinemia.

[a]Light-chain MGUS does not have a heavy-chain component.

[b]Smoldering myeloma or WM may have the diagnostic M protein level WITH OR WITHOUT the percentage of bone marrow clonal plasma or lymphoid cells.

Data from Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014 Nov;15(12):e538-48. [PMID: 25439696]

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Non-IgM MGUS, IgM MGUS, and light-chain MGUS transform into multiple myeloma or another PCD at 1%, 1.5%, and 0.3% per year, respectively. Patients with non-IgM and light-chain MGUS are more likely to develop multiple myeloma, whereas patients with IgM MGUS are more likely to develop Waldenström macroglobulinemia or other B-cell non-Hodgkin lymphoma. MGUS may infrequently transform to immunoglobulin light-chain (AL) amyloidosis. The presence of an IgA or IgM gammopathy, an M protein level of 1.5 g/dL or more, and an abnormal serum FLC ratio are predictive of progression to multiple myeloma or other PCD in non–light-chain MGUS (**Table 13**).

Patients with MGUS are reassessed 6 months after initial diagnosis, and, if stable, yearly thereafter. Patients with IgG MGUS, an M protein level less than 1.5 g/dL, and a normal serum FLC ratio may undergo follow-up once every 2 to 3 years. Evaluation should include a CBC, serum calcium and creatinine levels, and repeat M protein testing. Additional testing should be guided by history and physical examination. Imaging is not recommended in the absence of symptoms. The clinical value and economic impact of MGUS surveillance strategies have not been rigorously assessed. Patients with an increasing M protein level or new findings of a clinically symptomatic PCD (such as progressive anemia or kidney impairment) require additional evaluation. Patients with MGUS are at increased risk of osteoporosis and associated skeletal complications, most notably vertebral body compression fractures (hazard ratio 2.37) and should be considered for bone mineral density testing.

TABLE 13. Risk of MGUS Progression to a Clinically Symptomatic Plasma Cell Dyscrasia

Diagnosis	Risk Factors	Progression
Non-light chain MGUS (IgG, IgA, IgM)	M protein ≥1.5 g/dL	At 20 years:
	Non-IgG M protein	3 RFs: 58%
	Abnormal serum FLC ratio	2 RFs: 37%
		1 RF: 21%
		0 RFs: 5%
Smoldering myeloma	M protein ≥3 g/dL	At 5 years:
	Bone marrow plasma cells ≥10%	3 RFs: 76%
		2 RFs: 51%
	Serum FLC ratio <0.125 or >8 mg/dL	1 RF: 25%

FLC = free light chain; MGUS = monoclonal gammopathy of undetermined significance; RF = risk factor.

Data adapted from: Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005 Aug 1;106(3):812-7. [PMID: 15855274]; and Dispenzieri A, Kyle RA, Katzmann JA, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood. 2008 Jan 15;111(2):785-9. [PMID: 17942755].

KEY POINT

- Monoclonal gammopathy of undetermined significance is defined as an M protein level less than 3 g/dL (or less than 500 mg/24 hr of urinary monoclonal free light chains), clonal plasma cells comprising less than 10% of the bone marrow cellularity, and the absence of plasma cell dyscrasia–related signs or symptoms.

Multiple Myeloma

Multiple myeloma is a plasma cell malignancy involving the bone marrow. Patients may have smoldering (asymptomatic) disease or have symptomatic disease presenting with significant morbidity. Prompt recognition of symptomatic multiple myeloma is critical, because delayed diagnosis is associated with increased complications.

Clinical Manifestations and Findings

Smoldering myeloma is characterized by an M protein level of 3 g/dL or more (or ≥500 mg/24 hr of urinary monoclonal FLCs) or clonal plasma cells comprising 10% or more of the marrow cellularity and no evidence of myeloma-related signs or symptoms requiring therapy. It is typically diagnosed as part of an evaluation for an elevated serum total protein level on routine laboratory studies. Symptomatic myeloma is defined by the presence of an M protein, clonal plasma cells comprising 10% or more of the marrow cellularity, and myeloma-related end-organ damage (see Table 12).

For patients with symptomatic disease, fatigue and a normocytic anemia are common. Blood smear review may reveal rouleaux formation. Leukopenia and suppression of normal immunoglobulin production, from neoplastic plasma cell proliferation that replaces bone marrow precursors and normal plasma cells, can lead to frequent, sometimes life-threatening infections, particularly of the respiratory tract. Significant thrombocytopenia is uncommon.

Skeletal manifestations may include bone pain and nonvertebral or vertebral body compression fractures. A skeletal survey may reveal lytic bone lesions or osteopenia (**Figure 5**). Hypercalcemia due to osteolysis is common at diagnosis. Of those without initial bone complications, 25% will develop a skeletal-related event during the course of their disease.

Kidney dysfunction is found in 29% of patients, often due to cast nephropathy (also termed myeloma kidney), a condition in which excess monoclonal FLCs precipitate in the distal tubules and incite tubulointerstitial damage. Hypercalcemia and exposure to nephrotoxic agents are other frequent causes of kidney dysfunction, whereas AL amyloidosis, monoclonal immunoglobulin deposition disease, cryoglobulinemic glomerulonephritis, and proximal tubulopathy (with or without Fanconi syndrome) are less common.

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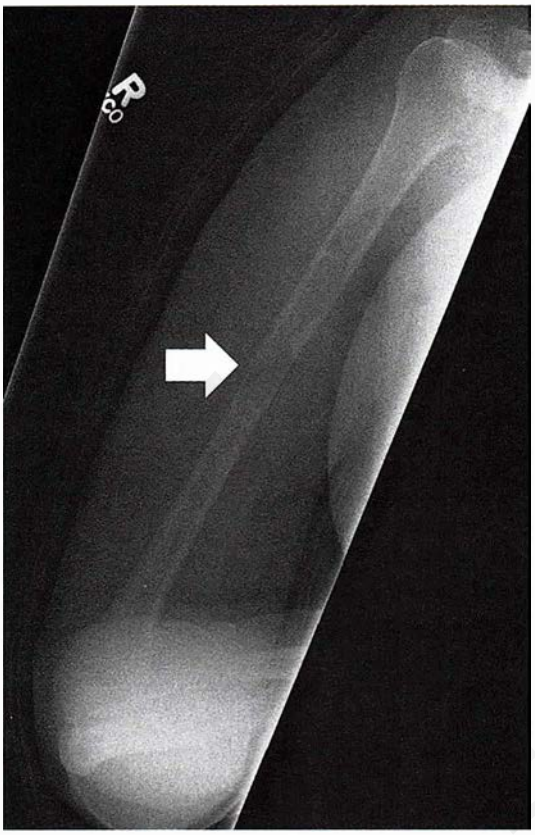

FIGURE 5. Lytic bone lesions in a patient with multiple myeloma. The *arrow* denotes an oblique pathologic fracture through a mid humerus lytic lesion. Other lesions can be seen both proximal and distal to the fracture.

KEY POINTS

- Smoldering multiple myeloma is characterized by a serum M protein level of 3 g/dL or greater (or ≥500 mg/24 hr of urinary monoclonal free light chains) or bone marrow plasma clonal cells of 10% or greater and no evidence of myeloma-related signs or symptoms requiring therapy.
- Symptomatic multiple myeloma is characterized by the presence of serum M protein, bone marrow plasma clonal cells of 10% or greater, and end-organ damage (hypercalcemia, kidney injury, anemia, bone disease).

Diagnosis and Prognosis

Criteria for diagnosing smoldering myeloma and multiple myeloma requiring treatment are outlined in Table 12. In addition to the initial testing noted previously (see Evaluation for Monoclonal Gammopathies), further diagnostic evaluation may be required to distinguish between the two. A skeletal survey is an important part of the initial evaluation of multiple myeloma, but more than 30% of trabecular bone loss must occur before lytic bone lesions are evident. An MRI or CT is more sensitive at detecting bone lesions than plain radiographs and should be considered when bone pain is present and radiographs are unrevealing. MRI should also be performed to assess for spinal cord impingement if back pain is present or a compression fracture is seen on radiographs. Bone scans are insensitive for detection of myeloma bone lesions. The role of whole body PET-CT in the initial evaluation of multiple myeloma and as a tool for assessing response to treatment is an area of active investigation. A kidney biopsy may be required when multiple myeloma-related kidney dysfunction is suspected if the results will impact treatment decisions. AL amyloidosis is found in 10% of patients with multiple myeloma, and appropriate testing should be pursued if clinically suspected (see Immunoglobulin Light-Chain Amyloidosis).

Most smoldering myeloma progresses to symptomatic myeloma or AL amyloidosis, the former being far more common; 51% and 66% of patients progress to symptomatic disease at 5 and 10 years, respectively, with a median time to progression of 4.8 years. Risk factors for progression include a high M protein level, a large burden of clonal plasma cells, and an abnormal serum FLC ratio (see Table 13). Additionally, markers of imminent progression include plasma cells comprising 60% or more of the bone marrow cellularity, more than one focal bone lesion on MRI, or a serum FLC ratio of 0.01 or less or 100 or more; these patients are not considered to have smoldering myeloma and should be considered for early treatment. Management of most patients with smoldering myeloma consists of evaluation every 3 to 6 months. Testing includes a CBC, serum calcium and creatinine levels, and repeat M protein assessment; other testing should be guided by history and physical examination.

After a diagnosis of multiple myeloma requiring treatment is established, additional testing can help determine prognosis and appropriate treatment. The serum β_2-microglobulin and albumin levels determine the stage of disease, which has prognostic significance.

KEY POINT

- Management of most patients with smoldering multiple myeloma consists of evaluation every 3 to 6 months, including a complete blood count, serum calcium and creatinine levels, and repeat M protein assessment.

Treatment

Studies evaluating the use of chemotherapy for patients with high-risk smoldering myeloma have been completed or are ongoing and will clarify whether early intervention can alter the course of the disease with acceptable toxicity. Pamidronate and zoledronic acid have no impact on time to progression to multiple myeloma requiring treatment or overall survival.

Patients with multiple myeloma requiring treatment are initially treated with induction chemotherapy, including some combination of a proteasome inhibitor (bortezomib), an immunomodulatory agent (thalidomide or lenalidomide), a glucocorticoid (prednisone or dexamethasone), or an

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CONT. alkylating agent (melphalan or cyclophosphamide). Autologous hematopoietic stem cell transplantation (HSCT) using high-dose melphalan after initial induction therapy is associated with improved progression-free and, in some studies, overall survival. The use of lenalidomide maintenance therapy after an initial course of treatment improves progression-free survival and may impact overall survival after autologous HSCT. Patients who relapse are typically treated with regimens containing the drug classes noted. Carfilzomib, a second-generation proteasome inhibitor, and the immunomodulatory agent pomalidomide in combination with dexamethasone are also effective in patients with relapsed and refractory disease.

Bortezomib and thalidomide are associated with a high risk of peripheral neuropathy. Patients taking thalidomide-, lenalidomide-, or pomalidomide-based therapy are at increased risk of venous thromboembolism (VTE). Patients with additional risk factors for VTE, including myeloma-related risk factors (concomitant use of dexamethasone, anthracyclines, or erythropoietin; immobilization; hyperviscosity), should be considered for prophylaxis with aspirin, low-molecular-weight heparin, or warfarin. Lenalidomide used as a maintenance therapy immediately after melphalan-based treatment is associated with an increased risk of secondary malignancies. The use of low-dose melphalan as part of initial chemotherapy for multiple myeloma may compromise future collection of hematopoietic stem cells and should be avoided in patients eligible for autologous HSCT.

Surgical stabilization may be required for established or impending pathologic fractures. Palliative therapy includes radiation therapy for bone pain from lytic bone lesions. Pamidronate reduces the risk of skeletal-related complications in symptomatic myeloma. Zoledronic acid protects against skeletal-related events, even in patients without evidence of bone disease on skeletal survey, and improves median overall survival. Guidelines recommend pamidronate or zoledronic acid once every 3 to 4 weeks for a minimum of 2 years in all newly diagnosed patients with symptomatic myeloma.

Cast nephropathy is managed with intravenous fluids, avoidance of nephrotoxic agents, and immediate initiation of chemotherapy to reduce the monoclonal FLC burden. Plasmapheresis clears FLCs inefficiently, and its role remains controversial. Hypercalcemia is managed with intravenous fluids and bisphosphonates.

Annual influenza vaccination is recommended. For adults with multiple myeloma, pneumococcal vaccination utilizing the 13-valent pneumococcal conjugate vaccine (PCV-13) and 23-valent pneumococcal polysaccharide vaccine (PPSV-23) should be performed in accordance with Advisory Committee on Immunization Practices guidelines (see MKSAP 17 General Internal Medicine). Intravenous immune globulin therapy may be used in select patients with low immunoglobulin levels and recurrent severe infections.

KEY POINTS

- The treatment of choice for patients with smoldering multiple myeloma at lower risk for progression is expectant management with monitoring every 3 to 6 months.
- For eligible patients with multiple myeloma requiring therapy, autologous hematopoietic stem cell transplantation with high-dose melphalan after initial induction therapy is associated with improved progression-free and, in some studies, overall survival.

Immunoglobulin Light-Chain Amyloidosis

The amyloidoses are characterized by the extracellular deposition of low-molecular-weight proteins in a β-pleated sheet configuration. The various types are outlined in **Table 14**. Proper identification of the amyloid type is critical and guides appropriate therapy. AL amyloidosis is the most common type

TABLE 14. The Amyloidoses

Type	Disease Association	Amyloid Protein
AL amyloidosis	Plasma cell dyscrasias (MGUS, multiple myeloma), Waldenström macroglobulinemia (rare)	Monoclonal free λ or κ light chains
Hereditary amyloidosis	Inherited	Mutated transthyretin (TTR), fibrinogen α chain[a]
AA amyloidosis	Rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever, chronic infection	Serum amyloid A protein
Age-related (senile) amyloidosis	Age	Wild type TTR
Dialysis-related amyloidosis	Dialysis for any reason	β_2-microglobulin

AA = secondary amyloidosis; AL = immunoglobulin light-chain amyloidosis; MGUS = monoclonal gammopathy of undetermined significance.

[a]Not an all-inclusive list.

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and is a PCD-related disease characterized by end-organ damage related to tissue deposition of monoclonal free λ or κ light-chain fibrils. Clinical symptoms and manifestations vary and are dictated by the tissue tropism of the amyloidogenic light chain (**Table 15**).

AL amyloidosis is diagnosed by an abdominal fat pad aspirate and bone marrow biopsy in most cases, although a more invasive biopsy of a clinically affected organ may be required if these tests are negative and clinical suspicion persists. Amyloid deposits in the biopsy sample demonstrate apple green birefringence under polarized light with Congo red staining. If amyloid deposits are identified, other types of amyloidosis should be excluded by typing, which can be done by κ/λ light-chain immunohistochemistry or immunofluorescence of a biopsy sample or mass spectroscopy–based protein sequencing of the amyloid deposits. A clonal plasma cell disorder should be confirmed, as defined by the presence of an M protein on serum or urine testing or the presence of clonal plasma cells in the marrow.

For patients with confirmed AL amyloidosis, in addition to the standard diagnostic tests noted previously (see Evaluation for Monoclonal Gammopathies), further studies should be conducted to assess organ involvement and establish a baseline for subsequent follow-up. Specific testing includes (1) serum troponin T, serum N-terminal proB-type natriuretic peptide (NT-proBNP), chest radiography, transthoracic echocardiography, and electrocardiography to assess cardiac involvement; (2) serologic liver tests, especially alkaline phosphatase, and abdominal ultrasonography to screen for hepatic amyloid; and (3) prothrombin and activated partial thromboplastin times to evaluate the presence of a coagulopathy (and, if abnormal, factor X level measurement). Pulmonary function tests, electromyography with nerve conduction studies, and gastric emptying studies should be considered for patients with symptoms of dyspnea, peripheral neuropathy, and gastroparesis, respectively.

The prognosis of systemic AL amyloidosis is driven by the extent of cardiac involvement and levels of affected serum FLCs. A prognostic model incorporates an elevated serum troponin T level or NT-proBNP level and a significant difference in the involved to uninvolved serum FLC level; patients with 0, 1, 2, or 3 risk factors have a median overall survival of 94.1, 40.3, 14.0, or 5.8 months, respectively.

Treatment algorithms are similar to those used in multiple myeloma. Retrospective studies have demonstrated high hematologic response rates, improvement in organ function, and durable progression-free and overall survival with autologous HSCT in carefully selected patients. Patients not eligible for HSCT are considered for chemotherapy, which commonly consists of low-dose melphalan with dexamethasone.

TABLE 15. Clinical Manifestations of AL Amyloidosis by Organ System

Organ System	Clinical Manifestations	Findings
Kidney	Anasarca, lower extremity edema, foamy urine	Nephrotic range proteinuria with bland urine sediment, hypoalbuminemia, elevated creatinine, nephromegaly on kidney ultrasonography
Gastrointestinal	Gastrointestinal bleeding, dysphagia, early satiety, abdominal distention, steatorrhea	Anemia, iron deficiency, submucosal hematomas on endoscopy, hypoalbuminemia, delayed gastric emptying, intestinal pseudo-obstruction, malabsorption, small bowel bacterial overgrowth
Liver	Weight loss, abdominal pain, features of chronic liver disease and portal hypertension	Cholestatic liver test abnormalities, hepatosplenomegaly, ascites, varices, evidence of portal hypertension
Neurologic	Distal numbness, paresthesias, neuropathic pain, weakness, autonomic nerve dysfunction	Distal sensorimotor polyneuropathy on electromyography/nerve conduction studies, autonomic neuropathy
Cardiac	Chest pain, symptoms from chronic heart failure or arrhythmia	Echocardiographic changes (ventricular hypertrophy with granular appearance, restrictive cardiomyopathy with diastolic heart failure greater than systolic heart failure), electrocardiographic changes (low voltages, pseudoinfarct pattern, conduction system changes, arrhythmias), abnormal cardiac MRI (late gadolinium enhancement)
Coagulation	Bleeding diathesis, periorbital purpura	Factor X deficiency with prolonged PT and aPTT, prolonged PT and aPTT from advanced liver impairment, blood vessel fragility from vascular amyloid deposition
Musculoskeletal	Macroglossia, muscle pseudohypertrophy, symmetric arthropathy, submandibular gland enlargement, carpal tunnel syndrome	Carpal tunnel syndrome on electromyography/nerve conduction studies, joint space widening on plain radiographs, periarticular soft tissue and muscle infiltration on MRI

aPTT = activated partial thromboplastin time; PT = prothrombin time.

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Bortezomib-based and immunomodulatory drug–based therapy have shown encouraging results in small studies. The treatment goal is attainment of complete hematologic response (undetectable M protein), because this is associated with a higher likelihood of improvement in organ function.

KEY POINTS

- AL amyloidosis is diagnosed by the presence of amyloid deposits in the tissue biopsy sample (whether from abdominal fat pad aspirate or bone marrow or organ biopsy), proof that amyloid deposits are monoclonal free light chains, and confirmation of a clonal plasma cell disorder.
- Treatment with autologous hematopoietic stem cell transplantation in select patients with AL amyloidosis has demonstrated high hematologic response rates, improved organ function, and durable progression-free and overall survival.

Waldenström Macroglobulinemia

Waldenström macroglobulinemia is an indolent B-cell non-Hodgkin lymphoma characterized by production of an IgM κ or λ M protein. Smoldering (asymptomatic) Waldenström macroglobulinemia is defined as a neoplastic infiltrate consisting of clonal lymphocytes, plasmacytoid lymphocytes, plasma cells, and immunoblasts comprising 10% or more of the bone marrow cellularity or an M protein level of 3 g/dL or more and the absence of disease-related signs, symptoms, or organ dysfunction. Waldenström macroglobulinemia requiring therapy is similarly defined, but symptoms are present (see Table 12).

Patients with symptomatic disease may experience fatigue, and anemia is common. Systemic symptoms, commonly referred to as "B symptoms," include unexplained drenching sweats, fever, and weight loss. A bleeding diathesis is present in one quarter of patients at diagnosis, attributable to hyperviscosity, qualitative platelet dysfunction, or, less commonly, dysfibrinogenemia. Symptoms attributable to hyperviscosity may include headache, blurred vision, hearing loss, tinnitus, dizziness, altered mental status, and nasal and oropharyngeal bleeding. Funduscopic evaluation may reveal hyperviscosity-related findings, including dilated retinal veins, papilledema, and flame hemorrhages. Lymphadenopathy, hepatomegaly, and splenomegaly are often found on physical examination. Twenty percent of patients have a distal sensorimotor polyneuropathy that is commonly caused by antimyelin-associated glycoprotein activity of the M protein. Other rare manifestations of Waldenström macroglobulinemia include amyloidosis, cryoglobulinemia, and cold agglutinin disease.

In addition to the initial diagnostic evaluation outlined previously (see Evaluation for Monoclonal Gammopathies), a prothrombin time, activated partial thromboplastin time, and thrombin time should be performed to screen for dysfibrinogenemia in those with a bleeding diathesis not attributable to hyperviscosity. Measurement of serum viscosity should be performed in those with symptoms or characteristic retinal findings. Patients with suspected cold agglutinin disease or cryoglobulinemia should have cold agglutinin titers or serum cryoglobulins and complement levels assessed. Assessment of serum β_2-microglobulin, albumin, and lactate dehydrogenase levels helps determine prognosis.

Symptomatic hyperviscosity is a medical emergency and requires immediate institution of plasmapheresis. Initial therapy may consist of rituximab as monotherapy or in combination with chemotherapy, which may consist of an alkylating agent (chlorambucil, cyclophosphamide, bendamustine) or a purine analog (fludarabine, cladribine) with or without a glucocorticoid. Autologous HSCT has been used in some patients. Bortezomib-based therapy may be used but is associated with high rates of peripheral neuropathy.

KEY POINTS

- Symptoms attributable to hyperviscosity, a medical emergency requiring immediate institution of plasmapheresis, are seen in 31% of patients with Waldenström macroglobulinemia and may include headache, blurred vision, hearing loss, tinnitus, dizziness, altered mental status, and nasal and oropharyngeal bleeding.
- In patients with Waldenström macroglobulinemia, funduscopic evaluation may reveal hyperviscosity-related findings, including dilated retinal veins, papilledema, and flame hemorrhages.

Cryoglobulinemia

Cryoglobulins are proteins that precipitate from serum at temperatures less than 37.0 °C (98.6 °F) and dissolve with warming. Cryoglobulins may cause no symptoms or lead to complications of hyperviscosity and thrombosis or manifestations of a small- to medium-vessel vasculitis. Cryoglobulinemias are classified by the composition of the cryoglobulin into types I, II, and III. Types II and III cryoglobulinemia are commonly referred to as mixed cryoglobulinemia. Type I cryoglobulinemia results from an underlying PCD or lymphoproliferative disorder (B-cell non-Hodgkin lymphoma), whereas mixed cryoglobulinemia can be caused by chronic infection, a PCD or lymphoproliferative disorder, or a systemic autoimmune disease. The most common disease associated with mixed cryoglobulinemia is hepatitis C. Although manifestations of vascular occlusion are more common in type I cryoglobulinemia, and vasculitis is common in mixed cryoglobulinemia, overlap is considerable. The clinical manifestations and disease associations for the various cryoglobulinemias are presented in **Table 16**.

Serologic testing for cryoglobulins should be performed using syringes and tubes prewarmed to 37.0 °C (98.6 °F) to avoid false-negative results. Rheumatoid factor and complement levels should be obtained. Additional testing may include evaluation for underlying disease states associated

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TABLE 16. The Cryoglobulinemias

Type	Cryoglobulin Characteristics	Disease Associations	Clinical Manifestations
I	Monoclonal immunoglobulin (IgG, IgM, or IgA) with no RF activity	PCDs and lymphoproliferative disorders (MGUS, multiple myeloma, Waldenström macroglobulinemia, B-cell non-Hodgkin lymphoma, CLL)	Acrocyanosis, digital ischemia, livedo reticularis, skin ulcers and necrosis, lower extremity purpura, peripheral neuropathy (more common with types II and III), hyperviscosity, arthralgia, membranoproliferative glomerulonephritis (more common with types II and III)
II[a]	Polyclonal immunoglobulins + monoclonal immunoglobulin (IgM, IgA) with RF activity	Infection (hepatitis C), connective tissue disease (Sjögren syndrome, SLE), lymphoproliferative disorders (Waldenström macroglobulinemia, B-cell non-Hodgkin lymphoma, CLL)	Acrocyanosis; digital ischemia; fatigue; arthralgia; lower extremity purpura; skin ulcers and necrosis; peripheral neuropathy; membranoproliferative glomerulonephritis; pulmonary, CNS, and gastrointestinal vasculitis
III[a]	Polyclonal immunoglobulins with RF activity	Connective tissue disease, lymphoproliferative disorders	Same as type II

CLL = chronic lymphocytic leukemia; CNS = central nervous system; MGUS = monoclonal gammopathy of undetermined significance; PCD = plasma cell dyscrasia; RF = rheumatoid factor; SLE = systemic lupus erythematosus.

[a]Types II and III are mixed cryoglobulinemias.

Data from Terrier B, Karras A, Kahn JE, et al. The spectrum of type I cryoglobulinemic vasculitis: new insights based on 64 cases. Medicine. 2013 Mar;92(2):61-8. [PMID: 23429354] and Terrier B, Krastinova E, Marie I, et al. Management of noninfectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey. Blood. 2012 Jun 21;119(25):5996-6004. [PMID: 22474249]

CONT.

with cryoglobulinemia, such as hepatitis C antibody testing in a patient with type II cryoglobulinemia or a bone marrow biopsy in a patient with a suspected PCD or lymphoproliferative disorder.

Treatment of type I cryoglobulinemia includes plasmapheresis for those with symptomatic hyperviscosity and treatment of the underlying PCD or lymphoproliferative disorder. Management of mixed cryoglobulinemia consists of treatment of the underlying disease and immunosuppressive therapy for patients with more severe manifestations of vasculitis (rituximab or cyclophosphamide with a short course of glucocorticoids). H

KEY POINTS

- The most common disease associated with mixed cryoglobulinemia is hepatitis C.
- Type I cryoglobulinemia with hyperviscosity is managed with plasmapheresis and treatment of the underlying plasma cell dyscrasia or lymphoproliferative disorder.
- Mixed cryoglobulinemia is managed by treating the underlying disease and immunosuppressive therapy for patients with more severe manifestations of vasculitis.

Erythrocyte Disorders

Approach to Anemia

The primary function of erythrocytes is to deliver oxygen to tissues. Anemia, defined as decreased circulating red blood cell mass or hemoglobin, can limit oxygen delivery and result in symptoms of fatigue, dizziness, shortness of breath, and palpitations. Anemia itself is not a diagnosis, but a sign of an underlying condition. Although a good medical and family history is essential, it may not always explain the cause of the anemia. A targeted laboratory evaluation is often a window into understanding the underlying disorder.

When considering a patient with anemia, it is important to first establish chronicity. This provides insight into potential inherited versus acquired conditions. Anemia generally results from blood loss or underproduction or destruction of erythrocytes. Gross blood loss can usually be ruled out by history, but microscopic or factitious (patient mediated) loss must be considered, especially when iron deficiency is present.

Underproduction can be distinguished from destruction by the reticulocyte count, a measure of bone marrow production of erythrocytes, which is typically low in underproduction and elevated in destruction. Reticulocytes are immature erythrocytes, and their count is reported as the absolute reticulocyte count. The corrected reticulocyte count adjusts for the patient's hematocrit value. Reticulocytes usually mature into erythrocytes within 24 hours of release into the circulation. In times of severe anemia, reticulocytes can be released into the circulation earlier and will take longer to mature into erythrocytes (2-3 days). This correction for immature reticulocytes is adjusted by the reticulocyte production index.

The mean corpuscular volume (MCV) reflects erythrocyte size and can characterize certain anemias (**Table 17**). Red cell distribution width (RDW), which is a measure of the variation in size of the circulating erythrocytes relative to the MCV, provides additional information for characterizing the cause of anemia. An elevated RDW usually reflects the presence of

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TABLE 17. Characterization of Anemia by Mean Corpuscular Volume

Microcytic (MCV <80 fL)	Normocytic	Macrocytic (MCV >100 fL)
Iron deficiency	Inflammatory anemia[a]	Cobalamin (vitamin B_{12}) or folate deficiency
Thalassemia	Anemia of kidney disease	Autoimmune hemolytic anemia[b]
	Hereditary spherocytosis	Liver disease
	Sickle cell disease	Hypothyroidism
		Myelodysplastic syndrome[c]
		Sideroblastic anemia[d]
		Alcohol
		Drugs (e.g., HU, ZDV)

HU = hydroxyurea; MCV = mean corpuscular volume; ZDV = zidovudine.

[a]Inflammatory anemia can occasionally be microcytic.

[b]Autoimmune hemolytic anemia can occur because of reticulocytosis.

[c]Myelodysplastic syndrome can present with a normocytic anemia.

[d]Either congenital or acquired (e.g., by lead poisoning, copper deficiency, or drugs such as isoniazid, chloramphenicol, cycloserine, and linezolid).

erythrocytes of different sizes and may indicate a mixed process. For example, concomitant iron deficiency (microcytic) anemia and vitamin B_{12} (macrocytic) anemia would result in a normal MCV but an elevated RDW. Examination of the peripheral blood smear will reveal possible causes by characteristic morphologies.

KEY POINT

- Anemia generally results from blood loss or underproduction or destruction of erythrocytes; underproduction can be distinguished from destruction by the reticulocyte count, which is typically low in the former and elevated in the latter.

Anemia Due to Erythrocyte Underproduction or Maturation Defects

Iron Deficiency

Iron is absorbed in the duodenum by enterocytes, which release it to the circulation destined for the bone marrow for incorporation into the hemoglobin molecule during erythropoiesis. Iron is transported in the plasma in its ferric form by the transport protein transferrin. Any excess iron is stored in the liver and reticuloendothelial system as ferritin for release as needed. Hepcidin, a peptide hormone produced in the liver, is a main regulator of iron homeostasis. It decreases intestinal iron absorption and release of iron stores by down-regulating the ferroportin-mediated release of iron from enterocytes, hepatocytes, and macrophages. Hepcidin is produced by hepatocytes when iron is abundant and in inflammatory anemia; it is suppressed in iron deficiency anemia (**Figure 6**).

Iron deficiency is the most common nutritional deficiency worldwide and is highly prevalent in developing countries. In the United States, it particularly affects children aged 1 to 2 years (7%-9% of toddlers) and girls and women aged 12 to 49 years (9%-16% of girls and women). The prevalence in the United States is higher in non-Hispanic black and Mexican American women (19%-22%). When diagnosing iron deficiency, it is crucial to consider, diagnose, and treat the underlying causes.

Approximately two thirds of iron is in the heme form and is incorporated into erythrocytes. The other one third is stored as ferritin or hemosiderin. A significant amount of iron is recycled from senescent erythrocytes. Dietary iron (1-2 mg/d) replaces natural losses of iron in urine, sweat, and stools. Insufficient dietary intake to replace this required amount and any additional loss (such as blood loss) will result in anemia over the course of a few months to years. Additionally, intestinal malabsorption of iron can lead to deficiency. Common causes of iron deficiency anemia are listed in **Table 18**.

Typical features of iron deficiency are identical to those of any symptomatic anemia but may be subtle owing to an insidious onset of the condition. Headache and pica (craving for typically undesirable items such as ice, dirt, clay, paper, and laundry starch) are frequently associated symptoms; other less common symptoms include restless legs syndrome and hair loss.

Recent blood transfusion or iron replacement may interfere with the accurate evaluation of iron deficiency. The hallmark of iron deficiency is a microcytic hypochromic anemia (**Figure 7**). However, this is usually only seen in advanced iron deficiency, and anemia tends to precede morphologic changes in the cells. On the other hand, abnormalities in iron studies typically precede the anemia. Serum iron concentrations tend to be low, but may be normal. Total iron-binding capacity (TIBC), a measure of the amount of transferrin in the plasma, is usually elevated. The transferrin saturation is a percentage calculated as serum iron/TIBC.

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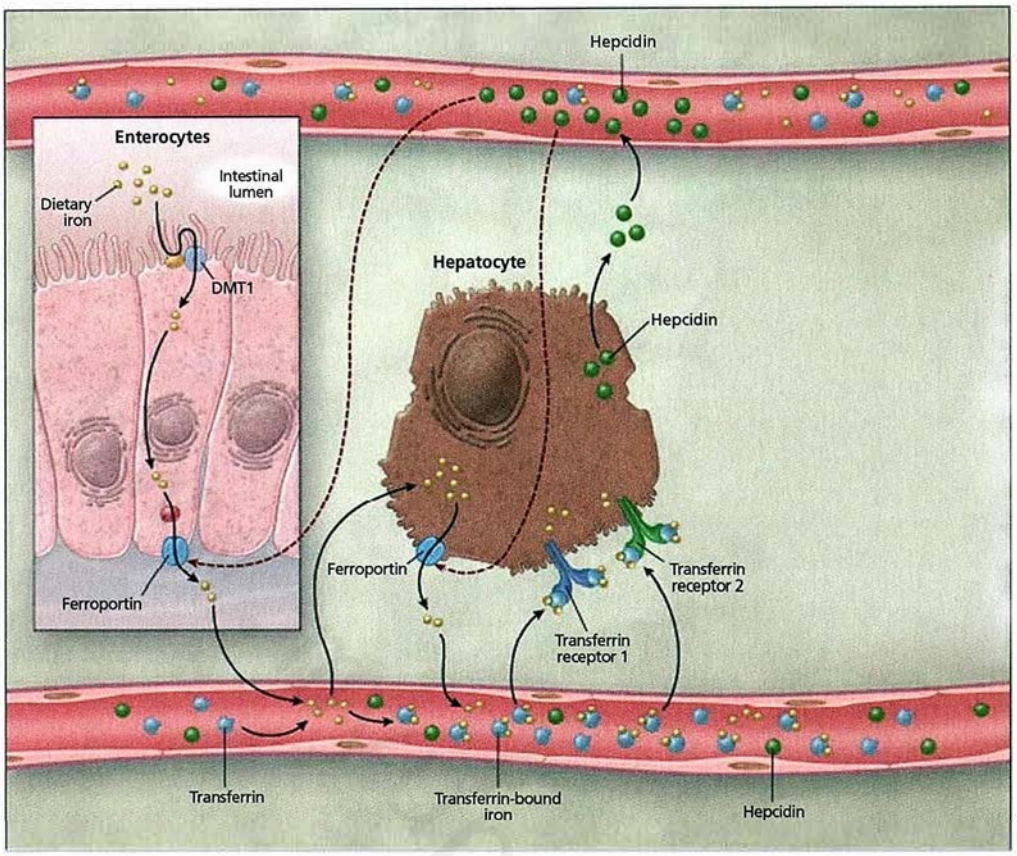

FIGURE 6. Dietary iron is absorbed from the gut (mainly the duodenum) into the blood stream via enterocytes (*inset*). This is facilitated by the divalent metal transporter-1 (DMT1) protein on the gut and the ferroportin on the vessel surface. Iron entering the vascular space is rapidly bound by transferrin and mostly transported to erythrocytes where it gets incorporated as hemoglobin. Excess iron is stored in the liver in hepatocytes and Kupffer cells utilizing transferrin receptors and ferroportin to transport it across the membrane. This transmembrane transport in the enterocyte and hepatic cells is down regulated by hepcidin, a hormone produced by hepatocytes in response to increased iron stores and inflammation.

TABLE 18. Causes of Iron Deficiency Anemia

- Loss of iron
  - Bleeding
    - Menstruation
    - Phlebotomy
    - Gastrointestinal bleeding (can be microscopic)
    - Genitourinary bleeding (can be microscopic)
    - Other blood loss (overt, microscopic, or factitious)
- Decreased intake
  - Nutritional deficiency
    - Decreased intake
  - Decreased absorption
    - After gastric/duodenal surgery
    - Celiac disease
    - *Helicobacter pylori* infection
    - Autoimmune atrophic gastritis
- Increased iron requirements
  - Pregnancy
  - Lactation

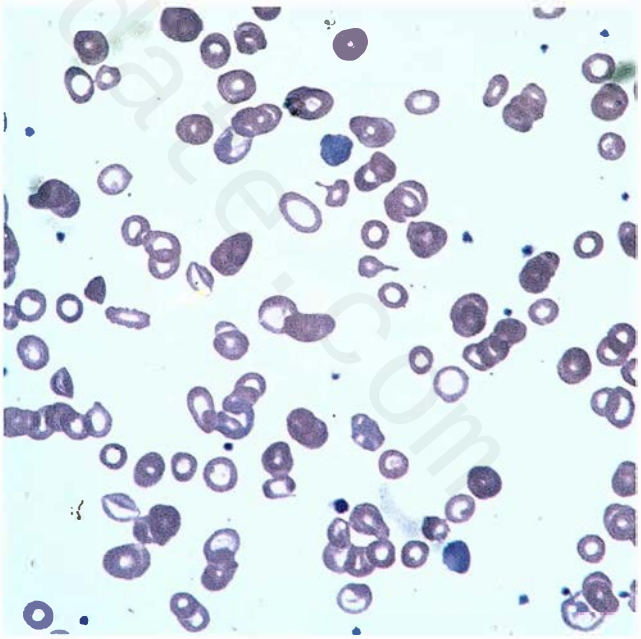

FIGURE 7. Iron deficiency anemia is characterized by microcytic (small) and hypochromic (pale-appearing) erythrocytes. The cells are often of various shapes and sizes as seen in this peripheral blood smear.

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Transferrin saturation is usually less than 15% in iron deficiency anemia. Serum ferritin levels, as a measure of total body iron, are typically no more than 12 ng/mL (12 µg/L) in iron deficiency anemia and may be slightly higher in iron deficiency without anemia. Serum ferritin levels can be in the normal range when an associated inflammatory condition exists (for example, rheumatoid arthritis, malignancy, Gaucher disease). In inflammatory states, a serum ferritin level of greater than 100 ng/mL (100 µg/L) usually excludes iron deficiency. It is important to distinguish iron deficiency anemia from inflammatory anemia.

The presence of reticulocytes reflects the bone marrow response to anemia. In iron deficiency, the reticulocyte count is typically low, although occasionally it can be normal or even elevated.

H Iron deficiency is managed by treating the underlying causes and by replacing iron. In premenopausal women, iron deficiency can result from menstrual blood loss, which need not imply any uterine or hormonal pathology and does not require further investigation. Further evaluation is warranted in all other persons with unexplained blood loss, and older men and women especially should be evaluated with colonoscopy, because a significant proportion will have colon cancer or premalignant polyps. Replacement can be achieved through oral supplementation, erythrocyte transfusion, or intravenous infusion (**Table 19**). One unit of packed red blood cells contains 225 to 250 mg of iron. Transfusion is an effective way to replace iron but is only indicated if the patient is profoundly anemic and symptomatic. Various oral replacement preparations are available. They should provide 30 to 100 mg of elemental iron (in the ferrous form) per dose and should be given two to three times per day to provide an approximate total of 150 to 200 mg of iron. The least expensive, ferrous sulfate, is as effective as any of the more expensive oral preparations; more costly oral preparations that are reported to cause fewer adverse effects typically do so by exposing the patient to less absorbed iron. Enteric-coated preparations can have decreased absorption. In general, oral iron supplementation is well tolerated but is commonly accompanied by gastrointestinal symptoms (nausea, vomiting, dark stools, constipation) and a metallic taste.

Iron deficiency seemingly refractory to oral iron supplementation may indicate a subclinical underlying *Helicobacter pylori* infection; treatment of the infection may lead to improved iron absorption. In patients with subclinical hypothyroidism, adding levothyroxine may improve the response to oral iron replacement.

In persons who cannot tolerate or adequately absorb oral iron, intravenous replacement is indicated. To determine adequate iron absorption, an oral challenge can be given (check a fasting serum iron level and compare it to a level 1-2 hours after giving 60 mg of oral elemental iron; an increase of >100 µg/dL [17.9 µmol/L] suggests adequate oral absorption). Several parenteral iron-carbohydrate complexes are available. Iron dextran has been associated with anaphylactic reactions and a test dose should be administered (see Table 19). H

In patients with chronic heart failure, iron deficiency is common and is associated with more severe disease and

TABLE 19. Approach to Iron Replacement

	Packed Red Blood Cell Transfusion	Oral Replacement	Intravenous Replacement
Dose	220-250 mg of iron/unit	Ferrous sulfate: 65 mg per 325-mg tablet Ferrous gluconate: 36 mg per 300-mg tablet Ferrous fumarate: 33 mg per 100-mg tablet	Ferric gluconate: 12.5 mg/mL Iron dextran: 50 mg/mL[a] Iron sucrose: 20 mg/mL Ferumoxytol: 30 mg/mL
Indication	Severe, symptomatic anemia Hemodynamically unstable patients End-organ damage	Iron deficiency not due to impaired intestinal absorption	GI malabsorption Inability to tolerate oral iron Poor response to oral iron Patients undergoing kidney dialysis receiving ESAs
Benefits	Rapid replacement of iron and lost blood	Inexpensive and readily available outpatient treatment	More rapid replacement, works in malabsorption, usually given in outpatient infusions
Side effects	Possible transfusion reaction	Often takes many months to fully replace stores, GI side effects	More expensive, allergic reactions

ESA = erythropoiesis-stimulating agent; GI = gastrointestinal.

[a]Requires test dose.

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higher mortality. Treatment with iron was shown to alleviate symptoms and improve functional capacity and quality of life in these patients regardless of the degree of anemia.

KEY POINTS

- The hallmark of iron deficiency is a microcytic hypochromic anemia, but anemia tends to precede morphologic changes in the cells, and abnormalities in iron studies typically precede the anemia.
- Transferrin saturation is usually less than 15% in iron deficiency anemia, and the serum ferritin level is typically no more than 12 ng/mL (12 µg/L).
- The least expensive iron replacement is ferrous sulfate, which is as effective as any of the more expensive oral preparations.

Inflammatory Anemia

Inflammatory anemia, also referred to as anemia of chronic disease, is the most common anemia found in hospitalized patients. It is caused by underlying proinflammatory states such as infection, cancer, and autoimmune disease and other conditions, including chronic heart failure and diabetes mellitus, not traditionally characterized as proinflammatory. Pathophysiologically, these proinflammatory states result in dysregulation of iron homeostasis, impaired erythropoiesis, and blunted erythropoietin response.

Hepcidin is upregulated in iron overload states as well as in inflammatory conditions, and proinflammatory cytokines such as interleukin-6, interleukin-1, and interferon-γ have been shown to induce hepcidin production. These inflammatory cytokines also blunt the erythropoietin response to anemia.

Inflammatory anemia is relatively mild, with most patients experiencing symptoms related to their underlying disease rather than the anemia. Inflammatory anemia and iron deficiency anemia can present with low serum iron levels but can be distinguished by other laboratory values (**Table 20**). Most significantly, inflammatory anemia is usually normocytic and has a low TIBC.

As with iron deficiency anemia, management includes maximizing treatment of or eliminating the underlying disorder. Studies targeting the hepcidin-ferroportin axis are ongoing and could present promising future treatment modalities.

KEY POINTS

- Inflammatory anemia is usually normocytic with a low serum iron level and total iron-binding capacity.
- Management of inflammatory anemia includes maximizing treatment of or eliminating the underlying disorder.

Anemia of Kidney Disease

Underproduction anemia is a very common association of chronic kidney disease (CKD) and affects about 90% of patients with a glomerular filtration rate (GFR) less than 25 to 30 mL/min/1.73 m^2; however, anemia can occur with higher GFR levels. The anemia is usually normochromic and normocytic and demonstrates a low reticulocyte count. In advanced kidney disease, typical echinocyte or "burr cell" morphology can be seen on peripheral blood smears. Although the primary cause of this anemia is decreased erythropoietin production by the failing kidney, erythropoietin levels measured in plasma do not accurately reflect functional or absolute erythropoietin deficiency and may appear normal. Measuring erythropoietin levels is thus not useful in diagnosing the anemia of kidney disease. Additional factors contributing to anemia are decreased lifespan of the erythrocytes, bone marrow suppression (from uremic toxins), and blood loss/destruction during hemodialysis. Diseases associated with kidney injury can also produce anemia by other mechanisms (for example, microangiopathic hemolytic anemia associated with hemolytic uremic syndrome–thrombotic thrombocytopenic purpura [see Platelet Disorders]). Anemia in kidney disease is discussed further in MKSAP 17 Nephrology.

TABLE 20. Laboratory Characteristics of Inflammatory Anemia, Iron Deficiency Anemia (IDA), and IDA with Inflammation

Finding	Type of Anemia		
	Inflammatory Anemia	Iron Deficiency Anemia	IDA with Inflammation
MCV	72-100 fL	<80 fL	<100 fL
MCHC	<36 g/dL (360 g/L)	<32 g/dL (320 g/L)	<32 g/dL (320 g/L)
Serum iron	<60 µg/dL (11 µmol/L)	<60 µg/dL (11 µmol/L)	<60 µg/dL (11 µmol/L)
TIBC	<250 µg/dL (45 µmol/L)	>400 µg/dL (72 µmol/L)	<400 µg/dL (72 µmol/L)
TIBC saturation	2%-20%	<15% (usually <10%)	<15%
Ferritin	>35 ng/mL (35 µg/L)	<15 ng/mL (15 µg/L)	<100 ng/mL (100 µg/L)
Serum soluble transferrin receptor concentration	Normal	Increased	Increased
Stainable iron in bone marrow	Present	Absent	Absent

MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; TIBC = total iron-binding capacity.

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KEY POINTS

- Underproduction anemia affects approximately 90% of patients with a glomerular filtration rate less than 25 to 30 mL/min/1.73 m^2; the anemia is usually normochromic and normocytic and demonstrates a low reticulocyte count.

HVC

- Measurement of erythropoietin levels is not useful in diagnosing the anemia of kidney disease.

Cobalamin (Vitamin B_{12}) Deficiency

Cobalamin (vitamin B_{12}) deficiency can result in a macrocytic underproduction anemia as well as a demyelinating nervous system disease.

Cobalamin is a cofactor needed by two enzymes in human cells: L-methylmalonyl-coenzyme A mutase and methionine synthase (**Figure 8**). Deficiency of cobalamin will thus cause increased methylmalonic acid and homocysteine levels and affect myelopoiesis as well as myelination of the central nervous system. Dyssynchronous development of the cytoplasm and the nucleus results in macrocytosis, hemolysis of erythrocytes within the bone marrow, and hypersegmentation in granulocytes.

Cobalamin deficiency is caused by insufficient intake or impaired absorption. Foods containing cobalamin are of animal origin, so vegetarians are at higher risk for cobalamin deficiency. Insufficient absorption can be caused by gastric, bariatric, or ileal surgery; inflammatory bowel disease; or pernicious anemia (autoimmune gastritis). Pernicious anemia is the most common cause of severe deficiency affecting all age groups, but especially older adults. It results in the destruction of gastric parietal cells, which synthesize intrinsic factor needed for cobalamin absorption. Because cobalamin is efficiently stored, and bile losses are effectively recycled by the enterohepatic circulation, it takes 2 to 3 years of insufficient intake or impaired absorption before cobalamin deficiency ensues.

H

Symptoms are those of anemia, hemolysis, or neurologic dysfunction. Common neurologic findings are symmetric paresthesias, numbness, decreased vibratory sense, and gait problems, and even neuropsychiatric symptoms, which can occur in the absence of anemia or other hematologic findings. Other associated symptoms include glossitis, hyperpigmentation, and infertility.

A thorough history to elicit potential causes of cobalamin deficiency and a neurologic examination must accompany laboratory evaluation. Patients with pernicious anemia often have other autoimmune disorders (for example, thyroid disease, diabetes mellitus, vitiligo).

Laboratory evaluation typically reveals macrocytic anemia and decreased reticulocyte count. Peripheral blood smears show large oval erythrocytes, hypersegmented neutrophils (≥6 lobes) (**Figure 9**), and possible pancytopenia. Measurement of the cobalamin level has poor sensitivity and specificity and can vary greatly between laboratories, especially in patients with anti-intrinsic factor antibodies. A reasonable first step in evaluating suspected vitamin B_{12} deficiency is a serum cobalamin level, with levels greater than 300 pg/mL (221 pmol/L) making deficiency unlikely and levels less than 200 pg/mL (148 pmol/L) strongly suggesting deficiency. If diagnostic uncertainty exists, methylmalonic acid and homocysteine measurement may be helpful. Both are elevated in 98% of patients with cobalamin deficiency, even in patients with neurologic symptoms without anemia. Levels should be measured before repletion therapy is initiated. Methylmalonic acid levels can be mildly elevated in kidney injury, but levels greater than 500 nmol/L are reasonably specific for cobalamin deficiency. Homocysteine levels are less specific and can be elevated in folate deficiency as well. Methylmalonic acid and total homocysteine levels are helpful in differentiating cobalamin deficiency (both levels are elevated) from folate deficiency (elevated homocysteine but normal methylmalonic acid level).

Bone marrow biopsy is not necessary to diagnose cobalamin deficiency and can be confusing, showing hypercellular, dysplastic changes that could be mistaken for myelodysplastic syndrome or an acute myeloid leukemia.

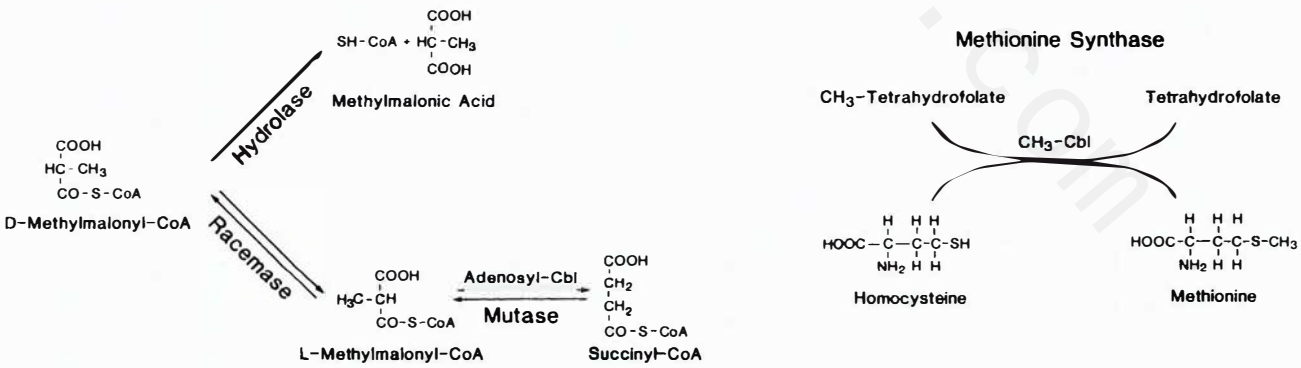

FIGURE 8. The two cobalamin (vitamin B_{12})-dependent enzymes, L-methylmalonyl-CoA mutase (*left*) and methionine synthase (*right*).

Reprinted with permission from Sumner AE, Chin MM, Abrahm JL, et al. Elevated methylmalonic acid and total homocysteine levels show high prevalence of vitamin B12 deficiency after gastric cancer. Ann Intern Med. 1996;124(5):469-476. Copyright 1996 American College of Physicians.

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FIGURE 9. Cobalamin deficiency is often accompanied by macrocytic (large) erythrocytes and hypersegmented neutrophils with six or more nuclear lobes as shown in the image.

CONT.

A bone marrow examination might be helpful if these disorders are suspected and the patient is not responding to replacement therapy.

Parietal cell antibody levels are sensitive for pernicious anemia, but can also be positive in chronic gastritis. Antibodies to intrinsic factor are more specific. Patients with unexplained cobalamin deficiency should be tested for pernicious anemia.

Deficiency resulting from insufficient dietary intake is rare and requires chronic, long-standing nutritional deficiency. It can be prevented by foods enriched with vitamin B_{12} and/or oral supplementation of more than 2 µg/d in persons with low dietary cobalamin intake. Malabsorption must be overcome with either high-dose oral supplementation or injections.

High-dose oral supplementation of 1000 to 2000 µg/d is usually as effective as parenteral administration, even in patients with intrinsic factor insufficiency, and should be the initial therapy for most patients.

In patients with severe anemia, neurologic dysfunction, or those not responding to oral replacement, cobalamin injections (intramuscular or subcutaneous) ensure adequate delivery, usually with 1000 µg several times per week for 1 to 2 weeks, then weekly until symptom relief or improved findings. Monthly injections thereafter are indicated if the underlying cause persists (for example, pernicious anemia).

The hematologic recovery is usually quick, with an increased reticulocyte count in 1 week and correction of megaloblastic anemia in 6 to 8 weeks. Neurologic recovery depends on the duration of symptoms before treatment, can include transient worsening, and may take weeks to months.

KEY POINTS

- Methylmalonic acid and total homocysteine levels are helpful in differentiating cobalamin deficiency (both levels are elevated) from folate deficiency (elevated homocysteine but normal methylmalonic acid level); bone marrow biopsy is not necessary and can be confusing.
- High-dose oral vitamin B_{12} supplementation of 1000 to 2000 µg/d is usually as effective as parenteral administration, even in patients with intrinsic factor insufficiency, and should be the initial therapy for most patients.

HVC

Folate Deficiency

Like cobalamin deficiency, folate deficiency leads to impaired DNA synthesis resulting in a megaloblastic anemia (MCV >100 fL). The bone marrow is characterized by erythroid hyperplasia with abnormal (megaloblastic) morphology.

Folate is available from animal and nonanimal sources (including asparagus, broccoli, spinach, lemons, mushrooms, fortified grains). Despite that, most folate deficiency is dietary in nature and particularly affects older adults, patients in nursing homes, and persons who consume large amounts of alcohol. Other causes of deficiency include malabsorption from entities such as celiac disease, inflammatory bowel disease, or short gut syndrome; medications accelerating folate metabolism, including phenytoin, trimethoprim, and methotrexate; and conditions requiring higher folate intake, including pregnancy, lactation, states of chronic hemolysis, and exfoliant dermatitis. Compared with cobalamin, folate is not well stored, and deficiency can occur in weeks rather than months. Symptoms of folate deficiency are usually related to the anemia, and neurologic deficits do not manifest.

Laboratory findings are similar to cobalamin deficiency (macrocytic anemia, hypersegmented neutrophils). Likewise, homocysteine levels are elevated in folate deficiency, although in contrast, methylmalonic acid levels will not be elevated. Serum folate levels have short-range fluctuations and are a poor measure of deficiency. Serum levels can normalize after a single folate-containing meal. However, they can be a good screening tool, especially if they are low in the absence of recent folate ingestion.

Folate deficiency can be treated with oral folic acid, 1 to 5 mg/d, until complete hematologic recovery; oral therapy is effective even in malabsorption conditions. Cobalamin deficiency should be excluded before initiating therapy, because large doses of folic acid may lead to improved hematopoiesis despite cobalamin deficiency, thus leaving patients vulnerable to central and peripheral nervous system injury from vitamin B_{12} deficiency.

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KEY POINTS

- Folate deficiency can be treated with oral folic acid, 1 to 5 mg/d, until complete hematologic recovery; oral therapy is effective even in malabsorption conditions.
- Cobalamin deficiency should be excluded before initiating folate deficiency therapy, because large doses of folic acid may lead to improved hematopoiesis despite cobalamin deficiency, leaving patients vulnerable to central and peripheral nervous system injury from vitamin B_{12} deficiency.

Hemolytic Anemias

Overview

Hemolytic anemias are characterized by early destruction of erythrocytes secondary to lysis. This happens within the circulatory system (intravascular); in the spleen, liver, or bone marrow (extravascular); or both. It can be due to an inherited defect (erythrocyte membrane or enzymatic defect, abnormal hemoglobin synthesis) or an acquired disorder (immune or nonimmune) (**Table 21**).

Hemolytic processes are characterized by compensatory increases in erythrocyte production (reticulocytosis) in many, but not all, cases; signs of erythrocyte destruction (elevated indirect bilirubin and lactate dehydrogenase [LDH]); and free hemoglobin secretion (hemosiderinuria, hemoglobinuria). If erythrocyte destruction and production do not balance, anemia results. A peripheral blood smear can be very useful in distinguishing different causes (**Table 22**).

Symptoms of hemolytic anemia depend on the severity and chronicity. Besides the usual symptoms of anemia, jaundice can be seen with acute hemolytic anemia and cholelithiasis can develop with chronic hemolysis. In severe cases, extramedullary hematopoiesis can occur and result in hepatosplenomegaly or lymphadenopathy that develops over years.

TABLE 22. Causes of Hemolytic Anemia Determined by Peripheral Blood Smear

Finding on Peripheral Blood Smear	Associated Disease State
Spherocytes	Hereditary spherocytosis
	Autoimmune hemolytic anemia
Target cells	Thalassemia
	Hemoglobin C
	Liver disease
Schistocytes	Microangiopathic hemolytic anemia
Bite cells	Glucose-6-phosphate dehydrogenase deficiency

Congenital Hemolytic Anemias

Hereditary Spherocytosis

Hereditary spherocytosis (HS) is a common form of inherited anemia in people of Northern European descent. It is usually autosomal dominant (75% of patients), but can also be recessive. Mutations causing deficiencies or dysfunction in five erythrocyte membrane proteins (α-spectrin, β-spectrin, ankyrin, band 3, and protein 4.2) have been identified. These will adversely affect the interaction between the lipid bilayer and cytoskeleton layer of the erythrocyte wall, reducing surface-to-volume ratio. Ultimately, this results in osmotically fragile spherocytes (hemolysis) and splenic sequestration (splenomegaly).

Symptoms of HS range from asymptomatic carrier states to severe hemolysis. Symptomatic patients usually present with anemia, jaundice, and splenomegaly and may have pigmented (bilirubin) gallstones.

Typical laboratory findings include spherocytes on peripheral blood smear and varying degrees of anemia, reticulocytosis, and bilirubin elevation. An increased mean corpuscular hemoglobin concentration reflecting membrane loss and erythrocyte dehydration is characteristic. Patients with representative

TABLE 21. Examples of Congenital and Acquired Causes of Hemolytic Anemia

Congenital Hemolytic Anemias	Examples
Defects in the erythrocyte membrane	Hereditary spherocytosis
Deficiencies in erythrocyte metabolic enzymes	Glucose-6-phosphate dehydrogenase deficiency
Defects in hemoglobin structure or synthesis	Sickle cell disease, α- and β-thalassemia
Acquired Hemolytic Anemias	**Examples**
Autoimmune hemolytic anemia	Warm autoimmune hemolytic anemia, cold agglutinin disease
Microangiopathic hemolytic anemias	Thrombotic thrombocytopenic purpura, disseminated intravascular coagulation
Paroxysmal nocturnal hemoglobinuria	
Infectious, chemical, and physical agents	*Plasmodium* species, *Babesia microti*, *Clostridium perfringens* (formerly *C. welchii*), *Bartonella bacilliformis*, copper, thermal injury, venoms and toxins (brown recluse spider bites)

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clinical and laboratory findings, especially if they have a family history of HS, do not require additional testing for the diagnosis. In less obvious presentations, the cryohemolysis test and eosin-5-maleimide binding test are effective screening tests with high predictive value, although they are not readily available at most hospitals. Additionally, the osmotic fragility test has not performed well as a screening test.

As in other hemolytic anemias, folate is consumed during active hemolysis, which could lead to a megaloblastic anemia. Folic acid supplementation is recommended in moderate and severe forms of HS. Splenectomy is effective in reducing hemolysis and should be considered in severe conditions. Partial splenectomy can be effective, especially in children in whom preserved splenic immune function is desired. It is important to appropriately vaccinate patients against encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* before splenectomy.

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked disorder, thus primarily affecting men. Women can be affected in the rare event of homozygous disease, lyonization with preference of expression of the defective gene, and in XO karyotypes. It is the most common enzyme deficiency in humans, with about 140 identified gene mutations. These affect the enzyme G6PD, the first enzyme in the pentose phosphate pathway, a crucial step in nicotinamide adenine dinucleotide phosphate reduction (NADP to NADPH), which is essential for cells to counterbalance oxidative stress. G6PD deficiency occurs most commonly in people of African, Asian, Mediterranean, and Middle Eastern descent.

It can cause various clinical phenotypes and presents with neonatal jaundice or acute hemolysis in response to a "trigger." Certain medications (sulfonamides, some antimalarials, rasburicase), naphthalene in mothballs, fava beans, and infection can trigger hemolysis within 24 to 72 hours. Clinical manifestations can range from asymptomatic mild hemolysis to severe hemolysis. The most common G6PD mutation found in blacks typically results in a very mild defect that may or may not lead to clinically relevant hemolysis following use of oxidative drugs or other stress. Some patients may have chronic nonspherocytic hemolysis. Patients often report fatigue, jaundice, shortness of breath, and dark urine. Typical laboratory markers for hemolysis are present and peripheral blood smears show typical bite cells (**Figure 10**) and Heinz bodies (**Figure 11**), which are denatured oxidized hemoglobin visualized as intranuclear inclusions seen on supravital stain. Severe hemolysis can lead to acute kidney injury and dialysis; chronic hemolysis can lead to cholelithiasis.

A fluorescent spot screening test for G6PD activity detects the formation of NADPH and is reliable in men who are not experiencing an acute hemolytic episode. This test is less useful in acute episodes, with reticulocytosis (young cells produce higher levels of enzyme), and in women (chimerism); measuring quantitative G6PD enzyme activity can provide a more specific diagnosis.

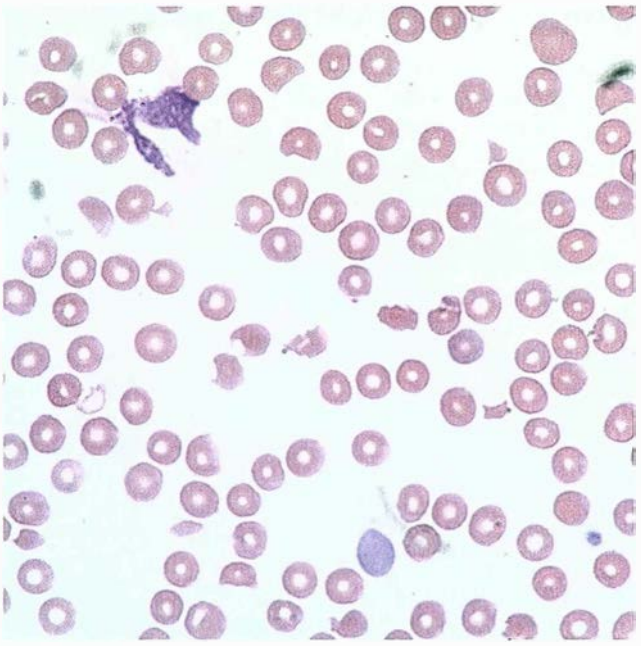

FIGURE 10. Bite cells seen at the center of this slide are typical findings in glucose-6-phosphate dehydrogenase (G6PD) deficiency and are characterized by a membrane defect that appears as though a semicircular bite has been taken out of the erythrocyte. The defect is caused by removal of denatured hemoglobin by macrophages in the spleen.

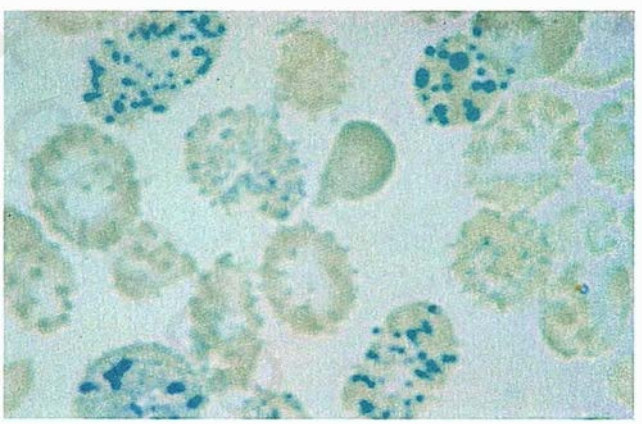

FIGURE 11. Erythrocytes with Heinz bodies in a patient with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a type of hemolytic anemia.

The most effective management of G6PD deficiency is prevention of hemolytic episodes by avoiding offending agents. When hemolysis occurs, treatment is supportive, with blood transfusions reserved for severe cases. The use of antioxidants such as vitamin E and selenium is controversial.

Thalassemia

The hemoglobin molecule in normal erythrocytes is made up of two α- and two β-globin subunits ($\alpha_2\beta_2$). Thalassemia is a common genetic disorder caused either by a mutation in the

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α globin (chromosome 16) or the β globin (chromosome 11) that leads to a quantitative deficiency in the synthesis of that globin chain. The imbalance in globin chain synthesis leads to impaired production of hemoglobin and ineffective erythropoiesis, with intramedullary hemolysis. Severity of the associated microcytic anemia depends on how many globin chains are affected and the severity of the mutation. Of the world population, 1% to 5% has a mutation in at least one β chain; mutations in an α chain are even more common. This incidence of thalassemia is especially high in Mediterranean countries, the Middle East, tropical and subtropical regions of Africa, Asia, and Southeast Asia.

Unlike iron deficiency, the overall erythrocyte count is normal to elevated in α- and β-thalassemia, and iron studies are in the normal range. Decreased β-chain synthesis leads to impaired production of hemoglobin A ($\alpha_2\beta_2$) and resultant increased synthesis of hemoglobin A_2 ($\alpha_2\delta_2$) and/or hemoglobin F ($\alpha_2\gamma_2$). The hemoglobin electrophoresis in α-thalassemia shows a normal pattern and cannot be differentiated from that of a person without thalassemia.

α-thalassemia

Duplication of the α-globin chain on chromosome 16 results in 4 α-globin genes (αα/αα); α-thalassemia results from deletion of one or more of these. The diagnosis is suspected in individuals with microcytic anemia not consistent with iron deficiency anemia and normal hemoglobin A_2 levels on electrophoresis.

The absence of one α gene (-α/αα) results in an asymptomatic carrier state. Absence of two α genes (-α/-α or --/αα) results in a mild microcytic anemia (α-thalassemia trait or α-thalassemia minor). Deletion of three α genes (--/-α), known as hemoglobin H disease, results in moderate microcytic anemia with hemoglobin levels of 8 to 10 g/dL (80-100 g/L), some hemolysis, and splenomegaly. α-Thalassemia trait and hemoglobin H disease are easily confused with iron deficiency anemia because of their microcytic nature. The complete absence of α-globin chains results in hydrops fetalis and intrauterine fetal demise.

Patients with α-thalassemia trait do not require treatment or further monitoring, but should be well educated regarding the condition to prevent unnecessary treatment with iron supplementation in the future. In hemoglobin H disease, blood transfusions occasionally become necessary if the patient is significantly symptomatic from the anemia, predisposing the patient to iron overload. As with any other hemolytic anemia, oral folic acid at 1 mg/d should be given.

β-thalassemia

More than 200 mutations in the β-globin chain have been described and may result in mild to severe reduction of β-chain expression (β^+-thalassemia) or complete gene deletion (β^0-thalassemia). This translates into a range of clinical diseases based on the degree of β-chain expression, classified into phenotypic subtypes of thalassemia minor, intermedia, and major.

Heterozygous gene mutations result in β-thalassemia trait (minor) characterized by an asymptomatic, microcytic (MCV 60-70 fL) mild anemia (hemoglobin 10-13 g/dL [100-130 g/L]), which is often confused with iron deficiency anemia. Homozygous or compound heterozygous (different mutations affecting the two genes) mutations result in more severe disease, depending on the type of mutation, and result in overstimulation of the bone marrow, ineffective erythropoiesis, and potential iron overload. Mild to moderate forms of β-thalassemia (intermedia) are associated with moderate hemolytic anemia, maintaining hemoglobin levels (>7 g/dL [70 g/L]) without transfusion support. Patients usually present during childhood with varying degrees of hemolytic anemia. Relatively normal growth without blood transfusions is common, but patients may require transfusions during periods of worsened and symptomatic anemia (such as aplastic crisis during infection). Complications from chronic hemolysis, such as folate deficiency and cholelithiasis, can occur. Folic acid supplementation is indicated. As in α-thalassemia, patients are often mistakenly diagnosed with iron deficiency anemia because of microcytosis, but iron replacement is only indicated if true iron deficiency can be demonstrated. Severe β-thalassemia (major) presents early in life with pallor, failure to thrive, severe hemolytic anemia, erythroid hyperplasia in the bone marrow, associated bone deformities, and massive hepatosplenomegaly due to extramedullary hematopoiesis. These patients, if untreated, usually die in the first or second decade of life.

Monthly erythrocyte transfusion should be initiated for hemoglobin levels less than 7 g/dL (70 g/L). Other contributing causes of anemia must be excluded (such as G6PD deficiency), and folic acid supplementation is required. However, risks of chronic transfusions include iron overload with subsequent cardiomyopathy, hepatic fibrosis, and endocrine dysfunction. Even patients not receiving transfusions are at risk for iron overload because of increased iron absorption as a result of ineffective erythropoiesis. Close monitoring and iron chelation therapy (if indicated) are crucial in all patients with thalassemia intermedia and major.

Subcutaneous desferrioxamine or an oral iron chelation agent (deferasirox, deferiprone), as monotherapy or combined, have shown good efficacy in reducing liver and myocardial iron load.

Allogeneic hematopoietic stem cell transplantation (HSCT) can be curative and should be considered with severe forms, preferably before the onset of end-organ damage.

Sickle Cell Syndromes

Sickle cell disease (SCD) is a recessively inherited hemoglobinopathy characterized by a single point mutation in the β-globin chain resulting in abnormal hemoglobin. This abnormal hemoglobin S (Hb S) results in polymerization of hemoglobin molecules under oxidative stress, leading to a formational change of the erythrocyte to a sickle shape and subsequent obstruction of the circulation as well as resultant

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hemolysis. Adhesion of cells to the endothelium, inflammation, decreased nitric oxide (due to binding with free hemoglobin released from lysing erythrocytes), and resulting vasoconstriction contribute to this complex pathophysiology.

Because most gene mutations are of African origin, most patients with homozygous sickle cell anemia (Hb SS) in the United States are black and about 1/200 blacks has sickle cell trait. The Hb S mutation can be coinherited with other hemoglobinopathies, resulting in differentiating values on hemogram and hemoglobin electrophoresis (**Table 23**).

Interestingly, these single point mutations causing Hb SS can result in a wide array of phenotypic expression in SCD, potentially affecting any organ system and leading to significantly decreased life expectancy.

Sickle Cell Disease Complications and Their Management

SCD results in a chronic hemolytic anemia, and maintenance of blood counts is dependent on a chronic, brisk reticulocytosis that is vulnerable to infections (particularly parvovirus B19) and vitamin deficiencies (folate deficiency). The three common disease-altering strategies are allogeneic HSCT, prophylactic transfusions, and hydroxyurea therapy. The timing and patient population for whom HSCT should be considered have not been clarified. Patients not considered for HSCT or prophylactic transfusions should be evaluated to receive hydroxyurea if they experience one or two vaso-occlusive episodes per year. Hydroxyurea therapy has been shown to decrease vaso-occlusive episodes and acute chest syndrome (ACS), to decrease transfusion requirements and hospitalizations, and to prolong overall survival.

The management of sickle cell complications is complex, benefits from a comprehensive care model, and must include preventive, acute, and chronic treatment approaches (**Table 24**).

Painful episodes are the hallmark of SCD resulting from vaso-occlusive ischemic episodes. Although most of these episodes seem to be spontaneous, precipitating factors (dehydration, temperature/climate changes, physical or emotional stress, infection, asthma, acidosis, sleep apnea, pregnancy) can cause them. The pain can occur anywhere in the body and take place only a few times over a lifetime or up to several episodes per month. Acute pain often requires treatment with scheduled narcotics with the exception of meperidine, which has been associated with a lower seizure threshold and is not recommended. H

Chronic pain is common in SCD and is poorly understood. The pain tends to be constant, lasting for months and years and can affect any body part. It is often triggered by frequent, severe, acute painful episodes and is thought to be a hypersensitization to normal environmental stimuli. Chronic pain is often accompanied by depression, anxiety, insomnia, and chronic narcotic use and dependency. Patients benefit from a multidisciplinary, multimodality approach (for example, opioids, NSAIDs, antidepressants, relaxation techniques, massage, acupuncture, biofeedback).

ACS results from vaso-occlusive involvement of the pulmonary vasculature and is diagnosed by new pulmonary infiltrates involving at least one complete lung segment that is consistent with alveolar consolidation with either chest pain, fever (>38.5 °C [101.3 °F]), tachypnea, wheezing, or cough. It is crucial to consider and rule out other causes that may present similarly, including infectious pneumonia, fat or bone marrow embolism, or more traditional venous thromboembolism. H

Infection, particularly with encapsulated bacteria such as pneumococcus, was previously the primary cause of death in SCD. It has now been surpassed by cardiopulmonary causes (pulmonary hypertension, pulmonary thromboembolism,

TABLE 23. Characteristics of Adult Sickle Cell Syndromes

Disease Type	Hb (g/dL)	MCV (fL)	Hb S (%)	Hb A (%)	Hb A_2 (%)	Peripheral Blood Smear Findings	Clinical Severity[a] 0 to +++
Sickle trait (AS)	NL	NL	40	60	<3.5	NL	0
Hb SS	6-8	NL	>90	0	<3.5	Sickle cells	+++
$S\beta^+$-Thalassemia	9-12	70-75	>60	10-30	>3.5	Rare sickle cells Target cells	+ to ++
$S\beta^0$-Thalassemia	7-9	65-70	>80	0	>3.5	Sickle cells Target cells	+++
SCD	10-15	75-NL	50	0	Hb A_2 = 0 Hb C = 50[b]	Fat sickle cells Target cells	+ to ++

Hb = hemoglobin; Hb SS = homozygous sickle cell anemia; MCV = mean corpuscular volume; NL = normal; $S\beta^+$ = sickle β^+; $S\beta^0$ = sickle β^0; SCD = sickle cell disease.

[a]Clinical severity is variable within each genotype.

[b]Note that Hb C comigrates with Hb A_2 on standard alkaline cellulose acetate electrophoresis but will separate on citrate agar electrophoresis.

NOTE: Hb percentages may not total 100% because Hb F is not included in this table.

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TABLE 24. Common Complications and Treatments in Adults with Sickle Cell Disease

Complications	Treatment
Vaso-occlusive pain episode	**Acute:** rest, relaxation, warmth, NSAIDs, oral and IV hydration, narcotic analgesia
	Recurring: HU, avoidance of triggers, nonnarcotic or narcotic analgesia
Acute chest syndrome	**Acute:** oxygen, incentive spirometry, analgesics, empiric antibiotics, IV fluids, simple or erythrocyte exchange transfusions
	Preventive: HU, incentive spirometry
Aplastic crisis	**Acute:** supportive care, blood transfusions as needed
Infection	**Acute:** Appropriate and immediate antibiotic management (particular concern for encapsulated bacteria)
	Prevention: Influenza, pneumococcal, and meningococcal vaccines
Hyperhemolytic crisis	**Acute:** supportive care, avoid further blood transfusions, immunosuppression might be helpful
	Preventive: avoid blood transfusions if possible, extended antibody screen can lessen but not eliminate recurrence
Multiorgan failure	**Acute:** Erythrocyte exchange transfusions
Ischemic stroke	**Acute:** Erythrocyte exchange transfusions, aspirin
	Preventive: Chronic simple transfusions or erythrocyte exchange transfusions (target Hb S <30%-50%)
Hepatic crisis	**Acute:** Supportive, transfusion or exchange transfusion if anemia is symptomatic
Cholelithiasis	**Acute:** If symptomatic, cholecystectomy with preoperative transfusions to hemoglobin of 10 g/dL (100 g/L)
Chronic kidney disease/ proteinuria	**Preventive:** good blood pressure control to <130/80 mm Hg
	Secondary preventive: ACE inhibitor or ARB
Priapism	**Acute:** relaxation, hydration, narcotic analgesics, aspiration of blood from corpora cavernosa and irrigation with dilute epinephrine, transfusions, shunt procedure
	Preventive: oral α-adrenergic agonists, HU. The role of leuprolide and sildenafil is not clear.
Pulmonary hypertension	No proven therapy established for prevention or treatment
Retinopathy	Annual ophthalmologic examination, laser phototherapy as needed
Osteopenia/osteoporosis	Supplementation with calcium and vitamin D
Avascular necrosis	Chronic narcotic analgesia, arthroplasty
Foot and leg ulcers	**Acute:** early aggressive treatment, debridement, bandage impregnated with zinc oxide
	Preventive: proper footwear to prevent pressure points

ARB = angiotensin receptor blocker; Hb S = hemoglobin S; HU = hydroxyurea; IV = intravenous.

CONT.

pulmonary microthrombi, sudden cardiac death) but remains a major factor in morbidity and mortality. In febrile patients, especially with leukocyte counts above baseline, infection with encapsulated bacteria must always be considered (even in vaccinated persons) and must be treated immediately.

Pulmonary hypertension can be a chronic and severe complication of SCD, and about 25% to 30% of persons with Hb SS or Hb Sβ⁰-thalassemia will have suggestive abnormalities on echocardiogram. Of those, 25% of patients will have confirmed pulmonary hypertension on right heart catheterization. In patients with confirmed pulmonary hypertension, an increased tricuspid regurgitation velocity on Doppler echocardiography has been associated with increased mortality. Advanced age; a history of leg ulcers; higher LDH, creatinine, alkaline phosphatase, and N-terminal proB-type natriuretic peptide levels; and a higher New York Heart Association functional class scoring are associated with increased mortality risk. No proven therapy is available for the prevention or treatment of pulmonary hypertension.

Persons with SCD are at increased risk for ischemic stroke during childhood and with advancing age. The Hb SS subtype is more affected than Hb SC, and stroke is rare in Hb Sβ⁰-thalassemia subtypes. In children, transcranial Doppler (TCD) ultrasonography of the middle cerebral arteries (to assess for increased velocity) has been shown to be a strong predictor of stroke risk, and prophylactic transfusion or exchange transfusion is proven to reduce this risk. Switching from transfusion to hydroxyurea therapy in these patients to lessen the risk of iron overload from overtransfusion increases the risk for ischemic stroke without improving iron concentration. Approximately 30% of patients with Hb SS or Sβ⁰-thalassemia without overt stroke may have silent infarcts. Lower hemoglobin levels, male sex, and higher blood pressure may be

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predisposing factors. Transfusion protocols to prevent or treat silent strokes have not been established.

Differing from strokes during childhood, strokes in the third and fourth decades of life tend to be hemorrhagic and are often attributable to underlying moyamoya disease (arterial narrowing at the basal ganglia and resulting fragile collateral circulation).

Adults with sickle cell anemia have lower neurocognitive performance than matched controls. This decreased neurocognitive performance (memory, processing speed, and executive function) is related to lower baseline hemoglobin levels (especially in older patients), but does not correlate with abnormal findings on MRI. No preventive measures have been established for decreasing neurocognitive function.

Hepatic crisis is characterized by right upper quadrant pain, elevated liver enzyme levels, and an enlarged liver. Hepatic crisis due to vaso-occlusive sickle cell episodes usually has a sudden onset and is self-limiting. It can be associated with hepatic sequestration typified by a rapid enlargement of the liver and decrease in hemoglobin level. Transfusion or exchange transfusion is the treatment of choice to support symptomatic anemia. Other causes such as acute or chronic hepatitis, liver involvement from hemosiderosis, and cholelithiasis should not be overlooked.

Nephropathy caused by decreased medullary blood flow, microinfarct, and papillary necrosis can result in CKD in SCD. Proteinuria is associated with progressively declining GFR and is evidence of glomerular injury. Impaired ability to concentrate urine, hematuria, urinary tract infections, and limited renal acidification and potassium secretion are common. Patients must be monitored periodically (serum creatinine level and testing for proteinuria every 3-6 months) for declining kidney function and require strict blood pressure control. Proteinuria should be treated with an ACE inhibitor or an angiotensin receptor blocker. Progression of kidney disease despite these measures may require dialysis and kidney transplantation.

Priapism is an unwanted, painful, sometimes recurrent penile erection lasting for hours to days. It is a common (35% of men with SCD) and often understated complication of SCD in young men and can lead to erectile dysfunction and impotence. The pathophysiology is not fully understood, but obstruction of venous outflow seems to be a contributing factor.

Decreased bone density is common in SCD and may be a result of vitamin D deficiency, increased bone resorption, or bone necrosis due to vaso-occlusion. Treatment with vitamin D, calcium, and bisphosphonates has not been studied. Avascular necrosis is common and poses a major problem because it presents with daily pain in children and young adults. It is uncertain what the best timing is for joint replacement in this relatively young population.

Spontaneous or traumatic leg ulcers are common in SCD, are related to impaired circulation, and are often complicated by prolonged wound healing. They are often located on the lower legs, particularly the medial and lateral ankle. Lower hemoglobin and increased hemolytic markers are associated with increased risk of skin ulcers.

Allogeneic HSCT to at least achieve chimerism between the donor and recipient (production of donor cells while retaining production of some recipient cells) has been investigated, and a small study in adults showed significant reduction in Hb S, increase in baseline hemoglobin level, and decrease in hemolysis in patients who received a nonmyeloablative transplant from a matched sibling. All of these patients were alive 1 year after the transplant and none had developed graft-versus-host disease.

Erythrocyte Transfusions in Sickle Cell Disease

Persons with SCD typically have baseline hemoglobin levels of 6 to 7 g/dL (60-70 g/L) in Hb SS and 8 to 10 mg/dL (80-100 g/L) in Hb SC; however, they have physiologically adjusted to this anemia. Transfusion to achieve hemoglobin levels of persons without SCD can be dangerous and lead to hyperviscosity. Therefore, persons with SCD should not receive transfusions unless they have significant symptoms from their anemia (dizziness, shortness of breath, chest pain that is significantly worse than their typical vaso-occlusive symptoms) or they have signs of end-organ failure (such as acute neurologic symptoms, ACS, multiorgan failure). Transfusions for simple vaso-occlusive pain are generally not indicated.

Transfusions may have significant adverse effects. The risk of infection was highlighted in the 1980s and 1990s with blood product contamination by HIV and hepatitis C virus. Patients who received transfusions in those years should be screened for these viruses. Better donor screening and disease surveillance have minimized, but not eliminated, this risk. Another significant risk is alloimmunization (see Transfusion), and as many as 18% of patients with SCD who undergo transfusion develop alloantibodies. This particularly affects women of childbearing age. Phenotypic matching for the C, E, and K antigens can decrease alloimmunization significantly and is done at some, but not all, institutions. Antibody formation may be immediate, but can cause delayed hyperhemolytic reactions (significant hemolysis with precipitous drop in hemoglobin level and increase in hemolytic markers such as LDH and indirect bilirubin) occurring 2 to 19 days after transfusion, presenting a significant, life-threatening challenge. Additionally, because mechanisms for eliminating iron are limited, erythrocyte transfusions carry an increasing cumulative risk of iron overload. This primarily results in liver damage, and close surveillance and iron chelation are indicated. In patients receiving regular transfusions (such as for stroke prevention), erythrocyte exchange transfusions can lessen the iron burden by removing some of the patient's erythrocytes.

Patients undergoing surgery should be transfused before their procedure to avoid complications. Transfusion to a hemoglobin level of 10 g/dL (100 g/L) has been shown to be equivalent to exchange transfusions in low- to medium-risk surgeries (low-risk surgery includes adenoidectomy,

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CONT. inguinal-hernia repair; medium-risk surgery includes cholecystectomy, joint replacement).

Other Hemoglobinopathies

More than 1000 mutations of the globin chains have been identified. Besides the most common hemoglobinopathies (sickle cell anemia and thalassemia), several rarer types can occur.

Hemoglobin C is a common mutation in black patients. Those with homozygous disease may have mild microcytic anemia and demonstrate numerous target cells on peripheral blood smear. Sickling only occurs if it is coinherited with Hb S, which typically leads to a milder form of SCD.

KEY POINTS

- Patients with chronic hemolytic anemias should receive folic acid supplementation and pneumococcal (13- and 23-valent), *Haemophilus influenzae* type b, influenza, and meningococcal immunizations.
- Acute hemolysis caused by glucose-6-phosphate dehydrogenase deficiency is characterized by typical laboratory markers for hemolysis and peripheral blood smears showing bite cells and Heinz bodies.
- The thalassemias are characterized by microcytosis, target cells, normal iron studies, and an elevated or normal erythrocyte count; electrophoresis in β-thalassemia shows slightly increased hemoglobin A_2 levels and fetal hemoglobin levels, whereas in α-thalassemia it shows a normal pattern.
- The three common disease-altering strategies in congenital hemolytic anemias are hematopoietic stem cell transplantation, prophylactic transfusions, and hydroxyurea therapy.

(Continued)

KEY POINTS *(continued)*

- In patients with sickle cell disease, hydroxyurea therapy has been shown to decrease vaso-occlusive episodes, acute chest syndrome, transfusion requirements, and hospitalization and to prolong overall survival.
- Persons with sickle cell disease should not receive transfusions unless they have symptomatic anemia or signs of end-organ damage. HVC

Acquired Hemolytic Anemias

Immune-Mediated Hemolysis

The mechanism underlying immune-mediated hemolysis involves antibodies binding to erythrocytes, with or without the activation of complement, leading to erythrocyte destruction. Antibodies causing hemolysis can be divided into two categories, warm and cold, referring to the optimal temperature for antibody-erythrocyte interaction. Antibodies reacting to erythrocytes at body temperature lead to warm autoimmune hemolytic anemia; those reacting at less than normal body temperature lead to a form of autoimmune hemolytic anemia also termed cold agglutinin disease. The characteristics of these conditions are listed in (**Table 25**). The hallmark of immune-mediated hemolytic anemia is the direct antiglobulin (Coombs) test, which tests for either IgG or C3 bound to erythrocytes.

Warm Autoimmune Hemolytic Anemia

In warm autoimmune hemolytic anemia, pathogenic IgG antibodies are directed against erythrocyte surface membrane molecules. IgG-coated membrane fragments are engulfed by macrophages in the reticuloendothelial system through Fc receptors, leading to loss of erythrocyte surface area, causing the erythrocytes to become progressively more spherocytic. Warm autoimmune hemolytic anemia can manifest as a primary disorder or

TABLE 25. Characteristics of Warm Autoimmune Hemolytic Anemia (WAIHA) and Cold Agglutinin Disease

	WAIHA	Cold Agglutinin Disease
Temperature for optimal antibody binding to erythrocytes	37.0 °C (98.6 °F)	<37.0 °C (98.6 °F)
Immunoglobulin class	IgG	IgM
Typical AGT pattern	IgG positive, C3 positive or negative	IgG negative, C3 positive
Peripheral blood smear findings	Spherocytes	Erythrocyte agglutination
Clinical manifestations[a]	Anemia, fatigue, dyspnea, jaundice, splenomegaly	Anemia, fatigue, dyspnea, jaundice, acrocyanosis, splenomegaly
Associated conditions	Autoimmune, lymphoproliferative (chronic lymphocytic leukemia, B-cell non-Hodgkin lymphomas), drug-induced[b]	Infectious (*Mycoplasma* and mononucleosis), lymphoproliferative (IgM MGUS, Waldenström macroglobulinemia, other B-cell non-Hodgkin lymphomas)
Treatment	Glucocorticoids, splenectomy, immunosuppression, treatment of underlying condition	Cold avoidance, rituximab, plasmapheresis, treatment of underlying condition

AGT = antiglobulin (Coombs) test; MGUS = monoclonal gammopathy of undetermined significance.

[a]Manifestations in cold agglutinin disease are worse upon exposure to the cold. Lymphadenopathy in either entity should raise suspicion of a lymphoproliferative disorder.

[b]Cephalosporins, penicillins, NSAIDs, isoniazid, procainamide, methyldopa, levodopa.

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can be a complication of another disorder such as an autoimmune condition or a lymphoproliferative disorder such as chronic lymphocytic leukemia. It can also be induced by certain medications (see Drug-induced Immune Hemolytic Anemia).

The severity of anemia symptoms depends on the rate of hemolysis and the compensatory rise in erythrocyte production. Patients may notice "tea-colored" urine. Clinical findings can include pallor, jaundice, and splenomegaly. Laboratory findings may reveal evidence of ongoing hemolysis, including an increased reticulocyte count, but more consistently reveal an elevated bilirubin level, decreased or absent haptoglobin, and increased LDH level. The direct antiglobulin test is positive, and spherocytes are seen on the peripheral blood smear.

Treatment is based on immunosuppression to halt immune-mediated erythrocyte destruction and allow the patient's own bone marrow to regenerate the erythrocytes, if possible. The physician must judge how well the patient tolerates the anemia and how the patient's marrow is responding. These two factors determine if the patient should receive erythrocyte transfusion. If erythrocytes must be transfused, it is recommended to give a single unit of blood at a time, assessing the patient's status after each unit. Because the autoantibody typically reacts against all erythrocytes, a completely cross-match-compatible unit may be impossible to find. The presence of autoantibodies can mask the presence of underlying alloantibodies that can lead to further hemolytic transfusion requirements, and these scenarios typically require consultation between a hematologist and a transfusion medicine physician. Nonetheless, if the patient is deemed to require additional oxygen-carrying capacity, transfusion of type-specific, cross-match-incompatible blood should be ordered. Patients should also receive glucocorticoids, either orally or parenterally. An inadequate response to glucocorticoids may indicate the need for splenectomy or alternative immunosuppression. Folic acid supplementation is indicated in all patients.

Cold Agglutinin Disease

Pathogenic IgM molecules bind best in colder temperatures, typically in the fingers, toes, and nose. IgM-coated erythrocytes will agglutinate and clump in the microvasculature, leading to cyanosis and ischemia in the cold extremities. IgM also fixes to complement, leading to erythrocyte destruction, either by completion of the complement cascade with intravascular hemolysis or by phagocytosis through complement receptors on macrophages. This disease can be primary, with no other underlying disorders, but may be associated with lymphoproliferative disorders such as Waldenström macroglobulinemia, other B-cell non-Hodgkin lymphomas, and IgM monoclonal gammopathy of undetermined significance. Cold agglutinin disease may also be precipitated by infections, typically *Mycoplasma pneumoniae* or Epstein-Barr virus.

The mainstay of treatment is cold avoidance and treatment of the underlying lymphoproliferative disorder, when appropriate. Treatment with rituximab has been effective, and plasmapheresis should be considered for those with more severe disease manifestations. Unlike in warm autoimmune hemolytic anemia, therapy with glucocorticoids or splenectomy is usually ineffective.

Drug-induced Immune Hemolytic Anemia

Medications can lead to an immune-mediated hemolytic anemia by one of two pathways. Erythrocyte antigens are altered, leading to the development of antibodies with cross-reactivity to unaltered erythrocyte antigens, or antierythrocyte antibodies develop, directed against antigenic drug-protein complexes on the erythrocyte cell surface. The former mechanism can occur with methyldopa, levodopa, or procainamide. Hemolysis ensues within a few weeks to months following therapy initiation and subsides within several months of discontinuing the implicated agent. The latter mechanism is commonly seen with cephalosporins, penicillins, NSAIDs, quinine, quinidine, and isoniazid; occurs within days of starting the drug; and subsides within days of stopping the medication.

Diagnosis is made on clinical grounds and requires a thorough medication history. The direct and indirect antiglobulin tests are typically positive with the former pathway, whereas the indirect antiglobulin test will only be positive with incubation in the presence of the offending agent with the latter pathway. Treatment consists of stopping the offending agent.

Nonimmune Hemolytic Anemia

Nonimmune hemolytic anemia may occur as the result of mechanical trauma to erythrocytes by a microangiopathic mechanism, abnormalities in the heart and large vessels leading to abnormal shear forces from flow through a large pressure gradient (such as in a leaky prosthetic aortic valve or a ventricular septal defect), or direct trauma (as in march hemoglobinuria) (see later section). Infections may lead to hemolysis either through direct infection of the erythrocytes or toxin-mediated membrane damage. Lastly, drugs, chemicals, and venoms may lead to hemolysis.

Microangiopathic Hemolytic Anemia

Microangiopathic hemolytic anemia (MAHA) represents shear damage to erythrocytes as the result of endothelial cell activation or endothelial cell damage. The hallmark of disease is the presence of schistocytes on the peripheral blood smear, typically accompanied by an elevated LDH level and other clues of intravascular hemolysis. Various disorders can cause MAHA and are listed in **Table 26**. Treatment is directed toward the underlying disorder. Thrombotic thrombocytopenic purpura is a catastrophic disorder manifested by MAHA and thrombocytopenia that may be associated with development of other symptoms, including fever, kidney failure, and neurologic findings. It is discussed further in the Platelet Disorders chapter.

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disease in which an abnormal progenitor cell clone develops, resulting in erythrocytes, leukocytes, and platelets that are missing

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TABLE 26. Causes of Microangiopathic Hemolytic Anemia

Cause
Thrombotic thrombocytopenic purpura
Hemolytic uremic syndrome
Disseminated intravascular coagulation
Malignant hypertension
Vasculitis
Eclampsia
HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome
Antiphospholipid antibody syndrome
Scleroderma renal crisis
Metastatic cancer
Calcineurin inhibitors
Solid organ transplant rejection

proteins normally attached to the cell surface by a glycophosphatidylinositol (GPI) anchor. The progenitor cell clone is defective in the gene *PIG-A*, which encodes the enzyme normally responsible for attaching these proteins to the cell surface via the GPI anchor. Among these proteins are CD55 and CD59, which are responsible for inactivating complement on the surface of erythrocytes. PNH cells are therefore more susceptible to complement-mediated lysis. Because complement-mediated lysis occurs more readily at lower pH levels, hemolysis typically occurs at night as the Pco_2 rises, so patients may report hematuria in the morning. For reasons that have not been fully explained, patients are at increased risk for developing thrombosis, especially at unusual sites. Arterial and venous clots are seen with increased frequency, including the Budd-Chiari syndrome (see Hematopoietic Stem Cell Disorders). Patients can also develop pancytopenia, which results from bone marrow hypoplasia. PNH may evolve into aplastic anemia and acute myeloid leukemia in some patients. Conversely, PNH clones may develop in patients with existing aplastic anemia or myelodysplastic syndrome (see Hematopoietic Stem Cell Disorders). Patients require folate repletion because of chronic hemolysis. Iron supplementation or transfusion may be necessary because of urine iron losses or symptomatic anemia, respectively. Eculizumab, a monoclonal antibody that binds C5 and inhibits activation of the terminal component of the complement cascade, decreases hemolysis and the need for erythrocyte transfusions and improves quality of life.

KEY POINTS

- Diagnosis of warm autoimmune hemolytic anemia includes physical and laboratory findings of pallor, jaundice, splenomegaly, increased reticulocyte count, elevated bilirubin level, decreased or absent haptoglobin, increased lactate dehydrogenase level, positive antiglobulin (Coombs) test, and spherocytes on the peripheral blood smear.

(Continued)

KEY POINTS *(continued)*

- The mainstay treatments for warm autoimmune hemolytic anemia and cold agglutinin disease are glucocorticoids and cold avoidance, respectively.

Other Causes of Hemolysis

Macroangiopathic Hemolytic Anemia

Abnormalities within the heart and the large vessels can cause shear damage to erythrocytes. Disorders can include problems with heart valves (especially mechanical heart valves), intracardiac tumors, or rupture of either chordae tendineae or an aneurysm of the sinus of Valsalva. This also produces schistocytes. Patients can become iron deficient because of chronic iron loss through hemosiderin in the urine. Development of hemolysis from a cardiac defect may require surgical correction.

March Hemoglobinuria

This disorder is caused by repetitive trauma to the soles of the feet or palms of the hands and can be provoked by marching, running, hand-drum playing, karate, or head banging. Many individuals who run long distances develop this condition. The Prussian blue stain for urine hemosiderin will be positive.

Hemolysis Associated with Chemical and Physical Agents

Arsenic, especially arsine gas used in the manufacture of semiconductors, can cause severe hemolysis. Elevated copper levels in the serum, either owing to Wilson disease or from copper contamination of dialysis fluid, can lead to hemolysis.

Insect and spider bites, especially the bite of the brown recluse spider, may cause severe intravascular hemolysis. Severe burns cause hemolysis through direct thermal injury to erythrocytes.

Hemolysis from Infections

Malarial infection invariably leads to hemolysis. At least part of the life cycle of all malarial forms occurs within the erythrocyte, requiring lysis to exit. *Babesia microti* is an intracellular parasite carried by the same tick as Lyme disease and leads to hemolysis. *Clostridium perfringens* (the agent of gas gangrene) toxin causes severe hemolysis; the bacteria produce a lysolecithinase, which attacks the membrane bilayer. *Bartonella bacilliformis*, the agent of Oroya fever, is an extracellular bacterium that can cause dramatic hemolytic episodes.

KEY POINTS

- Macroangiopathic hemolytic anemia can be caused by disorders of the heart valves (especially mechanical heart valves), intracardiac tumors, or rupture of chordae tendineae.
- March hemoglobinuria can be caused by repetitive trauma to the soles of the feet or palms of the hands, such as with marching or running.

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KEY POINTS (continued)

- *Plasmodium* species, *Babesia microti*, *Clostridium perfringens*, and *Bartonella bacilliformis* infections can cause hemolytic anemia.

Iron Overload Syndromes

Introduction

Despite iron's importance to living cells, it is toxic when present in excess. Excess iron may arise from increased absorption, related to mutations in iron regulatory genes; from chronic hemolytic states with ineffective erythropoiesis (such as thalassemia major); or from chronic transfusion therapy in diseases such as sickle cell anemia, aplastic anemia, and myelodysplasia.

Primary/Hereditary Hemochromatosis

Hereditary hemochromatosis affects approximately 1 in 400 persons of Northern European ancestry. It results from an autosomal recessive defect in the *HFE* gene, which leads to increased absorption of dietary iron. Two main defects in *HFE*, the *C282Y* and *H63D* mutations, account for most of the genotypic and phenotypic expression of hereditary hemochromatosis. Neither mutation is common in blacks or Asians with iron overload. Homozygosity for *C282Y* is found in 85% to 90% of phenotypically affected persons, and the likelihood of developing disease depends on many factors, including iron intake and rates of blood loss (women do not develop overt iron overload until after menopause). Only 10% of those homozygous for *C282Y* develop symptoms. Persons with one copy of *C282Y* and one copy of *H63D*, known as compound heterozygotes, are at much lower risk for iron overload than those who are homozygous for *C282Y*. Because other gene mutations or alternative causes may exist, approximately 5% to 10% of patients with iron overload have a negative hemochromatosis gene test. Therefore, the absence of *C282Y* does not eliminate the diagnosis of an iron overload disorder.

Most patients with hereditary hemochromatosis are diagnosed in the presymptomatic phase when iron test results are abnormal. In patients with symptoms, clinical presentation varies and often includes nonspecific findings such as chronic fatigue, weakness, nonspecific abdominal pain, arthralgia, and mildly elevated liver enzymes. A predilection for developing arthropathy is seen, especially in the second and third metacarpophalangeal joints. Endocrine organs are commonly affected, and diabetes mellitus, hypothyroidism, and gonadal failure may occur. Patients may present with heart failure or arrhythmias. An increased frequency of depression has been noted. As the disease advances and iron deposition goes untreated, hepatic fibrosis and cirrhosis may develop. When cirrhosis develops, a 200-fold increased risk of hepatocellular carcinoma has been documented.

Early diagnosis is essential to alter the disease course and avoid end-organ complications. The most sensitive and cost-effective initial diagnostic study in patients with suspected hemochromatosis is measurement of the fasting serum transferrin saturation. A consensus does not exist for transferrin saturation cut-off levels for diagnosis of hemochromatosis, with some guidelines recommending a value of greater than 60% in men or greater than 50% in women, and others suggesting a level of greater than 55% for all patients. Serum ferritin level measurement is indicated in patients with an elevated transferrin saturation; a markedly elevated level further supports the diagnosis and predicts the development of symptoms.

Universal screening for hereditary hemochromatosis is not recommended, but testing should be performed in first-degree relatives of patients with classic *HFE*-related hemochromatosis, those with evidence of active liver disease, and in patients with abnormal iron study results obtained for other indications. Screening for hepatocellular carcinoma is reserved for those with hereditary hemochromatosis and cirrhosis.

Patients who are *C282Y* homozygous but have a normal serum ferritin level can be monitored without treatment. In patients with abnormal ferritin levels, prompt and aggressive treatment with phlebotomy before end-organ complications occur will prevent subsequent morbidity and mortality. One unit of blood should be removed at weekly intervals until ferritin levels decrease to 10 to 50 ng/mL (10-50 µg/L), provided the hematocrit is maintained at greater than 30%. Subsequently, life-long maintenance phlebotomy is required. Iron chelation should be considered only rarely for patients in whom phlebotomy is contraindicated.

The risks of eating raw seafood or undercooked pork should be communicated, because the incidence of *Vibrio vulnificus* and *Yersinia enterocolitica* infections is increased in iron overload conditions. Patients with iron overload are also at risk for infection with mucormycosis, especially as they begin iron reduction therapy.

KEY POINTS

- An elevated transferrin saturation remains the most sensitive and cost-effective initial screening test for hemochromatosis. **HVC**
- Universal screening for hereditary hemochromatosis is not recommended and should be reserved for first-degree relatives of patients with classic *HFE*-related hemochromatosis, those with active liver disease, and patients with abnormal iron study results. **HVC**
- Prompt and aggressive treatment with phlebotomy before end-organ complications occur will prevent subsequent morbidity and mortality in patients with hemochromatosis.

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Secondary Iron Overload

In most cases, secondary iron overload occurs in patients with severe anemia who require chronic transfusion therapy. Because iron excretion has no regulated mechanism, multiple transfusions (for anemias not stemming from blood loss or iron deficiency) lead to iron overload, with subsequent secondary organ damage. If these anemias resolve (either from hematopoietic stem cell transplantation or remission from leukemias), phlebotomy should be initiated. When anemia is ongoing, iron chelation is required, for which deferoxamine, deferiprone, or deferasirox may be used. These agents are relatively toxic, leading to potential kidney and liver damage, agranulocytosis, or ocular and ophthalmic disorders.

KEY POINT

- Iron chelation is required in patients with secondary iron overload with ongoing anemia.

Platelet Disorders

Normal Platelet Physiology

Platelets are normally made in the bone marrow from stem cells known as megakaryocytes. The lifespan of a normal platelet is approximately 10 days, and every day one tenth of the total platelet population is replaced. A normal platelet count ranges from 150,000 to 440,000/μL ($150\text{-}440 \times 10^9$/L). The most important hormonal stimulus for platelet production is thrombopoietin.

Platelets play an important role in hemostasis and thrombosis. Platelets form the initial plug at the site of vascular injury in three coordinated steps: adhesion, aggregation, and secretion. At sites of vascular injury, von Willebrand factor (vWF) attaches to subendothelial collagen. Under shear conditions, the vWF exposes binding sites for glycoprotein Ib-IX-V complex on the platelet surface that allow it to become tethered to the vessel wall. Exposure to a variety of agonist agents arising from the injured vessel wall, damaged erythrocytes, and other activated platelets converts glycoprotein IIb-IIIa on the platelet surface to its activated state, allowing it to bind fibrinogen, which can thus aggregate numerous platelets together by providing binding sites for other platelets. Platelets activated by platelet agonists release the contents of their granules, including fibrinogen, epinephrine, and platelet agonists such as adenosine diphosphate, vWF, and factor V, thus propagating the platelet response. Additionally, platelets also serve as the phospholipid scaffold upon which other coagulation reactions occur, including generation of factor Xa and thrombin.

Approach to the Patient with Thrombocytopenia

In diagnosing thrombocytopenia, pseudothrombocytopenia, or platelet clumping, must be excluded. In some patients, platelets will clump in vitro when the anticoagulant ethylenediaminetetraacetic acid (EDTA) is present. The platelet count is thus spuriously low. This can be recognized by viewing platelet clumps on the peripheral blood smear. Drawing blood into a citrated tube frequently eliminates the clumping. No physiologic consequence to this finding exists, and it needs no treatment.

The next step in evaluating thrombocytopenia is to determine if the patient is experiencing symptoms related to the low platelet count. Severe thrombocytopenia leads to mucocutaneous bleeding (that is, epistaxis, gum bleeding, heavy menses, easy bruising, and petechiae). These symptoms are seldom seen at platelet counts greater than 30,000/μL (30×10^9/L). In general, patients with platelet counts greater than 100,000/μL (100×10^9/L) are asymptomatic. Patients with platelet counts between 50,000 and 100,000/μL ($50\text{-}100 \times 10^9$/L) are generally able to undergo abdominal surgery without risk of abnormal bleeding. However, patients with platelet counts less than 10,000/μL (10×10^9/L) are at risk for spontaneous intracranial hemorrhage.

The history should focus on previous platelet counts, if known. A careful list of all newly prescribed and over-the-counter medications should be obtained in patients with a new thrombocytopenia, because many medications can cause thrombocytopenia. A history of autoimmunity may point to immune thrombocytopenic purpura (ITP), and a history of fever, headache, hematuria, or abdominal pain may indicate thrombotic thrombocytopenic purpura (TTP). Physical examination should focus on the presence or absence of mucocutaneous bleeding. Stigmata of liver disease may point to the cause of thrombocytopenia, because splenomegaly can cause platelet sequestration.

Laboratory evaluation requires peripheral blood smear assessment, looking for schistocytes, which must be seen to diagnose TTP and may be seen in disseminated intravascular coagulation (DIC) and other causes of microangiopathic hemolytic anemia (MAHA) associated with thrombocytopenia. Prothrombin and activated partial thromboplastin times, fibrinogen level, and D-dimer measurement can be ordered if DIC is suspected. Thyroid function should be checked because both hyper- and hypofunction of the thyroid can lead to thrombocytopenia. It is recommended that antibodies to HIV and hepatitis C virus be determined in all patients being evaluated for thrombocytopenia. Other laboratory evaluations should be guided by the disease entity suspected.

Thrombocytopenic Disorders

The differential diagnoses for thrombocytopenia can be broadly attributed to three causes: disorders of underproduction, splenic sequestration, or peripheral destruction.

Underproduction thrombocytopenias are characterized by inadequate megakaryocyte numbers in the bone marrow. Other blood cell lines are usually decreased, as well. **Table 27**

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TABLE 27. Causes of Platelet Underproduction

Cause	Result
Marrow failure	Aplastic anemia
	Myelodysplasia
	Vitamin B_{12}/folate deficiency
	Fanconi anemia
Marrow invasion	Leukemias
	Tumors (small cell lung cancer metastatic to marrow)
	Granulomatous diseases (sarcoidosis)
	Fibrosis (primary myelofibrosis)
Marrow injury	Drugs (especially alcohol, chemotherapy)
	Radiation
	Infections (hepatitis C virus, HIV)
Congenital	Wiskott-Aldrich syndrome
	Thrombocytopenia absent radius (TAR) syndrome
	May-Hegglin anomaly
	Gray platelet syndrome
	Bernard-Soulier syndrome

includes some examples of conditions associated with inadequate platelet production.

Platelet sequestration in the spleen leads to decreases in the circulating platelet count. Unlike erythropoietin, which increases synthesis to increase the erythrocyte count in response to anemia, thrombopoietin synthesis is static in splenic sequestration. Circulating thrombopoietin binds to the surface of megakaryocytes and platelets and is internalized; thus, free thrombopoietin levels are negatively regulated by an increased platelet mass, including the platelets sequestered in an enlarged spleen. Therefore, the body is unable to mount a compensatory increase in platelet production in this clinical setting.

Thrombocytopenias due to peripheral destruction are classified as those being caused by either immune or nonimmune mechanisms.

Non-Immune-Mediated Thrombocytopenia

Nonimmune mechanisms of platelet destruction are typically microangiopathic (shear damage to erythrocytes and platelets as the result of endothelial cell activation or endothelial cell damage). This category encompasses three classic syndromes: DIC, TTP, and the hemolytic uremic syndrome (HUS). See the Bleeding Disorders chapter for a discussion of DIC.

Thrombotic Thrombocytopenic Purpura

TTP is characterized by abnormal activation of platelets and endothelial cells, deposition of fibrin in the microvasculature, and peripheral destruction of erythrocytes and platelets. The diagnosis is clinical and requires the presence of thrombocytopenia and MAHA in the absence of other causes of these findings such as malignant hypertension or scleroderma renal crisis. Additionally, patients may have fever, kidney disease, neurologic findings such as mental status changes or stroke, or abdominal pain. The most common cause of TTP is sporadic and is due to a deficiency in the protease ADAMTS-13, which cleaves the high-molecular-weight multimers of vWF. This deficiency can be congenital or produced by an autoantibody. The decrease in ADAMTS-13 activity leads to accumulation of clumps of ultra-large-molecular-weight vWF multimers, which bind to masses of platelets, leading to microvascular occlusion and thrombocytopenia. Schistocytes form as erythrocytes are damaged by these tangles of vWF and platelets. TTP can also be triggered by medications, especially quinine, ticlopidine, cyclosporine, and gemcitabine; with the latter two drugs, the cause may be endothelial cell damage rather than formation of antibodies against ADAMTS-13. MAHA leads to an increase in lactate dehydrogenase and bilirubin levels. Schistocytes are invariably seen on the peripheral blood smear. The blood urea nitrogen and creatinine levels may be elevated. Abdominal pain, with or without an increase in amylase level, is also a prevalent clinical feature.

Prompt and accurate diagnosis is critical, because TTP is fatal in 90% of patients without therapy. Patients require emergent treatment with plasma exchange, a form of therapeutic apheresis in which native plasma is removed and replaced with fresh frozen plasma. In a randomized clinical trial, plasma exchange was shown to be superior to simple plasma infusions. Platelet levels rarely decrease to less than 10,000/μL (10×10^9/L), and routine platelet transfusions are contraindicated, because transfusion of platelets can potentially precipitate microvascular occlusion.

Hemolytic Uremic Syndrome

HUS frequently overlaps in clinical presentation with TTP; however, HUS occurs more frequently in children and has more kidney and fewer neurologic manifestations. HUS can be precipitated by infectious diarrheal illnesses, especially *Escherichia coli* O157:H7 and others elaborating Shiga toxin. Plasma exchange is the standard of care for HUS in adults. Atypical HUS is a congenital syndrome that differs from typical HUS in that it is not preceded by a diarrheal illness. Rather, it is a disorder caused by overwhelming complement activation. The distinction between TTP and typical and atypical HUS is difficult but important to make, because atypical HUS is effectively treated by infusions of eculizumab, a monoclonal antibody directed against the terminal components of the complement cascade.

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KEY POINTS

- Clinical diagnosis of thrombotic thrombocytopenic purpura requires the presence of thrombocytopenia and microangiopathic hemolytic anemia in the absence of other causes of these findings and may include fever, kidney disease, neurologic findings, or abdominal pain.
- Atypical hemolytic uremic syndrome is effectively treated by infusions of eculizumab.

Immune-Mediated Thrombocytopenia

The pathophysiologic mechanism underlying immune-mediated thrombocytopenia involves antibodies binding to platelets, with platelet destruction mediated through Fc receptors on macrophages within the reticuloendothelial system.

Unlike autoimmune hemolytic anemia, there is no diagnostic test for immune-mediated thrombocytopenia. Antiplatelet antibody testing is not recommended because of low sensitivity and specificity. Like immune-mediated hemolytic anemia, certain medications can provoke immune-mediated thrombocytopenia. The mechanisms of drug-induced thrombocytopenia are identical to drug-induced hemolysis, including direct stimulation of antiplatelet antibodies and a hapten mechanism.

Immune Thrombocytopenic Purpura

ITP should be considered in patients with isolated new-onset thrombocytopenia. Unless the patient has been bleeding, the hemoglobin level and leukocyte count should be normal. The peripheral blood smear should show large platelets and no schistocytes. Splenomegaly and thyroid disease should be ruled out as causes of the thrombocytopenia (hypo- and hyperthyroidism can be causative). All new and unnecessary medications, supplements, and herbal therapies should be stopped. ITP may be a primary disorder or may be associated with any autoimmune conditions or lymphoproliferative disorders (such as chronic lymphocytic leukemia or Hodgkin and non-Hodgkin lymphomas). It may also present in pregnancy (see Hematologic Issues in Pregnancy). Certain viral illnesses may induce ITP, and for this reason, HIV and hepatitis C virus testing is warranted in patients with new-onset thrombocytopenia.

Specific therapy should be reserved for platelet counts less than 30,000/μL (30×10^9/L) or if the patient is bleeding. Initial therapy with glucocorticoids should be initiated with either prednisone, 1 mg/kg followed by a slow taper over the course of weeks, or dexamethasone, 40 mg/d for 4 days. Following a course of glucocorticoids, 25% of patients respond and never relapse, but the remainder do not respond or relapses after glucocorticoid taper. Intravenous immune globulin (IVIG) and anti-D immune globulin are other therapeutic first-line options, but anti-D immune globulin is effective only in Rh-positive patients. Second-line therapy is controversial and may include either splenectomy, use of off-label rituximab, or use of a thrombopoietin mimetic agent (either eltrombopag or romiplostim).

Patients with platelet counts less than 10,000/μL (10×10^9/L) or those with life-threatening bleeding may require more robust therapy. IVIG should be added and platelets transfused if bleeding is present. Routine transfusion of platelets is not recommended, because they are rapidly consumed, but their use for bleeding is not disputed.

KEY POINTS

- No diagnostic test can identify immune-mediated thrombocytopenia, and antiplatelet antibody testing is not recommended because of its low sensitivity and specificity.
- Patients with immune thrombocytopenic purpura may require therapy if the platelet count is less than 30,000/μL (30×10^9/L) or if bleeding is present.

HVC

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a specific, drug-induced thrombocytopenia in which the antigen is a complex between platelet factor 4 (PF4) and heparin. Antibodies directed against the heparin/PF4 complex can activate platelets via Fc receptors on platelets, leading to thrombocytopenia and, paradoxically in some patients, thrombosis. Risk factors for development of HIT include heparin treatment for more than 4 days, surgery, and treatment with unfractionated instead of low-molecular-weight heparin (LMWH); however, cases of HIT have been reported after use of LMWH, and LMWH should not be used in patients with a history of HIT. Platelet counts decrease by at least 50% 5 to 10 days after treatment with heparin. A scoring system for determining the pretest probability of a patient having HIT is shown in **Table 28**.

Diagnostic testing involves serologic testing (usually by enzyme-linked immunosorbent assay) for anti-heparin/PF4 antibodies and functional assays to determine platelet activation, of which the serotonin release assay is the gold standard. Serologic testing, although widely available, is limited by lack of specificity, which can be increased by testing for IgG rather than all anti-heparin/PF4 antibodies. Functional assays are more specific but are not readily available at all centers. As soon as HIT is suspected, heparin should be stopped, argatroban therapy should be initiated, and diagnostic testing ordered. Baseline Doppler ultrasound studies of all four extremities should be obtained, because the risk of thrombosis in HIT is more than 30%. Warfarin therapy should not be started until the platelet count normalizes because of the risk of developing warfarin skin necrosis. Platelet administration is relatively contraindicated. Anticoagulation should be continued at least until the platelet count is greater than 150,000/μL (150×10^9/L) in patients without thrombosis. Patients with thrombosis should complete the course of anticoagulation needed to treat their clot.

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TABLE 28. The 4T Scoring System for Predicting Heparin-Induced Thrombocytopenia and Thrombosis (HIT/T)

4 Ts	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count decrease >50% and platelet nadir ≥20,000/μL (20×10^9/L)	Platelet count decrease 30%-50% or platelet nadir 10,000-19,000/μL ($10\text{-}19 \times 10^9$/L)	Platelet count decrease <30% or platelet nadir <10,000/μL (10×10^9/L)
Timing of platelet count decrease	Clear onset between days 5-10 or platelet count decrease ≤1 day (with heparin exposure within 30 days)	Consistent with platelet count decrease between days 5-10, but unclear (e.g., missing platelet counts); onset after day 10; or decrease ≤1 day (heparin exposure 30-100 days ago)	Platelet count decrease <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction after intravenous unfractionated heparin bolus	Progressive or recurrent clot; nonnecrotizing (e.g., erythematous) skin lesions; suspected thrombosis (not proved)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

High probability: 6-8 points

Intermediate probability: 4-5 points

Low probability: 0-3 points

KEY POINT

- Diagnostic testing for heparin-induced thrombocytopenia includes serologic testing with the enzyme-linked immunosorbent assay and the functional assays, of which the serotonin release assay is the gold standard.

Qualitative Platelet Disorders

Acquired Platelet Dysfunction

Even if they are normal in number, dysfunctional platelets may lead to mucocutaneous bleeding. A qualitative platelet defect should be suspected in patients with clinical bleeding (suggesting a defect in hemostasis) whose platelet count, prothrombin time, and activated partial thromboplastin time are normal. A list of diagnoses leading to qualitative platelet disorders is given in **Table 29**. In general, platelet function defects are usually mild and unlikely to trigger bleeding without additional vascular injury or other hemostatic abnormalities. Some of these disorders may respond to desmopressin, whereas others require transfusion to treat or prevent bleeding.

Platelet Function Testing

Diagnostic evaluation starts with an abnormal bleeding time or Platelet Function Analyzer-100 (PFA-100®) result. In the PFA-100® test, whole citrated blood is aspirated through a small aperture into a microcapillary membrane infused with a mixture of collagen and either epinephrine or adenosine diphosphate. The shear stress produced by the rapid aspiration mimics arterial shear, leading to vWF binding to collagen. Platelets are activated by either collagen or epinephrine, and blood flow slows and eventually stops as platelets and erythrocytes obstruct the microcapillaries. If warranted, more specific platelet function assays such as platelet aggregation, flow cytometry, or electron microscopy can be performed at a specialized center.

Platelet function testing has been used to evaluate resistance to antiplatelet agents such as aspirin and clopidogrel. One such instrument, the Verifynow®, is a point-of-care instrument using the principle that fibrinogen-coated polystyrene beads will agglutinate in proportion to the number of glycoprotein IIb-IIIa receptors activated by specific agonists. Various cartridges use specific stimuli to monitor various antiplatelet drugs. Monitoring for aspirin therapy uses arachidonic acid as the platelet agonist and is given in aspirin-response units. Monitoring for clopidogrel uses adenosine diphosphate as the platelet agonist and is given in P2Y12 response units. Monitoring for glycoprotein IIb-IIIa inhibitors uses a peptide that activates the thrombin receptor. Although this test is currently available, guidelines recommend against routine monitoring of antiplatelet therapy with platelet function testing.

KEY POINT

- A qualitative platelet defect should be suspected in patients with clinical bleeding (suggesting a defect in hemostasis) whose platelet count, prothrombin time, and activated partial thromboplastin time are normal.

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TABLE 29. Causes of Platelet Dysfunction

	Comments	Severity	Treatment
Congenital Platelet Defects			
Glanzmann thrombasthenia	Defect in glycoprotein IIb-IIIa	Severe	Platelets or recombinant factor VIIa, ε-aminocaproic acid
Bernard-Soulier syndrome	Defect in glycoprotein Ib-IX	Severe	Platelets, ε-aminocaproic acid
Wiskott-Aldrich syndrome	Triad of eczema, thrombocytopenia, immunodeficiency	Moderate	Platelets, ε-aminocaproic acid
Gray platelet syndrome	Patients may develop myelofibrosis	Moderate	Platelets, ε-aminocaproic acid
Storage pool disease		Moderate to mild	Platelets, ε-aminocaproic acid; some may respond to desmopressin
Acquired Platelet Defects			
Uremia		Mild	Dialysis, desmopressin, ε-aminocaproic acid
Liver disease	Also associated with hyperfibrinolysis and coagulopathy	Mild to severe	Platelets, ε-aminocaproic acid
Myeloproliferative neoplasms	If platelet count is >1-1.5 million/μL (1000-1500 × 10^9/L), may be associated with acquired von Willebrand disease	Mild to severe	Before surgical procedures, normalize the platelet count Platelet transfusion may be necessary if bleeding occurs
Post-cardiac bypass		Mild	Platelets, if necessary
Antiplatelet drugs			
IIb-IIIa inhibitors		Severe	Platelets
Aspirin	Irreversible	Mild	Platelets, if necessary
Clopidogrel	Irreversible	Mild	Platelets, if necessary
NSAIDs	Temporary	Mild	None usually needed
Other drugs and herbs (β-lactams, vitamin E, ginkgo, turmeric, garlic, Chinese tree fungus)		Mild	None usually needed

Bleeding Disorders

Normal Hemostasis

Hemostasis encompasses the orderly, tightly regulated processes that occur in response to vascular injury to prevent bleeding. Primary hemostasis refers to the interaction between the injured vessel wall, von Willebrand factor (vWF), and platelets. Platelet adhesion, aggregation, and secretion were described previously in the section on platelets. Activated platelets also serve as the scaffold on which the series of proteolytic clotting factor reactions take place that culminate in the formation of a stable fibrin clot.

The "waterfall" model was initially used to describe hemostasis, but this model is now useful only to delineate the clotting factors necessary for testing prothrombin time (PT) and activated partial thromboplastin time (aPTT) (**Figure 12**). In this model, clotting factors X, V, II, and fibrinogen are

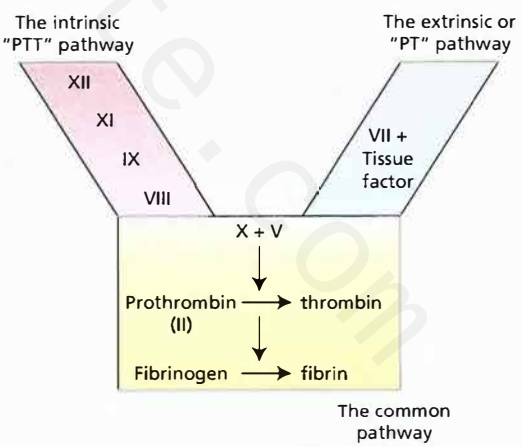

FIGURE 12. The "waterfall" model of hemostasis is useful for teasing out coagulation disorders affecting the prothrombin time (PT) and the activated partial thromboplastin time (aPTT). In this model, factors common to the PT and the aPTT are X, V, II, and fibrinogen. Factor VII is unique to the PT, and factors XII, XI, VIII, and IX are unique to the aPTT.

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common to the PT and the aPTT pathways; factor VII is unique to the PT pathway; and factors XII, XI, IX, and VIII are unique to the aPTT pathway. Limitations in the waterfall model have led to the development of a cell-based model of hemostasis, which characterizes the phases of coagulation as initiation, priming, and propagation (**Figure 13**). Thus, hemophilia A and B are understood to be defects in thrombin generation on the surface of activated platelets, and the hemorrhagic consequences are more clearly understood.

Table 30 lists the differential diagnoses for patients experiencing bleeding who have specific abnormalities in clotting assays.

Evaluation of Patients with Suspected Bleeding Disorders

The evaluation of a patient experiencing bleeding episodes is aimed at determining the likelihood that the patient has an underlying hemorrhagic disorder and at treating future bleeding episodes. Although the history and physical examination can increase suspicion for the presence of a bleeding disorder, laboratory confirmation is required for precise diagnosis and treatment.

A detailed history of bleeding episodes, including family history, is critical in elucidating whether a bleeding diathesis is present. The history should include an orderly description of bleeding episodes during infancy and childhood. Bleeding with dental procedures, including wisdom tooth removal, should be explored. Epistaxis may be a presenting symptom of von Willebrand disease (vWD) or hereditary hemorrhagic telangiectasia, and is especially notable if it does not stop with pressure and requires either cautery or an emergency department visit.

Other bleeding episodes, whether spontaneous or provoked, should be explored. Bleeding into muscles and joints is characteristic of disorders of humoral clotting factors (hemophilia), whereas mucosal bleeding is more common in disorders of primary hemostasis (vWD, thrombocytopenia of any cause). Easy bruisability is reported by many patients without underlying bleeding disorders, but certain historical features are worth noting. The new onset of bruising can herald a new thrombocytopenic disorder such as immune thrombocytopenic purpura or acute leukemia or can point to acquired hemophilia. Bruising that only occurs over the hands and forearms suggests the presence of senile purpura.

Each surgical procedure should be explored in depth. The details of bleeding, including timing (immediate or delayed), need for transfusion, comments by the surgeon concerning the characteristics of the bleeding, and any known anatomic sources of bleeding can shed light on the bleeding diathesis. Immediate bleeding may be more characteristic of a disorder of primary hemostasis, whereas delayed bleeding is more common in patients with deficiencies in humoral clotting factors.

TABLE 30. Differential Diagnoses for Patients Experiencing Bleeding

Clotting Assay Abnormality	Differential Diagnoses
Prolonged PT, normal aPTT	Factor VII deficiency
	DIC
	Liver disease
	Vitamin K deficiency
	Warfarin ingestion
Normal PT, prolonged aPTT	Deficiency of factors VIII, IX, XI, or XII
	von Willebrand disease (if severe and factor VIII level is quite low)
	Heparin exposure
Prolonged PT and aPTT	Deficiency of factors V, X, II, or fibrinogen
	Severe liver disease, DIC, vitamin K deficiency, warfarin use
	Heparin overdose
Normal PT and aPTT	Platelet dysfunction (acquired and congenital)
	von Willebrand disease (if mild and factor VIII level is not too low)
	Scurvy
	Ehlers-Danlos syndrome
	Hereditary hemorrhagic telangiectasia
	Deficiency of factor XIII

aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; PT = prothrombin time.

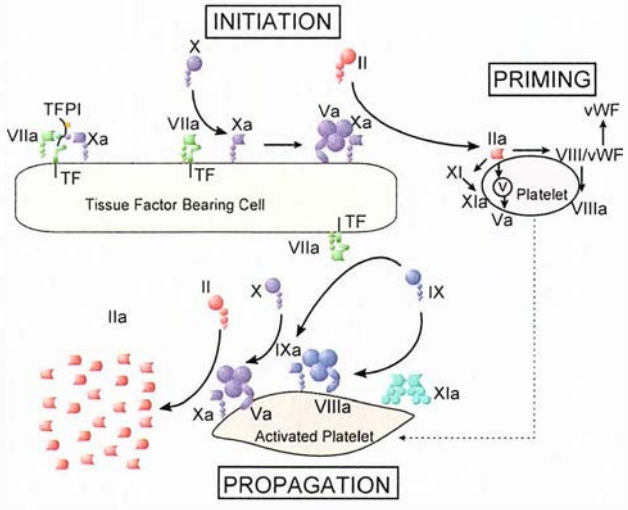

FIGURE 13. The cell-based model of hemostasis is useful for understanding coagulation as it occurs in vivo. The initiation of coagulation takes place on the surface of a tissue factor–bearing cell, such as a macrophage, tumor cell, or an activated endothelial cell. Tissue factor (TF) and a small amount of factor VIIa generate factor Xa, which joins with factor Va to form a small amount of thrombin (factor II). In the priming step, this small amount of thrombin proceeds to activate platelets and factor VIII, which joins with factor IX to generate factor Xa. On the platelet surface, the prothrombinase complex can generate a large thrombin burst in the propagation step, allowing for cleavage of fibrinogen into fibrin.

TFPI = tissue factor pathway inhibitor; vWF = von Willebrand factor.

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Bleeding in patients with an underlying hemorrhagic condition is typically described as "diffuse oozing," without a readily identifiable bleeding source such as a surgical mishap like a severed vessel. If a woman has bled with some procedures, but not others, she should be asked if she was taking oral contraceptive pills or hormone replacement therapy during the procedures in which she had good hemostasis, because these can increase levels of vWF, leading to normalization of hemostasis. If the patient's nonbleeding episodes correlate with times taking estrogen-containing contraceptives, a diagnosis of vWD could be suspected.

Women should be interviewed thoroughly about their menstrual history. Duration and severity of flow are more important than presence or severity of cramping. Features correlated with a higher likelihood of an underlying bleeding disorder include nighttime "flooding," passing clots larger than a quarter, duration longer than 8 days, and development of iron deficiency.

A family history of bleeding should also be elicited. A family history of bleeding with surgical procedures, bleeding requiring transfusions, and menorrhagia leading to hysterectomy at a young age should be queried. However, a negative family history does not rule out a hereditary bleeding disorder.

Certain medications or herbal and dietary supplements increase the risk of bleeding. The use of these agents may precipitate a hemorrhage in those with milder bleeding disorders. Aspirin and NSAIDs impair primary hemostasis, and their use should be avoided before surgery or evaluation of the hemostatic system. Their inclusion in over-the-counter products seems ubiquitous, and careful attention to cold and flu remedies is warranted.

The physical examination may provide useful clues to the cause of the patient's bleeding. Examining the skin may reveal petechiae, indicating thrombocytopenia, or the characteristic ecchymoses and lax skin seen with senile purpura. Telangiectasias around the lips or on the fingertips may signal the presence of hereditary hemorrhagic telangiectasia.

Splenomegaly can be associated with thrombocytopenia and may indicate underlying portal hypertension. Other stigmata of liver disease, such as spider angiomata, gynecomastia, asterixis, and jaundice, also suggest the patient may have liver coagulopathy. A loud systolic murmur radiating to the carotid arteries may indicate severe aortic stenosis, which can cause acquired vWD, with associated gastrointestinal bleeding from arteriovenous malformations. An enlarged tongue, carpal tunnel syndrome, and periorbital purpura may point to amyloidosis, which can lead to dysfibrinogenemia, factor X deficiency, or vascular fragility.

No available test serves as a screening test of global hemostasis, and none can include or exclude the presence of an underlying bleeding disorder. Screening tests may point to the presence of a factor deficiency or a defect in primary hemostasis, although more precise diagnoses require more detailed testing. See Table 30 for differential diagnoses for combinations of abnormal and normal PT and aPTT values.

KEY POINTS

- Bleeding into muscles and joints is characteristic of disorders of humoral clotting factors, whereas mucosal bleeding is more common in disorders of primary hemostasis.
- Features correlated with a higher likelihood of an underlying bleeding disorder in women being evaluated for menorrhagia include nighttime "flooding," passing clots larger than a quarter, duration longer than 8 days, and development of iron deficiency.

Congenital Bleeding Disorders

Hemophilia A and B

Hemophilia A and B are X-linked recessive disorders of hemostasis. Hemophilia A results from factor VIII deficiency and hemophilia B from factor IX deficiency. These disorders present identically and can only be distinguished by measuring the respective clotting factors. They will produce prolongation of the aPTT with a normal PT, and the aPTT mixing study will fully correct. The clinical symptoms are determined by the baseline factor activity in each patient. Those with severe hemophilia have less than 1% factor VIII or IX activity, and these persons will have severe spontaneous bleeding episodes that are clinically manifested at an early age as well as severe bleeding after surgery or trauma. The bleeding episodes occur predominantly in the ankle, knee, and elbow joints, but retroperitoneal, intramuscular, and intracranial bleeding can also occur. Children can present with bleeding after circumcision or have bleeding with loss of deciduous teeth. Patients with moderate hemophilia have factor levels between 1% and 5%, and those with mild disease have factor levels greater than 5%. These persons can occasionally present in adulthood, because they are less likely to experience spontaneous bleeding episodes, and trauma-induced bleeding may not be recognized as clinically significant. Older patients with hemophilia may have been infected with HIV and/or hepatitis C virus from contaminated factor concentrates made from pooled plasma, but transfusion-related risks of HIV and hepatitis B and C viruses are no longer a concern for younger patients with hemophilia.

Treatment relies on replacing the missing clotting factors with factor concentrates. Patients may take factor concentrates in response to bleeding episodes or on a prophylactic basis. Some patients may develop inhibitors, which are neutralizing alloantibodies against factor VIII (or occasionally IX). A patient may have developed an inhibitor if he or she does not clinically respond well to factor VIII or factor IX infusions. Diagnosis is confirmed by measuring a Bethesda titer, which is a measure of the strength of the inhibitor. Patients with hemophilia benefit from being monitored at a comprehensive hemophilia treatment center; this has been shown to decrease morbidity and mortality and reduce cost.

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All daughters of men with hemophilia are carriers of the factor deficiency and have a 50% chance of passing the disorder to their sons. They may also experience an increased bleeding tendency, especially if they have low factor VIII or IX levels owing to extreme lyonization, in which patients have a disproportionately inactivated X chromosome carrying the normal factor VIII or IX gene, leading to lower than expected factor levels.

KEY POINTS

- Hemophilia A (factor VIII deficiency) and B (factor IX deficiency) produce prolongation of the activated partial thromboplastin time (aPTT) with a normal prothrombin time, and the aPTT mixing study will fully correct; diagnosis is made by measuring the baseline factor activity.
- Treatment of patients with hemophilia relies on replacing the missing clotting factors with factor concentrates, which can be given in response to bleeding episodes or on a prophylactic basis.

von Willebrand Disease

vWD is the most common inherited bleeding disorder. As many as 1 in 100 persons have low levels of vWF, and approximately 1% of these experience mucocutaneous bleeding problems. Symptoms are similar to those experienced with platelet disorders and may include nosebleeds in children, easy bruising, bleeding gums, and postsurgical bleeding. Gynecologic problems are especially common. Most women with vWD experience heavy menstrual bleeding, and approximately 10% to 30% of women with menorrhagia may be diagnosed with vWD. Additionally, endometriosis (likely related to backflow of menses), miscarriages (unclear mechanism), and postpartum hemorrhage are more common in women with vWD. Type 1 vWD accounts for 80% of all vWD cases and is inherited in an autosomal codominant fashion. In this condition, vWF antigen and activity levels are 30% or less, and factor VIII levels may be normal or low owing to loss of vWF-provided protection from proteolysis. Results of the Platelet Function Analyzer-100 (PFA-100®) are usually prolonged. The PT is normal and the aPTT may be normal or slightly prolonged, because the factor VIII level may be slightly low. Despite this, the pattern of bleeding is similar to that of a platelet disorder rather than of a defect in humoral clotting factor; patients with hemophilia who have levels of factor VIII activity as low as those seen in patients with vWD are asymptomatic, thus the bleeding is due to defects in primary hemostasis from lack of vWF. Diagnosis may be difficult, because many elements influence vWF levels (**Table 31**).

Women with heavy menstrual bleeding may benefit from estrogen-containing oral contraceptives, which may regulate menstruation and raise vWF levels. Desmopressin causes preformed stores of vWF and factor VIII to be released from endothelial cells and may be given for treatment of menstrual or other bleeding or preoperatively as surgical prophylaxis.

TABLE 31. Elements Influencing von Willebrand Factor Levels

Factor	Effect on vWF Synthesis
ABO blood type	Type O persons have vWF levels 25% lower than average
Hypothyroidism	Decreases
Pregnancy and estrogen	Increases
Stress	Increases
Exercise	Increases
Inflammation	Increases
Smoking	Increases

vWF = von Willebrand factor.

Menorrhagia can be treated effectively with antifibrinolytic agents such as tranexamic acid or ε-aminocaproic acid during menses. Finally, factor concentrates consisting of factor VIII and vWF may be given as treatment for severe bleeding episodes or as perioperative therapy for major surgery. These are plasma derived but have undergone a number of steps to inactivate lipid-coated viruses such as HIV and hepatitis B and C. Patients should avoid taking aspirin or NSAIDs, which can worsen bleeding.

Other types of vWD are rare. The various subtypes of type 2 vWD result from production of an abnormally functioning vWF molecule. Type 3 vWD results from the near lack of vWF, and patients with this form of vWD have factor VIII levels low enough to produce defects in humoral hemostasis (for example, muscle hematomas and hemarthroses).

KEY POINTS

- Diagnosis of von Willebrand disease includes von Willebrand factor antigen and activity levels of 30% or less, factor VIII levels that may be normal or low, prolonged Platelet Function Analyzer-100 results, normal prothrombin time, and normal or slightly prolonged activated partial thromboplastin time.
- Treatment of von Willebrand disease depends upon the clinical severity of bleeding; estrogen-containing oral contraceptives and desmopressin can be given for treatment of menstrual or other minor bleeding or preoperatively for surgical prophylaxis.

Acquired Bleeding Disorders

Coagulopathy of Liver Disease

The liver is responsible for synthesis of all clotting factors as well as all anticoagulant and antifibrinolytic factors. Because of this, patients with severe liver failure will have prolonged PT and aPTT values resulting from decreased levels of coagulation factors. Despite this, patients are not protected against thrombosis, because protein C and S levels and antithrombin levels are low as well. Fibrinogen levels are low, and the fibrinogen

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CONT. may be dysfunctional because of abnormal glycosylation. Patients may also undergo accelerated fibrinolysis. Somewhat paradoxically, factor VIII levels are supranormal because it is produced in extrahepatic endothelial cells, and a hepatically synthesized factor is required for factor VIII clearance. Portal hypertension and associated splenomegaly may lead to a decreased platelet count, and qualitative platelet dysfunction is common in advanced liver disease, which may further exacerbate bleeding. Patients experiencing bleeding may require vitamin K, if deficiency is suspected, or transfusion with cryoprecipitate, fresh frozen plasma, and platelets. Antifibrinolytic agents may be beneficial for mucocutaneous bleeding.

KEY POINTS

- Laboratory evaluation for coagulopathy of liver disease will show prolonged prothrombin time and activated partial thromboplastin time, low fibrinogen levels and possibly dysfunctional fibrinogen because of abnormal glycosylation, and supranormal factor VIII levels.
- Patients with coagulopathy of liver disease who are experiencing bleeding may require transfusion with cryoprecipitate, fresh frozen plasma, and platelets or vitamin K supplementation if deficiency is suspected.

Acquired Hemophilia

Rarely, older patients without a personal or family history of bleeding may present with acute new-onset bleeding. Such bleeding can be mucocutaneous or intramuscular. The PT is normal, but the aPTT is significantly prolonged, and a 1:1 mixing study of the patient's plasma with normal plasma is unsuccessful at completely correcting the aPTT. This is the classic presentation for acquired hemophilia, in which autoantibodies form against factor VIII. This disorder, although rare, carries high morbidity and mortality and is a frequently missed diagnosis; a high level of suspicion is critical for prompt diagnosis and treatment. It may be associated with an underlying autoimmune condition such as systemic lupus erythematosus or malignancy (either lymphoproliferative or solid tumor) but is more commonly idiopathic. Bleeding episodes should be treated with recombinant activated factor VII, and the patient should undergo immunosuppression to decrease the inhibitor levels.

KEY POINT

- Bleeding episodes resulting from acquired factor VIII inhibitor should be treated with recombinant activated factor VII and patients should undergo immunosuppression to eradicate the inhibitor.

Disseminated Intravascular Coagulation

DIC is characterized by abnormal activation of coagulation, generation of thrombin, consumption of clotting factors, and peripheral destruction of platelets. Diagnostic laboratory findings are provided in **Table 32**, although not all of those features may be present. DIC may result from a variety of causes, including sepsis, obstetric emergencies (amniotic fluid embolism, fetal demise, placental abruption), acute leukemias (especially acute promyelocytic leukemia), severe burns, venoms, and shock. No specific therapy for DIC exists, and treatment relies on resolving the underlying cause. Supplemental supportive treatment for patients who are bleeding or who are at risk for bleeding can include administering platelets, fresh frozen plasma to replace clotting factors, or cryoprecipitate to replace fibrinogen.

TABLE 32. Laboratory Features of Disseminated Intravascular Coagulation (DIC)

Features
Elevated prothrombin time due to consumption of factor VII, which has the shortest half-life of the coagulation factors. Possibly elevated activated partial thromboplastin time if DIC is severe, because of consumption of other coagulation factors.
Low and progressively decreasing fibrinogen levels
Elevated D-Dimer or fibrin degradation products
Low platelets
Microangiopathic hemolytic anemia, which appears as schistocytes on the peripheral blood smear (seen in 50% of patients with DIC)

KEY POINT

- Management of disseminated intravascular coagulation focuses on treating the underlying cause.

Transfusion

Cellular Products

Erythrocytes

ABO/Rh System and Compatibility Testing

The ABO blood group system refers to carbohydrate antigens present on erythrocytes that include A or B antigens (blood group A or B, respectively), both (blood group AB), or neither (blood group O). Early in life, persons develop IgM antibodies to the A or B antigens not expressed on their erythrocytes. Thus, persons who have blood group A will have antibodies against B antigens and vice versa (**Table 33**). Anti-A and anti-B IgM antibodies bound to antigen on the erythrocyte cell surface activate complement and lead to life-threatening hemolytic reactions.

The Rh proteins on erythrocytes harbor the Rh antigens D, C, c, E, and e, the D antigen being the most immunogenic. Alloantibodies to Rh antigens develop from alloantigen exposure either through pregnancy or previous transfusion. Testing for D antigen is part of routine compatibility testing. IgG antibodies to Rh antigens can produce severe hemolytic transfusion reactions and hemolytic disease in the newborn if the mother is Rh(D)-negative and has been sensitized and the child is Rh(D)-positive; the use of anti-D immune globulin to

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TABLE 33. ABO Compatibility Between Donor and Recipient Erythrocytes and Fresh Frozen Plasma

	Recipient ABO Blood Group			
	A	**B**	**AB**	**O**
Recipient erythrocyte antigen	A	B	A and B	None
Recipient isohemagglutinins[a]	Anti-B	Anti-A	None	Anti-A, Anti-B
Compatible donor erythrocytes	A, O	B, O	Any	O
Compatible donor plasma	A, AB	B, AB	AB	Any

[a]Isohemagglutinins are IgM antibodies directed at ABO blood group antigens.

NOTE: Rh(D)-negative patients should receive Rh(D)-negative erythrocytes; Rh(D)-positive patients can receive Rh(D)-negative or Rh(D)-positive erythrocytes.

prevent sensitization in pregnant women who are Rh(D)-negative has decreased the incidence of the latter.

Compatibility testing consists of typing and screening, in which the ABO and Rh(D) phenotypes of the recipient's erythrocytes are determined, followed by screening of the recipient's serum for the presence of alloantibodies to erythrocyte antigens generated as a result of previous transfusion or pregnancy. The ABO type and Rh(D) status of the donor erythrocytes are then verified and cross-matched by incubating the recipient's serum with donor erythrocytes.

If alloantibodies to erythrocyte antigens are discovered, their specificity must be determined so that donor erythrocytes lacking that antigen can be identified. Patients with a history of alloimmunization should never receive erythrocytes containing that antigen, even if repeat alloantibody screening is negative, because anamnestic responses can occur, resulting in delayed hemolytic transfusion reactions.

Clinical Transfusion Issues

Persons with O-negative blood are considered universal erythrocyte donors. As such, O-negative blood should be given in emergencies when the recipient's blood type is not available. One unit of packed red blood cells is 250 to 300 mL and is expected to increase the hemoglobin level by 1 g/dL (10 g/L) in the absence of bleeding, erythrocyte destruction, or sequestration. Prestorage leukoreduction decreases the amount of contaminating leukocytes in the erythrocyte product and reduces the risk of febrile nonhemolytic transfusion reactions, cytomegalovirus transmission, and class I HLA alloimmunization and subsequent platelet transfusion refractoriness. Universal leukoreduction is mandated in many countries. In the United States, more than 80% of institutions have implemented universal leukoreduction policies. **Table 34** discusses modifications to erythrocyte and other cellular products.

The goal of erythrocyte transfusion is to improve oxygen delivery. Considering the potential risks associated with blood transfusion and compensatory mechanisms that exist to maintain oxygen delivery, physicians should use clinical judgment to determine when a transfusion is necessary based on symptoms, the extent of the anemia, and the presence of cardiopulmonary comorbidity.

TABLE 34. Cellular Transfusion Product Modifications

Modification[a]	Notes
Leukoreduction[b]	Reduces the number of leukocytes present in the transfused erythrocyte or platelet product. Reduces class I HLA alloantibody production and subsequent platelet transfusion refractoriness, febrile nonhemolytic transfusion reactions, and transmission of CMV. Leukoreduction cannot be relied on to prevent transfusion-associated GVHD.
Irradiation	Radiation destroys lymphocytes in erythrocyte and platelet transfusion products. Used to prevent transfusion-associated GVHD, which is mediated by donor lymphocytes. Indicated in patients with severe, inherited T-cell immunodeficiency syndromes or Hodgkin lymphoma or recipients of allogeneic or autologous hematopoietic stem cell transplantation; purine analog-based chemotherapy (fludarabine, cladribine, deoxycoformycin), alemtuzumab, or rabbit antithymocyte globulin therapy; and in immunocompetent patients receiving HLA-matched platelets or transfusions from relatives. Irradiation can weaken the erythrocyte membrane, causing reduced cell viability and potassium leakage.
Washing	Removes the proteins residing in the small amount of plasma of erythrocyte and platelet transfusions and is used in patients with a history of severe/recurrent allergic reactions, IgA deficiency (when IgA-deficient donors are unavailable), or complement-dependent autoimmune hemolytic anemia. Also reduces the amount of potassium transfused for use in patients who are at risk for hyperkalemia.

CMV = cytomegalovirus; GVHD = graft-versus-host disease; HLA = human leukocyte antigen.

[a]Transfusion of CMV-negative blood products for immunocompromised recipients who are CMV seronegative is controversial and not universally performed because modern era leukocyte filters are highly effective at reducing the inoculum of CMV-infected leukocytes.

[b]More than 80% of blood banks in the United States adhere to universal leukoreduction. For those that do not, leukoreduction should be performed for chronically transfused patients, those with a history of a febrile hemolytic transfusion reaction, patients who are potential candidates for or recipients of a solid-organ or hematopoietic stem cell transplant, and immunocompromised recipients who are CMV seronegative.

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Strategies to Minimize Blood Transfusion

CONT.

Randomized studies have shown that a more restrictive approach to erythrocyte transfusion is safe and reduces the need for erythrocyte transfusion in well-defined clinical scenarios. For hemodynamically stable, hospitalized medical and postsurgical patients, a transfusion threshold hemoglobin level of less than 7 to 8 g/dL (70-80 g/L) is recommended based on data demonstrating equivalent or improved outcomes for (1) patients in the ICU when transfused at a hemoglobin level of 7 g/dL (70 g/L) or less; (2) patients after surgical hip fracture repair who have pre-existing cardiovascular disease or risk factors for cardiovascular disease who are transfused at a hemoglobin level of 8 g/dL (80 g/L) or less or for symptomatic anemia; and (3) patients with acute upper gastrointestinal bleeding, no acute coronary syndrome, and no history of peripheral vascular disease or stroke when transfused at a hemoglobin level of 7 g/dL (70 g/L) or less. Evidence in patients with underlying cardiovascular disease is limited, but a transfusion threshold of 8 g/dL (80 g/L) or less or transfusion based on the presence of symptoms (chest pain, heart failure, hypotension, and tachycardia not responsive to intravenous fluids) has been proposed. Data on appropriate transfusion thresholds in acute coronary syndromes are lacking and decisions must be made on a case-by-case basis.

Erythropoiesis-stimulating agents (ESAs; erythropoietin and darbepoetin) are used to promote erythrocyte production and reduce the need for transfusion. However, several studies have shown a detrimental impact with the use of ESAs in select clinical situations, especially when a higher hemoglobin level is targeted. ESAs used to target a higher hemoglobin level increase the risk of cerebral infarction, hypertension, and vascular access thrombosis in patients with anemia of chronic kidney disease. A study in patients with chronic heart failure targeting a hemoglobin level of 13 g/dL (130 g/L) demonstrated a similar increased risk of thromboembolic events. ESAs are associated with an increased risk of venous thrombosis and mortality in patients with cancer. In light of these safety concerns, ESA use must be carefully individualized.

Preoperative autologous blood donation can reduce the need for donor blood and reduces many of the risks associated with blood transfusion (febrile nonhemolytic reactions, hemolytic and allergic reactions, graft-versus-host disease [GVHD], alloimmunization). Other strategies include intraoperative hemodilution or use of intraoperative cell salvage technology, a method for retaining and reusing erythrocytes lost during intraoperative bleeding.

KEY POINTS

- Patients with a history of alloimmunization should never receive erythrocytes containing antigens to which they are alloimmunized, even if repeat alloantibody screening is negative, because anamnestic responses can occur, resulting in delayed hemolytic transfusion reactions.

(Continued)

KEY POINTS *(continued)*

- O-negative blood, which is considered the universal erythrocyte donor type, should be given in emergencies when the recipient's blood type is not available.
- For hemodynamically stable, hospitalized medical and postsurgical patients, a hemoglobin threshold of less than 7 to 8 g/dL (70-80 g/L) is recommended based on data demonstrating equivalent or improved outcomes compared with a nonrestrictive transfusion approach. HVC

Platelets

ABO/Rh System, Human Leukocyte Antigen System, and Compatibility Testing

ABO blood group antigens are expressed on platelets, and transfusion of ABO-matched platelets produces a modestly increased platelet count compared with ABO-mismatched platelets. Although ABO-mismatched platelets may be used, anti-A or -B antibodies in the plasma of the platelet product can uncommonly lead to hemolytic transfusion reactions. Rh antigens are not expressed on platelets but are present at trace levels owing to contaminating erythrocytes. As such, alloimmunization after exposure to Rh(D)-positive platelets can infrequently occur in Rh(D)-negative recipients. If Rh(D)-positive platelets must be given to a woman of childbearing potential who is Rh(D)-negative, anti-D immune globulin should be coadministered to reduce the low risk of alloimmunization.

Class I HLA proteins are expressed on the surface of platelets, and alloantibody generation to these antigens may lead to platelet transfusion refractoriness and necessitate the use of class I HLA-matched platelets in affected patients (see Platelet Transfusion Refractoriness).

Clinical Transfusion Issues

Sources for platelet transfusion include random donor-pooled platelets, which include platelets from four to six combined blood donors, and single-donor platelets obtained through apheresis. Random donor-pooled and apheresis platelets are expected to increase the platelet count by 20,000 to 30,000/μL ($20\text{-}30 \times 10^9$/L). Advantages to the use of single-donor platelets include the ability to select a platelet product for a patient based on HLA type, platelet cross-match compatibility, and ABO blood group. Leukoreduction of platelet products yields the same benefits seen with erythrocyte leukoreduction (see Table 34).

Patients with thrombocytopenia with clinically significant active bleeding or patients without bleeding in whom nonneuraxial surgery is planned should be transfused to a target platelet count of 50,000 to 100,000/μL ($50\text{-}100 \times 10^9$/L) depending on the clinical circumstances. For patients with central nervous system bleeding or undergoing neurosurgery, the target platelet count is greater than 100,000/μL

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(100×10^9/L). Platelet transfusions may also be indicated for patients with qualitative platelet function defects and clinically significant bleeding.

Prophylactic platelet transfusion for platelet counts of 10,000/μL (10×10^9/L) or less in patients with thrombocytopenia due to decreased bone marrow production (hematologic malignancies undergoing chemotherapy or hematopoietic stem cell transplantation) decreases the risk of bleeding compared with platelet transfusion at the onset of clinical bleeding and is recommended for hospitalized patients. Patients with active fever or infection or acute promyelocytic leukemia, however, require a higher platelet transfusion threshold.

The AABB (formerly the American Association of Blood Banks) also recommends prophylactic platelet transfusion to platelet count of 20,000/μL (20×10^9/L) or greater in patients having an elective central venous catheter placed and to 50,000/μL (50×10^9/L) or greater for patients undergoing elective diagnostic lumbar puncture.

Platelet Transfusion Refractoriness

Platelet transfusion refractoriness is defined as an increase in the platelet count of less than 10,000/μL (10×10^9/L), measured 10 to 60 minutes after transfusion on at least two separate occasions. Refractoriness to platelet transfusion occurs in 10% to 25% of patients receiving chemotherapy for acute myeloid leukemia and is associated with an increased risk of bleeding and mortality. Nonimmune causes of platelet transfusion refractoriness include sepsis, disseminated intravascular coagulation (DIC), medications that can lead to decreased platelet survival (for example, amphotericin B), and platelet sequestration due to splenomegaly.

Alloimmunization is an important cause of platelet transfusion refractoriness due to production of alloantibodies to class I HLA antigens (and less commonly platelet-specific antigens) on donor platelets. Patients at risk are those who have previously been transfused or exposed to fetal antigens during pregnancy. HLA-matched platelets are used for transfusion if available. If the recipient is heterozygous for an HLA haplotype for which the donor is homozygous, the recipient may not reject the contaminating lymphocytes in the platelet product and is at risk of transfusion-associated GVHD. As such, HLA-matched platelets must be irradiated to prevent this complication, regardless of the state of the recipient's immune system. Other options for the alloimmunized patient include the use of HLA-compatible platelets missing the antigen to which the patient is alloimmunized or platelet crossmatching, a process in which the patient's serum is incubated with donor platelets. Class II HLA antigens present on transfused leukocytes are important in the initial immune response to class I HLA antigens on donor platelets. Thus, the use of leukoreduced blood products significantly decreases the risk of alloimmunization.

KEY POINTS

- If Rh(D)-positive platelets must be given to a woman of childbearing potential who is Rh(D)-negative, anti-D immune globulin should be coadministered to reduce the risk of alloimmunization.
- Platelet transfusion refractoriness, defined as an increase in platelet count less than 10,000/μL (10×10^9/L) when measured within 1 hour after transfusion, may be caused by alloimmunization or nonimmune factors, including sepsis, hypersplenism, disseminated intravascular coagulation, and some medicines, such as amphotericin B.
- In patients with hematologic malignancies undergoing chemotherapy or hematopoietic stem cell transplantation, prophylactic platelet transfusions for platelet counts less than 10,000/μL (10×10^9/L) decrease the risk of bleeding compared with platelet transfusion at the onset of clinical bleeding.

Plasma Products

Fresh Frozen Plasma

Fresh frozen plasma (FFP) is plasma collected from whole blood through centrifugation or collected through apheresis and stored at −18 °C (0.04 °F) or colder within 6 to 8 hours of donation. FFP contains all of the coagulation factors. One unit of FFP is 200 to 280 mL. The appropriate dose of FFP and administration schedule must take into account the patient's plasma volume, the factor activity goal, and the half-life of the affected factor(s). In general, an effective dose of FFP can range from 10 to 15 mL/kg. When used to treat patients with multiple clotting factor deficiencies and clinically significant active bleeding (advanced liver impairment or DIC), FFP may need to be administered every 8 to 12 hours to achieve adequate hemostasis. Redosing should be guided by monitoring the prothrombin and activated partial thromboplastin times, clotting factor levels, and achievement of hemostasis. FFP use is excessive in the United States and other countries despite published guidelines regarding its use. FFP is ineffective at treating mild coagulopathies characterized by an INR of 1.85 or less. Indications for the use of FFP, as well as other plasma-based products, are outlined in **Table 35**.

Antibodies to A and B antigens may be present in FFP, and ABO-identical or ABO-compatible FFP must be used (see Table 33). Rh(D) compatibility is not necessary. FFP is an acellular product. As such, infections caused by intracellular pathogens like cytomegalovirus are significantly reduced. The risk of other transfusion-associated infections is similar (see Transfusion Complications).

Cryoprecipitate

When FFP is thawed at 4 °C (39.2 °F), a cryoprecipitate remains enriched for factors VIII and XIII, fibrinogen, and

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transfused product, an evaluation to exclude other transfusion reactions is important, because signs and symptoms of a transfusion-transmitted bacterial infection can be similar to other serious reactions. Management of suspected bacterial infection includes antibiotic therapy with gram-positive and gram-negative coverage. Preventive measures include surveillance cultures of stored platelet products. Table 36 includes other transfusion-transmissible pathogens.

KEY POINT

- Management of a suspected transfusion-associated bacterial infection includes antibiotic therapy with gram-positive and gram-negative coverage.

Therapeutic Apheresis

Therapeutic apheresis is a procedure in which blood is passed through an extracorporeal device that separates the various blood components. The affected component is either discarded (as in leukapheresis or plasmapheresis) or treated (as in photopheresis), and the unaffected components are returned to the patient. Plasma exchange and erythrocyte exchange entail the removal of plasma or erythrocytes through apheresis followed by infusion of a crystalloid/colloid or plasma solution or donor erythrocytes to replace what was removed. Although simple erythrocyte transfusion and erythrocyte exchange have not been compared rigorously in sickle cell disease, exchange has the advantage of not increasing blood viscosity, avoiding iron overload, and decreasing the concentration of hemoglobin S more effectively. **Table 37** reviews the indications for therapeutic apheresis.

Apheresis complications include potential transfusion reactions if donor erythrocytes, plasma, or albumin is used (see Transfusion Reactions). Hypotension may occur as a result of volume depletion or in combination with flushing and abdominal pain in patients taking ACE inhibitors who are undergoing plasma exchange, especially when albumin is used as the replacement solution. This is thought to be the result of decreased clearance of bradykinin generated during plasma exchange for those taking ACE inhibitors. As such, ACE inhibitors should be withheld for 24 hours before plasma exchange, if appropriate. Other complications may include the development of hypocalcemia resulting from binding of ionized calcium to citrate. Plasma exchange with crystalloid or non-plasma-containing colloid can lead to coagulopathy caused by clotting factor depletion.

KEY POINT

- Erythrocyte exchange does not increase blood viscosity, avoids iron overload, and more effectively decreases the concentration of hemoglobin S compared with erythrocyte transfusion.

TABLE 37. Indications for Therapeutic Apheresis[a]

Plasmapheresis/Plasma Exchange
Thrombotic thrombocytopenic purpura
Clopidogrel/ticlopidine-associated thrombotic microangiopathy
Hyperviscosity syndrome (Waldenström macroglobulinemia and multiple myeloma)
Paraproteinemic polyneuropathies
Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy)
Chronic inflammatory demyelinating polyradiculoneuropathy
Myasthenia gravis
ANCA-associated rapidly progressive glomerulonephritis
Anti-glomerular basement membrane disease
Recurrent focal segmental glomerulosclerosis
Severe, symptomatic cryoglobulinemia
Antibody-mediated renal allograft rejection
Fulminant Wilson disease
Erythrocyte Exchange
Severe babesiosis[b]
Sickle cell disease with acute cerebral infarct
Sickle cell disease with severe acute chest syndrome[c]
Leukapheresis
Hyperleukocytosis syndrome
Plateletpheresis
Symptomatic extreme thrombocytosis[d]
Extracorporeal Photopheresis
Cardiac allograft rejection, prophylaxis
Erythrodermic cutaneous T-cell lymphoma/ Sézary syndrome
Selective Blood Component Removal
LDL cholesterol for familial hypercholesterolemia

[a]This list includes diseases for which apheresis is an accepted part of frontline therapy for a particular indication, either as the sole therapeutic modality or in combination with other therapy. It is not an all-inclusive list.

[b]Erythrocyte exchange for severe malaria is a category II indication (accepted second-line therapy).

[c]Erythrocyte exchange for acute chest syndrome is a category II indication but recommended by many as first-line therapy for those severely affected.

[d]The use of plateletpheresis is a category II indication for patients with life-threatening thrombosis or hemorrhage associated with thrombocytosis (for example, in a patient with essential thrombocytosis).

Data from Szczepiorkowski ZM, Winters JL, Bandarenko N, et al; Apheresis Applications Committee of the American Society for Apheresis. Guidelines on the use of therapeutic apheresis in clinical practice--evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher. 2010;25(3):83-177. [PMID: 20568098]

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Allergic Reactions and Anaphylaxis

Rarely, anaphylaxis occurs within seconds to several minutes of transfusion of erythrocytes, platelets, plasma, cryoprecipitate, or other plasma-derived blood product. Patients with IgA deficiency are at higher risk because of the presence of anti-IgA antibodies (see MKSAP 17 Infectious Diseases). Manifestations include the sudden onset of respiratory distress, bronchospasm, angioedema, urticaria, nausea and vomiting, abdominal pain, tachycardia, and hypotension. Management consists of transfusion discontinuation, exclusion of other transfusion reactions, and appropriate management of anaphylaxis (see MKSAP 17 Pulmonary and Critical Care Medicine). Prevention includes the use of donors who are IgA deficient for those with anti-IgA antibodies or washing of erythrocyte and platelet products to reduce the volume of allergen-containing plasma in the product.

Less severe allergic reactions occur because of recipient IgE antibodies with reactivity to allergens in the plasma of the transfused product. Signs and symptoms are largely restricted to urticaria. Management consists of transfusion discontinuation to exclude a more severe allergic reaction and administration of antihistamines. Transfusion can be safely resumed for those with waning urticaria and no signs or symptoms of a more serious reaction. Cellular blood product washing reduces the risk of a reaction and should be considered for those with more severe reactions.

KEY POINTS

- Patients with IgA deficiency are at high risk for an anaphylactic transfusion reaction because of the presence of anti-IgA antibodies.
- Treatment of patients experiencing anaphylaxis from transfusion consists of transfusion discontinuation, exclusion of other transfusion reactions, and appropriate anaphylaxis management.
- Management of allergic reactions consists of transfusion discontinuation to exclude a more severe allergic reaction and administrations of antihistamines.

Transfusion-associated Graft-versus-Host Disease

Transfusion-associated GVHD is a rare but fatal complication of erythrocyte and platelet transfusion in which viable donor lymphocytes generate an immune response to recipient tissues. This typically occurs in recipients who are immunocompromised and unable to destroy the donor lymphocytes or in immunocompetent patients who are heterozygous for an HLA haplotype for which the donor is homozygous. Signs and symptoms occur several days to 1 month after transfusion and include a diffuse maculopapular rash, jaundice, abdominal pain, nausea and vomiting, diarrhea, abnormal liver chemistries, and severe pancytopenia. Irradiation of blood products before transfusion destroys donor lymphocytes and has largely eliminated this complication.

KEY POINT

- Signs and symptoms of transfusion-associated graft-verus-host disease occur several days to 1 month after transfusion and include a diffuse maculopapular rash, jaundice, abdominal pain, nausea and vomiting, diarrhea, abnormal liver chemistries, and severe pancytopenia.

Infectious Complications

Transmission of bacterial infection from contaminated blood products is an uncommon but potentially life-threatening complication of transfusion. Various gram-positive and gram-negative bacteria have been implicated, including skin, enteric, and environmental organisms (**Table 36**). Platelets must be stored at room temperature and are associated with a higher risk of bacterial contamination. Signs and symptoms occur within minutes to several hours after transfusion and include fever, chills, rigors, tachycardia, and hypotension. In addition to blood cultures from the patient and culture of the

TABLE 36. Transfusion-Transmitted Infections

Pathogen	Risk of Transmission (when known)
Bacterial pathogens	
Staphylococcus aureus	1 in 2500 platelet transfusions
Escherichia coli	
Acinetobacter	
Klebsiella	
Anaplasma (human granulocytic ehrlichiosis)	
Viral pathogens	
Hepatitis A	
Hepatitis B[a]	1 in 280,000 erythrocyte units
Hepatitis C[a]	1 in 1,150,000 erythrocyte units
HIV[a]	1 in 1,500,000 erythrocyte units
HTLV-1/2[a]	1 in 1,900,000 erythrocyte units
West Nile virus[a]	
Dengue fever	
Parasitic pathogens	
Babesiosis	
Malaria	
Leishmaniasis	
Chagas disease[a]	
Prion diseases	
Variant Creutzfeldt-Jakob disease	

HTLV = human T-cell lymphotropic virus type 1/2.

[a]Donated blood is screened for these pathogens. Syphilis is also screened, as is cytomegalovirus on a subset of donated blood to serve as a source for immunocompromised recipients who are cytomegalovirus seronegative.

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Transfusion Complications

Hemolytic Reactions

Acute Hemolytic Transfusion Reaction

Intravascular acute hemolytic transfusion reactions are characterized by the immediate destruction of donor erythrocytes by recipient antibodies. These reactions are most commonly caused by ABO incompatibilities or, occasionally, alloantibodies to other erythrocyte antigens. Signs and symptoms include fever, chills, dyspnea, red urine, flank pain, kidney injury, DIC, and hypotension/shock. Therapy consists of transfusion discontinuation, intravenous hydration, and appropriate cardiovascular support. Blood should be sent for transfusion reaction evaluation. A direct antiglobulin (Coombs) test is positive if blood is drawn before the destruction of all donor erythrocytes. Extravascular acute hemolytic transfusion reactions are caused by non-complement-fixing alloantibodies and are usually not life threatening. Patients may have fever, chills, jaundice, or worsening anemia but are often asymptomatic. Treatment is supportive.

Delayed Hemolytic Transfusion Reaction

Delayed hemolytic transfusion reactions are typically caused by an anamnestic alloantibody response upon re-exposure to an erythrocyte antigen. The alloantibody is undetectable at the time of initial antibody screening but increases rapidly after erythrocyte transfusion. These reactions occur 2 to 10 days after transfusion, are often extravascular, and produce similar clinical signs and symptoms as an extravascular acute hemolytic transfusion reaction. A repeat antibody screen and direct antiglobulin test will be positive. Treatment is supportive. The rate of onset of delayed hemolytic transfusion reactions is slower than that of intravascular acute reaction and signs and symptoms are not as severe. Intravenous fluid hydration and close monitoring are typically sufficient. H

KEY POINTS

- Signs and symptoms of acute hemolytic transfusion reaction include fever, chills, dyspnea, red urine, flank pain, kidney injury, disseminated intravascular coagulation, and hypotension/shock.
- Therapy for acute hemolytic transfusion reaction consists of transfusion discontinuation, intravenous hydration, and appropriate cardiovascular support.
- Delayed hemolytic transfusion reactions occur 2 to 10 days after transfusion, are often extravascular, and present with fever, jaundice, and worsening anemia.

Nonhemolytic Transfusion Reactions

Transfusion-associated Circulatory Overload

Transfusion-associated circulatory overload is a common, underreported adverse event in which hypervolemia develops toward completion or within several hours of a blood product transfusion. Signs and symptoms include dyspnea, hypoxia, tachycardia, headache, and hypertension, and physical examination demonstrates evidence of pulmonary edema or other signs of volume overload. Risk factors include age older than 60 years, chronic kidney disease, heart failure, number of blood products transfused, and volume transfused per hour. Management consists of transfusion discontinuation, diuretic therapy, and supportive care. Prevention includes a slower infusion rate (1 mL/kg/hour) and diuretic therapy between transfusions to maintain euvolemia for those at risk.

Transfusion-related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related mortality. It is characterized by the development of acute lung injury within 6 hours of transfusion of erythrocytes, platelets, or FFP. TRALI is mediated by initial priming of neutrophils in the recipient's lung parenchyma (endothelial damage, for example) followed by their activation by anti-HLA and antineutrophil antibodies present in donor plasma. Signs and symptoms escalate quickly and include dyspnea, hypoxia, fever, chills, and hypotension. Chest radiograph reveals diffuse bilateral pulmonary infiltrates. Preventive measures include excluding multiparous women from donating plasma-rich blood products, deferring any blood product donation from those implicated in a previous TRALI reaction, and using solvent/detergent-treated plasma. Management includes transfusion discontinuation and supportive care, which frequently includes a brief course of mechanical ventilation.

Febrile Nonhemolytic Transfusion Reaction

Febrile nonhemolytic transfusion reactions are common and occur within several hours of an erythrocyte or platelet transfusion. Febrile nonhemolytic transfusion reactions are mediated by the generation of leukocyte-derived cytokines during erythrocyte and platelet storage. Symptoms include fever, chills, rigors, or dyspnea. Management consists of transfusion discontinuation to exclude a more serious transfusion reaction, acetaminophen for fever, and meperidine for rigors. Leukoreduction of packed red blood cells and platelets before storage significantly reduces the rate of febrile nonhemolytic transfusion reactions. H

KEY POINTS

- Signs and symptoms of transfusion-associated circulatory overload include dyspnea, hypoxia, tachycardia, headache, and hypertension, and physical examination demonstrates evidence of volume overload.
- Transfusion-related acute lung injury is characterized by the development of acute lung injury within 6 hours of transfusion of erythrocytes, platelets, or fresh frozen plasma, with signs and symptoms escalating quickly to include dyspnea, hypoxia, fever, chills and hypotension.
- Transfusion discontinuation and supportive care are the primary interventions for all nonhemolytic transfusion reactions.

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TABLE 35. Plasma-Derived Therapeutic Products

Product	Indication(s) for Use
Fresh frozen plasma	Replacement solution for plasma exchange
	Prevention of coagulopathy from massive transfusion
	Treatment of bleeding associated with multiple acquired clotting factor deficiencies (liver disease, disseminated intravascular coagulation)
	Major warfarin-associated hemorrhage (when a 4-factor prothrombin complex concentrate is not available)
Cryoprecipitate	Congenital or acquired fibrinogen deficiency
	Dysfibrinogenemia
	Factor XIII deficiency
	Treatment of hemophilia A and von Willebrand disease when another more suitable product is not available
Immune globulin	Acquired or congenital hypogammaglobulinemia
	Autoimmune disorders
Albumin	Replacement solution for plasma exchange
	Spontaneous bacterial peritonitis
Prothrombin complex concentrates[a]	Major warfarin-associated hemorrhage
Factor VIII[b]	Hemophilia A, treatment and prevention of bleeding
von Willebrand protein-rich factor VIII[c]	Von Willebrand disease, treatment and prevention of bleeding
Factor IX[b]	Hemophilia B, treatment and prevention of bleeding
Fibrinogen	Congenital fibrinogen deficiency, treatment of bleeding
Thrombin[b]	Small vessel bleeding despite standard surgical techniques or when surgical intervention is not feasible (topical application)
Protein C concentrate	Severe congenital protein C deficiency (prevention and treatment of venous thrombosis and purpura fulminans)
Antithrombin[b]	Hereditary antithrombin deficiency (perisurgical and obstetrical procedure prophylaxis and treatment of established venous thrombosis)
α_1-antitrypsin	Congenital α_1-antitrypsin deficiency (high-risk phenotype, α_1-antitrypsin level <11 µmol/L, ≥18 years of age and airflow obstruction by spirometry)
C1-esterase inhibitor	Hereditary angioedema, acute attacks

[a]4-Factor prothrombin complex concentrate (containing factors II, VII, IX, and X) is preferred over 3-factor prothrombin complex concentrates in which factor VII is missing.

[b]Recombinant product available and preferred as a way of reducing risk of transmissible infections.

[c]Select plasma-derived factor VIII products are rich in von Willebrand protein.

von Willebrand factor (vWF). A unit is 10 to 20 mL. Cryoprecipitate is used to treat fibrinogen deficiency, dysfibrinogenemia, and factor XIII deficiency (see Table 35). Cryoprecipitate can be used as a source of vWF for patients with von Willebrand disease, but vWF-containing factor VIII concentrates are preferred. The widespread availability of plasma-derived and recombinant factor VIII products has largely eliminated the use of cryoprecipitate in the management of hemophilia A.

Other Plasma-Derived Transfusion Products

Inactivated 4-factor prothrombin complex concentrate contains factors II, VII, IX, and X and is indicated for the treatment of major warfarin-associated bleeding in conjunction with vitamin K. If unavailable, FFP can be used in its place or a 3-factor prothrombin complex concentrate (missing factor VII) with a supplemental dose of FFP or recombinant activated factor VII (see Table 35).

KEY POINTS

- Fresh frozen plasma is ineffective for treating mild coagulopathies characterized by an INR of 1.85 or less.
- Inactivated 4-factor prothrombin complex concentrate contains factors II, VII, IX, and X and is indicated in conjunction with vitamin K for the treatment of major warfarin-associated bleeding.

HVC

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Thrombotic Disorders

Pathophysiology of Thrombosis and Thrombophilia

The balance of multiple procoagulant and anticoagulant factors, including coagulation proteins, platelets, leukocytes, erythrocytes, and components of the vascular wall, prevents thrombosis development. Procoagulant activity necessary for hemostasis is modulated by the natural anticoagulant system (proteins C and S, antithrombin, tissue factor pathway inhibitor). Fibrinolysis limits thrombus growth and facilitates clot resolution, resulting in reestablishment of intravascular blood flow. Thrombosis occurs when this balance is disturbed. The contributing factors of reduced blood flow (stasis), blood hypercoagulability (thrombophilia), and vascular wall abnormalities have been described as Virchow triad. Thrombosis is typically multifactorial, with genetic and acquired factors contributing.

Thrombophilia

Blood hypercoagulability is referred to as thrombophilia and can be inherited or acquired. Venous thromboembolism (VTE) is often multifactorial, and risk factors potentiate each other, often in more than just additive fashion.

Inherited Thrombophilic Conditions

Thrombophilia Testing

When thrombophilia testing is contemplated, a four-component strategy (the "4Ps") should be considered: Patient selection, Pretest counseling, Proper laboratory test interpretation, and Provision of education and advice. No general consensus exists on who should undergo thrombophilia testing. Identifying a thrombophilia often does not change treatment decisions in a patient with VTE. The evidence-based 2012 anticoagulation treatment guidelines of the American College of Chest Physicians and a 2012 guidance document of the International Society on Thrombosis and Haemostasis recommend against routine thrombophilia testing because identification of inherited abnormalities does not alter the duration of recommended anticoagulation or reliably predict risk of VTE recurrence. However, in patients with VTE assessed to be at intermediate risk for recurrence by traditional predictors, finding a strong thrombophilia (homozygous factor V Leiden [FVL] or II20210; double heterozygous FVL plus II20210; deficiency of protein C, S, or antithrombin; antiphospholipid antibody [APLA] syndrome) may be one motivator for long-term anticoagulation (**Table 38**).

TABLE 38. Risk of Venous Thromboembolism Associated with Various Thrombophilias

Thrombophilia	Risk Relative to Persons Without the Respective Thrombophilia	
	First VTE	**Recurrent VTE**
Thrombophilia not present	Reference group	Reference group
Heterozygous *G20210A*	3.8 (95% CI, 3.0-4.9)[a]	1.45 (95% CI, 0.96-2.21)[b]
Heterozygous FVL	4.9 (95% CI, 4.1-5.9)[a]	1.56 (95% CI, 1.14-2.12)[b]
Homozygous *G20210A*	Insufficient data	Insufficient data
Heterozygous FVL + heterozygous *G20210A*	20 (95% CI, 11.1-36.1)[a]	4.81 (95% CI, 0.50-46.3)[b]
Homozygous FVL	18 (95% CI, 4.1-41)[c]	2.65 (95% CI, 1.18-5.97)[b]
Protein S deficiency	30.6 (95% CI, 26.9-55.3)[d]	Increased, but insufficient data for accurate risk assessment
Protein C deficiency	24.1 (95% CI, 13.7-42.4)[d]	
Antithrombin deficiency	28.2 (95% CI, 13.5-58.6)[d]	
APLA	Increased, but data insufficient and too heterogeneous for accurate risk assessment	Available evidence is of very low quality: Any APLA positive: 1.41 (95% CI, 0.99-2.00)[e] Anticardiolipin positive: 1.53 (95% CI, 0.76-3.11)[e] Lupus anticoagulant positive: 2.83 (95% CI, 0.83-9.64)[e]

APLA = antiphospholipid antibody; FVL = factor V Leiden; VTE = venous thromboembolism.

Data from: [a]Emmerich J, Rosendaal FR, Cattaneo M, et al. Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism--pooled analysis of 8 case-control studies including 2310 cases and 3204 controls. Study Group for Pooled-Analysis in Venous Thromboembolism [erratum in: Thromb Haemost 2001 Dec;86(6):1598]. Thromb Haemost. 2001 Sep;86(3):809-16. [PMID: 11583312] [b]Segal JB, Brotman DJ, Necochea AJ, et al. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. JAMA. 2009 Jun 17;301(23):2472-85. [PMID: 19531787] [c]Juul K, Tybjaerg-Hansen A, Schnohr P, Nordestgaard BG. Factor V Leiden and the risk for venous thromboembolism in the adult Danish population. Ann Intern Med. 2004 Mar 2;140(5):330-7. [PMID: 14996674] [d]Lijfering WM, Brouwer JL, Veeger NJ, et al. Selective testing for thrombophilia in patients with first venous thrombosis: results from a retrospective family cohort study on absolute thrombotic risk for currently known thrombophilic defects in 2479 relatives. Blood. 2009 May 21;113(21):5314-22. [PMID: 19139080] [e]Garcia D, Akl EA, Carr R, Kearon C. Antiphospholipid antibodies and the risk of recurrence after a first episode of venous thromboembolism: a systematic review. Blood. 2013 Aug 1;122(5):817-24. [PMID: 23760616]

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CONT.

Guidelines have not addressed whether screening family members of patients in whom a strong thrombophilia has been detected is beneficial. Consultation with a thrombosis specialist in these circumstances is advisable.

Factor V Leiden

FVL is the most common inherited thrombophilia. It results from a point mutation (G1691A) in the factor V gene, which leads to an amino acid substitution that renders factor V resistant to inactivation by activated protein C (APC). FVL accounts for greater than 90% of APC resistance, with other causes being less common factor V mutations and acquired conditions, including APLA syndrome, pregnancy, and cancer. FVL is inherited in an autosomal dominant fashion; its prevalence is 3% to 8% in whites and 1.2% in blacks in the United States. It is rarely found in African and Asian populations. Homozygous FVL occurs in 1 in 500 to 1600 whites. FVL is diagnosed by polymerase chain reaction (PCR) testing of the FVL gene. However, the presence of FVL can be detected through an APC resistance assay that assesses the ability of protein C to inactivate factor Va. This is a very sensitive test that effectively excludes FVL if normal and is the preferred initial screening test, because it is usually less expensive than the genetic test. An abnormal result suggests heterozygous or homozygous FVL, depending on the degree of abnormality, but must be followed up by PCR testing of the FVL gene.

Additional factors that further increase VTE risk include age, smoking, obesity, and estrogen use. A systematic review showed that FVL heterozygosity is only a very mild risk factor for VTE recurrence compared with absence of FVL; FVL homozygosity is a stronger risk factor. It is unknown whether homozygous FVL is a risk factor for arterial thrombosis, but heterozygous FVL is not.

Prothrombin *G20210A* Gene Mutation

The prothrombin *G20210A* gene mutation (PGM) occurs in the noncoding region and is the second most common inherited risk factor for VTE. It is inherited in an autosomal dominant fashion, and persons with the mutation have slightly higher levels of circulating prothrombin (factor II) than those without it; this has been speculated to be the mechanism of the increased VTE risk. The prevalence in the United States is 2% in whites and 0.5% in blacks. Homozygosity for PGM occurs in approximately 1 in 4000 persons of white European descent. It is diagnosed by PCR testing of the prothrombin gene. Obtaining factor II activity levels is not helpful.

Heterozygous PGM confers a three-fold increased risk of first-time VTE. The VTE risk in persons homozygous for the mutation has not been defined. A systematic review showed that heterozygosity compared with absence of the mutation was not associated with an increased risk of VTE recurrence. No clinically meaningful association has been demonstrated between PGM and arterial thromboembolism. However, a mild association has been suggested between PGM and stroke and myocardial infarction risks in certain subpopulations, such as younger patients.

Antithrombin Deficiency

Antithrombin is an enzyme that interrupts the coagulation process, mainly by inhibiting thrombin and activated factors X and IX (factors Xa and IXa). Antithrombin deficiency (ATD) is inherited in an autosomal dominant fashion. Quantitative (type I) and qualitative (type II) defects exist, and the risk for VTE appears to depend on the genetic defect and deficiency subtype, ranging from mildly thrombogenic to more pronounced. Inherited ATD is uncommon. The prevalence in the general population is 1 in 500 to 5000. Deficiencies are typically heterozygous; homozygous deficiencies are typically not compatible with life. Many causes exist for acquired low antithrombin levels (**Table 39**). ATD is diagnosed by assaying antithrombin activity. Acquired causes must be ruled out. Genetic testing is not feasible for routine clinical practice. A thrombosis specialist can conduct further testing to clarify the subtype of ATD to assess thrombosis risk.

ATD is considered a risk factor for VTE, but the risk depends on the subtype. It is unclear whether ATD is a risk factor for arterial thromboembolism. A large family study showed no association between ATD and arterial thrombosis. Antithrombin concentrates may be used as adjunctive therapy with routine pharmacologic VTE prophylaxis or as a supplement when treating acute VTE.

Protein C Deficiency

Protein C is a vitamin K–dependent natural anticoagulant; it is converted during the coagulation process to APC, which inactivates coagulation factors Va and VIIIa. Quantitative

TABLE 39. Conditions Associated with Decreased Coagulation Factor Levels

Coagulation Factor	Condition
Protein C	Acute thrombosis
	Warfarin therapy
	Liver disease
	Protein-losing enteropathy
Protein S	Acute thrombosis
	Warfarin therapy
	Liver disease
	Inflammatory states
	Estrogens (contraceptives, pregnancy, postpartum state, hormone replacement therapy)
	Protein-losing enteropathy
Antithrombin	Acute thrombosis
	Heparin therapy
	Liver disease
	Nephrotic syndrome
	Protein-losing enteropathy

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CONT. (type I) and qualitative (type II) defects exist, but their clinical appearance is almost identical. Protein C deficiency is inherited in an autosomal dominant fashion. The diagnosis is made by obtaining a protein C activity assay, also referred to as functional protein C. Genetic testing is not feasible for routine clinical practice. See Table 39 for causes of acquired low levels.

The prevalence of inherited protein C deficiency is 1 in 500 to 600. Homozygous or double heterozygous protein C deficiency may develop in fetuses in approximately 1 in 1,000,000 pregnancies. Protein C deficiency is a risk factor for primary VTE, recurrent VTE, and arterial thromboembolism. H

Plasma-derived protein C concentrate is indicated in infants with catastrophic thrombotic complications (purpura fulminans) due to severe protein C deficiency at birth.

Protein S Deficiency

Protein S is another natural vitamin K-dependent anticoagulant. It is a cofactor for APC. Protein S deficiency is inherited in an autosomal dominant fashion and is classified into three types, although their clinical manifestations are nearly identical. Evaluation of protein S deficiency includes measurement of protein S activity (also referred to as functional protein S) and free protein S antigen; interpretation of these studies is often challenging and may be facilitated by a thrombosis specialist. Genetic testing is not feasible for routine clinical practice. See Table 39 for causes of acquired low levels.

The prevalence of inherited protein S deficiency is between 1 in 800 and 1 in 3000; however, rates of VTE vary among individuals and families with the deficiency. It is considered a higher risk thrombophilia.

The heterogeneity in the clinical phenotype of patients with protein S deficiency must be taken into consideration when deciding duration of anticoagulant therapy and family counseling. A large family study showed that protein S deficiency is a risk factor for arterial thromboembolism in persons younger than 55 years. No protein S concentrate exists. H

Other Inherited Thrombophilic Disorders

A family history of VTE is a risk factor for first-time VTE whether a thrombophilia is detectable in the family or not. This risk is conferred by unknown factors. Having one first-degree relative with a history of VTE increases a person's risk of VTE 2.2-fold; having one or more affected relatives increases the risk 3.9-fold.

Dysfibrinogenemias are rare inherited disorders that can lead to a clotting or bleeding phenotype. An elevated serum homocysteine level is a risk factor for arterial and venous thrombosis. However, lowering levels with vitamins B_6 or B_{12} or folic acid does not influence the risk of a first or recurrent thrombotic event. Polymorphisms in the methylene tetrahydrofolate reductase (*MTHFR*) gene exist that, in the homozygous or double heterozygous state, sometimes lead to increased homocysteine levels. Meta-analyses show that the *MTHFR* polymorphisms in North America, where food is supplemented with folic acid, are not risk factors for venous or arterial thrombosis or pregnancy complications.

Elevated plasma factor VIII levels are an independent and dose-dependent risk factor for a first episode of VTE. Population-based controlled studies have demonstrated that elevations in factor VIII greater than 150% confer a 4.8-fold greater risk for first-episode VTE than levels less than 100%. Results of studies investigating whether elevated factor VIII levels are also a risk factor for recurrent VTE have been inconclusive. Therefore, decisions on duration and intensity of anticoagulation cannot be made based on factor VIII levels. Consequently, clinical testing for factor VIII levels is not part of a thrombophilia evaluation.

Studies of abnormalities of fibrinolysis (protein and activity levels and genetic polymorphisms) as risk factors for arterial or venous thrombosis have yielded conflicting or indecisive results. Therefore, testing for abnormalities in the fibrinolytic pathway (plasminogen, tissue plasminogen activator, plasminogen activator inhibitor-1, and thrombin-activatable fibrinolysis inhibitor) is not meaningful. Results neither explain the cause of a thrombotic event nor influence decisions on duration of anticoagulant therapy.

KEY POINTS

- Evidence-based guidelines recommend against routine thrombophilia testing because identification of inherited abnormalities does not alter the duration of recommended anticoagulation or reliably predict the risk of recurrence. HVC
- Factor V Leiden (FVL) is the most common inherited thrombophilia, diagnosed by polymerase chain reaction test and activated protein C (APC) resistance assay; an abnormal APC assay result suggests heterozygous or homozygous FVL, but must be confirmed by a genetic test.
- Heterozygous prothrombin *G20210A* gene mutation confers a three-fold increased risk for initial venous thromboembolism (VTE) but is not associated with increased risk for VTE recurrence.

Acquired Thrombophilic Conditions

Overview

Several environmental and medical conditions lead to an increased risk for VTE. The most significant risk factors are surgery (OR 21.7), trauma (OR 12.7), hospital or nursing home confinement (OR 8.0), and malignant neoplasm undergoing chemotherapy (OR 6.6); other factors (active malignancy not undergoing chemotherapy, central venous catheter or pacemaker placement, superficial vein thrombosis, neurologic disease with extremity paresis) have an OR between 3.0 and 5.6. Central venous access catheters, estrogen therapy and pregnancy, obesity, inflammatory disorders, chemotherapy, glucocorticoid therapy, and smoking are additional risk factors.

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Surgery, Trauma, Hospitalization, Immobility

Hip and knee arthroplasty, cancer surgery, and pelvic and abdominal surgery are associated with a particularly high VTE risk. Although outpatient and minor inpatient surgeries can increase the VTE risk, particularly if additional VTE risk factors are present, the overall risk is very low. Approximately 40% of VTEs are associated with hospitalization, occurring either in the hospital or shortly after discharge, typically within 3 months. Therefore, patient awareness of VTE symptoms and postdischarge VTE prophylaxis in patients at high risk may be important, even if the patient is mobile after discharge. Forty percent or more of hospital VTEs are preventable with VTE prophylaxis.

Cancer

Approximately 20% of all VTEs occur in patients with cancer. The risk for VTE is determined by general risk factors (age, obesity, personal or family history of VTE, coexisting medical conditions, inherited and acquired thrombophilias) and cancer-specific risk factors (cancer type, stage, chemotherapy type, hormonal therapy, surgery, central venous catheters). Active cancer or cancer actively being treated with chemotherapy or radiation therapy increases the VTE risk approximately five- to six-fold, but a history of cancer, or cancer that has undergone curative therapy without evidence of residual disease, does not.

Approximately 6% of patients with unprovoked VTE have an undiagnosed cancer at the time of the VTE, and about 10% of patients with unprovoked VTE will be diagnosed with a cancer in the year following the VTE diagnosis. It is unknown whether extensive screening for cancer in a patient with unprovoked VTE is beneficial and leads to decreased cancer-associated morbidity or improved survival. Cancer should be considered in select patients, such as those with recent weight loss and other unexplained symptoms or abnormalities on routine laboratory testing, such as anemia. Routine extensive screening for underlying cancer in all patients with unprovoked VTE, beyond that recommended for age and gender, is not recommended.

Antiphospholipid Antibody Syndrome

APLAs are acquired autoantibodies against phospholipids and phospholipid-binding proteins such as cardiolipin and β_2-glycoprotein I (β_2-GPI). In vitro, they can prolong clotting tests, but in vivo they increase the risk of venous and arterial thrombosis. Antiphospholipid syndrome (APS) can be a primary disorder with no underlying comorbidity or a secondary disorder associated with autoimmune diseases, malignancy, or drugs.

APLAs **(Figure 14)** may be detected and measured in several ways. Lupus anticoagulants (also termed lupus inhibitors) are APLAs that prolong clotting times (such as the prothrombin time [PT], activated partial thromboplastin time [aPTT], dilute Russell viper venom time). This prolongation is not corrected with a normal plasma mixing study, but corrects when excess phospholipids are added. Anticardiolipin antibodies (ACAs) are APLAs that react with cardiolipin or proteins associated with cardiolipin and are also responsible for false-positive tests for syphilis (such as the rapid plasma reagin test) that use cardiolipin in their assays.

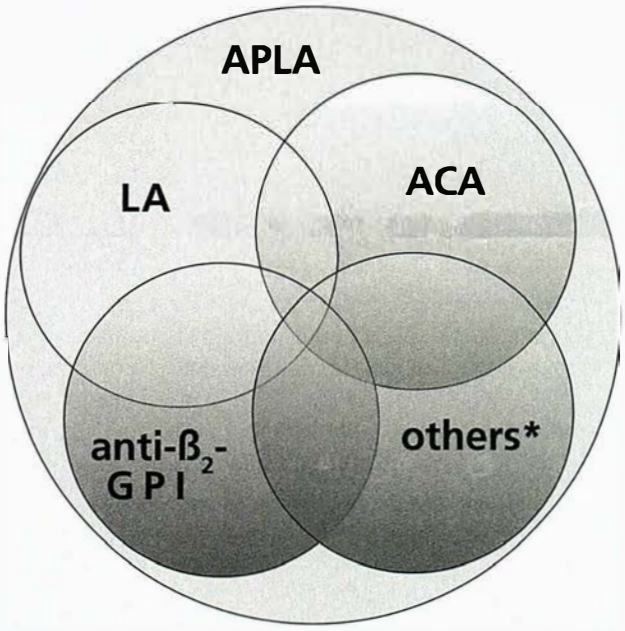

FIGURE 14. APLAs are acquired autoantibodies against phospholipids and phospholipid-binding proteins such as cardiolipin and β_2-GPI; LAs are APLAs that prolong clotting times although patients are actually thrombophilic. Some patients may have one or more APLAs present.

APLA = antiphospholipid antibody; ACA = anticardiolipin antibody, anti-β_2-GPI = anti-β_2-glycoprotein-I antibody; LA = lupus anticoagulant.

*Other antibodies, of unclear clinical significance: antiphosphatidyl-serine, -ethanolamine, and -inositol antibodies.

The diagnostic criteria for APS include venous or arterial thrombosis or pregnancy loss plus moderate to high antibody titers or a lupus anticoagulant that is positive on repeat testing at least 3 months apart (**Table 40**).

No full consensus exists regarding which APLAs to test for in suspected APS. The Sydney criteria include IgG and IgM ACAs and anti-β_2-GPI antibodies, as well as lupus anticoagulant (see Table 40). The clinical significance of IgA antibodies and antibodies against other phospholipids is unclear. The prevalence of APS is poorly defined, but APLAs are found in nearly 50% of patients with systemic lupus erythematosus, but only 1% to 5% of the general population. Not infrequently, APLAs are transiently positive at the time of an acute thrombotic event, but the clinical significance of these elevations is questionable.

Positivity of all three APLA tests (lupus anticoagulant, ACA, and anti-β_2-GPI antibodies) is associated with the highest risk for thrombosis and pregnancy loss. APS is also implicated in recurrent VTE when anticoagulation is discontinued. However, limited data exist on the degree to which APLAs increase the risk of recurrence, particularly in patients whose index event was provoked. Presence of a

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TABLE 40. Diagnostic Criteria for Antiphospholipid Syndrome

Clinical Criteria	Definitions
Vascular events	One or more objectively confirmed symptomatic episodes of arterial, venous, or microvascular thrombosis. Histopathologic specimens must demonstrate thrombosis in the absence of vessel wall inflammation to qualify
Pregnancy morbidity	One or more unexplained fetal deaths at or beyond the 10th week of gestation, with normal fetal morphology; or
	One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia, or placental insufficiency; or
	Three or more unexplained, consecutive, spontaneous abortions before the 10th week of gestation in the absence of maternal anatomic, chromosomal, or hormonal abnormalities or paternal chromosomal abnormalities
Laboratory Criteria	**Definitions**
Lupus anticoagulant	Positive result for a lupus anticoagulant using a phospholipid-dependent clotting assay (aPTT, dilute Russell viper venom assay, kaolin clotting time, dilute PT) with evidence of phospholipid dependence present on two or more occasions at least 12 weeks apart; or
Anticardiolipin antibody	Medium- or high-titer IgG or IgM anticardiolipin antibody measured using a standardized ELISA on two or more occasions at least 12 weeks apart; or
β_2-Glycoprotein I antibody	High-titer anti-β_2-glycoprotein I IgG or IgM antibody measured using a standardized ELISA on two or more occasions at least 12 weeks apart

aPTT = activated partial thromboplastin time; ELISA = enzyme-linked immunosorbent assay; PT = prothrombin time.

Data from Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295-306. [PMID: 16420554]; and Devreese K, Hoylaerts MF. Laboratory diagnosis of the antiphospholipid syndrome: a plethora of obstacles to overcome. Eur J Haematol. 2009;83(1):1-16. [PMID: 19226362]

CONT. lupus anticoagulant is a stronger risk factor for recurrence than ACA and anti-β_2-GPI antibodies; triple positivity confers the highest risk of recurrence. Finally, warfarin therapy is unsuccessful in preventing recurrent thrombosis in 5% to 15% of patients. Occasionally, this is a result of invalidity of the INR for assessing warfarin therapy, because the INR may be inappropriately elevated in some patients because of a lupus anticoagulant, potentially leading to inaccurate measurement of anticoagulation.

Because of the high rate of recurrent VTE, patients with APS and a history of unprovoked VTE should receive anticoagulation therapy indefinitely. A target INR range of 2 to 3 is as effective in preventing recurrent VTE as an INR range of 3 to 4. Whether patients with arterial thrombosis and APS are more effectively treated with antiplatelet or anticoagulant therapy is unknown. Rituximab has been shown to decrease APLA titers in some patients, but whether decreasing or eliminating APLAs leads to a decreased thrombosis risk has not been studied.

Catastrophic APS is a rare, life-threatening condition that results in multiorgan failure from widespread microvascular thrombosis. Anticoagulation, high-dose glucocorticoids and other immunosuppressants, and plasma exchange are the treatment modalities.

Medications

Many medications increase the risk for thrombosis, often in conjunction with acquired hypercoagulable states (such as obesity, smoking, and age) or inherited thrombophilias. The VTE risk with estrogen-progestin contraceptives is highest with the fourth-generation pills (containing the progestin drospirenone) and contraceptive patches and rings, followed by third generation pills, and then second-generation pills. Somewhat limited data exist regarding the risk of VTE with progestin-only contraceptives. It appears that injectable progestin-only contraceptives do increase the risk of VTE, but oral progestin contraceptives (mini-pill) carry less risk, and progestin-releasing intrauterine devices do not increase risk (see MKSAP 17 General Internal Medicine for more information on contraceptives by generation).

Hormone replacement therapy with estrogen-progestin agents also increases the risk for VTE. Whether so-called "bioidentical hormones," compound hormonal preparations, or phytoestrogens increase the risk for thrombosis is unknown. Chemotherapy, particularly combination therapy, increases the risk for thrombosis in patients with cancer, as do specific drugs such as tamoxifen and anastrozole. Bevacizumab increases the risks for thrombosis and bleeding. Erythropoiesis-stimulating agents confer a mild risk for VTE in patients with cancer, increasing the VTE risk 1.6-fold.

Other Acquired Thrombophilic Conditions

Thrombosis may occur as a complication of systemic or local infection. Head and neck infections may trigger cerebral and sinus vein thrombosis, likely through inflammation of the jugular vein. Inflammatory conditions slightly increase the risk of VTE, as do glucocorticoids. Nephrotic syndrome

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predisposes to VTE, sometimes owing to urine antithrombin loss but often because of unknown factors. Liver disease can lead to an increased risk of thrombosis because of decreased synthesis of anticoagulants (for example, antithrombin, proteins C and S) and fibrinolytic factors. Myeloproliferative neoplasms (MPNs) (polycythemia vera, essential thrombocythemia, and myelofibrosis) are strong risk factors for thrombosis, more often arterial but also venous. Complete blood count abnormalities may be the first indicator of an MPN, and the presence of the *JAK2 V617F* mutation is a helpful diagnostic tool. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder that predisposes patients to arterial and venous thrombosis with a predilection for splanchnic vein thrombosis.

KEY POINTS

IVC

- Routine extensive screening for underlying cancer in all patients with unprovoked venous thromboembolism is not recommended.
- Because of the high rate of recurrent venous thromboembolism (VTE), patients with antiphospholipid syndrome and a history of unprovoked VTE should undergo anticoagulation indefinitely.
- The risk of venous thromboembolism with estrogen-progestin contraceptives is highest with the fourth-generation pills and contraceptive rings and patches; progestin-releasing intrauterine devices do not increase risk.
- Polycythemia vera, essential thrombocythemia, and myelofibrosis are strong risk factors for arterial and venous thrombosis.

Deep Venous Thrombosis and Pulmonary Embolism

VTE encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE). Superficial thrombophlebitis is not included in this term.

Prevention

VTE prophylaxis should be considered for every hospitalized patient based on individual risk assessment for VTE and bleeding and formal VTE prophylaxis guidelines used in all hospitals (see MKSAP 17 General Internal Medicine). If prophylaxis is indicated, pharmacologic agents are the preferred choice. Mechanical VTE prophylaxis with graded compression stockings or intermittent pneumatic compression devices is not recommended either with or in place of pharmacologic prophylaxis, although intermittent pneumatic compression devices have shown some efficacy in surgical patients and may be an option for nonsurgical patients with a contraindication to pharmacologic therapy. VTE prophylaxis is often only given during a patient's hospitalization. However, for many patients, some degree of VTE risk persists for weeks after discharge, and a heightened level of suspicion that extremity or pulmonary symptoms may be caused by VTE is appropriate, particularly if additional VTE risk factors are present. The benefit of postdischarge prophylaxis (up to 5 weeks) is well established in patients after hip fracture, hip replacement, and major cancer surgery. Prolonged prophylaxis may also be considered in other patients at high risk, such as patients with previous VTE or significant immobility after hospital discharge. The role of inferior vena cava (IVC) filters in patients considered at high risk for PE, such as trauma patients, is unclear.

Diagnosis

The symptoms and signs of VTE, including extremity pain, swelling, warmth, and reddish discoloration in DVT and shortness of breath, chest pain, nonproductive cough, and tachycardia in PE, are notoriously nonspecific, and sensitivity and specificity of these signs and symptoms are low. Because of this, pretest probability models such as the Wells criteria have been developed and validated to assist in clinical decision making when evaluating patients with either potential diagnosis. In patients with low pretest probability for DVT (Wells DVT score ≤1; **Table 41**) or PE (Wells PE score ≤4; **Table 42**), obtaining a D-dimer blood test is suggested; if negative, no further testing is needed, because a VTE has been effectively excluded. However, if the D-dimer assay is positive or the Wells score indicates that DVT or PE is likely (Wells DVT score >1; Wells PE score >4), an imaging study is indicated. When

TABLE 41. Wells Criteria for Deep Venous Thrombosis

Variables	Points
Leg Symptoms and Findings	
Calf swelling ≥3cm	+1
Swollen unilateral superficial veins (nonvaricose)	+1
Unilateral pitting edema	+1
Swelling of the entire leg	+1
Localized tenderness along the deep venous system	+1
History	
Previously documented DVT	+1
Active cancer or treatment in previous 6 months	+1
Paralysis, paresis, recent cast immobilization of legs	+1
Recently bedridden for ≥3 days; major surgery	+1
Alternative explanation for leg symptoms at least as likely	−2

DVT = deep venous thrombosis

0-1 points = DVT unlikely; obtain D-dimer assay. If negative, no further evaluation; if positive, obtain Doppler ultrasonography.

>1 point = DVT likely; obtain Doppler ultrasonography.

From Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003 Sep 25;349(13):1228. [PMID: 14507948]. Reprinted with permission from Massachusetts Medical Society.

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TABLE 42. Wells Criteria for Pulmonary Embolism

Variables	Points
Symptoms and Signs	
Hemoptysis	1
Heart rate >100/min	1.5
Clinical signs and symptoms of DVT	3
History	
Previously documented DVT or PE	1.5
Active cancer	1
Bedridden ≥3 days or major surgery in previous 4 weeks	1.5
Other	
PE is most likely diagnosis	3

DVT = deep venous thrombosis; PE = pulmonary embolism.

≤4 points = PE unlikely.

4-6 points = moderate possibility of PE.

>6 points = high probability of PE.

Republished with permission of Schattauer, from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000 Mar;83(3):418. [PMID: 10744147]

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using the D-dimer for pretest probability assessments, a moderately or highly sensitive assay should be used.

Knowledge of superficial versus deep vein anatomy is important when making VTE treatment decisions. The femoral vein (previously termed superficial femoral vein) is the main deep vein in the thigh; because the term "superficial" can lead to confusion, this vein was renamed. The soleal vein is a deep intramuscular distal leg vein. In the arm, the brachial vein is a deep vein and the basilic vein is a superficial vein. Lower extremity DVTs are termed "proximal" if they involve the popliteal or more proximal veins and "distal" if only calf veins are affected.

When imaging is indicated, duplex ultrasonography and CT angiography (CTA) are the diagnostic tests of choice for DVT and PE, respectively. Duplex ultrasonography interpretations are operator dependent; the diagnosis of recurrent DVT can be particularly challenging. PEs are categorized as "massive" if associated with cardiovascular shock or persistent hypotension, "submassive" if associated with right ventricular dysfunction on echocardiography or chest CT or with serum cardiac enzyme elevation (troponin or B-type natriuretic peptide), and "low risk" if cardiac enzyme level and echocardiography are normal. The categories correspond to mortality rates, ranging from greater than 30% to less than 1%. Although chest CTA is a sensitive test for the detection of PE, suboptimal contrast filling of pulmonary arteries, intravascular flow artifacts, and over- and underinterpretation of changes can lead to false-positive and false-negative readings, particularly of subsegmental PEs. When a discrepancy occurs between clinical pretest probability assessment of PE and CTA imaging findings, review of the CTA by an experienced radiologist and additional testing for VTE (Doppler ultrasonography of the legs, ventilation-perfusion lung scan, D-dimer testing) are indicated to confirm the diagnosis.

Treatment

Outpatient management and early discharge for patients with PE or DVT are safe, feasible, cost-effective management options. Hospital admission is appropriate for patients who are too ill to be managed at home (those needing supplemental oxygen or intravenous pain medications) or for whom social and financial circumstances make this the better option. Outpatient management is safe for up to 50% of patients with PE, even some with mild right heart strain on cardiac echocardiography. Early ambulation rather than bedrest is suggested for patients with DVT and PE.

In patients with acute isolated distal DVT with only mild symptoms and no risk factors for progression (such as immobility or cancer), no anticoagulation is necessary, but serial Doppler ultrasonography approximately 5 to 7 days after initial diagnosis and then 10 to 14 days later is suggested, because approximately 15% of these DVTs progress to proximal veins. Risk factors for extension are a positive D-dimer assay, thrombosis that is extensive or close to the proximal veins, no reversible provoking factor for DVT, active cancer, history of VTE, and inpatient status. Patients with acute isolated distal DVT with severe symptoms or risk factors for extension, and those with proximal DVT, require anticoagulation. For patients with incidentally found asymptomatic proximal DVT or PE, the same initial and long-term anticoagulation is suggested as for comparable patients with symptomatic DVT. Because of radiation exposure with lung scanning, patients with diagnosed DVT and no PE symptoms should not routinely undergo chest CTA.

The role of thrombolytic therapy in the management of DVT is unclear and a matter of clinical investigation. At publication, anticoagulant therapy alone is preferred to pharmacomechanical thrombectomy/thrombolysis for proximal DVT.

Systemic thrombolytic therapy with anticoagulation is suggested for PE with hypotension. The best treatment for patients with submassive PE is unknown, but thrombolytics may be considered in younger patients at low risk for bleeding.

Anticoagulant treatment options in the acute setting are a parenteral anticoagulant (low-molecular-weight heparin [LMWH], fondaparinux, or unfractionated heparin [UFH]) and initiation of warfarin or monotherapy with a new oral anticoagulant (NOAC), including apixaban, dabigatran, edoxaban, and rivaroxaban. When choosing a NOAC, differences between the drugs, dosing regimens, and FDA approval must be considered. Dabigatran and edoxaban were studied in patients with acute VTE only after patients had received at least 5 days of parenteral anticoagulant therapy. In studies of rivaroxaban and apixaban, no such initial bridging therapy was required. Parenteral anticoagulant administration must overlap with

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warfarin for at least 5 days and until the INR is greater than 2 for 24 hours. In most patients, LMWH or fondaparinux is preferred to UFH, because they have less nonspecific protein binding and lead more rapidly to therapeutic anticoagulation. Intravenous UFH is indicated in severely ill patients with VTE who may require thrombolytic therapy or medical intervention such as central venous catheters or arterial lines, during which temporary dose reduction or anticoagulant interruption may become necessary. Therapy with a NOAC is an option in many patients with acute VTE, unless intravenous UFH is necessary. NOACs should not be used in patients who must be hospitalized, who have an extreme BMI (>40), have kidney disease with a creatinine clearance less than 30 mL/min, or, given the nonreversibility of the NOACs, who are at significantly increased risk for bleeding.

Decisions on anticoagulation therapy duration depend on the recurrent VTE risk without anticoagulation, the bleeding risk with anticoagulants, and the patient's preference. Treatment recommendations are summarized in **Table 43**. Patients with distal leg DVT have a low risk for recurrence. In patients with proximal leg DVT or PE, the cumulative VTE recurrence risk after discontinuation of anticoagulation is (1) 1% after 1 year and 3% after 5 years for VTE provoked by major surgery; (2) 5% after 1 year and 15% after 5 years for VTE provoked by a nonsurgical reversible risk factor; and (3) 10% after 1 year and 30% after 5 years for unprovoked VTE. Risk scoring systems have been developed to predict the risk of recurrence in individual patients (HERDOO-2 score, DASH score, Vienna model), but have not been sufficiently validated for use in routine clinical care. When extended (long-term) anticoagulation therapy is chosen, the risks, benefits, and burden of long-term therapy must be re-evaluated periodically. Aspirin appears to lower the risk of recurrent VTE in some patients with unprovoked VTE treated for a standard length of time with full-dose anticoagulant therapy, but it is much less effective than continued anticoagulant therapy. Therefore, aspirin is not an alternative to anticoagulation. However, in patients with unprovoked VTE who discontinue anticoagulant therapy, daily aspirin therapy is reasonable if it is well tolerated and the patient does not have a high bleeding risk.

The only clear indication for an IVC filter is in patients with acute pelvic or proximal leg DVT who cannot undergo anticoagulation because of active bleeding or a very high bleeding risk. It is unclear whether an IVC filter is beneficial in patients with recurrent leg DVT despite therapeutic anticoagulation. H

Long-term Complications

Fifty percent of patients with DVT recover completely, but 33%, 9%, and 7% develop mild, moderate, or severe post-thrombotic syndrome (PTS), respectively, most often within 1 to 2 years of the acute DVT. PTS manifests as painful extremities, edema, stasis dermatitis, and skin ulcers.

TABLE 43. Duration of Anticoagulant Therapy for Venous Thromboembolism[a]

Type of Thrombotic Event	Duration of Anticoagulant Therapy
Distal leg DVT	
Provoked or unprovoked, mild symptoms	No anticoagulation suggested, but monitor with serial duplex ultrasonography for 2 weeks
Provoked or unprovoked, moderate-severe symptoms	3 months
Proximal leg DVT or PE	
Provoked (by surgery, trauma, immobility)	3 months
Unprovoked	Extended[b]
Recurrent	Duration of therapy depends on whether VTE events were provoked or unprovoked
Two provoked VTE events	3 months after each event
Second unprovoked VTE	Extended[b]
Upper extremity DVT, proximal	At least 3 months
Cancer-associated DVT or PE	As long as the cancer is active or being treated. LMWH is the preferred anticoagulant.
Chronic thromboembolic pulmonary hypertension	Extended[b]

DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; VTE = venous thromboembolism.

[a]Decisions regarding duration of anticoagulation must always weigh the risk of VTE recurrence, risk of bleeding, and patient preference.

[b]Indicates long-term anticoagulation therapy with periodic (such as once per year) re-evaluation of the risks, benefits, and burdens of long-term therapy and discussion of new clinical study results and new anticoagulant drugs.

Data from Kearon C, Akl EA, Comerota AJ, et al; American College of Chest Physicians. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [erratum in: Chest. 2012 Dec;142(6):1698-1704]. Chest. 2012 Feb;141(2 Suppl):e419S-94S. [PMID: 22315268]

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Although compression stockings do not appear to prevent PTS, they may be effective in alleviating symptoms. Venous stents may improve PTS in select patients if significant pelvic vein narrowing is demonstrated. Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as an elevated mean pulmonary artery pressure of greater than 25 mm Hg. Patients with large or recurrent PEs are at risk. Chronic shortness of breath and general malaise are key symptoms. Ventilation-perfusion lung scanning is the appropriate test to evaluate for CTEPH; chest CTA is not a sensitive test. Long-term anticoagulant therapy is indicated if CTEPH is present. See MKSAP 17 Pulmonary and Critical Care Medicine for full discussion.

KEY POINTS

- Venous thromboembolism (VTE) prophylaxis should be considered for every hospitalized patient based on individual risk assessment for VTE and bleeding.
- HVC A low-probability Wells score with a negative D-dimer blood test rules out venous thromboembolism.
- Anticoagulant therapy alone is preferred for proximal deep venous thrombosis, and thrombolytic therapy with anticoagulation is suggested for pulmonary embolism with hypotension.
- Anticoagulation duration is 3 months for provoked venous thromboembolism (VTE) and extended for unprovoked VTE or following a second unprovoked VTE episode.
- HVC The only clear indication for an IVC filter is in patients with acute pelvic or proximal leg DVT who cannot be anticoagulated because of active bleeding or a very high risk for bleeding

Other Sites of Thrombosis

Superficial Venous Thrombophlebitis

Superficial venous thrombophlebitis (SVT) may occur unprovoked or in the setting of varicose veins, trauma, phlebotomy, intravenous catheters, underlying hypercoagulable states, cancer, infections, or inflammatory disorders (inflammatory bowel disease, thromboangiitis obliterans [Buerger disease], and Behçet syndrome). Because patients may have concurrent DVT, duplex ultrasonography is indicated when SVT of the great or small saphenous vein is present, if extremity swelling is more pronounced than would be expected from the SVT alone, and if symptoms progress. DVT or PE develops in up to 3.3% of patients with isolated SVT. Nonextensive SVT (less than 5 cm in length and not near the deep venous system) requires only symptomatic therapy consisting of analgesics, anti-inflammatory medications, and warm or cold compresses for symptom relief. Patients with extensive SVT may benefit from a short course of anticoagulant therapy. The only randomized trial in the management of SVT showed that 6 weeks of a prophylactic dose of fondaparinux compared with placebo is beneficial for preventing local thrombosis progression and development of DVT and PE. However, because of a lack of data, optimal length of anticoagulation and drug choice are not known.

KEY POINT

- Nonextensive superficial venous thrombophlebitis requires only symptomatic therapy with analgesics, anti-inflammatory medications, and warm or cold compresses.

Upper Extremity DVT

Upper extremity DVT accounts for 1% to 4% of all DVTs. Approximately 80% are secondary to central venous catheters or cancer, and 20% are primary events. Little direct evidence exists to support any particular duration of anticoagulant therapy after a first unprovoked upper extremity DVT. Management consists of anticoagulation for at least 3 months (see Table 43) for unprovoked or catheter-associated proximal DVT and maintaining catheter placement if the central venous catheter is functional and still needed. Anticoagulation should be continued as long as the catheter remains in place. If the catheter is removed, anticoagulation should be given for 3 months. DVT may also be due to thoracic outlet syndrome (effort thrombosis, Paget-Schroetter syndrome) from external compression of the axillary vein by the clavicle, a cervical rib, or enlarged or aberrantly inserted muscles. No uniform approach exists for treatment of these patients. Upper extremity DVTs carry a risk of PE, but it has not been well quantified. H

KEY POINT

- Approximately 80% of upper extremity deep venous thromboembolisms occur secondary to central venous catheters or cancer, with only 20% occurring as primary events.

Budd-Chiari Syndrome

Presentations of hepatic vein thrombosis (Budd-Chiari syndrome) range from asymptomatic and incidentally discovered to fulminant liver failure. Patients can have various degrees of right upper quadrant or diffuse abdominal pain. The cause is often multifactorial. The most common risk factor, present in nearly 50% of patients, is an MPN such as polycythemia vera, essential thrombocythemia, and primary myelofibrosis. The *JAK2* mutation is frequently present in patients with Budd-Chiari syndrome (29%) even if no hematologic abnormalities suggesting an MPN are present. Any of the inherited and acquired thrombophilias can also contribute to the development of Budd-Chiari syndrome, as can estrogens and pregnancy. PNH can be detected in almost 20% of patients with Budd-Chiari syndrome. The diagnosis is made by Doppler ultrasonography, contrast-enhanced CT, or MRI. Thrombolytic therapy can be considered in the acute setting of fulminant

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thrombosis but must be balanced against the increased risk for bleeding associated with liver failure. Anticoagulation is usually appropriate. The duration may be long term, but depends on a patient's risk for bleeding, which may be significant owing to esophageal varices, coagulopathy from liver synthetic dysfunction, and thrombocytopenia from hypersplenism.

KEY POINT

- The most common risk factor for Budd-Chiari syndrome is a myeloproliferative neoplasm such as polycythemia vera, essential thrombocythemia, and primary myelofibrosis.

Portal and Mesenteric Vein Thrombosis

Portal vein thrombosis (PVT) is often silent and may only be discovered during evaluation of variceal gastrointestinal bleeding. The most common symptom is nonspecific right upper quadrant abdominal pain of acute or subacute onset. It is associated with inherited and acquired thrombophilias, MPNs, *JAK2* positivity without overt MPN, PNH, intra-abdominal neoplasia, infection, trauma, surgery, and neonatal umbilical vein catheterization. PVT occurs in up to 26% of patients with cirrhosis. It is diagnosed by Doppler ultrasonography, CT, or magnetic resonance venography. Cavernous transformation of the portal vein (collateral vessel formation in the porta hepatis) reflects old PVT. In acute PVT, extension of thrombus into the mesenteric veins may lead to intestinal infarction. Superior mesenteric vein thrombosis typically presents with nonspecific abdominal pain and nausea. Symptoms are vague, often leading to a delay in diagnosis. By the time of diagnosis, small bowel ischemic changes may be present. Gastrointestinal bleeding and peritonitis develop when transmural ischemia has occurred. The causes of superior mesenteric vein thrombosis are similar to those of portal vein thrombosis. Patients with acute portal or mesenteric vein thrombosis typically undergo anticoagulation for at least 3 months. Decisions regarding long-term anticoagulation in these patients, as well as patients with incidentally discovered thrombosis, must balance the often unknown risk of recurrent thrombosis with the risk of bleeding.

KEY POINT

- Patients with acute portal or mesenteric vein thrombosis should typically receive anticoagulation for at least 3 months.

Splenic Vein Thrombosis

Pancreatitis and pancreatic malignancies are the main causes of splenic vein thrombosis. Abdominal surgery and trauma, intra-abdominal infection, and thrombophilias are also causative. Symptoms are often subtle, and diagnosis frequently occurs coincidentally during abdominal imaging studies ordered for other reasons. Anticoagulant treatment duration depends on the triggering factors. Incidentally discovered splenic vein thrombosis likely does not require anticoagulation after appropriate evaluation for an underlying, treatable cause (MPN, PNH) has been concluded. Pancreatitis-associated thrombosis may not require anticoagulation therapy either, particularly because the risk for intra-abdominal bleeding with such therapy may be high.

Cerebral and Sinus Vein Thrombosis

Thrombosis of the cerebral, cortical, and sinus veins is also referred to as cerebral and sinus vein thrombosis (CSVT). The cause is often multifactorial, with risk factors being thrombophilias, estrogen therapy and pregnancy, and infections such as mastoiditis, otitis, sinusitis, and meningitis. A cause for CSVT is identified in 85% of patients. The most frequent but least specific symptom is severe headache of subacute or acute onset, which is present in 90% of patients. Routine noncontrast and contrast head CT and brain MRI scans are often unrevealing, resulting in missed diagnoses; CT venography or magnetic resonance venography are the appropriate studies if CSVT is suspected. Approximately 40% of patients with CSVT have a hemorrhagic infarct, a consequence of the venous occlusion. In the acute setting, even with hemorrhagic infarct, heparin is given followed by oral anticoagulation, unless the hemorrhage is very pronounced. The optimal duration of anticoagulant therapy is unknown. Expert opinion suggests 3 to 6 months if the thrombosis was associated with a transient risk factor, 6 to 12 months if the event was unexplained and no higher risk thrombophilia has been detected, and long term if a higher risk thrombophilia is detected or the event is recurrent. Increased intracranial pressure (pseudotumor cerebri) can be a late complication. CSVT accounts for up to 10% of patients with presumed idiopathic intracranial hypertension.

KEY POINTS

- CT venography and magnetic resonance venography are the diagnostic tests of choice for cerebral and sinus vein thrombosis.
- Expert opinion suggests an anticoagulation duration of 3 to 6 months if cerebral and sinus vein thrombosis was associated with a transient risk factor, 6 to 12 months if the event was unexplained and no higher risk thrombophilia has been detected, and long term if a higher risk thrombophilia is detected or the event is recurrent.

Retinal Vein Thrombosis

Central retinal vein occlusion (CRVO) leads to sudden, extensive vision loss. A branch retinal vein occlusion (BRVO) causes a painless sectorial decrease in vision resulting in misty or distorted vision. BRVO is more common than CRVO and typically results from pressure on the vein from the overlying arteriosclerotic thickened branch retinal artery. Risk factors for BRVO and CRVO include hypertension, hyperlipidemia, and diabetes mellitus. Management by an ophthalmologist and a thrombosis specialist may be the best approach for optimal treatment of patients with CRVO, because indications for

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anticoagulant use are not clearly defined (see MKSAP 17 General Internal Medicine section for further information).

Unexplained Arterial Thrombosis

Arterial thrombotic and thromboembolic events in young persons (younger than 50 years) are uncommon unless significant arteriosclerotic risk factors, or atrial fibrillation, are present. A systematic evaluation can be helpful in identifying causes (**Table 44**). Relatively little is known about thrombophilias predisposing to arterial thrombosis. Whether patients found to have a strong thrombophilia should be treated with antiplatelet therapy or anticoagulant therapy is also unknown.

Anticoagulants

The most common anticoagulants used in VTE prevention and treatment are UFH, LMWH, fondaparinux, and warfarin. NOACs apixaban, dabigatran, edoxaban, and rivaroxaban are FDA approved for VTE treatment. The parenteral direct thrombin inhibitors argatroban and lepirudin are reserved for the treatment of heparin-induced thrombocytopenia (HIT), and bivalirudin is used for patients during percutaneous transluminal coronary angioplasty, including patients who also have HIT.

Unfractionated Heparin

UFH potentiates the natural anticoagulant activity of antithrombin and acts as a nonspecific anticoagulant, mostly against thrombin and factor Xa. UFH bioavailability varies greatly because of avid protein binding. It is typically monitored by the aPTT, although anti-factor Xa plasma levels may be used. Whether either monitoring method leads to superior safety or efficacy of heparin therapy is unknown. UFH is mostly cleared by the reticuloendothelial system and, to a lesser degree, by the kidneys. Lower doses may be required for therapeutic anticoagulation in patients with kidney injury and higher doses needed during extensive acute VTE. Weight-based heparin dosing nomograms achieve therapeutic aPTTs faster than other approaches to selecting a UFH dose. The half-life of UFH depends on the dose given: it is 60 minutes with a bolus dose of 100 U/kg. A patient receiving continuous intravenous UFH at therapeutic doses will likely return to the baseline aPTT within 3 to 4 hours after discontinuing heparin. Protamine can be used to reverse anticoagulation with UFH. Long-term use of UFH leads to an increased risk of osteoporosis.

KEY POINTS

- Weight-based heparin dosing nomograms achieve therapeutic activated partial thromboplastin times faster than other approaches to selecting an unfractionated heparin dose.
- Protamine can be used to reverse anticoagulation with unfractionated heparin.

Low-Molecular-Weight Heparin

LMWH is made from UFH through chemical and physical processes that select the smaller polysaccharides; these lower weight molecules have different properties than UFH. Like UFH, LMWH potentiates antithrombin action, although this effect is greater against factor Xa than against thrombin. Because of this, aPTT measurement does not reflect LMWH activity; if it is necessary to assess anticoagulant effect, anti-Xa activity must be measured. LMWH also has greater bioavailability, more predictable pharmacokinetics, and a prolonged half-life when administered subcutaneously. This allows administration once or twice daily based on weight and without routine monitoring. Other differences between LMWH and UFH include less risk for HIT development and decreased osteoporosis risk. Monitoring is generally unnecessary. LMWH should be used cautiously, in reduced doses or not at all, in patients with severe kidney disease (creatinine clearance <30 mL/min). Dosing in obese patients should be based on actual body weight, but anti-Xa activity measured 3 to 4 hours after subcutaneous injection may be helpful in select patients with extreme BMIs (>40) to assess actual anticoagulant effect. LMWH is only partially reversible by protamine. It is unknown whether fresh frozen plasma (FFP), nonactivated prothrombin complex concentrates (PCCs), activated PCCs, or recombinant factor VIIa are beneficial in LMWH-associated major bleeding. Use of these reversal agents is not evidence based.

KEY POINTS

- Low-molecular-weight heparin's predictable pharmacokinetics enable weight-based dosing without laboratory monitoring.
- Low-molecular-weight heparin should be used cautiously, in reduced doses or not at all, in patients with severe kidney disease (creatinine clearance <30 mL/min).

Fondaparinux

Fondaparinux is a synthetic pentasaccharide that acts as an anticoagulant by potentiating antithrombin inhibition of factor Xa. It is administered subcutaneously, reaches its peak plasma level after approximately 3 hours, and, because of a half-life of approximately 17 hours, is dosed once daily. Because fondaparinux does not bind significantly to plasma proteins, it can be given without laboratory monitoring as a fixed dose for VTE prophylaxis and in body-weight-adjusted dosing for VTE treatment. It is cleared by the kidneys, so it should be used with caution in patients with a creatinine clearance of 30 to 50 mL/min. It is contraindicated in patients with a creatinine clearance less than 30 mL/min. No agent is available to reverse anticoagulation with fondaparinux. It is unknown whether FFP, nonactivated PCCs, activated PCCs, or recombinant factor VIIa are beneficial as reversal agents.

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TABLE 44. Structured Approach for the Evaluation of Patients with Unexplained Arterial Thromboembolism

Is Arteriosclerosis the Underlying Problem?
Arteriosclerotic changes demonstrated on imaging studies (CT, contrast arteriogram, or other radiologic imaging studies) or pathology specimens?
Arteriosclerosis risk factors present?
Cigarette smoking
High blood pressure
High LDL cholesterol
Low HDL cholesterol
High lipoprotein(a)
Diabetes mellitus
Obesity
Family history of arterial disorders in young relatives (<50 years)
Has the Heart Been Thoroughly Evaluated as an Embolic Source?
Atrial fibrillation evaluated by ECG or ambulatory or event monitor
Cardiomyopathy with possible left ventricular or atrial thrombus
Patent foramen ovale on cardiac echocardiography with bubble study and Valsalva maneuver
Other Causes
Is the patient receiving estrogen therapy (contraceptive pill, ring, or patch; hormone replacement therapy)?
Does the patient use cocaine or anabolic steroids?
Is there evidence for Buerger disease (does patient smoke cigarettes or cannabis)?
Does patient have symptoms suggesting a vasospastic disorder (Raynaud phenomenon)?
Were anatomic abnormalities seen in the artery leading to the ischemic area (web, fibromuscular dysplasia, dissection, vasculitis, external compression)?
Does patient have evidence of a rheumatologic or autoimmune disease (arthritis, purpura, or vasculitis)? Consider laboratory evaluation for vasculitis and immune disorder.
Is there a suggestion of an infectious arteritis?
Could the patient have hyperviscosity or cryoglobulins?
Thrombophilia Evaluation
Hemoglobin and platelet count
Antiphospholipid antibodies
Anticardiolipin IgG and IgM antibodies
Anti-β_2-glycoprotein I IgG and IgM antibodies
Lupus anticoagulant
Protein C activity
Protein S activity and free protein S antigen
Antithrombin III activity
Homocysteine (in younger patients)
Consider factor V Leiden and prothrombin *G20210A* mutation[a]
JAK2 mutation and PNH testing if CBC abnormalities
Do not test for *MTHFR* polymorphisms, PAI-1 or tPA levels or polymorphisms, or fibrinogen or factor VIII activities.

CBC = complete blood count; ECG = electrocardiography; *MTHFR* = methylene tetrahydrofolate reductase; PAI-1 = plasminogen activator inhibitor 1; PNH = paroxysmal nocturnal hemoglobinuria; tPA = tissue plasminogen activator.

[a]The purpose of testing is to detect the homozygous or double heterozygous state.

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KEY POINTS

- Fondaparinux can be dosed once daily because of a half-life of approximately 17 hours and can be given without laboratory monitoring because it does not bind significantly to plasma proteins.
- Fondaparinux should be used with caution in patients with a creatinine clearance of 30 to 50 mL/min and is contraindicated in those with a creatinine clearance less than 30 mL/min.

Warfarin

Vitamin K antagonists such as warfarin inhibit vitamin K epoxide reductase, an enzyme complex needed for synthesis of coagulation factors II, VII, IX, and X and proteins C and S. Warfarin's effect is measured by the PT, expressed as the INR.

Dosing nomograms should be used when initiating warfarin and at follow-up evaluations. Individual dosage requirements vary between 0.5 and 50 mg/d and depend on the patient's diet, medications, comorbidities, age, and genetic factors. Warfarin is metabolized by the cytochrome P-450 enzyme complex, including the cytochrome P-2C9 (CYP2C9) enzyme. Clinical testing for individual polymorphisms is available but has not been convincingly shown to lead to improved clinical outcomes and is not recommended as part of routine care.

Because warfarin leads to a gradual onset of anticoagulation, and paradoxically leads to hypercoagulability in the first 5 days of initiation owing to its rapid effect of lowering protein C activity levels, it must be administered initially with a rapidly acting parenteral anticoagulant when treating an acute thrombotic event. Both should be administered together for at least 5 days regardless of the INR, because decrease of the shorter half-life coagulation factor VII may lead to an increase in INR that does not reflect protective anticoagulation. During this time, the INR should be checked several times. If the INR increases to greater than 2 during these first 5 days, the parenteral anticoagulant should be continued and the warfarin dose interrupted or decreased. After this period, and with the INR greater than 2 for 24 hours, the short-acting anticoagulant should be discontinued; thereafter, monitoring can decrease to weekly, then monthly, with a stable, therapeutic INR. In patients with very stable INRs, monitoring can be extended to every 12 weeks. Point-of-care full-blood fingerstick monitors yield reliable results and are available for clinical practices and for appropriately selected patients to self-test their INR at home.

Dietary vitamin K intake influences the INR. Patients should not avoid all foods containing vitamin K, but rather consume a consistent diet. In some patients with fluctuating INRs, daily supplementation with vitamin K (100-150 µg/d) can stabilize the INR. Many medications also influence the metabolism of warfarin, leading to INR elevations or decreases. Preemptive dose adjustments and close monitoring are warranted when interacting medications are started or stopped.

Warfarin's half-life is 20 to 60 hours (mean, 32-40 hours). The bleeding risk associated with a procedure determines whether warfarin must be stopped beforehand and when. Warfarin must be discontinued at least 5 days before major surgery. The patient's thromboembolic risk should determine whether bridging therapy with a parenteral anticoagulant is needed perioperatively (see MKSAP 17 General Internal Medicine). Managing elevated INRs and bleeding in patients taking warfarin depends on the degree of INR elevation and bleeding risk factors or active bleeding (**Table 45**). PCCs are plasma products from human donors. Four-factor PCC contains all vitamin K-dependent coagulation factors and has been available in the United States since 2013; 3-factor PCCs contain factors II, IX, and X, but relatively little factor VII. Four-factor PCC is capable of restoring individual clotting factor activity in nearly 100% of patients within minutes of administration, whereas 3-factor PCCs must be supplemented with FFP or a low dose of recombinant factor VIIa to more optimally lower the INR (see Transfusion).

TABLE 45. Management Strategy for Elevated INRs and Bleeding in Patients Taking Vitamin K Antagonists

INR	Bleeding	Risk Factors for Bleeding[a]	Intervention
Supratherapeutic but <5	No	No/yes	Lower or omit next VKA dose(s)
			Reduce subsequent dose(s)
5-9	No	No	Omit next VKA dose(s)
			Reduce subsequent dose(s)
	No	Yes	Vitamin K, 1-2.5 mg PO
>9	No	No/yes	Vitamin K, 2.5-5 mg PO
Serious bleed at any INR	Yes	NA	Vitamin K, 10 mg IV + 4f-PCC (or 3f-PCC + FFP or rVIIa)

3f-PCC = 3-factor prothrombin complex concentrate; 4f-PCC = 4-factor PCC; FFP = fresh frozen plasma; IV = intravenous; NA = not applicable; PO = by mouth; rVIIa = recombinant activated factor VII; VKA = vitamin K antagonist.

[a]Coagulopathy, moderate or severe thrombocytopenia, recent major surgery, previous major bleeding episode.

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KEY POINTS

- In some patients taking warfarin with fluctuating INRs, daily supplementation with vitamin K (100-150 µg/d) can stabilize the INR.
- Four-factor prothrombin complex concentrate (PCC) can restore individual clotting factor activity in nearly 100% of patients, whereas 3-factor PCCs must be supplemented with fresh frozen plasma or a low dose of recombinant activated factor VIIa.

New Oral Anticoagulants

The NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban), also referred to as target-specific oral anticoagulants, share several features, including (1) rapid onset of action (maximal anticoagulant plasma levels in 3 or fewer hours after oral intake), (2) no need for routine monitoring of their anticoagulant effect in most patients, (3) no dietary restrictions, (4) relatively few clinically important interactions with medications, (5) short half-lives of about 12 hours when kidney function is normal, (6) contraindications or need for dose modifications in moderate to severe kidney disease, and (7) lack of established reversal agents and strategies for patients with major hemorrhage. These medications are FDA approved and available for specific indications (**Table 46**). NOACs influence routine coagulation tests (PT, aPTT) to various degrees. Additionally, coagulation-based thrombophilia tests (proteins C and S, antithrombin activities, lupus anticoagulant) and coagulation factor levels are influenced by these medications, rendering the obtained results unreliable.

When to discontinue these medications before surgery depends on the expected bleeding risk with the surgery and the patient's kidney function. For standard-risk procedures and in a patient with normal kidney function, discontinuation is typically 24 to 36 hours before surgery; for surgeries and interventions with high risk for bleeding, the NOAC should be discontinued at least 60 hours (2.5 days) beforehand. When kidney function is impaired, the half-lives of the drugs are increased, so the drug must be discontinued sooner before

TABLE 46. Key Features of the New Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Class of anticoagulant	Direct factor IIa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
T_{max} (h)	2	3	3	1-2
Half-life (h)	12-17	7-11	9-14	9-11
Protein binding	35%	95%	87%	54%
Renal elimination	80%	66% (33% as active metabolite)	25%	35%
FDA-approved indications	Atrial fibrillation VTE treatment	Atrial fibrillation VTE treatment VTE prevention	Atrial fibrillation VTE treatment VTE prevention	Atrial fibrillation VTE treatment
Dosing				
Atrial fibrillation	CrCl >30 mL/min: 150 mg twice daily CrCl 15-30 mL/min: 75 mg twice daily CrCl ≤15 mL/min: do not use	CrCl >50 mL/min: 20 mg once daily CrCl 15-50 mL/min: 15 mg once daily CrCl ≤15 mL/min: do not use	5 mg twice daily 2.5 mg twice daily if ≥2 criteria present: ≥80 years of age Weight ≤60 kg (132 lb) Creatinine ≥1.5 mg/dL (133 µmol/L)	60 mg once daily CrCl 15-50 mL/min: 30 mg once daily CrCl >95 mL/min: do not use
VTE prevention	NA	10 mg once daily	2.5 mg twice daily	NA
VTE treatment	CrCl >30 mL/min: 150 mg twice daily CrCl <30 mL/min: do not use	CrCl >30 mL/min: 15 mg twice daily × 3 wks, then 20 mg once daily CrCl ≤30 mL/min: do not use	VTE treatment: 10 mg twice daily × 1 wk, then 5 mg twice daily Reduction in VTE recurrence: 2.5 mg twice daily	60 mg once daily 30 mg once daily with the following criteria: CrCl 30-50 mL/min Weight ≤60 kg (132 lb) Concomitant p-glycoprotein inhibitor use

CrCl = creatinine clearance; h = hour; NA = not applicable; T_{max} = time to maximum concentration; VTE = venous thromboembolism.

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CONT.

surgery. If major bleeding occurs with any of the NOACs, therapy with oral charcoal is appropriate for patients who ingested the medication within approximately 2 hours of presentation. Further management is supportive. Dabigatran is dialyzable; apixaban, edoxaban, and rivaroxaban, because of their higher plasma protein-binding, are not. Because of a lack of data, it is unknown whether treatment with activated or nonactivated PCCs, recombinant factor VIIa, or FFP is clinically beneficial, or whether antifibrinolytic therapy with tranexamic acid or ε-aminocaproic acid has any beneficial reversal effect.

In clinical treatment trials of acute VTE, some NOACs (rivaroxaban, apixaban) were used immediately upon diagnosis of acute VTE, whereas others (dabigatran, edoxaban) were started after initial therapy with parenteral anticoagulants. Few patients with cancer, extreme body weight, very old age, multiple comorbidities, or APS were included in the VTE treatment trials of the NOACs. Therefore, they should be used with caution, if at all, in these special populations.

KEY POINT

- Apixaban, dabigatran, edoxaban, and rivaroxaban share several features, including rapid onset of action, no need for routine monitoring, no dietary restrictions, short half-lives, contraindications or need for dose modifications in moderate to severe chronic kidney disease, and lack of reversal agents.

Hematologic Issues in Pregnancy

Gestational Anemia

Pregnancy results in significant changes in metabolism, fluid balance, and circulation, all of which impact the hemoglobin value. Starting in the sixth week of gestation, maternal plasma volume begins to increase, but no increase in erythrocyte mass occurs in response. The result is a dilutional anemia evident by the seventh or eighth week of pregnancy, with a hemoglobin value that should not be less than 11 g/dL (110 g/L) in the first trimester or 10 g/dL (100 g/L) in the second or third trimesters. Hemoglobin values less than these should prompt a search for other causes of anemia, of which iron deficiency is the overwhelming culprit.

Iron and folate deficiencies commonly occur during pregnancy independent of fluid shifts induced by the gravid state (see Erythrocyte Disorders).

KEY POINT

- Hemoglobin values less than 11 g/dL (110 g/L) in the first trimester or less than 10 g/dL (100 g/L) in the second and third trimesters of pregnancy should prompt a search for causes of anemia other than the expected gestational anemia.

Sickle Cell Disease

Care of pregnant patients with sickle cell disease (SCD) should be multidisciplinary and ideally involves a hematologist specifically trained in hemoglobinopathies and a maternal-fetal medicine specialist.

Women with SCD considering pregnancy should take prenatal vitamins without iron because of the predisposition to iron overload from frequent blood transfusions; however, folic acid supplementation should be continued throughout pregnancy. Other medications taken for SCD should be reviewed for possible contraindications in pregnancy. Hydroxyurea should be discontinued even though adverse effects in human fetuses have not been demonstrated. Other therapies, such as ACE inhibitors or iron chelation, are contraindicated in pregnancy. Pneumococcal and yearly influenza vaccines are safe to administer during pregnancy (see General Internal Medicine for further information on vaccination recommendations).

Compared with women without SCD, those with SCD are at increased risk for maternal pregnancy complications. Although maternal mortality risk has improved with better care, it remains nine-fold higher than in women without SCD (0.16% in SCD vs. 0.01% in non-SCD).

A recent study showed a significantly increased relative risk of venous thromboembolism (VTE) (pregnancy-related VTE was 0.09% in normal controls, 0.15% in sickle cell trait, and 2.9% in SCD), but no guidelines provide clear indications for prophylactic anticoagulation. Other complications include preeclampsia, eclampsia, infection, cardiomyopathy, intrauterine fetal demise, and intrauterine growth restriction. Vaso-occlusive crises are overall increased during pregnancy, and 28% of women have vaso-occlusive pain episodes at the time of delivery (mostly in women with hemoglobin SS subtype). Development of vaso-occlusive episodes appears to be a predictor for increased maternal morbidity and mortality. Preventing dehydration, for example from pregnancy-induced vomiting, may decrease the incidence of vaso-occlusive crises. If vaso-occlusive crises occur, NSAIDs for pain control are considered safe before 30 weeks' gestation. Opiate analgesics are safe to use in pregnant patients with SCD, but increased narcotic tolerance must be considered during peripartum anesthesia. Chronic opioid use during pregnancy can lead to fetal narcotic withdrawal syndrome.

Although prophylactic transfusions during pregnancy can reduce pain crises, neither transfusion nor exchange transfusion has been shown to reduce pregnancy-related morbidity or mortality, and increased risk for alloantibody production in this population must be considered.

Because pregnant women with SCD have a higher risk of morbidity and mortality, they should be closely monitored for SCD-related complications and promptly treated.

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KEY POINTS

- Hydroxyurea, ACE inhibitors, and iron chelation therapy should be discontinued during pregnancy.
- IIVC Although prophylactic transfusions during pregnancy can reduce pain crises in patients with sickle cell disease, neither transfusion nor exchange transfusion has been shown to reduce pregnancy-related morbidity or mortality, and increased risk for alloantibody production in this population must be considered.

Thrombocytopenia in Pregnancy

Thrombocytopenia in pregnancy is common, occurring in approximately 7% to 12% of pregnant women. Most cases of thrombocytopenia in pregnancy are mild and have no adverse outcomes for the mother or fetus, although occasionally a low platelet count may signal a more complex, potentially life-threatening condition. Therefore, it is critical to distinguish between different causes of thrombocytopenia in pregnancy.

Gestational Thrombocytopenia

Gestational thrombocytopenia is the cause of a low platelet count in 75% of pregnant women with thrombocytopenia. It generally occurs in the latter half of pregnancy and causes no complications of maternal or fetal health. The patient should have no history of thrombocytopenia outside of pregnancy, and the platelet count should never be less than 50,000/μL (50×10^9/L). No laboratory studies can confirm the diagnosis. It requires no treatment, but careful monitoring is necessary, especially in the final month of pregnancy to ensure the platelet count remains greater than 50,000/μL (50×10^9/L). The mechanism is thought to be the result of a mild consumptive process, but unlike true disseminated intravascular coagulation, the prothrombin and activated partial thromboplastin times are normal, and fibrinogen levels are not depressed. The peripheral blood smear should show an absence of schistocytes, thus proving the thrombocytopenia is not due to a microangiopathic process.

KEY POINT

- In patients with gestational thrombocytopenia, the platelet count should never decrease to less than 50,000/μL (50×10^9/L), and no schistocytes should appear on peripheral blood smear.

Immune Thrombocytopenic Purpura

If a patient has a history of immune thrombocytopenic purpura (ITP), any thrombocytopenia that occurs during pregnancy is assumed to be due to ITP. Additionally, a platelet count that decreases to less than 50,000/μL (50×10^9/L) with normal coagulation values and an absence of schistocytes on peripheral blood smear is considered consistent with a diagnosis of ITP. Management in the first 8 months of pregnancy should be the same as for any nonpregnant patient, which includes avoiding therapy unless the patient is bleeding or has a platelet count less than 30,000/μL (30×10^9/L). In the final month, a target platelet count of 50,000/μL (50×10^9/L) is desirable, which allows for an emergent cesarean section to be performed safely if needed. If immunosuppressive therapy is required, glucocorticoids such as prednisone are considered relatively safe in pregnancy, although they can increase blood pressure and plasma glucose level, cause weight gain, and may contribute to adverse pregnancy outcomes. Glucocorticoids given to the mother have no effect on fetal platelet counts. Intravenous immune globulin is another first-line therapeutic option for patients with ITP because it is also considered safe for use in pregnancy. Splenectomy should be deferred, if possible. See Platelet Disorders chapter for more information about ITP.

KEY POINT

- Therapy for immune thrombocytopenic purpura during pregnancy is generally not necessary unless the platelet count decreases to less than 30,000/μL (30×10^9/L); however, a platelet count of 50,000/μL (50×10^9/L) is desirable in the final month of pregnancy so a cesarean section can be performed safely if necessary.

Microangiopathy of Pregnancy H

The HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome, preeclampsia, and acute fatty liver of pregnancy are part of a spectrum of disorders called the "thrombotic microangiopathy of pregnancy." Symptoms and laboratory features for each overlap (**Table 47**), but making the distinction among the disorders may not be critical, because the most effective therapy for each is emergent delivery of the fetus. If microangiopathic hemolytic anemia and thrombocytopenia worsen following delivery, thrombotic thrombocytopenic purpura should be suspected and plasma exchange therapy initiated. H

KEY POINT

- The most effective therapy for HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome, preeclampsia, and acute fatty liver of pregnancy is emergent delivery of the fetus.

Thrombophilia and Venous Thromboembolism in Pregnancy

Epidemiology, Pathophysiology, and Risk Factors H

Pregnant women have an approximately five-fold increased risk of thromboembolism compared with nonpregnant women. Eighty percent of events are venous, and the remaining 20% are arterial. Approximately 50% of VTEs occur antepartum. The incidence of VTE declines quickly in the 6 weeks following delivery, and returns to baseline 4 months postpartum. However, the postpartum period is often

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TABLE 47. Clinical and Laboratory Features of the Thrombotic Microangiopathies of Pregnancy

Feature	Preeclampsia	HELLP	AFLP	TTP
Hypertension	+++	+++	+	+
Proteinuria	+++	++	+/−	+/−
Abdominal pain	+/−	++	++	+/−
Jaundice	+/−	+/−	++	+/−
Neurologic findings	+	+	+	++
Thrombocytopenia	+	+++	+	+++
Hemolysis	+/−	+++	+	+++
Kidney disease	+/−	+	++	+
Disseminated intravascular coagulation	+/−	++	+++	+/−
Elevated liver chemistry tests	+	+++	+++	+/−
Hypoglycemia	+/−	+/−	+++	+/−

AFLP = acute fatty liver of pregnancy; HELLP = Hemolysis, Elevated Liver enzymes, and Low Platelets; TTP = thrombotic thrombocytopenic purpura.

+++ = always present

++ = usually present

+ = likely to be present

+/− = may or may not be present

CONT.

considered to be the 6 weeks after delivery. VTE complicates one to two of 1000 pregnancies. Deep venous thrombosis of the leg is left-sided in 80% of patients, probably because of stenosis of the left common iliac vein from the overlying right common iliac artery and the lumbar vertebral body posteriorly (May-Thurner syndrome) accentuated by the pregnant uterus. Other contributors to hypercoagulability during pregnancy are a decrease in protein S and increase in fibrinogen, factors VII and VIII, von Willebrand factor, and other procoagulant levels.

The strongest risk factor for pregnancy-associated VTE is a history of VTE. Risk factors for pregnancy-associated VTE are typically the same as those in nonpregnant women, including obesity, advanced age, comorbid conditions such as heart disease, and thrombophilias. Delivery by cesarean section carries up to a 3.6-fold increased risk for postpartum VTE. An association has been suggested between inherited thrombophilias and adverse pregnancy outcomes, such as recurrent early pregnancy loss (<10 weeks), one or more losses after 10 weeks' gestation, intrauterine growth restriction, preeclampsia, and eclampsia, but this association is controversial.

KEY POINT

- Pregnancy is associated with an approximately five-fold increased risk for thromboembolism, with the highest risk for venous thromboembolism occurring in the first 6 weeks postpartum.

Prevention

Despite the increased risk for thrombosis associated with pregnancy, anticoagulation is not indicated for women at average risk in the antepartum or postpartum periods. However, prophylactic anticoagulation should be considered in select women with increased risk for VTE. Unfortunately, adequate data are not available to definitively determine which patients should receive anticoagulant prophylaxis or at what doses. Expert recommendations exist to help guide clinical decision making. Consultation with a thrombosis expert or maternal-fetal medicine specialist is suggested. In patients with a very high risk of VTE, prophylaxis should be started as soon as pregnancy is documented, because VTE risk is relatively evenly distributed throughout pregnancy. Because the postpartum period carries the highest VTE risk, women at high risk should also receive postpartum anticoagulation for 6 weeks.

Diagnosis

When symptoms and signs suggest new deep venous thrombosis, duplex compression ultrasonography of the extremity is the recommended initial diagnostic test. If results are normal or unclear, pelvic magnetic resonance venography may be appropriate. For suspected pulmonary embolism, Doppler ultrasonography of the legs should be performed whether leg symptoms are present or not. If ultrasonography is normal, chest radiography is the next test, followed by a ventilation-perfusion lung scan if normal. If chest radiography is abnormal, CT pulmonary arteriography is appropriate. D-dimer testing is not useful in pregnant women, because it is always positive and lacks predictive value.

Treatment

For pregnant women with acute VTE, full-dose, weight-adjusted, low-molecular-weight heparin (LMWH), rather than unfractionated heparin (UFH), is the treatment of choice.

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CONT. Anticoagulants should be continued for at least 6 weeks postpartum, for a minimum therapy duration of 3 months. It is unclear whether periodic anti-Xa level determination and LMWH dose adjustment based on the results is beneficial. In the final month of pregnancy, a switch from LMWH to UFH can be considered because of UFH's shorter half-life. This allows an epidural catheter for anesthesia to be placed when the activated partial thromboplastin time for UFH is normal, whereas a 24-hour period is necessary after the last LMWH dose before placing a catheter. In addition, UFH can be completely reversed with protamine if major bleeding occurs, whereas LMWH is only partially reversible. An alternative is continued LMWH and labor induction. Patients should stop LMWH at least 24 hours before epidural anesthesia. LMWH and warfarin are acceptable to take while breastfeeding but fondaparinux and the new oral anticoagulants are not. H

KEY POINTS

- During pregnancy, weight-based, low-molecular-weight heparin is the treatment of choice for venous thromboembolism.
- Anticoagulation therapy for venous thromboembolism should be continued for at least 6 weeks postpartum, for a therapy duration of at least 3 months.

Issues in Oncology

Introduction

Medical oncology is currently at a threshold between the old and the new. Conventional approaches to histologic diagnosis and clinical staging are being supplemented and sometimes replaced by molecular profiling. New treatment paradigms, including targeted therapy, immunotherapy, and the use of immunoconjugates, are emerging to supplant the long-standing treatment strategies of surgery, radiation therapy, and chemotherapy.

Although the primary site of the tumor and its histology may eventually be of secondary importance to the molecular characteristics of the tumor, clinical evaluation remains fundamental to the management of patients with cancer. Before patients can be treated, staging and an individualized clinical assessment must be done, and mutually determined goals of therapy must be established. Additionally, determining the goals of therapy requires an understanding of the unique terminology used in cancer care, particularly when interpreting the results of clinical trials and discussing with patients whether certain therapeutic options should be considered.

Staging

Once cancer is diagnosed, clinicians must order appropriate tests to identify disease extent. This workup constitutes staging. Although newer methods for describing the extent of disease exist and several tumor-specific systems are used (such as for certain lymphomas and small cell lung cancer), most solid tumor malignancies are described using the "TNM" classification, in which "T" describes the primary tumor and is designated as T1-4, and the numerals increase with increasing tumor size or extent of local invasion; "N" represents the degree of locoregional lymph node involvement and is designated by N0-3, with N0 indicating no involvement and N1 or greater representing increasing lymph node involvement; and "M" represents the absence or presence of nodal metastasis and is designated by M0 or M1. Differing T, N, and M classifications may then be grouped into disease-specific stages (such as stage I or stage II) to characterize the extent of certain cancers in individual patients and potentially provide prognostic information and help guide appropriate therapy.

The patterns of disease spread as well as the selection of appropriate tests and imaging modalities vary depending on cancer type. Therefore, a proper cancer workup requires knowledge of the individual disease entity so that the necessary tests can be obtained. Tests with a very low yield should not be ordered in the absence of specific directing symptoms. For example, imaging is appropriate in the staging of patients with lung cancer because bone and brain metastases are common in the early course of this disease. However, patients with presumed locoregional colorectal cancer rarely present with bone and brain metastases; consequently, routine imaging as part of staging is not necessary. Thoughtfully performed staging is generally the most accurate prognostic indicator and largely dictates the therapeutic strategy for patients with cancer.

KEY POINTS

- Most solid tumor malignancies are staged according to the "TNM" classification, in which "T" reflects tumor size or extent of local invasion (T1-4); "N" represents the degree of locoregional lymph node involvement (N0-N3), and "M" represents the absence or presence of nodal metastasis (M0-M1).
- During staging of patients with cancer, tests with a very low yield should not be ordered in the absence of specific directing symptoms. HVC

Performance Status

A primary consideration in managing patients with cancer is an individual's performance status, which indicates a patient's well-being and ability to perform daily activities. Two measures of performance status are widely used: the Karnofsky score and the Zubrod score (also called the Eastern Cooperative Oncology Group/World Health Organization Performance Scale) (**Table 48**).

Patients with an excellent performance status typically have a better overall prognosis and the ability to tolerate more aggressive therapies compared with those with a poor performance status. Less toxic regimens or no chemotherapy may be warranted in patients with a poor performance status and in those for whom supportive, comfort-oriented care may be most appropriate. Patients who are otherwise medically well

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TABLE 48. Oncology Performance Status Systems

ECOG/WHO Performance Scale[a]
0 - Fully active; no restrictions on activities
1 - Unable to do strenuous activities, but able to carry out light housework and sedentary activities
2 - Able to walk and manage self-care, but unable to work; out of bed more than 50% of waking hours
3 - Confined to a bed or a chair more than 50% of waking hours; capable of limited self-care
4 - Completely disabled. Totally confined to a bed or chair; unable to do any self-care
5 - Death
Karnofsky Performance Scale
100 - Normal; no symptoms or evidence of disease
90 - Minor symptoms, but able to carry on normal activities
80 - Some symptoms; normal activity requires effort
70 - Unable to carry on normal activities, but able to care for self
60 - Needs frequent care for most needs; some occasional assistance with self-care
50 - Needs considerable assistance with self-care and frequent medical care
40 - Disabled; needs special care and assistance
30 - Severely disabled; hospitalized
20 - Very ill; significant supportive care is needed
10 - Actively dying
0 - Death

ECOG/WHO = Eastern Cooperative Oncology Group/World Health Organization.

[a]Also called the Zubrod Score.

but in whom a poor performance status score has acutely developed based on tumor-related symptoms and whose performance status would be expected to improve with tumor regression should be considered for aggressive therapy, with recognition of the higher risks involved.

Virtually all clinical oncology trials enroll only patients with good performance status. Therefore, the applicability of the results of these trials to patients with a poorer performance status is limited. Chronologic age is rarely, if ever, a major contraindication to aggressive therapy. Patients in their 80s who are otherwise healthy may be able to tolerate more aggressive therapy, whereas younger patients with multiple medical comorbidities, such as liver or kidney conditions that affect the ability to tolerate treatment, may be unable to receive aggressive therapy.

KEY POINTS

- The term *performance status* is used to indicate a patient's well-being and ability to perform daily activities.
- HVC Less toxic regimens or no chemotherapy may be warranted in patients with cancer and a poor performance status and for whom supportive, comfort-oriented care may be most appropriate.
- Chronologic age is rarely, if ever, a major contraindication to aggressive cancer therapy.

Goals of Therapy

Establishing clear and realistic treatment goals is essential in the care of patients with cancer. When considering goals, it is important for physicians to discuss with patients that virtually all therapies are associated with risks and side effects. In medically fit patients with locoregional disease, cure is often the stated goal. As the cancer stage increases, the likelihood of cure becomes more remote. For most patients with unresectable, metastatic solid tumors, cure is not a realistic goal, and alternative goals need to be established. In patients who are unfit for aggressive therapy because of medical comorbidities and poor performance status, who have been intolerant to treatment, or who have experienced disease progression despite use of standard therapies, a focus on comfort-oriented management may be most appropriate. Acknowledging that a patient's disease is incurable often leads to appropriate and adequate use of analgesics and other comfort-oriented measures, whereas establishing unrealistic measures for outcomes may impede adequate symptom management. Goals of care other than cure may include lengthening of overall survival time, control of disease growth, amelioration or prevention of disease-related symptoms, and maintaining a level of quality of life acceptable to the patient. Clinicians should reassure patients who express fear of cancer-related pain that their pain will be controlled. Palliative care consultation is appropriate at

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any point in the treatment process to assist patients in establishing goals of care and help develop comprehensive management strategies.

KEY POINT

- In patients with incurable cancer, acknowledging that disease is incurable often leads to appropriate and adequate use of analgesics and other comfort-oriented measures, whereas establishing unrealistic measures for outcomes may impede adequate symptom management.

Understanding Cancer Terminology

Several terms and concepts are important in understanding the potential benefits and harms of specific therapeutic interventions as they are commonly reported.

The *mitotic rate* is a measure of how fast cancer cells are dividing and growing. To find the mitotic rate, the pathologist determines the number of cancer cells that are in mitosis per mm^2 in a histologic section of the tumor. Mitotic rate is used to help find the stage of melanoma and other types of cancer. Higher mitotic rates are linked with lower survival rates.

The term *overall survival* refers to the time from initiation of therapy until death. This period is frequently quoted as the *median survival time* for a population of patients in a published study. Such medians are not necessarily applicable to any one individual as some patients may live considerably shorter and some considerably longer than the median survival time. Because it is difficult to extrapolate data from studies regarding overall or median survival, physicians should take care when discussing such information with their patients to avoid setting unrealistic expectations. In addition, it should be noted that as a result of increased screening and improved imaging techniques, primary cancer diagnoses and recurrences are being identified earlier in the course of the patient's disease. This "lead time bias" in more recent reports may make comparisons with older data problematic. Improvements in overall survival by a new treatment are thus best determined from randomized controlled trials and should not be inferred from comparisons with historical controls.

Progression-free survival, or more accurately, *progression-free interval*, refers to the time from initiation of therapy until the time therapy is no longer controlling tumor growth. This term is frequently misunderstood to indicate improved overall survival, just as improvements in overall survival are often misunderstood to indicate improvements in the cure rate.

An additional metric of clinical activity is the *overall response rate*, which refers to the percentage of patients involved in a clinical trial whose tumor undergoes a prespecified degree of shrinkage on imaging studies such as CT scan or MRI. Although tumor shrinkage is both encouraging and a clear indicator of an agent's antitumor activity, it does not tend to correlate well with long-term outcome such as overall survival, and its true benefit to the patient is not always clear. If, however, a patient is symptomatic due to tumor bulk, then shrinking of that tumor may provide good palliation of symptoms.

It is imperative that clinicians understand the practical meaning of these measures as they relate to various treatment options and are able to convey their significance to their patients to facilitate informed discussions and development of realistic treatment goals.

KEY POINTS

- The term *overall survival* refers to the time from initiation of therapy until death and is frequently quoted as the *median survival time* for a population of patients in a published study.
- *Progression-free survival*, or more accurately, *progression-free interval*, refers to the time from initiation of therapy until the time therapy is no longer controlling tumor growth and does not intrinsically indicate improved overall survival.
- *Overall response rate* refers to the percentage of patients involved in a clinical trial whose tumor undergoes a prespecified degree of shrinkage on imaging studies.

Treatment Approaches

Cancer treatments traditionally have comprised of local treatment for the primary tumor with either surgery or radiation therapy and systemic treatment with chemotherapy. New approaches based on molecular characteristics of the tumor, or personalized medicine, have recently been becoming part of clinical practice.

Traditional Cancer Therapies

The primary treatment of locoregional solid tumor malignancies is surgical resection. A general goal is usually resection of all known gross disease with clear surgical margins, which is potentially curative.

Following surgery, TNM classification, and staging, further therapeutic interventions may be warranted. Chemotherapy or radiation therapy is often used in conjunction with surgery to potentially increase the cure rate. When these therapies are given after definitive surgery with curative intent, they are referred to as *adjuvant* therapy, and when they are given before planned definitive surgery with curative intent, they are referred to as *neoadjuvant* therapy. Adjuvant or neoadjuvant chemotherapy or chemoradiotherapy is incorporated into management strategies for most solid tumors and is given for eradication of micrometastatic disease. Whether local or distant recurrence is more likely and whether radiation therapy, chemotherapy, or a combination of the two is most appropriate depends on the tumor type.

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Unfortunately, adequate technology to accurately identify which patients will truly benefit from adjuvant or neoadjuvant therapies does not yet exist, although progress has been made in this area. For example, *predictive assays* are highly desirable as they can identify who is at risk for recurrence and who will benefit from treatment. In breast cancer, a commercially available assay analyzes 21 genes within an individual tumor to demonstrate the patient's likelihood for recurrence and benefit from adjuvant chemotherapy; a value of less than 18 indicates a low recurrence score (RS), a value of 18 to 30 indicates an intermediate RS, and a value of greater than 30 indicates a high RS. This tool is useful in discriminating between patients who should or should not receive treatment, and, as such, is a predictive test. However, similar assays in patients with colorectal cancer have been unable to discriminate between which patients will or will not benefit from therapy despite identifying which patients are at higher risk for recurrence; these are called *prognostic assays*. Although prognostic assays may lead to increased emotional comfort in patients and clinicians, they add expense and do not provide information that is useful in therapeutic decision making.

For a small number of cancers, *conversion therapy* may be administered before surgery in patients with surgically unresectable disease that might become resectable with a favorable response to chemotherapy, radiation, or both. This therapy is intended to shrink visible metastatic disease away from critical vascular structures to facilitate resection. The incidence of truly unresectable disease converted to resectable disease is, unfortunately, relatively low.

KEY POINTS

- The primary treatment for locoregional solid tumor malignancies is surgical resection, which is often combined with chemotherapy or radiation to potentially increase the cure rate.
- Adjuvant therapy is given after and neoadjuvant therapy is given before definitive surgery with curative intent to eradicate micrometastatic disease in patients with cancer.
- *Predictive assays* can identify who is at risk for cancer recurrence and who will benefit from treatment, whereas *prognostic assays* can identify who is at risk for recurrence but not who will benefit from treatment.

Personalized Medicine

Traditional cancer chemotherapy has involved cytotoxic agents with minimal selectivity for tumor cells over normal cells. More recently, increased understanding of tumor growth and survival mechanisms has led to development of the so-called targeted agents. These agents are designed to have more selective toxicity on tumor cells based on specific tumor biology; however, many still confer substantial toxicities, the risk for which should not be understated in therapeutic decisions.

The goal of personalized medicine is to direct therapeutic approaches that are optimally beneficial to an individual patient through a better understanding of the molecular makeup of the individual and the tumor. One aspect of personalized medicine is identification of specific tumor markers that can help clinicians decide whether to include or exclude certain therapies in individual patients. For example, the anti-epidermal growth factor receptor monoclonal antibodies cetuximab and panitumumab are active against metastatic colorectal cancer, but only in patients whose tumors do not have mutations in the K-*ras* or N-*ras* genes. Performing genotypic analysis of all patients with metastatic colorectal tumors to exclude use of these agents in patients with colorectal cancer in whom *ras* mutations have been identified (50% of all patients with colorectal cancer) has become standard practice. Identification of this *exclusionary* marker does not make available any new treatment options to patients with colorectal cancer because these therapies were available before the utility of *ras* genotyping was understood; however, identification of the *ras* mutations in these patients will preclude the use of agents that will not be beneficial and may even cause unnecessary harm, toxicity, and expense.

Conversely, approximately 20% to 25% of breast cancer tumors and a similar percentage of gastroesophageal tumors demonstrate *HER2* growth factor receptor overexpression on the cell surface. Although *HER2* overexpression has been identified as a poor prognostic factor, the development of the anti-*HER2* therapies, such as the monoclonal antibody trastuzumab, has led to availability of specific therapies that are used only against tumors with demonstrated *HER2* overexpression. Thus, the presence of *HER2* constitutes an *inclusionary* marker that has made available a previously unavailable therapeutic strategy.

Other examples include the use of the tyrosine kinase inhibitor imatinib against a growth factor–activating mutation in gastrointestinal stromal tumors; the small molecule inhibitor vemurafenib that acts against a mutation in the *BRAF* gene, which is present in 40% of patients with melanoma; and erlotinib, another tyrosine kinase inhibitor active against an activating mutation present in some patients with non-small cell lung cancer. In these scenarios, pretesting for the presence of tumor mutations dictates appropriate therapy.

Other technologies are evolving. Antibodies that target overexpression of specific factors on tumor cells are being conjugated to radiotherapeutic agents or toxins; these agents have demonstrated clinical activity and are routinely used to treat many malignancies. Active immunotherapeutic strategies have also been developed over the past several years, including the monoclonal antibody ipilimumab, which has demonstrated benefit in patients with metastatic melanoma by blocking innate immune regulatory mechanisms and allowing the immune system to more effectively attack tumors. Development of other immunostimulatory strategies is currently in progress and appears promising.

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KEY POINT

- The goal of personalized medicine is to direct therapeutic approaches that are optimally beneficial to an individual patient through a better understanding of the molecular makeup of the individual and the tumor.

Breast Cancer

Introduction

In the United States, breast cancer is the most common cancer among women, excluding skin cancer, and is the second leading cause of cancer-related death in women, exceeded only by lung cancer. The lifetime risk of developing invasive breast cancer is about one in eight. In 2013, approximately 232,340 new cases of invasive breast cancer; 64,640 new cases of ductal carcinoma in situ; and 39,620 breast cancer–related deaths were estimated to have occurred. Breast cancer incidence in men is less than 1% that of women.

Epidemiology and Risk Factors

Breast cancer incidence increases with age. Ninety-five percent of new cases occur in women aged 40 years or older, with a median age at diagnosis of 61 years. Breast cancer incidence rates in the United States are highest in non-Hispanic white women and second highest in black women. Other risk factors for breast cancer are listed in **Table 49**.

Women with a strong family history of breast cancer should be referred to a qualified genetic counselor for possible genetic testing for breast cancer susceptibility genes such as *BRCA1* and *BRCA2*. The most common features suggestive of a familial breast cancer syndrome are detailed in the highlights of the National Comprehensive Cancer Network guidelines in **Table 50** on page 76. The United States Preventive Services Task Force guidelines for *BRCA1/2* testing are listed in **Table 51** on page 76.

KEY POINTS

- Breast cancer incidence increases with age, with 95% of cases developing in women older than 40 years, and incidence is highest in non-Hispanic white women and second highest in black women.
- Women with a strong family history of breast cancer should be referred to a qualified genetic counselor for possible genetic testing for breast cancer susceptibility genes such as *BRCA1/2*.

Chemoprevention and Other Risk Reduction Strategies

Breast cancer screening is discussed in MKSAP 17 General Internal Medicine.

The Gail Model Risk Assessment Tool (www.cancer.gov/bcrisktool/) can be used to estimate any woman's 5-year and lifetime breast cancer risk. Women older than 35 years with a 5-year breast cancer risk of 1.7% or higher or with lobular carcinoma in situ are candidates for breast cancer prophylaxis with antiestrogen treatments such as tamoxifen prior to menopause and, in addition, raloxifene or exemestane after menopause (**Table 52**, on page 77). Atypical ductal hyperplasia is associated with a high risk of breast cancer independent of the Gail Model risk.

The American Cancer Society (ACS) recommends screening certain high-risk women with breast MRI and annual mammography. These recommendations are listed in **Table 53** on page 77.

Women with *BRCA1/2* mutations should undergo breast cancer screening with MRI beginning at age 25 years and mammography beginning at age 30 years. Ovarian cancer screening with semiannual pelvic examinations, pelvic ultrasonography, and serum CA-125 measurement should begin at age 30 years. However, the effectiveness of ovarian cancer screening is not known, and surgical prophylaxis as detailed below is strongly recommended for *BRCA1/2* mutation carriers. Ovarian cancer screening is not recommended in women at average risk of ovarian cancer.

In women who are *BRCA1/2* carriers with one prior diagnosis of breast cancer, tamoxifen decreases the risk of contralateral breast cancer by 40% to 60%. Surgical prophylaxis options for carriers of *BRCA1/2* mutations include prophylactic bilateral mastectomy, which decreases the risk of breast cancer by greater than 90%, and prophylactic bilateral salpingo-oophorectomy (BSO), which decreases the risk of ovarian cancer by 80%, whether done before or after menopause. If done before menopause, prophylactic BSO also decreases the risk of breast cancer by 50%. Prophylactic BSO is recommended in women who carry deleterious *BRCA1/2* mutations between ages 35 and 40 years, once childbearing is complete. A recent registry study recommends risk-reducing BSO by age 35 years in women with *BRCA1* mutations because of a 4% risk of ovarian cancer between ages 35 and 40 years. Women with *BRCA2* mutations in this study did not develop ovarian cancer until after age 40 years.

KEY POINTS

- Women older than 35 years with a 5-year breast cancer risk of 1.7% or higher or with lobular carcinoma in situ or atypical ductal hyperplasia are candidates for breast cancer prophylaxis with tamoxifen prior to menopause and with tamoxifen, raloxifene, or exemestane after menopause.
- Women with *BRCA1/2* mutations should undergo breast cancer screening with MRI beginning at age 25 years and mammography beginning at age 30 years.
- Surgical prophylaxis options for *BRCA1/2* mutation carriers include prophylactic bilateral mastectomy (90% decreased risk of breast cancer) and prophylactic bilateral salpingo-oophorectomy (80% decreased risk of ovarian cancer).

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TABLE 49. Breast Cancer Risk Factors

Breast Cancer Risk Factor Category	Breast Cancer Risk Factors	Increase in Breast Cancer Risk or Lifetime Breast Cancer Risk
Reproductive factors	Early menarche, late menopause, first full-term pregnancy after age 30 years, or nulliparous	RR 1.2-3.5
Lifestyle	Obesity (BMI ≥30), lack of regular exercise, vitamin D deficiency, alcohol intake	RR 1.2-1.6 Obesity: RR 1.6 for BMI >30.7 versus BMI <22.9 in postmenopausal women[a] Regular exercise: RR decreased by 25% in physically active women compared with the least active women[b] Vitamin D deficiency: Postmenopausal breast cancer risk decreased by 12% for each 5 ng/mL (12.5 nmol/L) increase in 25(OH)D levels between 27 and 35 ng/mL[c] (67.4 and 87.4 nmol/L) Alcohol: mildly increased risk (RR 1.05) with 2 to 3 drinks per week. RR 1.41 for women consuming 2 to 5 drinks per day[d]
Treatment related: radiation	Prior chest wall radiation in patients younger than age 30 years (e.g., mantle radiation for Hodgkin lymphoma)	RR 5.0, with highest risk for younger age at radiation therapy; risk remains increased for at least 40 years after radiation therapy, with 30% to 50% lifetime risk of breast cancer[e]
Treatment related: HRT	Combination estrogen and progesterone HRT after menopause	RR 1.2-1.4; increased risk begins after 3 years of therapy[a]
Breast density[f]	Increased breast density	Risk increases with each category of breast density; for ≥75% density, RR is 4.7 compared with <10% density[g]
Atypical breast lesions	Atypical ductal or lobular hyperplasia, LCIS	RR 3.8-5.3 for atypical hyperplasia[h] and RR 5.4-8.0 for LCIS[i]; 30% to 35% lifetime risk of breast cancer (bilateral risk)[h,i]
Family history of breast cancer and familial breast cancer syndromes	*BRCA1/2* mutation represents the most common familial breast cancer syndrome (5% to 10% of all breast cancer tumors); others are rare	*BRCA1/2* mutations (RR 3.0 to 7.0) confer a 50% to 87% lifetime risk of breast cancer and a 20% to 45% lifetime risk of ovarian cancer

25(OH)D = 25-hydroxyvitamin D; HRT = hormone replacement therapy; LCIS = lobular carcinoma in situ; RR = relative risk.

[a]Data from Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med. 2001 Jan 25;344 (4):276-85. Erratum in: N Engl J Med. 2001 Jun 7;344(23):1804. [PMID: 11172156]

[b]Data from Lynch BM, Neilson HK, Friedenreich CM. Physical activity and breast cancer prevention. Recent Results Cancer Res. 2011;186:13-42. [PMID: 21113759]

[c]Data from Bauer SR, Hankinson SE, Bertone-Johnson ER, Ding EL. Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies. Medicine (Baltimore). 2013 May;92(3):123-31. [PMID: 23625163]

[d]Data from Bagnardi V, Rota M, Botteri E, et al. Light alcohol drinking and cancer: a meta-analysis. Ann Oncol. 2013 Feb;24(2):301-8. [PMID: 22910838] and Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA. 1998 Feb 18;279(7):535-40. [PMID: 9480365]

[e]Data from Swerdlow AJ, Cooke R, Bates A, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol. 2012 Aug 1;30(22):2745-52. [PMID: 22734026]

[f]Breast density refers to the amount of radiologically dense breast tissue appearing on a mammogram.

[g]Data from Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007 Jan 18;356(3):227-36. [PMID: 17229950]

[h]Data from Degnim AC, Visscher DW, Berman HK, et al. Stratification of breast cancer risk in women with atypia: a Mayo cohort study. J Clin Oncol. 2007 Jul 1;25(19):2671-7. [PMID: 17563394] and Marshall LM, Hunter DJ, Connolly JL, et al. Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol Biomarkers Prev. 1997 May;6(5):297-301. [PMID: 9149887]

[i]Data from Bodian CA, Perzin KH, Lattes R. Lobular neoplasia. Long term risk of breast cancer and relation to other factors. Cancer. 1996 Sep 1;78(5):1024-34. [PMID: 8780540]

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TABLE 50. Highlights of NCCN Criteria for Breast and/or Ovarian Cancer Syndrome Genetic Testing[a]
Individual with a family history of a known deleterious *BRCA1/2* mutation
Individual with breast cancer diagnosed before age 45 years
Individual with breast cancer diagnosed before age 50 years if family history includes very few female first- or second-degree relatives or if one relative is diagnosed with breast cancer at any age
Individual with breast cancer diagnosed at any age if one or more relatives is diagnosed with epithelial ovarian cancer
Breast cancer in women of Ashkenazi (Eastern European) Jewish ancestry
Men with breast cancer diagnosed at any age
Individual with more than three family members[b] with breast cancer, ovarian cancer, pancreatic cancer, and/or aggressive prostate cancer
Individual with triple-negative breast cancer[c] diagnosed before age 60 years
Individual with epithelial ovarian cancer diagnosed at any age

BCRA1/2 = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes; NCCN = National Comprehensive Cancer Network.

[a]Full testing guidelines can be accessed at www.nccn.org/professionals/physician_gls/f_guidelines.asp.

[b]First-, second-, or third-degree relatives.

[c]Negative for estrogen receptors, progesterone receptors, and *HER2* amplification.

TABLE 51. U.S. Preventive Services Task Force Recommendations[a] for Breast and/or Ovarian Cancer Syndrome Genetic Testing[b]
Women of Non-Ashkenazi Jewish Heritage:
Two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50 years or younger
A combination of three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis
A combination of both breast and ovarian cancer among first- and second-degree relatives
A first-degree relative with bilateral breast cancer
A combination of two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis
A first- or second-degree relative with both breast and ovarian cancer at any age
A history of breast cancer in a male relative
Women of Ashkenazi Jewish Heritage:
Any first-degree relative (or two second-degree relatives on the same side of the family) with breast or ovarian cancer

[a]Full testing recommendations can be accessed at: www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing.

[b]Applies to patients without a personal history of breast or ovarian cancer and without a known deleterious breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*) mutation present in their family. Both maternal and paternal family histories are important.

Staging and Prognosis of Early-Stage Breast Cancer

Breast cancer staging and prognosis is detailed in **Table 54**.

Stage I and II disease are classified as early breast cancer. According to the American Society of Clinical Oncology guidelines, imaging studies to identify occult metastatic disease are not needed for staging of early breast cancer unless worrisome signs or symptoms are present. The risk of distant metastases at diagnosis in these patients is very low. Clinical features associated with a more favorable prognosis include hormone receptor–positive cancer, small tumor size, low tumor grade, negative lymph nodes, and lack of *HER2* overexpression or extensive lymphovascular invasion. Based on these clinical characteristics, the benefit of adjuvant therapy in terms of recurrence and survival can be estimated using risk calculators such as www.adjuvantonline.com.

Women with hormone receptor–positive breast cancer (about 75% of cases) respond to antiestrogen therapy and have the best prognosis. *HER2* overexpression or gene amplification is present in approximately 20% of patients with breast cancer and predicts response to anti-*HER2* agents. Tumors negative for estrogen receptor, progesterone receptor, and *HER2* overexpression are called triple-negative tumors and are a particularly aggressive subtype.

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TABLE 52. Chemoprophylaxis Agents for Breast Cancer Risk Reduction

	Medications		
Considerations	**Tamoxifen**	**Raloxifene**	**Exemestane**
Mechanism of action	SERM	SERM	Aromatase inhibitor: prevents conversion of androgens to estrogens
Dose (all are 5 years in duration)	20 mg/d orally	60 mg/d orally	25 mg/d orally
Breast cancer risk reduction	49%	Less effective than tamoxifen: retains 76% of the effectiveness of tamoxifen	65%
Important toxicities	Vasomotor symptoms, cataracts, vascular events (stroke, TIA, DVT and PE), and endometrial cancer and uterine sarcoma in postmenopausal women	Vasomotor symptoms, cataracts, vascular events (25% lower risk of vascular events than tamoxifen)	Vasomotor symptoms, arthralgia, headaches, and insomnia
Indicated for use in premenopausal women	Yes	Not studied; should not be used unless part of a clinical trial	Not effective in premenopausal women
Other	Contraindicated in women with prior thromboembolic events	Contraindicated in women with prior thromboembolic events	At 3-year follow-up, no increase in osteoporosis, fractures, endometrial cancer, vascular events, or cardiac disease

DVT = deep venous thrombosis; PE = pulmonary embolism; SERM = selective estrogen receptor modulator; TIA = transient ischemic attack.

TABLE 53. American Cancer Society Recommendations for MRI Breast Cancer Screening

Women with *BRCA1/2* mutations
Women who are a first-degree relative of a *BRCA1/2* carrier, but are untested[a]
Women with a strong family history of breast cancer with a lifetime breast cancer risk of ≥20% to 25% as calculated by models[b] largely dependent on family history
Women who had radiation to the chest wall between ages 10 and 30 years (e.g., mantle radiation therapy for Hodgkin lymphoma)
Women with a history of other rare familial breast cancer syndromes

BRCA1/2 = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes.

[a]Testing for the *BRCA1* or *BRCA2* mutation that is present in the family is strongly recommended, but some patients decide to defer testing. In this situation where their carrier status is unknown, breast MRI screening is recommended. If they are later tested and do not carry the mutation, MRI screening should be stopped.

[b]Models that can be used to estimate lifetime risk of breast cancer to determine if MRI screening is appropriate (please note that the Gail Model is not recommended for this use):

- BRCAPRO: www4.utsouthwestern.edu/breasthealth/cagene/default.asp
- Claus model: Claus EB, Risch N, Thompson WD. The calculation of breast cancer risk for women with a first degree family history of ovarian cancer. Breast Cancer Res Treat. 1993 Nov;28(2):115-20. [PMID: 8173064]
- Tyrer-Cuzick (also called IBIS Breast Cancer Risk Evaluation Tool): www.ems-trials.org/riskevaluator

TABLE 54. Breast Cancer Stage and Survival

Stage	Tumor Size and Nodes	5-Year Relative Survival
I	≤2 cm, negative lymph nodes	95%
IIA	≤2 cm if 1 to 3 positive lymph nodes; 2.1-5 cm if negative lymph nodes	85%
IIB	2.1-5 cm with 1 to 3 positive lymph nodes; or >5 cm tumor with negative lymph nodes	70%
III	Any tumor size with ≥4 positive axillary lymph nodes; positive infraclavicular or supraclavicular nodes, and/or positive ipsilateral internal mammary nodes (clinically detected, or on sentinel node biopsy if ≥4 positive axillary nodes); tumors >5 cm with ≥1 positive nodes; or tumor extension to chest wall or skin	52%
IV	Distant metastases	18%

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KEY POINTS

- Clinical features associated with a more favorable prognosis of early-stage breast cancer include hormone receptor–positive cancer, small tumor size, low tumor grade, and negative lymph nodes.
- HVC Imaging studies to identify occult metastatic disease are not needed in patients with stage I and II breast cancer unless worrisome symptoms or the following poor prognostic features are present: hormone receptor–negative cancer, *HER2* overexpression, large tumor size, high tumor grade, positive lymph nodes, and the presence of extensive lymphovascular invasion.

Primary Breast Cancer Therapy

Ductal Carcinoma in Situ

Ductal carcinoma in situ (DCIS), classified as stage 0 breast cancer, usually presents as calcifications on mammography but can occasionally present as a palpable mass.

Given that DCIS is a cancer that is not life-threatening while it remains noninvasive, whether DCIS is being overdiagnosed and overtreated in many women is controversial. The ultimate goal would be to identify, potentially through molecular techniques, the patients in whom risk of progressing to invasive cancer is low enough that they could safely be monitored and forego surgical and radiation treatment (see Issues in Oncology). However, currently, it is not possible to accurately determine which patients are at such minimal risk.

The goal of treatment of DCIS is to prevent progression to invasive cancer. Excision alone without radiation is associated with a 30% risk of local recurrence at 10 years, with half of these recurrences consisting of invasive cancers. Risk factors for recurrence include young age, high tumor grade, the presence of comedo-type necrosis (necrosis in the center of the involved spaces), margin width, and tumor size.

DCIS can be treated with breast-conserving therapy, which consists of wide excision (lumpectomy) followed by breast radiation, or mastectomy. Mastectomy may be necessary if the DCIS is more extensive or if clear margins cannot be obtained by a wide excision. Sentinel lymph node biopsy is recommended if there is microinvasion (≤1 mm foci of invasion) or if a mastectomy is done in those in whom invasion is found on final pathologic results.

Approximately 80% of DCIS is estrogen receptor positive. In patients with estrogen receptor–positive DCIS, adjuvant tamoxifen decreases the risk of local recurrence of both DCIS and invasive cancer by 20% to 25% and of contralateral breast cancer by 50%. Because tamoxifen in DCIS confers no apparent benefit for survival, a discussion about treatment decisions should focus on potential toxicities and patients' needs and preferences. With treatment, patients with DCIS have a 15-year cause-specific survival rate of 97%.

KEY POINTS

- Ductal carcinoma in situ (DCIS) can be treated with breast-conserving therapy or mastectomy if the disease is more extensive or if clear margins cannot be obtained by a wide excision.
- In patients with estrogen receptor–positive DCIS, adjuvant tamoxifen decreases the risk of local recurrence of both DCIS and invasive cancer by 20% to 25% and of contralateral breast cancer by 50%, but it does not confer a survival advantage.

Invasive Breast Cancer

Breast-conserving therapy (wide excision followed by breast radiation) and mastectomy are the two surgical options used to treat invasive breast cancer. Breast-conserving therapy is an effective option in patients with tumors measuring 5 cm or less involving a single quadrant of the breast and with clear margins after excision. Mastectomy is recommended for tumors involving the skin, chest wall, or more than one quadrant of the breast, and for inflammatory breast cancer. Patients with tumors measuring 5 cm or greater who would otherwise be candidates for breast-conserving therapy may receive chemotherapy or antiestrogen treatment before surgery to decrease tumor size to facilitate breast conservation. Mastectomy may be appropriate for patients in whom radiation is contraindicated and is an option for women with familial breast cancer syndromes (including *BRCA1/2* mutations) owing to the increased risk of subsequent ipsilateral and contralateral breast cancers.

At the time of definitive breast surgery, lymph nodes in the ipsilateral axilla are routinely sampled to complete breast cancer staging and guide treatment decisions. In patients with no palpable lymph nodes and no abnormal nodes seen on ultrasound (if an ultrasound is done), a sentinel lymph node biopsy is usually done. The sentinel lymph node procedure uses radioactive colloid and/or blue dye injected near the area of the tumor or in the subareolar area to identify and then remove the lymph node or a few lymph nodes to which breast cancer would initially spread. If the sentinel lymph node biopsy is negative, or if there are less than three positive sentinel nodes in a woman who is to receive whole breast radiation and adjuvant therapy, axillary lymph node dissection is not required. In patients with clinically involved lymph nodes or with three or more involved sentinel lymph nodes, axillary lymph node dissection is done to remove additional lymph nodes. The sentinel lymph node procedure is associated with a much lower risk of lymphedema, sensory loss, and shoulder abduction defects than is axillary lymph node dissection.

Primary breast radiation usually consists of whole breast radiation with a boost given to the lumpectomy bed. Chest wall radiation after mastectomy is recommended in patients with tumors measuring greater than 5 cm, positive tumor margins, skin or chest wall involvement,

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inflammatory breast cancer, or four or more positive axillary lymph nodes. Depending on other risk factors, it may be recommended in women with one to three positive axillary lymph nodes. Postmastectomy radiation in these patients decreases the risk for local recurrence and systemic metastases.

For women aged 70 years and older with tumors measuring less than 2 cm, no clinically involved lymph nodes, and estrogen receptor–positive breast cancer, wide excision without sentinel lymph node biopsy or whole breast radiation followed by antiestrogen therapy alone is an acceptable treatment option. Whole breast radiation in this setting does decrease the risk for local recurrence, but does not increase breast cancer–specific or overall survival.

Men with breast cancer have the same surgical options as women; however, owing to smaller breast size and more frequent involvement of the areola, many men are not candidates for breast-conserving therapy, and most are treated with mastectomy. Sentinel lymph node sampling is appropriate in men with clinically lymph node–negative breast cancer, and the indications for postmastectomy radiation are the same for men as for women with breast cancer.

KEY POINTS

- Breast-conserving therapy is effective for patients with invasive breast cancer with tumors 5 cm or less involving a single quadrant of the breast and clear margins after excision.
- Mastectomy is recommended for patients with invasive breast cancer with tumors involving the skin, chest wall, or more than one quadrant of the breast and for inflammatory breast cancer.
- Chest wall radiation therapy after mastectomy is recommended in patients with invasive breast cancer with tumors greater than 5 cm, positive tumor margins, skin or chest wall involvement, inflammatory breast cancer, and for many patients with any positive axillary lymph nodes.

Adjuvant Systemic Therapy for Nonmetastatic Breast Cancer

Adjuvant systemic therapy is used to eradicate occult microscopic foci of breast cancer to prevent or delay systemic recurrence for stages I to III breast cancer, stages in which the cancer is not metastatic and is potentially curable. The type of adjuvant therapy recommended depends on tumor characteristics such as stage and tumor biology as well as patient status and preferences.

Adjuvant Endocrine Therapy

Most patients with hormone receptor–positive breast cancer receive adjuvant antiestrogen therapy which includes aromatase inhibitors, tamoxifen, and ovarian suppression in premenopausal women. Hormonal therapies reduce the overall risk of local and distant recurrence by 40% to 50% and the risk of contralateral cancer by 50% to 65%.

For premenopausal women, tamoxifen, a selective estrogen receptor modulator, is routinely recommended. Recent results from two large international studies, the ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) and aTTom (Adjuvant Tamoxifen Treatment Offers More) trials, are showing superior results with 10 rather than 5 years of tamoxifen adjuvant therapy, changing the standard of care for premenopausal women. Premenopausal women who previously completed 5 years of tamoxifen also benefit further from taking an aromatase inhibitor for 5 years once they become postmenopausal. Ovarian ablation or suppression decreases the risk of breast cancer recurrence by 25% and is sometimes used in premenopausal women with contraindications to tamoxifen. Clinical trials are investigating whether ovarian suppression may provide additional benefit to patients receiving adjuvant antiestrogen therapy and/or chemotherapy.

For women who are postmenopausal at breast cancer diagnosis or who become postmenopausal after the first 2 to 3 years of tamoxifen therapy, treatment should include an aromatase inhibitor. A meta-analysis of postmenopausal women with early breast cancer who took adjuvant tamoxifen for 5 years or an adjuvant aromatase inhibitor for 5 years reported a decreased rate of breast cancer recurrence (12% versus 15% at 5 years, rate ratio 0.77) in the aromatase inhibitor arm. Current antiestrogen adjuvant therapy options for postmenopausal women include 2 years of tamoxifen therapy followed by 3 to 5 years of an aromatase inhibitor, or 5 years of an aromatase inhibitor. Women who cannot tolerate more than 2 to 3 years of an aromatase inhibitor can switch to tamoxifen to complete 5 years of antiestrogen therapy.

The three approved aromatase inhibitors, anastrazole, letrozole, and exemestane, have comparable efficacy. Aromatase inhibitors prevent peripheral conversion of androgens to estrogens in postmenopausal women. They should not be used in premenopausal women as they are inactive in women with intact ovarian function. The main side effects of aromatase inhibitors are arthralgia and bone pain; vaginal dryness; sexual dysfunction; and higher risks of osteoporosis, fractures, cardiovascular risk, and hyperlipidemia. Compared with tamoxifen, the aromatase inhibitors confer a lower risk of venous thrombosis and endometrial cancer. Patients taking aromatase inhibitors should have their bone density monitored, and if the T score falls below -2.5, bisphosphonate treatment can be initiated.

Tamoxifen increases the risk of endometrial cancer and venous thromboembolic events in women over age 55 years. Other toxicities include hot flushes, vaginal discharge, and sexual dysfunction. Yearly pelvic examinations are recommended, and abnormal vaginal bleeding should be reported to their physicians.

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Men with hormone receptor–positive breast cancer (85% of male breast cancers) are treated adjuvantly with tamoxifen. Data supporting the use of aromatase inhibitors in men are insufficient.

KEY POINTS

- In women with hormone receptor–positive breast cancer, antiestrogen therapy reduces the overall risk of local and distant recurrence by 40% to 50% and the risk of contralateral breast cancer by 50% to 65%.
- Women with hormone receptor–positive breast cancer experienced superior benefit when they took adjuvant tamoxifen for 10, rather than 5, years.
- Treatment of women who are postmenopausal at breast cancer diagnosis or who become postmenopausal after the first 2 to 3 years of tamoxifen therapy should include an aromatase inhibitor.

Adjuvant Chemotherapy

Adjuvant chemotherapy is usually recommended for patients with high-risk breast cancer features, such as hormone receptor–negative status, *HER2* amplification, high-grade tumor, extensive lymphovascular invasion, and positive lymph nodes. For all women with hormone receptor–positive and lymph node–negative cancer and for postmenopausal women with one to three positive lymph nodes, commercially available molecular prognostic profiles can help determine the benefit of adjuvant chemotherapy. The most commonly used molecular prognostic profile in the United States is the 21-gene recurrence score (see Issues in Oncology).

Patients with hormone receptor–negative breast cancer generally have a greater benefit from adjuvant chemotherapy, with a proportional reduction in risk of recurrence and breast cancer–related death of more than 50% compared with a risk reduction of 25% in patients with hormone receptor–positive breast cancer. The decision to use adjuvant chemotherapy is individualized to the patient and involves assessment of the degree of benefit in decreasing risk of distant recurrence, potential toxicities, comorbidities, and patient preferences.

Adjuvant chemotherapy usually consists of two or three agents given sequentially or concurrently for 3 to 6 months. Commonly used agents include the anthracyclines (doxorubicin or epirubicin), cyclophosphamide, and the taxanes (paclitaxel or docetaxel). Common side effects of these regimens include bone marrow suppression with anemia and neutropenia, alopecia, hypersensitivity reactions, neuropathy, nausea, and premature menopause and infertility when given to premenopausal women (see Effects of Cancer Therapy and Survivorship). Rare but serious toxicities include cardiomyopathy from anthracyclines, interstitial pneumonitis from cyclophosphamide or the taxanes, and myelodysplasia and acute leukemia from the anthracyclines and/or cyclophosphamide. The risk of cardiomyopathy after four cycles of anthracycline therapy is 1.5%. The risk of acute leukemia after regimens with cyclophosphamide and doxorubicin is 0.5%.

For women with *HER2*-positive breast tumors measuring 0.5 cm or larger and/or positive lymph nodes, adjuvant chemotherapy combined with trastuzumab is recommended. Trastuzumab is a monoclonal antibody directed against the *HER2* receptor. When added to adjuvant chemotherapy, trastuzumab decreases the risk of breast cancer recurrence by 53% and the risk of breast cancer–related death by 34%. Adjuvant trastuzumab is given for 1 year. Trastuzumab toxicities include infusion reactions and cardiomyopathy. The risk of cardiomyopathy is higher in patients receiving anthracycline-containing regimens (2% to 4%) compared with non–anthracycline-containing regimens (0.4%) and is higher in older women or those with preexisting cardiac risk factors. Cardiac function should be evaluated at baseline with echocardiography or multigated acquisition scan and every 3 months during adjuvant trastuzumab therapy (see Effects of Cancer Therapy and Survivorship). Other anti-*HER2* agents are being studied in adjuvant clinical trials.

Nearly half of all breast cancers are diagnosed in women older than age 65 years, yet many adjuvant chemotherapy trials have not included older women owing to comorbidities or upper-age–limit eligibility. Consequently, evidence-based guidelines for women in this age group are lacking. Studies support treating healthy older women the same as younger women with early-stage breast cancer. Older women have a higher risk for cardiotoxicity, which should be considered when clinicians formulate treatment recommendations.

The indications for adjuvant chemotherapy in men with breast cancer and the regimens used are the same as those for women with early-stage breast cancer.

KEY POINTS

- Patients with hormone receptor–negative breast cancer generally have a greater benefit from adjuvant chemotherapy, with a proportional reduction in risk of recurrence compared with patients with hormone receptor–positive breast cancer.
- Patients with *HER2*-positive breast tumors measuring 0.5 cm, or larger and/or positive lymph nodes, should receive a combination of adjuvant chemotherapy and trastuzumab; the addition of trastuzumab decreases the risk of breast cancer recurrence by 53% and the risk of breast cancer–related death by 34%.

Locally Advanced and Inflammatory Breast Cancer

Locally advanced breast cancer (stages IIIA-IIIC) is characterized by tumors measuring greater than 5 cm with lymph node involvement, skin or chest wall involvement, and/or

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extensive axillary lymph node involvement. This type of cancer is treated with initial chemotherapy (neoadjuvant chemotherapy), followed by surgery, and then radiation. Patients with tumors measuring greater than 5 cm without other locally advanced features such as skin or chest wall involvement can often have breast-conserving surgery after chemotherapy. Tumors with chest wall or skin invasion (T4 cancers) require mastectomy after chemotherapy; surgical staging of the axilla is also required. Postmastectomy or postlumpectomy radiation is recommended for these locally advanced breast cancers, which often also require radiation of draining lymph nodes. Locally advanced cancer is associated with a high risk of distant and local recurrence.

Inflammatory breast cancer is an aggressive and rapidly progressive type of cancer characterized by erythema and edema of the skin of the breast called "peau d'orange" for its resemblance to the skin of an orange (**Figure 15**).

In the United States, inflammatory breast cancer constitutes 1% to 2% of cases of breast cancer. The inflammatory appearance mimicking mastitis is caused by tumor emboli in the dermal lymphatics, which are often seen on skin biopsy but are not required for the diagnosis; an underlying breast mass may also be palpable. The diagnosis is established based on the clinical appearance of the breast. Tumors of inflammatory breast cancer are usually high grade, most are hormone receptor negative, and many have *HER2* amplification. At diagnosis, nearly all patients have axillary lymph node involvement and approximately one third have distant metastases. Because of the high risk for metastases in patients with inflammatory cancer, staging with CT and bone scanning is recommended.

Inflammatory breast cancer is treated with neoadjuvant chemotherapy, followed by mastectomy with axillary node dissection, and then postmastectomy chest wall radiation therapy. Despite multimodality treatment, prognosis is still worse for patients with inflammatory breast cancer than for those with other types of locally advanced breast cancer, with a 5-year relative survival rate of approximately 40%.



FIGURE 15. Inflammatory breast cancer often has this characteristic "p'eau d'orange" (orange peel) appearance of the skin, due to tumor emboli in the dermal lymphatics. Erythema is often present as well.

KEY POINTS

- Inflammatory breast cancer is characterized by erythema and edema of the skin of the breast, which can resemble the skin of an orange ("peau d'orange"); the diagnosis is established based on the clinical appearance of the breast.
- Because of the high risk for metastases in patients with inflammatory breast cancer, staging with CT and bone scanning is recommended.
- Inflammatory breast cancer is treated with neoadjuvant chemotherapy, followed by surgery, and then radiation.

Breast Cancer Follow-up and Survivorship

After completing surgery, radiation therapy, and chemotherapy, patients with early-stage breast cancer should receive follow-up monitoring every 3 to 6 months for 2 years, every 6 months during years 2 through 5, and then annually. Monitoring should include annual mammography, whereas screening MRI of the breast is reserved for patients who have a high risk for subsequent breast cancer from *BRCA1/2* mutations, a strong family history of breast cancer, or other indications as based on the ACS guidelines (see Table 53).

Surveillance blood tests and other imaging studies are not recommended, as these have not been shown to improve survival. Investigative laboratory tests and imaging studies should be reserved for patients with worrisome symptoms or findings on examination. Most hormone receptor–negative breast cancer recurrences develop within 5 years of diagnosis. However, in patients with hormone receptor–positive breast cancer, half of the recurrences arise 5 years or more after diagnosis.

Quality-of-life issues should be monitored in survivors of breast cancer. Vasomotor symptoms are common in younger women owing to chemotherapy-induced early menopause and antiestrogen treatment in patients with hormone receptor–positive breast cancer. Hot flushes may be improved with selective serotonin reuptake inhibitors such as escitalopram, or with serotonin-norepinephrine reuptake inhibitors such as venlafaxine. However, in patients taking tamoxifen, it is important to avoid the use of strong and moderately strong CYP2D6 inhibitors, such as bupropion, fluoxetine, and paroxetine, as these drugs can inhibit tamoxifen activation. Testing patients for CYP2D6 polymorphisms is not currently recommended. Gabapentin at bedtime can help decrease night sweats. Aromatase

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inhibitor–induced arthralgia can be treated with NSAIDs, a break in treatment, or changing to another aromatase inhibitor or to tamoxifen. Regular exercise can ameliorate aromatase-inhibitor arthralgia. Other common problems facing survivors of breast cancer include sexual dysfunction, fatigue, insomnia, and cognitive dysfunction, including impaired memory, decreased concentration, and word-finding difficulty. Patients can experience a treatment-related decrease in bone density caused by chemotherapy-induced early menopause or aromatase inhibitors. Bone density should be monitored every 1 to 2 years during, as well as initially after, aromatase inhibitor treatment and should be monitored in patients with chemotherapy-induced premature menopause. Additionally, patients should be monitored for decreased arm mobility and lymphedema, with prompt referral to physical therapy if such symptoms occur. Patients who wish to preserve fertility after breast cancer treatment should be referred to fertility specialists before starting chemotherapy. Clinicians should reassure patients that becoming pregnant following breast cancer diagnosis and treatment does not increase the risk of breast cancer recurrence nor does it decrease survival. Premenopausal women with breast cancer who do not wish to become pregnant should use a nonhormonal method of birth control.

An established fertility preservation option for a woman with a partner is in vitro fertilization with embryo freezing. Newer options, often done as part of clinical trials, include freezing of unfertilized eggs and ovarian cryopreservation with future reimplantation. Embryo preservation also gives parents with *BRCA1/2* mutations the option of preimplantation genetic diagnosis (if desired by the parents, embryos without the mutation can be selected for implantation).

KEY POINTS

IIVC
- After completion of treatment, follow-up monitoring in patients with early-stage breast cancer should occur every 3 to 6 months for 2 years, every 6 months during years 2 through 5, and then annually, with annual mammography for all survivors, and MRI of the breast reserved for those at high risk for recurrence.

IIVC
- Surveillance blood tests and other imaging tests should not be routinely performed and are reserved for patients with symptoms or findings of disease.
- Therapy-related hot flushes in breast cancer survivors may be improved with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, with avoidance of strong and moderately strong CYP2D6 inhibitors, which can inhibit tamoxifen activation.
- Breast cancer survivors should undergo monitoring for decreased arm mobility and lymphedema, with prompt referral to physical therapy in the presence of such symptoms.

Metastatic Breast Cancer

Recurrent breast cancer with distant metastases is not curable. The average overall survival from the start of systemic chemotherapy to death is 2 years, although patients with hormone-sensitive breast cancer are often treated for years with antiestrogen therapy before chemotherapy is begun. The goals of treatment in this setting are to improve survival, palliate symptoms, and minimize treatment toxicity. Clinical trials of new treatments, including new molecularly targeted therapies, should be considered for patients with metastatic breast cancer whenever possible. It is important to discuss goals of care with patients and involve palliative care teams when appropriate.

Patients with a history of early-stage breast cancer who develop findings suspicious for metastatic disease should undergo biopsy of the suspected metastatic lesions if possible to confirm the diagnosis and facilitate repeat assessment of hormone receptor status and *HER2* overexpression. Most patients with recurrence outside the central nervous system can undergo imaging-guided needle biopsies in locations such as the spine. Discordance between the status of these molecular markers in the primary tumor and the metastatic site occurs in 10% to 15% of patients with breast cancer for both estrogen receptor status and *HER2* amplification, usually resulting in a change in treatment.

Systemic treatment is the mainstay of therapy for patients with metastatic breast cancer; surgery and radiation have ancillary roles. Radiation is used to treat painful bone metastases. Surgery can stabilize impending pathologic fractures. Either may be used to treat oncologic emergencies, such as spinal cord compression and brain metastases. Patients who present with de novo metastatic disease currently do not undergo resection of the primary breast cancer, although randomized trials are currently studying whether this approach may confer survival benefits in patients in whom the systemic disease is responding to therapy.

Initial treatment for metastatic breast cancer depends on hormone receptor and *HER2* status, disease sites, and patient comorbidities and preferences. For hormone receptor–positive cancer, antiestrogen therapy usually is given initially. Antiestrogen therapy works best in patients with bone and soft tissue metastases and in those with a longer disease-free interval since the initial breast cancer diagnosis. Antiestrogen treatments for metastatic breast cancer include aromatase inhibitors, tamoxifen, ovarian suppression in premenopausal women, fulvestrant (an estrogen receptor down-regulator), megestrol acetate, and estradiol. A newer approach combines antiestrogen treatment with molecularly targeted therapy affecting downstream pathways. The combination of exemestane and the mammalian target of rapamycin (mTOR) inhibitor, everolimus, is effective in patients in whom resistance to aromatase inhibitor therapy has developed.

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Patients with hormone receptor–negative cancer, those with impending visceral crisis due to extensive metastases, or those who do not respond to antiestrogen therapy are treated with chemotherapy. Generally, single-agent chemotherapy is given, although combination therapy is appropriate in patients with extensive visceral metastases in whom a higher response rate is needed. Chemotherapeutic agents can be used sequentially in patients with good performance status who wish to continue palliative treatment.

Patients with *HER2*-amplified metastatic breast cancer are treated with monoclonal antibodies against the *HER2* receptor. These drugs can be used as single agents, in multiple anti-*HER2* drug combinations, given with antiestrogen therapy in hormone receptor–positive cancer, or combined with nonanthracycline-based chemotherapies. A more recent approach uses an antibody drug conjugate of trastuzumab linked to the antimitotic agent ado-trastuzumab emtansine. Trastuzumab delivers the potent chemotherapeutic agent directly to the cancer cells that overexpress *HER2*.

Patients with breast cancer with lytic bone metastases are treated with bisphosphonates to decrease bone pain and skeletal-related events such as bone fractures and reduce the need for palliative radiation therapy. These agents can cause transient aches as well as fever, kidney injury, hypocalcemia, and osteonecrosis of the jaw. Denosumab, a monoclonal antibody against the receptor activator of nuclear factor κB ligand (RANKL), is an alternative option for reducing the morbidity related to metastatic bone lesions. Denosumab can also cause hypocalcemia and osteonecrosis of the jaw. Patients who take bisphosphonates or denosumab should receive a baseline dental evaluation, schedule regular dental appointments during treatment, maintain good oral hygiene, and report any jaw pain or areas of poor gingival healing. Coordination with an oral surgeon is needed to minimize risk before any invasive dental procedures are performed.

KEY POINTS

- Recurrent breast cancer with distant metastases is not curable, and the goals of treatment in such patients are to improve survival, palliate symptoms, and minimize treatment toxicity.
- Patients with a history of early-stage breast cancer who develop findings suspicious for metastatic disease should undergo biopsy of a suspected metastatic lesion, if possible, to confirm the diagnosis and facilitate repeat assessment of hormone receptor status and *HER2* overexpression.
- Recurrent metastatic hormone receptor–positive breast cancer is usually treated with initial antiestrogen therapy, which works best in patients with bone and soft tissue metastases and in those with a longer disease-free interval since the initial breast cancer diagnosis.

Ovarian Cancer

Epidemiology and Risk Factors

Ovarian cancer is the leading cause of gynecologic cancer-related deaths, with an estimated 22,240 new cases and 14,230 deaths in the United States in 2013. The lifetime risk for developing ovarian cancer is 1.4%, and the median age at diagnosis is 63 years. Epithelial cancer accounts for 95% of ovarian cancer and is the type discussed in this section.

The most important risk factor for ovarian cancer is family history. Ten percent to 15% of ovarian cancer is hereditary, mostly due to *BRCA1/2* mutations. The lifetime risk of ovarian cancer in hereditary syndromes is detailed in **Table 55**. Current guidelines recommend *BRCA1/2* testing for all women with ovarian cancer (see Breast Cancer).

Factors that decrease the risk of ovarian cancer include previous pregnancy, prior oral contraceptive pill (OCP) use, and tubal ligation or hysterectomy. OCP use for 15 years or

TABLE 55. Lifetime Risk of Ovarian Cancer

Family History or Mutation Status	Lifetime Risk of Ovarian Cancer
Average population risk (no family history of ovarian cancer or related cancers)	1.4%
Family history of ovarian cancer with negative testing for a familial ovarian cancer syndrome	Previously listed as 5%, but now uncertain if risk is increased above population baseline if genetic testing is negative
BRCA1 mutation	35% to 46%
BRCA2 mutation	13% to 23%
Lynch syndrome[a] (also called HNPCC)	3% to 14%

BRCA1 = breast cancer susceptibility 1 gene; *BRCA2* = breast cancer susceptibility 2 gene; HNPCC = hereditary nonpolyposis colon cancer.

[a]Also has increased risks of colon cancer, other gastrointestinal cancers, endometrial cancer, and urinary tract cancers.

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more decreases the risk of ovarian cancer by 50%, with the protective effect lasting approximately 30 years after OCP cessation, but even shorter use results in some protection. Endometriosis, polycystic ovary syndrome, infertility, intrauterine device use, and cigarette smoking all increase the risk. Ovulation induction for treatment of infertility does not increase ovarian cancer risk.

KEY POINTS

- All women with ovarian cancer are eligible for *BRCA1/2* testing.
- Oral contraceptive pill (OCP) use for 15 years or more decreases the risk of ovarian cancer by 50%, with the protective effect lasting 30 years after OCP cessation, but even shorter use results in some protection.

Screening and Risk-Reduction Strategies

Women at average risk of ovarian cancer should not undergo screening. The predictive value of serum CA-125 testing and ultrasonography are each less than 3% and lead to a high rate of false-positive results and unnecessary surgeries. Prospective randomized studies have shown no difference in the stage of ovarian cancer at detection or in the rate of ovarian cancer–related deaths when annual serum CA-125 assays and transvaginal ultrasounds are used. Despite a lack of data showing that screening in high-risk patients is effective, most guidelines recommend women with hereditary ovarian cancer syndromes undergo ovarian cancer screening beginning at age 30 years (or 5 to 10 years younger than the age at which ovarian cancer was diagnosed in the youngest relative) with pelvic examinations, serum CA-125 measurement, and transvaginal ultrasonography performed every 6 months.

In women who carry deleterious *BRCA1/2* mutations, prophylactic bilateral salpingo-oophorectomy (BSO) is recommended between ages 35 and 40 years, once childbearing is complete. A recent registry study recommends risk-reducing BSO by age 35 years in women with *BRCA1* mutations because of a 4% risk of ovarian cancer between ages 35 and 40 years. Women with *BRCA2* mutations in this study did not develop ovarian cancers until after age 40 years.

KEY POINTS

HVC
- Women at average risk for ovarian cancer should not receive ovarian cancer screening; the predictive values of serum CA-125 testing and ultrasonography are each less than 3% and lead to a high rate of false-positive results and unnecessary surgeries.
- Prophylactic bilateral salpingo-oophorectomy reduces ovarian cancer risk by 80%, with a residual 1% to 3% risk of primary peritoneal cancer in women with hereditary syndromes.

Diagnosis

Although ovarian cancer is sometimes diagnosed early when an ovarian mass is felt on examination or seen on imaging, ovarian cancer is usually advanced at diagnosis owing to the absence of effective screening tests and usual lack of symptoms in patients with early-stage disease. Severe or persistent symptoms such as abdominal or pelvic pain, bloating, early satiety, or anorexia should raise suspicion for ovarian cancer, particularly in postmenopausal women. Dyspnea due to pleural effusion or symptoms of bowel obstruction may be presenting symptoms.

Ultrasound findings suggestive of a malignant ovarian mass include a solid component that is often nodular or papillary and the presence of ascites and/or peritoneal masses. If ovarian cancer is suspected, CT or MRI of the abdomen and pelvis and chest imaging are usually done to assess disease extent.

Serum CA-125 levels are elevated in most women with advanced ovarian cancer, but this finding is less sensitive for detecting earlier-stage disease. In addition, the finding of elevated serum CA-125 levels is not specific and levels can be elevated in other malignancies; in several benign gynecologic conditions common in premenopausal women; and in liver failure, colitis, peritonitis, diverticulitis, and heart failure. The decision to proceed to surgery should depend more on imaging findings than on biomarkers such as the serum CA-125 level. If ovarian cancer is diagnosed, it is helpful to measure preoperative serum CA-125 levels to determine whether this marker will be useful for assessing treatment response.

In patients with an adnexal mass without ascites, diagnosis is usually established by surgical exploration, as there is survival benefit from intact removal of the adnexal mass in early-stage disease. In patients with advanced disease, diagnosis may be made by cytologic evaluation of ascites or pleural fluid, or by image-guided biopsy of peritoneal masses.

KEY POINTS

- Severe or persistent symptoms such as abdominal or pelvic pain, bloating, early satiety, or anorexia should raise suspicion for ovarian cancer, particularly in postmenopausal women.
- Ultrasound findings suggestive of a malignant ovarian mass include a solid component that is often nodular or papillary and the presence of ascites and/or peritoneal masses.
- Ovarian cancer diagnosis is usually established by surgical exploration, cytologic evaluation of ascites or pleural fluid, or by image-guided biopsy of peritoneal masses in patients with more advanced cancer.

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Treatment

Ovarian cancer staging, treatment, and prognosis are detailed in **Table 56**. Stage I ovarian cancer without high-risk features is treated with surgery alone. Patients with stage I ovarian cancer with high-grade or clear cell histology, cyst rupture, or positive peritoneal cytologic results should receive adjuvant chemotherapy after surgery. Patients with stages II, III, and IV ovarian cancer and initially resectable disease can undergo surgery first followed by postoperative chemotherapy. If disease is not resectable initially, neoadjuvant chemotherapy is given, usually for two to three cycles, followed by resection in patients with an adequate response to chemotherapy; chemotherapy is completed after surgery.

Optimal surgical debulking (residual masses <1 cm), ideally performed by a gynecologic oncologist, improves survival. Surgery involves total abdominal hysterectomy and BSO; staging by examination of the abdomen and pelvis, including peritoneal washings and lymph node evaluation; and tumor debulking by removal of all neoplastic tissue that can be safely excised.

For stage II and optimally debulked stage III cancer, intraperitoneal chemotherapy through an indwelling peritoneal catheter should be considered. It results in a 16-month improvement in overall survival in patients with stage III disease compared with intravenous chemotherapy regimens, but is associated with more toxicity. Physicians and patients should discuss the risks and benefits of this approach.

KEY POINTS

- Surgical treatment of ovarian cancer should be done by a gynecologic oncologist and involves total abdominal hysterectomy and bilateral salpingo-oophorectomy; staging by examination of the abdomen and pelvis, including peritoneal washings and lymph node evaluation; and optimal tumor debulking.
- Intraperitoneal chemotherapy results in a 16-month improvement in overall survival in patients with stage II and optimally debulked stage III ovarian cancer compared with intravenous chemotherapy, but it is associated with more toxicity.

Monitoring and Follow-up

Patients with ovarian cancer undergo follow-up monitoring every 2 to 4 months for the first 2 years following completion of surgery and first-line chemotherapy, with subsequent monitoring every 3 to 6 months through 5 years after treatment, and then annually. Follow-up visits include a thorough history, physical examination, and pelvic examination. Guidelines differ on whether to monitor serum

TABLE 56. International Federation of Gynecology and Obstetrics Ovarian Cancer Staging, Treatment, and Survival

Stage	Definition	Treatment	5-Year Overall Survival
Stage I disease (favorable)	Cancer in one or both ovaries, not high grade or clear cell, negative peritoneal washings, no rupture	Surgery alone	>90%
Stage I disease (unfavorable); stage II disease	Unfavorable stage I disease: Confined to ovaries but with high-grade or clear cell histology, rupture, or positive peritoneal washings Stage II disease: spread beyond ovaries but confined to pelvis	Surgery followed by chemotherapy	Stage I: 75% to 80% Stage II: 60% to 70%
Optimally debulked stage III disease	Spread to abdomen, with residual tumor masses <1 cm after debulking surgery	Surgery followed by intravenous or intraperitoneal chemotherapy	Intravenous chemotherapy: 40% Intraperitoneal chemotherapy: 50%
Suboptimally debulked stage III disease or stage IV disease	Stage III (suboptimal) disease: spread to abdomen with residual masses >1 cm after debulking surgery Stage IV disease: spread beyond abdomen	Surgery (usually done even for stage IV disease) and chemotherapy, with order of treatment depending on initial tumor resectability	Stage III: 20% to 30% Stage IV: 10% to 15%

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CA-125 levels, although a recent trial suggested that such monitoring might result in earlier initiation of treatment for recurrence, but no difference in overall survival. Imaging studies and other blood tests are reserved for addressing specific clinical concerns. If not given on initial diagnosis, a referral for genetic counseling should be provided at initial follow-up.

KEY POINT

HVC
- Follow-up for patients who have completed treatment for ovarian cancer includes a periodic history, physical examination, and pelvic examination for 5 years after treatment; routine monitoring of CA-125 levels, other laboratory testing, and imaging studies does not improve survival and should be reserved for addressing specific clinical concerns.

Management of Recurrent Ovarian Cancer

More than 70% of women with advanced ovarian cancer will experience a relapse after first-line chemotherapy, and recurrent ovarian cancer is not curable. The goal of treatment of recurrent ovarian cancer is to improve cancer-related symptoms and extend survival. Discussion and shared decision making about goals of care and referral to a palliative care team are appropriate in the management of patients with recurrent disease.

Secondary cytoreductive surgery is best considered for patients with a progression-free interval of at least 12 months, good performance status, and a local recurrence that can potentially be rendered free of gross disease with surgery.

An elevated serum CA-125 level in a patient with a normal physical examination and CT scan and no disease symptoms constitutes the most common presentation at relapse. Patients with an isolated serum CA-125 recurrence who are not comfortable with surveillance alone can be treated with tamoxifen or an aromatase inhibitor. Initiating cytotoxic treatment confers no known benefit in this setting.

Cytotoxic chemotherapy is indicated for patients with significant disease on CT scan or physical examination or in those with disease progression–related symptoms. Treatment options include single-agent or combination chemotherapy, often involving a platinum agent if the cancer has not developed resistance, as well as anti-angiogenesis inhibitors such as bevacizumab.

Ascites can be managed with periodic paracentesis for symptomatic relief. Patients with bowel obstruction from advanced ovarian cancer are unlikely to benefit from surgery. Chemotherapy benefit in patients with bowel obstruction is often limited, and treatment should focus on comfort and palliation.

KEY POINTS

- The goal of treatment of recurrent ovarian cancer is to improve cancer-related symptoms and extend survival.
- Secondary cytoreductive surgery is best considered for patients with ovarian cancer and a progression-free interval of at least 12 months, good performance status, and a local recurrence that can potentially be rendered free of gross disease with surgery.

Cervical Cancer

Epidemiology and Risk Factors

Over 12,000 new cases of invasive cervical cancer and approximately 4000 cervical cancer–related deaths occur in the United States each year. The mean age at diagnosis is 48 years. Invasive cervical cancer incidence in the United States has decreased by more than 80% since the 1940s, largely owing to Pap smear screening. The incidence and mortality rates are higher in countries lacking screening programs.

Nearly all cases of cervical cancer are precipitated by persistent human papillomavirus (HPV) infection. HPV, most commonly subtypes 16 and 18, is detected in more than 99% of patients with cervical cancer. Both squamous cell carcinoma and adenocarcinoma are associated with HPV infection. The HPV vaccine is ideally given before sexual activity begins: if given to adolescents and young women before they develop HPV infection, it is 90% effective at preventing infection and 97% to 100% effective at preventing cervical intraepithelial neoplasia and invasive cervical cancer.

Cervical Pap smears can detect precancerous lesions that occur several years before the development of invasive disease. See MKSAP 17 General Internal Medicine for cervical cancer screening guidelines and HPV vaccine recommendations.

KEY POINTS

- Nearly all cases of cervical cancer are precipitated by human papillomavirus infection (subtypes 16 and 18).
- The human papillomavirus vaccine, given before infection develops, is 90% effective at preventing infection and 97% to 100% effective at preventing cervical intraepithelial neoplasia and invasive cervical cancer. HVC

Diagnosis, Staging, and Treatment

The most common presenting symptoms of cervical cancer are abnormal vaginal discharge, postcoital bleeding, or vaginal bleeding between menstrual cycles or after menopause. Diagnosis of cervical cancer is established by biopsy of the

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cervix. Colposcopy with directed biopsy is done if there is no visible lesion, with cervical conization done if colposcopy is nondiagnostic. The most common histologies are squamous cell carcinoma (69% of cervical cancers) and adenocarcinoma (25%).

Staging, most often performed using the International Federation of Gynecology and Obstetrics system (**Table 57**), is done clinically and includes a pelvic examination and chest radiograph. CT, MRI, and PET/CT are often useful in planning therapy, although they are not part of the formal staging evaluation.

Primary treatment of cervical cancer based on clinical stage is outlined in Table 57. Chemotherapy given with radiation therapy improves survival in patients with intermediate-risk and high-risk cervical cancer but not in the neoadjuvant or adjuvant setting.

KEY POINTS

- The most common presenting symptoms of cervical cancer are abnormal vaginal discharge, postcoital bleeding, or vaginal bleeding between menstrual cycles or after menopause.
- Chemotherapy given with radiation therapy improves survival in patients with intermediate- and high-risk cervical cancer but not in the neoadjuvant or adjuvant setting.

Prognosis and Surveillance

The most important prognostic factor in cervical cancer is clinical stage followed by involvement of pelvic or paraaortic lymph nodes. The 5-year overall survival rate is 90% to 95% for patients with early-stage clinical disease and negative lymph nodes; the survival rate in patients with positive lymph nodes decreases to 70%. Patients with regionally advanced tumors have a 40% to 50% survival rate at 5 years.

Surveillance of patients with cervical cancer includes clinical evaluation every 3 to 6 months for 2 years, followed by evaluation every 6 months until year 5, and then annually. Surveillance evaluation should include a history, physical examination, and pelvic examination with cervicovaginal cytology. Yearly chest radiography is optional, and other imaging is done only as clinically indicated. In appropriate candidates, localized pelvic recurrence may be cured with pelvic exenteration.

KEY POINT

- In patients with cervical cancer, surveillance evaluation (a history, physical examination, and pelvic examination with cervicovaginal cytology) should occur every 3 to 6 months for 2 years, followed by evaluation every 6 months until year 5, and then annually.

Gastroenterological Malignancies

Colorectal Cancer

This section discusses staging through follow-up and prognosis of patients with colorectal cancer. Epidemiology, pathophysiology, risk factors, and clinical manifestations will be discussed in MKSAP 17 Gastroenterology and Hepatology. Colorectal cancer screening is discussed in MKSAP 17 General Internal Medicine.

Colorectal cancer is a common malignancy in both men and women in developed countries and is second only to lung cancer as a cause of cancer-related deaths in the United States. Symptoms and signs of bowel disease include bleeding per rectum, melena, persistent cramping or bloating, and chronic diarrhea or constipation and may indicate the presence of a

TABLE 57. International Federation of Gynecology and Obstetrics Cervical Cancer Staging

Stage	Treatment
I: Carcinoma is strictly confined to the cervix IA: Microscopic disease only	I: Radical hysterectomy or radiation; ovarian preservation can be done if fertility desired IA: Simple hysterectomy, cone biopsy, or removal of cervix alone are options
IIA (nonbulky) and IIB (bulky): Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or lower third of the vagina	IIA: same as for stage I IIB: same as for stage III
III: The tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney	III: Radiation with concurrent platinum-based chemotherapy
IV: The carcinoma extends beyond the true pelvis or involves (biopsy proven) the mucosa of the bladder or rectum IVA: spread to adjacent organs IVB: distant metastases	IVA: same as for stage III IVB: palliative chemotherapy, with palliative radiation for local symptoms such as bleeding or pain

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benign polyp, another nonmalignant process, or cancer. Such symptoms and signs warrant investigation regardless of age.

Colorectal cancer is a cancer of the large intestine. The most distal 12 to 15 centimeters of the large intestine, the portion below the peritoneal reflection and therefore within the pelvis, is referred to as the rectum; the rest of the organ is referred to as the colon. Metastatic disease from either the colon or the rectum is referred to as colorectal cancer. The need for a permanent colostomy is one of the most common fears in patients in whom colorectal cancer is diagnosed, and usually this fear is unfounded.

KEY POINT

- The need for a permanent colostomy is one of the most common fears in patients in whom colorectal cancer is diagnosed, and usually this fear is unfounded.

Staging

The preoperative staging workup should include a complete colonoscopy (if technically feasible) and contrast-enhanced CT scans of the chest, abdomen, and pelvis. Preoperative measurement of serum carcinoembryonic antigen (CEA) levels is also routinely done. PET scans have not been demonstrated to improve preoperative staging and should not be used routinely. Patients with local or locoregional rectal cancer require further preoperative staging with endorectal ultrasonography or a pelvic MRI to assess the depth of tumor penetration (T stage), degree of lymph node involvement (N stage), and any metastasis (M stage).

Staging using the TNM cancer staging system is the most accurate predictor of outcome in patients with colorectal cancer (**Table 58**).

KEY POINT

HVC
- PET scans have not been demonstrated to improve preoperative staging in patients with colorectal cancer and should not be routinely used.

TABLE 58. Staging of Colorectal Cancer

Stage	Description	Approximate 5-Year Disease-Free Survival
I	Tumor does not invade the full thickness of bowel wall (T1, T2); lymph nodes not involved (N0)	90%-95%
II	Tumor invades full thickness of the bowel and may invade into pericolonic or perirectal fat (T3, T4); lymph nodes not involved (N0)	70%-85%
III	One or more lymph nodes involved with cancer (N1, N2); any T stage	25%-70%
IV	Metastatic tumor spread to distant site (M1); any T stage; any N stage	0%-10%

Surgical Management

Colon Cancer

Patients with colon cancer without preoperative evidence of metastatic disease should undergo surgical resection of the primary tumor and the regional lymph nodes. Surgery of the colon should almost never result in a need for permanent colostomy, although a temporary colostomy, usually reversed after a few months, may be needed for emergent surgery due to obstruction or perforation or if the bowel is not evacuated properly before surgery. Surgery involving tumors of the upper two thirds of the rectum also should only very rarely require permanent colostomy, although temporary ostomies may be needed more frequently. Patients with colon cancer confirmed as stage I at surgery require no further treatment. In stage II colon cancer, data do not show a clear survival advantage for administration of adjuvant chemotherapy; consequently, surgery alone is acceptable standard practice for most patients. An exception is patients with stage II colon cancer with characteristics associated with a high risk for recurrence (T4 disease and inadequate lymph node sampling [<12 lymph nodes examined], lymphovascular invasion, poorly differentiated histology, or clinical perforation or obstruction). In these patients, the prognosis is similar to that of patients with stage III disease, and adjuvant chemotherapy may be appropriate.

Rectal Cancer

Patients with rectal tumors that are not full thickness and do not have lymph node involvement (stage I) on pretreatment imaging usually undergo surgery, with a total mesorectal excision being the preferred procedure. The mesorectum is a fatty sheath covering the rectum that contains the regional lymph nodes. A total mesorectal excision entails a sharp dissection of the pelvis outside of the mesorectum to allow removal of the mesorectum fully intact en bloc with the rectum. However, considerable expertise is required to avoid complications with this procedure, which should be performed only by a subspecialized surgeon. If local lymph node metastases or full-thickness tumor penetration is found after surgery in those patients thought to be stage I preoperatively, then postoperative chemotherapy and radiation therapy are indicated. Otherwise, if pathology confirms stage I cancer, no further therapy is needed. In patients with tumors that are too distal to permit an adequate margin of resection without resection of the anal sphincter muscles, an abdominal-peritoneal resection is likely to be required, which results in a permanent colostomy. Patients who have full-thickness rectal tumors (T3-T4) or clearly enlarged lymph nodes on preoperative imaging require combined-modality therapy with neoadjuvant radiation and chemotherapy and adjuvant chemotherapy alone. More recently, an accepted alternative has been chemotherapy first, followed by chemoradiotherapy, and then surgery, with no postoperative treatment ("total neoadjuvant therapy").

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KEY POINTS

- Patients with colon cancer without preoperative evidence of metastatic disease should undergo surgical resection of the primary tumor and the regional lymph nodes.
- Treatment for patients with rectal tumors that are not full thickness and with no lymph node involvement (stage I) on pretreatment imaging is usually surgery alone.

Adjuvant Treatment of Colorectal Cancer

Colon Cancer

The first drug successfully used for adjuvant treatment of colorectal cancer was 5-fluorouracil (5-FU), and this agent, now in its sixth decade of clinical use, remains at the center of current treatment strategies. Newer drugs are most typically used in combination with 5-FU. 5-FU is usually given with the reduced folate leucovorin, which is inactive alone but causes 5-FU to bind more tightly to its target enzyme. Capecitabine is an oral prodrug that is converted to 5-FU in the body. Use of this agent requires a highly reliable, motivated patient who is able to adhere to a complex oral medication schedule. In patients with stage III disease, adjuvant 5-FU–based chemotherapy given for approximately 6 months after surgery has been shown to reduce the risk of cancer recurrence and death; therefore, all patients with stage III disease, regardless of age, should receive adjuvant chemotherapy barring specific medical or psychiatric contraindications. The FOLFOX (leucovorin, 5-FU, and oxaliplatin) regimen and the CAPOX (capecitabine plus oxaliplatin) regimens have been shown to be modestly but statistically significantly more effective than the same regimens without oxaliplatin in patients with stage III disease (but not in those with stage II disease); these two regimens are equally acceptable. Not all drugs that are useful for treating metastatic disease are active in the adjuvant setting. Irinotecan, bevacizumab, and cetuximab have all been shown to be ineffective in improving survival in the adjuvant setting, yet, as discussed below, all are part of standard treatment of metastatic disease. For patients with stage II disease and a high risk for recurrence, treatment with 5-FU/leucovorin or capecitabine may be appropriate. Whether the addition of oxaliplatin in patients with high-risk stage II disease is appropriate has been challenged by recent data, and patient care must be individualized based on the extent of risk factors for recurrence and the patient's overall medical condition. Although no definitive standards exist, a consensus statement from the American Society of Clinical Oncology recommends that all patients with stage II colon cancer consult with a medical oncologist to discuss the risks and benefits of adjuvant treatment.

Rectal Cancer

Radiation therapy is not routinely indicated for completely resected colon cancer. However, because of the anatomic location of rectal cancer and the difficulty in obtaining adequate tumor-free margins, local recurrence rates tend to be higher than those for completely resected colon cancer. Therefore, neoadjuvant chemoradiotherapy is indicated in patients with locally advanced (T3-T4) rectal cancer, in addition to adjuvant therapy. Clinical trials have established that 5-FU given by protracted intravenous infusion or capecitabine is an equally acceptable chemotherapeutic option to be given concurrently with radiation therapy. Data evaluating the addition of oxaliplatin during radiation have been disappointing, and this therapy is not currently recommended. The FOLFOX or CAPOX regimen is typically used after neoadjuvant chemoradiotherapy and surgery for approximately 4 months to complete a total of approximately 6 months of therapy (inclusive of pre- and postoperative treatments). More recently, use of this 4-month combination chemotherapy as an initial treatment, followed by chemoradiation and then surgery, has become an acceptable alternative.

KEY POINTS

- Adjuvant 5-fluorouracil–based chemotherapy given for approximately 6 months after surgery reduces the risk of cancer recurrence and death in patients with stage III colon cancer.
- For patients with stage II colon cancer and a high risk for recurrence, the prognosis is similar to that for patients with stage III disease, and treatment with 5-fluorouracil/leucovorin or capecitabine may be appropriate.
- Neoadjuvant and adjuvant chemotherapy is indicated in patients with stage III or IV rectal cancer.

Metastatic Disease

Most patients with stage IV colorectal cancer have treatable, but not curable, disease. A long disease-free interval, a limited number of metastases, and metastases confined to a single organ (such as liver or lung) are favorable prognostic factors. A few such patients may have disease amenable to curative surgical resection. Patients with a limited number of liver-only lesions (≤3) have been reported to have long-term disease-free survival rates of 25% to 50% in selected studies. Results are less encouraging as the number of lesions increases. Otherwise, the primary treatment modality is chemotherapy. 5-FU, often modified by the reduced folate leucovorin, is the basis of most chemotherapy regimens used in colorectal cancer. Often, the drugs oxaliplatin or irinotecan are added to these agents. The FOLFOX regimen or the 5-FU, leucovorin, and irinotecan (FOLFIRI) regimen are equally acceptable. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), modestly improves outcome when added to chemotherapy regimens. Recent data support the use of either continued bevacizumab or ziv-aflibercept, another anti-VEGF agent, together with second-line chemotherapy.

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All patients with metastatic colorectal cancer should undergo tumor genotyping to identify mutations in the K-*ras* and N-*ras* genes because the anti-epidermal growth factor receptor antibodies, cetuximab and panitumumab, are inactive in the 50% of tumors that harbor mutations. Cetuximab and panitumumab typically cause an acneiform rash, which can be uncomfortable and socially debilitating; however, for reasons that remain unclear, antitumor activity and the development of rash are tightly correlated, and patients who do not experience a substantial skin rash are extremely unlikely to benefit from these agents.

KEY POINTS

- In some patients, metastatic colorectal cancer confined to a single organ may be curable with surgical resection of the primary tumor and metastasis.
- 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin are used to treat patients with metastatic colorectal cancer.
- Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, modestly improves outcome in patients with metastatic colon cancer when added to chemotherapy regimens.
- All patients with metastatic colorectal cancer should undergo tumor genotyping to identify mutations in the K-*ras* and N-*ras* genes because the anti-epidermal growth factor receptor antibodies, cetuximab and panitumumab, are inactive in the 50% of tumors that harbor mutations.

Postoperative Surveillance

The role of postoperative surveillance in patients with colorectal cancer, regardless of whether postoperative therapy has been given, is to identify surgically curable recurrence, such as oligometastatic liver disease or lung metastases, rather than to assess for more disseminated disease. Treatment of small-volume, widely metastatic, but asymptomatic, disease discovered on surveillance has not been associated with improved outcomes and may subject patients to significant treatment toxicity. CT scans of the chest, abdomen, and pelvis are recommended annually for at least the first 3 years postoperatively. PET scanning should not be used for routine surveillance but may be used to further evaluate an equivocal finding on CT scans in some patients. Colonoscopy is typically recommended 1 year after resection, 3 years later, and then every 5 years unless abnormalities are found. The main purpose of colonoscopy is to identify new polyps rather than survey for local recurrence, which is relatively rare. Serum CEA levels are measured every 3 to 6 months for the first 2 years, and then every 6 months, to complete a total of 5 years. The finding of abnormal serum CEA levels, if testing has been repeated and confirmed, warrants additional investigation, as it may indicate recurrent disease. However, therapy should not be started based on serum CEA elevation alone.

KEY POINTS

- Postoperative surveillance of patients with colorectal cancer includes CT scans of the chest, abdomen, and pelvis annually for at least the first 3 years postoperatively and colonoscopy 1 year after resection, 3 years later, and then every 5 years with the goal of identifying surgically curable recurrence.
- Treatment of small-volume, widely metastatic, but asymptomatic, disease discovered on surveillance has not been associated with improved outcomes and may subject patients to significant treatment toxicity. **HVC**
- PET scanning should not be used for routine surveillance of patients with colorectal cancer but may be used to further evaluate an equivocal finding on CT scans in some patients. **HVC**

Anal Cancer

Anal cancer is an epidermoid, or squamous cell carcinoma, in contradistinction to rectal cancer, which is an adenocarcinoma. Anal cancers are typically associated with human papillomavirus (HPV) infection and also have increased incidence in patients with HIV infection. Whereas current management of rectal cancer uniformly involves surgical resection, anal cancer is often curable with radiation therapy and concurrent chemotherapy with mitomycin plus 5-FU. This chemotherapeutic regimen was established in the 1970s, and results of studies that have explored newer, alternative agents have not demonstrated improved outcomes. Anal tumors may continue to regress for at least 6 months up to 1 year after completion of chemoradiation therapy. Therefore, treatment failure should not be declared unless unequivocal growth or metastases are documented after completion of radiation therapy. Salvage surgery is performed in patients with local tumor growth after radiation plus chemotherapy; however, this procedure necessarily removes the sphincter muscle, thus requiring a permanent colostomy.

See MKSAP 17 General Internal Medicine for discussion of HPV vaccination.

KEY POINTS

- Anal cancer is often curable with radiation therapy and concurrent chemotherapy with mitomycin plus 5-fluorouracil.
- Because anal tumors may continue to regress for 6 months to 1 year following completion of radiation therapy, treatment failure should not be declared unless unequivocal growth or metastases are documented after completion of radiation therapy.

Pancreatic Cancer

To determine the extent of disease in pancreatic cancer, clinicians use the American Joint Committee on Cancer (AJCC)

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TNM cancer staging system. To determine treatment approach, exocrine pancreatic cancer is typically classified based on whether it is surgically resectable, borderline resectable, or either locally advanced or metastatic unresectable disease.

Resectable tumors are confined to the pancreas or just beyond it that correspond to stage IA (tumor limited to the pancreas and ≤2 cm in diameter), IB (tumor limited to the pancreas but >2 cm in diameter), and IIA (tumor extension beyond the pancreas but without involvement of the celiac axis) without involved lymph nodes or evidence of metastatic disease.

Borderline resectable pancreatic cancer is that which extends to nearby blood vessels but that may be removed completely with surgery, such as some stage III tumors (involving the celiac axis or superior mesenteric artery with or without involved lymphadenopathy) without evidence of metastatic disease.

Unresectable cancers cannot be removed entirely by surgery and may include locally advanced disease that has not yet spread to distant organs but still cannot be completely surgically removed (stage IIB [localized tumor or with extension beyond the pancreas but with associated involved lymph nodes] and most stage III cancers).

Metastatic cancer has spread to distant organs and might involve surgery to ameliorate symptoms, but surgery cannot excise the tumor completely or cure the cancer.

Surgical resection is the only potential curative intervention for pancreatic cancer. Patients with a clinical presentation and CT or MRI scans consistent with a resectable pancreatic cancer should undergo definitive resection of the pancreatic mass. Endoscopic or percutaneous needle biopsy should not be attempted prior to definitive surgery, as these procedures have a high false-negative rate in this setting, and would therefore not change management; a suspicious pancreatic mass would require resection whether the needle biopsy showed cancer or not. Although only 15% to 20% of cases are considered resectable at presentation and the overall cure rate in patients undergoing surgical resection is low, patients without evidence of metastatic disease who appear to have resectable disease should undergo resection because it is the only potentially curative option. For patients with locally unresectable disease, neoadjuvant chemoradiation remains controversial.

Postoperative adjuvant therapy with chemotherapy, local radiation, or the combination is also controversial.

For decades, gemcitabine alone was considered an appropriate standard treatment for metastatic pancreatic cancer. More recently, a combination regimen of oxaliplatin, irinotecan, 5-FU, and leucovorin (FOLFIRINOX), has been shown to provide better outcomes; however, this regimen has substantial toxicity and is only a reasonable option in patients who are both medically well (have an excellent performance status) and who are highly motivated. A more recent trial has shown that the addition of liposomally encapsulated paclitaxel (nab-paclitaxel) to gemcitabine also improves outcome modestly, albeit with some increased toxicity.

KEY POINT

- Patients with pancreatic cancer without evidence of metastatic disease who have technically resectable disease should undergo resection because it is the only potentially curative option.

Gastroesophageal Cancer

This section discusses treatment of patients with gastroesophageal cancer. Epidemiology, risk factors, and clinical manifestations of esophageal cancer are discussed in MKSAP 17 Gastroenterology and Hepatology, Disorders of the Esophagus. The same aspects of gastric cancer are discussed in MKSAP 17 Gastroenterology and Hepatology, Disorders of the Stomach and Duodenum.

Staging of gastroesophageal cancer is based on the TNM cancer staging system. In simple terms, stage I disease is a superficial lesion that has not spread and does not penetrate the full thickness of the esophagus or stomach wall, whereas stage II disease is a full-thickness lesion. Stage III disease is defined by spread to locoregional lymph nodes, and stage IV disease is defined by the presence of distant metastatic disease. Virtually all gastric and gastroesophageal junction cancers are adenocarcinomas, as are approximately 95% of esophageal cancers. About 5% of esophageal cancers are of squamous cell histology, although currently, patients with adenocarcinomas and squamous cell carcinoma receive the same treatments.

Although only 30% to 40% of patients have potentially resectable disease at presentation, patients with local and locoregional disease (AJCC stages I, II, and III) are typically treated surgically. Unfortunately, recurrence rates are high and cure rates with surgical resection remain low. Studies have shown that administration of neoadjuvant chemotherapy improves outcome to a modest, but statistically significant, degree. The addition of preoperative radiation therapy, as well as chemotherapy, is also supported by some—although less robust—clinical data. As such, surgery alone is no longer the preferred approach, and neoadjuvant chemotherapy or chemoradiation therapy is routinely used.

Because of the low cure rates for locoregional therapy for esophageal cancer, chemotherapy has been added to many treatment regimens, and many patients are currently treated with combination chemoradiation therapy following surgery for resectable disease. However, the optimal treatment regimen and the overall effectiveness of different treatment approaches have not yet been established.

Treatment of metastatic (stage IV) gastroesophageal cancer remains unsatisfactory and palliative. Numerous agents

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have shown modest activity, and combination cisplatin-based regimens are typically used owing to the insufficient activity of single agents.

Up to 20% of gastric cancers and 30% of gastroesophageal junction adenocarcinomas recently have been found to overexpress the *HER2* growth factor receptor, which is a target for the anti-*HER2* monoclonal antibody trastuzumab. Therefore, evaluation of all metastatic gastroesophageal carcinomas for *HER2* is performed, and trastuzumab is added to chemotherapy regimens in patients whose tumors express *HER2*.

KEY POINTS

- Patients with local and locoregional gastroesophageal cancer (American Joint Committee on Cancer stages I, II, and III) are typically treated surgically.
- Treatment of metastatic gastroesophageal cancer is palliative and usually consists of cisplatin-based therapy or cisplatin-based therapy plus trastuzumab in patients with *HER2* tumor expression.

Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are rare in incidence, but because of their often relatively indolent course, the prevalence of NETs in the population is disproportionately higher than the incidence. NETs arising from the endocrine cells of the pancreas are called pancreatic NETs, whereas those arising from all other neuroendocrine tissues of the aerodigestive tract are called carcinoid tumors. Although older literature categorized pancreatic NETs (previously called islet cell tumors) and carcinoids together, these two entities clearly behave differently, with several anticancer agents showing activity against pancreatic NETS but not against carcinoid tumors. Typically, NETs of the gastrointestinal tract are well to moderately differentiated and indolent in growth pattern. However, NETs may be poorly differentiated, in which case they typically exhibit a very aggressive growth pattern and are treated like small cell lung cancer. Most NETs are hormonally nonfunctioning, but about 25% are hormone producing. For example, carcinoid tumors typically produce serotonin, which can cause the classic carcinoid syndrome of diarrhea and facial flushing. Pancreatic NETs, when hormonally active, may produce any of the pancreatic endocrine hormones, including insulin, gastrin, glucagon, somatostatin, or vasoactive intestinal peptide, with resulting hormonal syndromes based on the type of hormone elaborated.

Although patients with hormonally functioning tumors may present with hormonal symptoms, those with nonfunctioning tumors may be asymptomatic and have metastatic disease for many years before diagnosis. The liver is overwhelmingly the most common site of metastasis, and diagnosis is often established through an incidental finding of hepatomegaly.

Because well-differentiated NETs are so indolent, patients often can be effectively managed with expectant observation and serial imaging. Triple-phase contrast-enhanced CT scanning or MRI with gadolinium are the preferred imaging modalities. Indium 111 pentetreotide scanning can be used to establish the presence of somatostatin receptors, which are commonly expressed on these tumors. Tumors that have demonstrated somatostatin receptors and are hormonally symptomatic or show clear growth under observation may be treated with the somatostatin analogues octreotide or lanreotide. Mechanical interventions, such as hepatic arterial embolization, radiofrequency ablation, or surgical debulking, may be used to reduce symptomatic tumor bulk in the liver or to decrease hormone production.

In pancreatic NETs, the small-molecule inhibitors sunitinib (an anti-VEGF agent) and everolimus (an anti–mammalian target of rapamycin [mTOR] agent), and the oral cytotoxic combination of capecitabine and temozolomide, are active. However, these agents have not demonstrated the same activity in carcinoid tumors. Chemotherapy is minimally effective in carcinoid tumors, and no specific agents are FDA approved for this indication.

KEY POINTS

- Most neuroendocrine tumors are hormonally nonfunctioning, but about 25% that manifest are hormone producing.
- Because well-differentiated neuroendocrine tumors are so indolent, patients often can be effectively managed with expectant observation and serial imaging using triple-phase contrast-enhanced CT scanning or MRI with gadolinium.
- In pancreatic neuroendocrine tumors, the small-molecule inhibitors sunitinib and everolimus and combination capecitabine and temozolomide are active.

HVC

Gastrointestinal Stromal Tumors

Although gastrointestinal stromal tumors (GISTs) were once considered rare, significant improvements in molecular diagnostics and therapy have led to increased recognition of these tumors. GISTs are the most common tumor of mesenchymal origin, or sarcoma, of the gastrointestinal tract, representing 1% to 3% of all gastrointestinal tumors, and are derived from the precursors of the intestinal cells of Cajal. Almost all GISTs have an activating mutation in the c-*kit* proto-oncogene, leading to constitutive activation of the KIT receptor tyrosine kinase. CD-117, the immunohistochemical marker for the KIT protein, is the hallmark of most GISTs. GISTs may also present with mutations in the platelet-derived growth factor-α receptor.

Localized GISTs typically appear as isolated, discrete masses anywhere along the digestive tract. Localized GISTs

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are managed with surgical resection. For patients undergoing a potentially curative resection of a localized GIST, tumors with favorable risk factors require no further treatment, whereas patients with higher-risk tumors are treated with an extended course of the small-molecule receptor tyrosine kinase inhibitor imatinib, which blocks c-*kit* tyrosine kinase phosphorylation. In such patients, recurrence-free survival and overall survival are superior in patients who receive 3 years of imatinib therapy versus 1 year of therapy.

Metastatic disease is extremely refractory to standard cytotoxic chemotherapy agents; however, imatinib is remarkably effective in this setting, and lifelong treatment with this drug typically is recommended until disease progresses or treatment toxicity becomes unacceptable. However, despite its outstanding efficacy, imatinib is not curative. More recently, other agents such as sunitinib and dasatinib have shown activity in the treatment of GISTs that have become refractory to imatinib.

KEY POINTS

- Patients with localized gastrointestinal stromal tumors are managed with surgical resection.
- Following surgery, patients with localized gastrointestinal stromal tumors and tumors with favorable risk factors require no further treatment, whereas those with higher-risk tumors are treated with an extended course of imatinib.
- Patients with metastatic gastrointestinal stromal tumors are treated with lifelong imatinib until disease progresses or treatment toxicity is no longer tolerable.

Lung Cancer

This section will focus on treatment and follow-up of patients with lung cancer. See MKSAP 17 Pulmonary and Critical Care Medicine for discussion of epidemiology, risk factors, screening, diagnosis, and staging.

The initial step in developing a therapeutic plan for lung cancer is to obtain a tissue diagnosis to determine whether the tumor is non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) and to exclude metastatic disease from another site. It is important to obtain an adequate biopsy sample (with at least a core biopsy) to allow for additional molecular studies that may be helpful in guiding therapy in some patients.

NSCLC constitutes 80% to 90% of cases, SCLC is responsible for approximately 10% of cases, and the management of these two forms of lung cancer differs significantly. Unfortunately, most patients with lung cancer have advanced, and often incurable, disease at diagnosis, reflecting the relatively asymptomatic nature of early-stage disease. Nonetheless, lung cancer research efforts have led the way in improving therapy through molecular targeting, resulting in multiple targeted therapies that are now readily available to patients and have dramatically affected treatment efficacy and tolerability.

KEY POINTS

- The initial step in developing a therapeutic plan for lung cancer is to obtain a tissue diagnosis to determine whether the tumor is non-small cell lung cancer or small cell lung cancer and to exclude metastatic disease from another site.
- Most patients with lung cancer have advanced, and often incurable, disease at diagnosis, reflecting the relatively asymptomatic nature of early-stage disease.

Non-Small Cell Lung Cancer

Diagnosis and Staging

The clinical manifestations and diagnosis of lung tumors are discussed in MKSAP 17 Pulmonary and Critical Care Medicine.

NSCLC includes several different histologic types, including squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and other less commonly occurring tumors. It may also be characterized by various paraneoplastic syndromes, including hypercalcemia due to secretion of parathyroid hormone–related protein, hypertrophic pulmonary osteoarthropathy, and inflammatory myopathies. Adenocarcinoma is the most common subtype, accounting for about 50% of cases. Correct assignment of subtype, especially adenocarcinoma versus squamous cell carcinoma, is important to allow for proper treatment in patients with metastatic disease. Additionally, adenocarcinoma can be associated with genetic mutations that help predict the response to tyrosine kinase inhibitors.

The histologic subtypes of NSCLC are all staged similarly; selection of therapy is based primarily on disease stage. Stage I disease is characterized by a solitary tumor without regional (peribronchial or hilar) or mediastinal lymph node involvement. Stage IA disease consists of tumors measuring less than 3 cm, whereas stage IB disease consists of tumors measuring greater than 3 cm but less than 5 cm. Patients with stage II disease have tumors greater than 5 cm; regional lymph node involvement; tumor invasion into local structures, such as the pleura or chest wall; or tumors that are located near the carina. Most patients with stage III disease have mediastinal lymph node involvement. Patients with stage IV disease have metastatic disease or an ipsilateral malignant pleural effusion.

KEY POINTS

- Non-small cell lung cancer may be characterized by various paraneoplastic syndromes, including hypercalcemia due to secretion of parathyroid hormone–related protein, hypertrophic pulmonary osteoarthropathy, and inflammatory myopathies.

(Continued)

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KEY POINTS *(continued)*

- Correct assignment of subtype, especially adenocarcinoma versus squamous cell carcinoma, is important to allow for proper treatment in patients with metastatic disease.

Treatment

Lung cancer treatment varies significantly based on cancer stage, as noted below. A vital component of treatment, regardless of stage, is smoking cessation. Continued smoking has been shown to increase the risk of complications associated with treatment as well as reducing the potential efficacy of treatment. Furthermore, it is associated with higher risks of secondary cancers in patients with lung cancer.

Surgery with curative intent is recommended for patients with stage I or II NSCLC. Because many patients with lung cancer have concomitant chronic obstructive pulmonary disease, evaluating baseline pulmonary function with measurement of DLCO and spirometry in all potential surgical candidates is necessary. Depending on results of baseline pulmonary function testing, further evaluation to assess predicted postoperative pulmonary function and exercise capacity may be indicated. Some patients are considered to have unresectable disease based on poor pulmonary function or the presence of extensive medical comorbidities rather than disease stage. In these patients or those of advanced age, stereotactic ablative radiation therapy may be an alternative treatment option, as phase II trials have found it can result in tumor control rates similar to surgery. Patients with stage III disease with mediastinal lymph node involvement and those with metastatic disease or an ipsilateral malignant pleural effusion (stage IV) are not typically treated with surgery.

Although adjuvant chemotherapy is not usually recommended following surgery for stage I disease, it may be beneficial in patients with high-risk tumors (poorly differentiated histology, vascular invasion, need for wedge resections, tumors greater than 4 cm, visceral pleural involvement, and incomplete lymph node sampling). Adjuvant chemotherapy has a proven role in patients with resected stage II and resected stage III disease. Cisplatin-based combination therapy has demonstrated a clear survival advantage in these settings.

Adjuvant radiotherapy has been shown to decrease the risk of locoregional recurrence, although its effect on overall survival in patients with stage I and II NSCLC has not been established. Consequently, radiotherapy is not typically given to patients with negative tumor resection margins but may be considered for those with an incompletely resected tumor.

For most patients with stage III NSCLC, combined chemoradiation therapy given with curative intent is the preferred treatment approach. There is no single standard chemotherapy regimen used, but treatment with cisplatin- or carboplatin-based chemotherapy can be given. Adjuvant chemotherapy does not improve survival following definitive chemoradiation. In highly selected patients with stage III disease, surgery may be considered an appropriate therapeutic option. For patients with T3N1 disease, surgery can be done as initial therapy, although the procedure should include mediastinal lymph node dissection. If mediastinal lymph nodes are negative, adjuvant chemotherapy should be given. In patients with positive mediastinal lymph nodes, sequential chemotherapy and radiation is recommended. For patients with limited mediastinal lymph node involvement, chemotherapy or chemoradiation can be given initially, followed by surgery in patients without disease progression. However, no data indicate that this approach is superior to definitive chemoradiation therapy. Following surgery, patients with positive margins or multistage mediastinal lymph node involvement who were treated with chemotherapy only before surgery should be offered adjuvant radiotherapy.

Metastatic disease (stage IV) is not curable, and treatment in these patients is, by definition, palliative. Proper assessment of performance status using a validated measure is vital, as the benefit of chemotherapy in this patient population is confined to those with an adequate performance status (see Issues in Oncology for discussion of performance status scales). In addition, it is important to address issues surrounding goals of care and provision of palliative care in patients with metastatic NSCLC (see Issues in Oncology for discussion of palliative care goals and benefits).

Selected patients with a single site of metastasis can be treated with resection of the metastatic lesion and aggressive treatment of the primary tumor. However, most patients who present with metastatic disease have multiple sites of metastasis and are treated with systemic therapy. Recommended treatments for patients with metastatic disease are based on the pattern of metastatic spread and the results of histologic and molecular assessment. Recent evidence has indicated that squamous cell carcinoma and adenocarcinoma each respond differently to certain chemotherapeutic agents. Additionally, mutations in the epidermal growth factor receptor (EGFR), translocation of the *ALK* and *EML-4* genes, or mutation of the *ROS1* gene have been identified in a few non-squamous cell lung cancers, usually adenocarcinomas. Patients with EGFR mutations have been found to derive significant benefit from treatment with erlotinib, whereas those with *ALK* translocations and *ROS1* mutations derive similar benefit from crizotinib; these agents are recommended as initial therapy in these patients when mutation status is known before treatment is initiated. In patients who must start treatment before mutation test results are available, these agents can be used later in treatment.

Patients without an activating mutation are treated with chemotherapy. Platinum-containing doublet regimens are widely used in the first-line treatment of metastatic NSCLC and are typically combined with pemetrexed for

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patients with adenocarcinoma or gemcitabine for squamous cell tumors. For patients in whom the histologic subtype is uncertain, paclitaxel or docetaxel can be used. Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, can be combined with chemotherapy for patients with non-squamous cell histology. Patients receiving platinum-based chemotherapy are typically treated for an initial four to six cycles because more than six cycles has not been shown to be beneficial.

Following the initial course of therapy, management options include observation and maintenance chemotherapy. Maintenance therapy is typically given until the patient experiences disease progression or an unacceptable level of toxicity. In such cases, the platinum-containing drug is stopped, and patients continue to receive the same drug that was used in combination with the platinum-based agent (continuation maintenance) or a different drug (switch maintenance). Bevacizumab should be continued along with maintenance therapy in patients receiving this agent, as it has been shown to improve progression-free survival. Patients with an activating mutation detected after initial platinum-based chemotherapy is started should receive the appropriate tyrosine kinase inhibitor as maintenance therapy if it was not used sooner. Maintenance chemotherapy results in improved progression-free survival and is therefore considered an accepted treatment option in patients with responsive or stable disease following four to six cycles of a platinum-based treatment. If disease progression occurs while on or after first-line chemotherapy, patients are often treated with single-agent chemotherapy consisting of docetaxel or pemetrexed (for non-squamous cell cancers). However, response rates in patients receiving second-line therapy are low, and median survival is relatively short following progression after first-line treatment. Patients with an EGFR mutation or *ALK* translocation can be treated with erlotinib or crizotinib, respectively, as maintenance therapy if they were initially treated with chemotherapy. It is especially important to address goals of care and symptom management in patients whose disease progresses after they receive first-line chemotherapy.

Following curative-intent treatment for NSCLC, patients should undergo follow-up monitoring with a periodic history, physical examination, and CT of the chest. Follow-up monitoring is important in the detection of recurrence and new primary lung cancers, which occur at a rate of approximately 3% per year. In addition, smoking cessation counseling is important in the care of lung cancer survivors.

Despite these treatment interventions, the 5-year survival rate for patients with NSCLC is only 10% to 15%. This low survival rate is largely attributable to the finding that 70% of patients present with stage III or IV disease. However, 5-year survival rates for patients with stage IA disease is only 73%, decreasing to 36% for those with stage IIB disease, and lower for those with stage III disease.

KEY POINTS

- Surgery is recommended for patients with stage I or stage II non-small cell lung cancer.
- Adjuvant chemotherapy is appropriate for patients with resected stage II and stage III non-small cell lung cancer.
- For patients with stage III non-small cell lung cancer, the preferred treatment is combined chemotherapy and radiation.
- Metastatic non-small cell lung cancer (stage IV) is not curable and treatment is palliative; the benefit of systemic therapy in this patient population is confined to those with adequate performance status. **HVC**
- Patients with metastatic non-small cell lung cancer and adequate performance status should be treated with systemic therapy selected based on the pattern of metastatic spread and the results of histologic and molecular assessment. **HVC**

Small Cell Lung Cancer

Diagnosis and Staging

SCLC is a neuroendocrine tumor that is seen almost exclusively in smokers. Large cell neuroendocrine carcinoma is a form of lung cancer that is distinct from small cell carcinoma histologically but behaves and is treated similarly to SCLC. SCLC is characterized by rapid growth, with most patients presenting with locally advanced or metastatic disease. Like NSCLC, SCLC can be associated with several paraneoplastic syndromes, including hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion, hypertrophic pulmonary osteoarthropathy, inflammatory myopathies, Cushing syndrome caused by ectopic adrenocorticotropic hormone deficiency, and other various hematologic and neurologic syndromes. SCLC is also associated with superior vena cava syndrome (see Oncologic Urgencies and Emergencies).

Staging of SCLC involves a two-stage system that was first used in early clinical trials conducted by the Veterans Administration Lung Study Group. Limited-stage disease is defined as cancer confined to a single hemithorax, which could include ipsilateral supraclavicular lymph node disease, and requires that all disease be encompassed by a single radiation portal. Extensive disease refers to disease that extends beyond a single hemithorax. Typically performed staging studies include CT of the chest, abdomen, and pelvis; whole-body bone scintigraphy; and MRI of the brain. The most recent update of lung cancer staging has recommended that SCLC be staged with the TNM system used for staging NSCLC; however, because most patients with SCLC present with locally advanced or metastatic disease, the use of the TNM staging system does not alter treatment decisions in most patients.

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KEY POINTS

- Limited-stage small cell lung cancer is defined as cancer confined to a single hemithorax, which could include ipsilateral supraclavicular lymph node disease, and requires that all disease be encompassed by a single radiation portal.
- Extensive-stage small cell lung cancer refers to disease that extends beyond a single hemithorax.

Treatment

The role of surgery in the management of patients with SCLC is limited to those with very early-stage disease (<10% of patients). Although no firm criteria can be used to identify patients for surgery, eligible patients should optimally have single, small primary tumors without associated lymph node involvement (T1-2 and N0). Patients require extensive preoperative evaluation to exclude occult disease, including invasive staging of the mediastinum with endobronchial ultrasonography or mediastinoscopy. Although no prospective data are available to guide clinical decision making, retrospective data indicate 5-year survival rates of 15% to 48% following resection depending on disease stage. Patients treated with surgery typically receive adjuvant chemotherapy, as currently available data indicate that surgery alone is suboptimal.

Limited-stage SCLC that is too advanced for surgical resection is potentially curable, but treatment outcomes are poor, with 5-year survival rates of only 10% to 15%. The mainstay of treatment is combined chemotherapy and radiation therapy. The addition of radiation to chemotherapy in patients with limited-stage disease has been shown to improve survival compared with chemotherapy alone, which is associated with a high risk of local recurrence. Radiation is typically started with cycle 1 or cycle 2 of chemotherapy. Cisplatin or carboplatin can be used in combination with etoposide. Patients who experience a complete response or a significant partial response to primary chemoradiation should be offered treatment with prophylactic cranial irradiation to reduce the incidence of brain metastases and improve overall survival.

Extensive-stage SCLC is treated with chemotherapy usually consisting of cisplatin or carboplatin combined with etoposide or irinotecan and given for four to six cycles. Although response rates to chemotherapy are high, overall treatment outcomes remain poor. Nonetheless, survival in patients with extensive-stage SCLC who receive chemotherapy is superior to those who do not receive chemotherapy. As with limited-stage disease, cisplatin or carboplatin is used as initial therapy, but carboplatin is most commonly used owing to its more favorable side effect profile. Patients with extensive-stage disease who respond to initial chemotherapy also should be offered prophylactic cranial irradiation.

Unfortunately, even in the setting of significant tumor response, patients with extensive-stage SCLC will likely experience recurrent disease. The median survival following relapse of extensive disease is 4 months, but patients can still benefit from treatment depending on the timing and extent of the relapse and response to initial therapy. Patients with a good performance status who had a good response to initial therapy and whose disease progresses more than 90 days after initial treatment are most likely to benefit from second-line chemotherapy. Conversely, patients who experience relapse less than 90 days after completion of first-line chemotherapy, whose disease progresses while being treated with first-line chemotherapy, or who have a poor performance status are less likely to benefit from second-line chemotherapy. Although second-line chemotherapy can be offered, best supportive care is often more appropriate for these patients. In particular, patients with a poor performance status should not be treated with additional chemotherapy. Except in patients with extensive-stage SCLC who have experienced a late relapse following first-line therapy, combination chemotherapy is not used in the second-line setting because it provides no benefit compared with single-agent chemotherapy, and single-agent chemotherapy confers a reduced risk for side effects.

KEY POINTS

- Patients with small cell lung cancer who are considered eligible for surgery optimally have single, small primary tumors without associated lymph node involvement (T1-2 and N0) and require invasive staging of the mediastinum with endobronchial ultrasonography or mediastinoscopy to exclude occult disease.
- The mainstay of treatment for patients with limited-stage small cell lung cancer that is too advanced for surgical resection is combined chemotherapy and radiation therapy.
- Extensive-stage small cell lung cancer is treated with chemotherapy usually consisting of a platinum-containing doublet.

Head and Neck Cancer

Cancers arising in the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, paranasal sinuses, thyroid, and salivary glands are grouped together as head and neck cancer. Squamous cell carcinoma, which arises from the mucosa, constitutes 90% to 95% of cases of head and neck cancer and will be the focus of this chapter. Thyroid cancer is discussed in MKSAP 17 Endocrinology and Metabolism.

Risk Factors

Head and neck cancer constitutes approximately 3% of cancer diagnoses in the United States and is more common among men than women. Tobacco and alcohol use are well-described and potent risk factors that also can cause global mucosal

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alterations, markedly increasing the risk for second primary cancers involving other head and neck subsites. More recently, human papillomavirus (HPV) infection has emerged as an important risk factor for head and neck cancer, particularly for oropharyngeal cancer. HPV-associated oropharyngeal cancer has dramatically increased in incidence in North America over the past 30 to 40 years, accounting for 70% to 80% of oropharyngeal cancers diagnosed in the United States. This is mostly related to oral sexual contact. While not yet definitively proved, it is hoped that use of the HPV vaccine will be able to reduce the incidence of HPV-associated oropharyngeal cancers.

HPV-associated tumors differ markedly from conventional squamous cell carcinoma of the head and neck. These tumors occur almost exclusively within the oropharynx, develop in younger individuals, and are associated with a significantly improved prognosis, even when diagnosed at an advanced stage. However, despite the improved prognosis of patients with HPV-associated oropharyngeal cancer, HPV status does not currently factor into treatment decisions. Other risk factors for head and neck cancer include Epstein-Barr virus infection, HIV infection, various occupational exposures, and betel nut chewing. Persons with occupations placing them at risk for head and neck cancer include painters, wood workers, textile workers, farmers, and construction workers.

KEY POINTS

- Tobacco, alcohol, and human papillomavirus infection are important risk factors in the development of head and neck cancer.
- Human papillomavirus tumors differ markedly from squamous cell carcinoma of the head and neck as they occur almost exclusively within the oropharynx, develop in younger individuals, and are associated with a significantly improved prognosis.

Clinical Manifestations

Head and neck cancer is characterized by various presenting symptoms, many of which are nonspecific and therefore important for physicians to recognize to avoid unnecessary delays in diagnosis. An isolated neck mass is a common presentation prompting further evaluation. Other symptoms and signs suggestive of head and neck cancer are less obvious and include hearing loss (often unilateral), tinnitus, ear pain, nonhealing oral ulcers, loosening of teeth, ill-fitting dentures, throat pain, dysphagia, hoarseness, bleeding, and unilateral nasal obstruction. Weight loss also occurs in patients with more advanced disease at diagnosis.

KEY POINT

- An isolated neck mass is a common symptom in head and neck cancer and should prompt further evaluation.

Evaluation and Staging

Patients with suspected head and neck cancer require prompt referral to an otolaryngologist. The basis of diagnosis is the history and physical examination, which includes flexible fiberoptic laryngoscopy to facilitate direct visualization of the mucosa of the entire pharynx and larynx. Examination under anesthesia with diagnostic panendoscopy (laryngoscopy, bronchoscopy, and esophagoscopy) is done to obtain a biopsy, better characterize the anatomic extent of disease, and identify second primary cancers. Imaging studies, particularly CT and MRI, are important in evaluating the primary site and regional lymph nodes. PET and PET/CT are especially effective in detecting metastatic disease, and they can also help to clarify the results of MRI and CT imaging.

Staging of head and neck cancer follows the TNM staging system (**Table 59**). Although tumors arising from different anatomic locations are staged differently with regard to T stage, staging of cervical lymph node metastases is similar for all the different anatomic sites. Generally, patients with stage I and II disease have clinically negative lymph nodes, whereas patients with stage III to IVb disease have varying degrees of lymph node involvement. Stage IVc disease is typically limited to patients with distant metastatic disease. Patients with stages I and II disease are generally considered to have localized disease, whereas those with stages III and IVa disease are considered to have locally advanced disease. Although it occurs infrequently, metastatic disease must be excluded, particularly in patients with locally advanced head and neck cancer.

KEY POINTS

- The basis of diagnosis of head and neck cancer is the history and physical examination, which includes flexible fiberoptic laryngoscopy to facilitate direct visualization of the mucosa of the entire pharynx and larynx.
- In patients with head and neck cancer, imaging studies, including CT and MRI, are important in evaluating the primary site and lymph nodes, and PET and PET/CT detect metastatic disease and clarify results of CT and MRI.

Treatment

Treatment of clinical early-stage (typically stage I and II) head and neck cancer consists of surgical resection or definitive radiotherapy. One exception to this is nasopharyngeal cancer, which is treated with radiation alone for stage I disease and combined chemotherapy and radiation for stage II and higher (nonmetastatic) disease. Recurrence rates are generally similar for patients treated surgically or with radiation, and the selected modality most commonly is chosen based on expected morbidity and functional outcomes. For patients treated with surgery, the use of adjuvant radiation or combined chemotherapy and radiation is recommended based on findings at surgery. Factors indicating a need for adjuvant therapy include

(Text continued on page 100)

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TABLE 59. AJCC TNM Staging System for Head and Neck Cancer

Stage	Anatomic Sites						
	Nasopharynx	**Lip and Oral Cavity**	**Oropharynx**	**Hypopharynx**	**Supraglottis**	**Glottis**	**Subglottis**
Primary Tumor (T)							
T1	Confined to nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal extension[a]	≤2 cm	≤2 cm	≤2 cm and limited to 1 subsite of hypopharynx	Limited to 1 subsite of supraglottis with normal vocal cord mobility	Limited to vocal cord(s) with normal mobility; T1a: 1 vocal cord; T1b: both vocal cords	Limited to subglottis
T2	Parapharyngeal extension[a]	≥2-4 cm	≥2-4 cm	≥2-4 cm and/or invades >1 subsite of hypopharynx or an adjacent site and without fixation of hemilarynx	>1 area of invasion in adjacent subsite of supraglottis or glottis or region outside supraglottis without fixation of the larynx	Extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility	Extends to vocal cord(s) with normal or impaired mobility
T3	Involves bony structures of skull base and/or paranasal sinuses	>4 cm	>4 cm or extension to lingual surface of epiglottis	>4 cm or fixation of hemilarynx or extension to esophagus	Limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage	Limited to larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of thyroid cartilage	Limited to larynx with vocal cord fixation
T4a	T4 (no subcategories): Intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to infratemporal fossa/masticator space	Moderately advanced local disease[b]. Lip: invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face; Oral cavity: invades adjacent structures only	Moderately advanced local disease: invades larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible[c]	Moderately advanced local disease: invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue[d]	Moderately advanced local disease: invades through thyroid cartilage and/or invades tissues beyond larynx	Moderately advanced local disease: invades through outer cortex of thyroid cartilage and/or invades tissues beyond larynx	Moderately advanced local disease: invades cricoid or thyroid cartilage and/or invades tissues beyond larynx
T4b	n/a	Very advanced local disease: invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery	Very advanced local disease: invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery	Very advanced local disease: invades prevertebral fascia, encases carotid artery, or involves mediastinal structures	Very advanced local disease: invades prevertebral space, encases carotid artery, or invades mediastinal structures	Very advanced local disease: invades prevertebral space, encases carotid artery, or invades mediastinal structures	Very advanced local disease: invades prevertebral space, encases carotid artery, or invades mediastinal structures

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TABLE 59. AJCC TNM Staging System for Head and Neck Cancer *(Continued)*

Stage	Anatomic Sites						
	Nasopharynx	**Lip and Oral Cavity**	**Oropharynx**	**Hypopharynx**	**Supraglottis**	**Glottis**	**Subglottis**
Regional Lymph Nodes (N)[e]							
N1	Unilateral metastasis in cervical lymph node(s), ≤6 cm, above supra-clavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, ≤6 cm[f]			Single ipsilateral node ≤3 cm			
N2a	N2 (not divided into sub-categories): Bilateral metastasis in cervical lymph node(s), ≤6 cm, above supra-clavicular fossa[f]			Single ipsilateral node >3 cm and ≤6 cm			
N2b	n/a			Multiple ipsilateral nodes, none >6 cm			
N2c	n/a			Bilateral or contralateral nodes, none >6 cm			
N3	Metastasis in a lymph node(s)[f] >6 cm (N3a) and/or to supraclavicular fossa (N3b)[f,g]			One or more nodes >6 cm			
Distant Metastasis (M)							
M0	No distant metastasis			No distant metastasis			
M1	Distant metastasis			Distant metastasis			
Anatomic Stage/Prognostic Groups							
Stage I	T1N0M0			T1N0M0			
Stage II	T2N0M0 or T1-2N1M0			T2N0M0			
Stage III	T1-2N2M0 or T3N0-2M0			T3N0M0 or T1-3N1M0			
Stage IVA	T4N0-2M0			T4aN0-2M0 or T1-3N2M0			
Stage IVB	Any T,N3,M0			Any T, N3, M0 or T4b, any N, M0			
Stage IVC	Any T, any N, M1			Any T, any N, M1			

AJCC = American Joint Committee on Cancer; n/a = not applicable.

[a]Parapharyngeal extension denotes posterolateral infiltration of tumor.

[b]Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

[c]Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.

[d]Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

[e]For hypopharynx, metastases at level VII are considered regional lymph node metastases.

[f]Midline nodes are considered ipsilateral nodes.

[g]Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder. Note that this would include caudal portions of levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

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close or positive surgical margins, the presence of lymphovascular or perineural invasion, and identification of T3 or T4 disease. The expected 5-year survival rate for patients with early-stage disease is 70% to 90%, although patients with tobacco- or alcohol-related cancer have a substantial risk of developing a second primary cancer.

Initial treatment of locally advanced disease consists of surgery or combined-modality therapy, depending on the expected morbidity and functional outcomes associated with these treatments. In general, surgery is preferred for oral cavity cancers because these tumors are usually easily accessible and can be resected with good functional outcomes using modern reconstruction techniques. Locally advanced tumors arising from other anatomic sites are more commonly treated with combined-modality therapy to preserve organ function. Concurrent chemotherapy and radiation is the accepted standard of care, with sequential chemotherapy and radiation or radiation alone for patients who cannot tolerate combined-modality therapy. The most commonly used agent is high-dose cisplatin. Cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor, is also an accepted standard of care in this setting. In patients treated with combined chemotherapy and radiation, surgery for removal of the primary tumor is reserved for identification of residual cancer at the time of posttreatment assessment. Posttreatment neck dissection in patients treated with chemoradiotherapy is used only in those with residual disease in the cervical lymph nodes following treatment as assessed by PET/CT (or MRI in patients in whom contrast is contraindicated). The expected 5-year survival for patients with locally advanced disease is approximately 40% to 60%.

Patients treated with primary surgery for locally advanced disease almost always require adjuvant radiation or combined chemotherapy. Although many patients can receive radiation alone, patients with positive surgical margins or those with extracapsular extension of metastatic disease with lymph node involvement are at especially high risk of recurrence and should receive combined chemotherapy and radiation. Neck dissection is recommended based on T stage and lymph node status at diagnosis.

Chemotherapy is used in patients with metastatic disease, and treatment outcomes are generally poor, with a median survival of typically less than 1 year. Various agents are active against metastatic head and neck cancer and are chosen based on prior treatment history, timing of recurrence, and performance status. Cetuximab has also been shown to be effective in this setting as a single agent or combined with chemotherapy. Given the poor prognosis of patients with metastatic disease, early discussions about goals of care and symptom management are essential.

The treatment of head and neck cancer can result in significant functional impairment and disfigurement, dramatically affecting quality of life. Optimal management of patients with head and neck cancer requires a multidisciplinary treatment team consisting of not only physicians, but also nurses, speech and swallowing therapists, and nutritionists. Surgery can result in permanently altered speech and swallowing and disfigurement. Radiation or combined-modality therapy often causes xerostomia, thickening of saliva, mucositis, dysphagia, odynophagia, and malnutrition. Insertion of a percutaneous gastrostomy tube prior to treatment is recommended for some patients, particularly those with significant dysphagia or malnutrition at diagnosis. Late complications can include trismus, peripheral neuropathy, kidney failure, chronic pain, hypothyroidism, tooth decay, and second cancers.

KEY POINTS

- Treatment of clinical early-stage (typically stage I and II) head and neck cancer consists of surgical resection or definitive radiotherapy depending on expected morbidity and functional outcomes.
- Initial treatment of locally advanced head and neck cancer consists of surgery (most likely with adjuvant radiation or combined chemotherapy) or combined-modality therapy.
- Patients treated with primary surgery for locally advanced head and neck cancer almost always require adjuvant radiation or combined chemotherapy.
- Chemotherapy is used in patients with metastatic head and neck cancer, and treatment outcomes are generally poor, with a median survival of typically less than 1 year.

Posttreatment Surveillance

Posttreatment surveillance of patients with head and neck cancer is particularly important, especially in patients with tobacco- or alcohol-related cancers owing to the increased risk for second primary cancers. Surveillance in these patients is directed at both assessment of cancer recurrence and identification of potential second cancers. Conversely, patients with HPV-associated oropharyngeal cancer experience a much lower rate of second primary cancers.

The primary means of surveillance monitoring of patients with head and neck cancer is direct examination, most commonly by flexible fiberoptic laryngoscopy combined with conventional physical examination. Use of imaging, other than to establish a posttreatment baseline assessment, is recommended only as signs or symptoms warrant. Posttreatment surveillance should be done every 1 to 3 months for the first year, every 2 to 6 months for the second year, every 4 to 8 months for years 3 through 5, and yearly thereafter. Tobacco and alcohol cessation counseling is a vital component of posttreatment care because continued cigarette smoking or alcohol use is associated with decreased head and neck cancer–specific survival. Other recommendations include assessment of thyroid function every 6 to 12 months for patients treated with neck radiation and periodic dental evaluation for those treated with oral cavity radiotherapy. Speech, hearing, and swallowing

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evaluations are also performed as needed. Low-dose CT surveillance should be considered for patients with a history of alcohol- or tobacco-related cancer because of the documented survival benefit associated with its use in this setting.

KEY POINTS

- The primary means of surveillance monitoring of patients with head and neck cancer is direct examination, most commonly by flexible fiberoptic laryngoscopy combined with conventional physical examination.
- Tobacco and alcohol cessation counseling is a vital component of posttreatment care of patients with head and neck cancer because continued cigarette smoking or alcohol use is associated with decreased head and neck cancer–specific survival

Genitourinary Cancer

Prostate Cancer

Epidemiology and Risk Factors

Prostate cancer is the second most common cancer in the United States, with an estimated 238,590 cases diagnosed in 2013. The mortality rate of prostate cancer is disproportionally low to its high incidence. The incidence of prostate cancer varies significantly throughout the world, although these data are confounded significantly by the use of prostate-specific antigen (PSA) screening (see MKSAP 17 General Internal Medicine for a discussion of current issues relating to PSA screening).

Risk factors for developing prostate cancer are numerous and include ethnicity, certain genetic and dietary factors, and age, the most important risk factor. Currently available data indicate markedly increasing prostate cancer prevalence with advancing age. Black men have a significantly higher age-adjusted incidence of prostate cancer than white or Hispanic men and receive a diagnosis at an earlier age, with a higher serum PSA level and Gleason score, and they have more advanced disease at diagnosis.

KEY POINT

- Risk factors for developing prostate cancer are numerous and include ethnicity, certain genetic and dietary factors, and age, which is the most important risk factor.

Diagnosis and Staging

An estimated 80% of newly diagnosed cases of prostate cancer in the United States are based on initial identification of an elevated serum PSA level. However, digital rectal examination (DRE) remains an important component of diagnosis because 20% of men diagnosed with prostate cancer undergo biopsy after identification of a palpable nodule on DRE. In addition to identification of actual nodules on DRE, prostate asymmetry or focal induration should prompt referral for biopsy, regardless of the serum PSA level. Prostate biopsy is performed by urologists, commonly using transrectal ultrasonography for guidance. Twelve specimens are taken, with six samples taken from each lobe. A negative biopsy, although reassuring, does not exclude prostate cancer, and in a man with an elevated PSA level or abnormal findings on DRE, close follow-up with possible repeat biopsy is warranted.

Mostly all cases of prostate cancer are adenocarcinomas (approximately 95%), which will be the focus of this section. Other histologies include transitional cell carcinoma, small cell carcinoma, and lymphoma. Important components of the pathology report include the Gleason score, the location and extent of cancer, and the presence of perineural invasion and extraprostatic extension. The Gleason score is a scoring system in which architectural features of prostate cancer cells are graded, with 1 representing the most well-differentiated histology and 5 representing the least well-differentiated histology. Two scores, representing the two most prevalent differentiation patterns identified in a biopsy specimen, are added together to derive a composite score (for example, 3 + 4 = 7). The most prevalent differentiation pattern identified is listed first. The Gleason score has been correlated closely with the prevalence of nonorgan-confined disease and outcomes after definitive local therapy.

Staging of prostate cancer follows the TNM system. The most common stage at diagnosis is T1c, referring to clinically silent prostate cancer diagnosed on the basis of an elevated serum PSA level. Clinical staging is based on information obtained from the prostate biopsy, DRE, and, in some patients, imaging studies. Use of these data, along with the serum PSA level and Gleason score, facilitates risk stratification into five different risk categories (**Table 60**). This information is instrumental in guiding decisions on the need for imaging evaluation and local therapy. Imaging studies to assess for possible metastatic disease or regional lymph node involvement are only indicated for men with poor-risk features (typically men with intermediate, high, or very high–risk cancer).

KEY POINTS

- A negative biopsy, although reassuring, does not exclude prostate cancer; patients with an elevated serum prostate-specific antigen level or abnormal findings on digital rectal examination require close follow-up with possible repeat biopsy.
- In patients with prostate cancer, imaging studies to assess for possible metastatic disease or regional lymph node involvement are only indicated for men with poor-risk features (typically men with intermediate, high, or very high–risk cancer). HVC

Treatment

Management options in men with clinically localized prostate cancer include observation, active surveillance, radiation therapy, brachytherapy, and radical prostatectomy. Active

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TABLE 60. Prostate Cancer Risk Stratification

Risk Category	Definition
Very Low	Stage T1c, serum PSA <10 ng/mL (10 µg/L), Gleason score ≤6, fewer than 3 biopsy cores positive, ≤50% cancer in each core, PSA density <0.15 ng/mL/g
Low	T1-T2a, Gleason score ≤6, PSA <10 ng/mL (10 µg/L)
Intermediate	T2b-T2c OR Gleason score 7 OR PSA 10-20 ng/mL (10-20 µg/L)
High	T3a OR Gleason score 8-10 OR PSA >20 ng/mL (20 µg/L)
Very High	T3b-T4, primary Gleason pattern 5, >4 cores with Gleason score 8-10

PSA = prostate-specific antigen.

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surveillance is the postponement of definitive local therapy coupled with surveillance using serum PSA measurement, DRE, and repeat prostate biopsy. It is only appropriate for men with very low-risk or low-risk prostate cancer with a life expectancy of at least 10 years. Men undergoing active surveillance receive referral for definitive local therapy if there is any evidence of disease progression. As of this writing, no randomized trials have compared the use of active surveillance with initial, definitive local therapy.

Options for local therapy include external-beam radiotherapy, brachytherapy, and radical prostatectomy. At the present time, there are no data supporting the use of proton beam radiotherapy in the treatment of prostate cancer. Unfortunately, no randomized trials to date have compared treatment outcomes or incidence of complications among these modalities. Furthermore, comparison of different studies is complicated by selection bias. However, some conclusions can be drawn. For men with low-risk, clinically localized prostate cancer, all three modalities offer excellent disease control. Radiation is often associated with symptoms of urinary irritation (urgency, frequency, dysuria), with brachytherapy causing these symptoms more commonly than external-beam radiotherapy. Radical prostatectomy is more commonly associated with urinary incontinence, with approximately 60% to 70% of patients having urinary leakage 2 months following surgery. Problems with sexual function are frequent in men treated with both radiation and surgery, although these complications occur more commonly following surgery. Bowel complications are associated with radiation therapy and include increased urgency, increased frequency, and diarrhea; however, these complications occur in only approximately 10% to 20% of men. Prostate cancer treatment-related complications occur most commonly in the first few months after treatment, and they improve or resolve over time in most men.

Men with intermediate and high-risk disease, who were treated with surgery, should be treated with adjuvant androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) if found to have lymph node metastasis. For men treated with external beam radiation, those with high-risk disease should be treated with ADT with a GnRH agonist for 2 to 3 years, while those with intermediate risk disease only require treatment for 4-6 months. For all men who have completed local therapy, follow-up monitoring for relapse and treatment-related complications is vital. Follow-up monitoring consists of a history and physical examination with serum PSA measurement. After radical prostatectomy, the serum PSA level should be undetectable; a PSA of 0.2 ng/mL (0.2 µg/L) or greater indicates active prostate cancer. However, after radiation therapy, the serum PSA level declines to a nadir but does not typically become undetectable; a PSA rise of 2 ng/mL (2 µg/L) or more above the nadir is considered a recurrence following radiotherapy.

Patients with a biochemical recurrence (a rising serum PSA level and no evidence of local disease progression) are treated with ADT, but the optimal timing of therapy remains to be defined. Studies have indicated that early initiation of therapy, before identification of clinical evidence of metastasis, is associated with decreased prostate cancer mortality rates but no improvement in overall survival. ADT consists of inhibiting androgen synthesis by using a GnRH agonist or blocking the androgen receptor with an antiandrogen agent. Bilateral orchiectomy is a reasonable alternative to GnRH agonist therapy, particularly in the very elderly. Initial treatment consists of a GnRH agonist alone or a GnRH agonist with an antiandrogen agent (a so-called complete androgen blockade). ADT is associated with a response rate of 80% to 90%. As of this writing, no evidence supports one approach over the other, and consensus guidelines indicate that either is appropriate. ADT is associated with significant side effects, including fatigue, loss of muscle mass, osteoporosis, dyslipidemia, hyperglycemia, and sexual dysfunction. Although intermittent androgen deprivation has been studied as a means of limiting ADT-associated morbidity, insufficient evidence exists indicating an improvement in morbidity without sacrificing efficacy; therefore, this approach is not recommended as a routine standard of care.

KEY POINTS

- Active surveillance, with the use of serum prostate-specific antigen measurement, digital rectal examination, and repeat prostate biopsy, is appropriate only for men with very low-risk or low-risk prostate cancer who have a life expectancy of at least 10 years. HVC
- Options for local therapy of patients with prostate cancer include external-beam radiotherapy, brachytherapy, and radical prostatectomy; proton beam radiotherapy is not recommended.

(Continued)

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KEY POINTS *(continued)*

- Any identifiable level of prostate specific antigen (PSA) following surgery indicates active prostate cancer, whereas a progressive increase in the serum PSA level is required to demonstrate recurrence following radiotherapy.

Metastatic Prostate Cancer

Metastatic disease invariably develops in men with a biochemical recurrence. The most common site of metastasis is bone, and men with osseous metastatic disease are at risk for pain and fracture. Treatments available to target bone metastases include external-beam radiotherapy and bone-targeted radiopharmaceutical agents. Radiation is most appropriate for men with pain limited to one or a few metastatic sites. For men with multifocal bone pain due to metastatic disease, treatment with a radiopharmaceutical agent is indicated. Radium-223 has recently been approved by the FDA for this indication, and it has been shown to relieve symptoms and improve overall survival. Another important treatment for men with osseous metastatic disease is osteoclast inhibition. This form of therapy, using zoledronic acid or denosumab, reduces the incidence of skeletal-related events such as fracture or pain and mitigates bone loss due to ADT.

Whether they are being treated for biochemical recurrence or overt metastatic disease, men who receive ADT eventually experience disease progression. Prostate cancer that progresses despite ADT is considered castrate resistant. Disease in men who are treated with only a GnRH agonist may respond to the addition of an antiandrogen agent in this setting. In addition, castrate-resistant disease may be responsive to secondary endocrine therapies, including ketoconazole, megestrol, glucocorticoids, and estrogens. In addition, two newer therapies that target pathways of androgen biosynthesis have recently been approved by the FDA for treatment of castrate-resistant prostate cancer: abiraterone and enzalutamide. Both of these agents have been shown to improve overall survival in placebo controlled trials. Sipuleucel-T, an autologous dendritic cell–based therapeutic vaccine, has also been shown to improve survival in men with asymptomatic or minimally symptomatic castrate-resistant metastatic prostate cancer. Patients whose disease does not respond to these therapies or in whom disease progresses after an initial response eventually require chemotherapy. Docetaxel plus prednisone is the most commonly used first-line regimen. This combination has been found to improve survival compared with mitoxantrone, which was the standard of care previously. Cabazitaxel is a newer taxane that also has demonstrated efficacy in the treatment of metastatic castrate-resistant prostate cancer. Although chemotherapy is effective in patients with advanced prostate cancer, the median survival of such patients is less than 2 years. Given this prognosis, the use of chemotherapy in the setting of metastatic castrate-resistant prostate cancer should be discussed within the context of goals of care and palliative care.

KEY POINTS

- In patients with prostate cancer, zoledronic acid and denosumab reduce the incidence of skeletal-related events such as fracture or pain and mitigate bone loss due to androgen deprivation therapy.
- Painful bone metastases in patients with prostate cancer can be treated with external-beam radiotherapy and bone-targeted radiopharmaceutical agents.
- Patients with a biochemical recurrence of prostate cancer (a rising serum prostate-specific antigen level and no evidence of local disease progression) are treated with androgen deprivation therapy.

Testicular Cancer

Although the most common cancer among male adolescents and men aged 15 to 35 years, testicular cancer is rare among cancers, accounting for only 1% of all adult cancers in the United States. Testicular cancer management represents a true success story among solid tumors because it has been one of the most curable cancers since the late 1970s. The 5-year survival rate for all patients with testicular germ cell tumors is approximately 95%. Mostly all testicular cancers are germ cell tumors, which will be discussed in this section. Germ cell tumors can be pure seminomas or nonseminomas.

For most men, testicular cancer symptoms are attributable to local disease and include testicular swelling, identification of a testicular mass, or, occasionally, a dull pain in the lower abdomen, perianal region, or scrotum. Occasionally, men will present with symptoms caused by metastatic disease. Physical examination typically reveals a firm, often painless, testicular mass.

After a palpable mass is identified, testicular ultrasonography is performed to confirm the presence of a solid mass, following which radical inguinal orchiectomy is usually performed. Needle biopsy is contraindicated, as this can result in an increased recurrence rate. In conjunction with histologic sampling, it is important to measure serum tumor marker levels, which include β-human chorionic gonadotropin, lactate dehydrogenase, and α-fetoprotein. The serum α-fetoprotein level is never elevated in patients with pure seminomas, and β-human chorionic gonadotropin is only elevated in approximately 20% of patients with pure seminomas. Nonseminomatous germ cell tumors can contain elements of seminoma, but those elements are mixed with tumors with nonseminomatous histologies, which include yolk sac tumor, choriocarcinoma, and embryonal carcinoma. This distinction is important for determining the correct treatment. Once a diagnosis is made, a clinical stage is determined by tumor marker assessment and CT to identify metastatic disease and assess retroperitoneal lymph nodes.

Treatment depends on stage, histology, and, in patients with advanced disease, risk assessment based on disease extent and tumor marker levels. Because many testicular cancer treatments can affect future fertility, obtaining a sperm

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count and discussing sperm banking should occur before treatment is initiated unless treatment needs to start emergently. For patients with seminoma confined to the testis (stage I), orchiectomy is usually curative. Options following surgery include active surveillance, single-agent carboplatin, and radiation to para-aortic lymph nodes. Active surveillance consists of regular tumor marker and imaging assessments with the purpose of evaluating for evidence of recurrence. Patients with stage II seminomas receive adjuvant radiotherapy or cisplatin-based chemotherapy depending on the extent of lymphadenopathy. Conversely, in patients with stage I nonseminomatous germ cell tumors, depending on pathologic risk factors, post-surgical therapy can include active surveillance, one cycle of cisplatin-based chemotherapy, or retroperitoneal lymph node dissection (RPLND). High-risk patients usually receive RPLND or chemotherapy. Patients with stage II disease receive RPLND if retroperitoneal lymph nodes are small, with possible adjuvant chemotherapy depending on the extent of disease identified at surgery. For patients with bulky retroperitoneal lymphadenopathy identified on CT, cisplatin-based chemotherapy is recommended. Treatment of advanced disease depends on both histology and risk assessment based on clinical extent of disease and tumor marker levels. All patients with advanced disease receive chemotherapy, most commonly bleomycin, etoposide, and cisplatin, given for three to four cycles. Following treatment, patients are observed closely with periodic history, physical examination, and imaging and tumor marker assessments. For patients with residual radiographic abnormalities following treatment, surgery is sometimes recommended. Patients with relapsed or refractory disease are treated with salvage chemotherapy, and sometimes, autologous hematopoietic stem cell transplantation.

Survivorship issues are particularly important in men with testicular germ cell tumors because of the risk for various treatment-related complications, such as infertility from chemotherapy or RPLND, and the risk for second cancers, including some solid tumors and acute leukemia. There is an increased risk for metabolic syndrome (insulin resistance, hypertension, dyslipidemia, abdominal obesity) after chemotherapy or radiation treatment. Other potential complications include pulmonary toxicity, kidney failure, peripheral neuropathy, ototoxicity, Raynaud phenomenon, and cardiovascular disease.

KEY POINTS

- For most patients with testicular cancer, symptoms are attributable to local disease and include testicular swelling, a testicular mass, or occasionally, a dull pain in the lower abdomen, perianal region, or scrotum.
- After a palpable testicular mass is identified, patients undergo testicular ultrasonography to confirm the presence of a solid mass, following which radical inguinal orchiectomy is usually performed.
- For patients with seminoma confined to the testis (stage 1), orchiectomy is usually curative.

Renal Cell Carcinoma

Renal cell carcinomas arise in the renal cortex and are the most common type of tumors affecting the kidney. The next most common tumor, transitional cell carcinoma of the renal pelvis, is not considered a renal cell carcinoma and is treated similarly to bladder cancer. Patients with renal cell carcinoma are often asymptomatic until they have advanced disease, but possible symptoms include hematuria, an abdominal mass, abdominal pain, and unexplained weight loss. However, the classic triad of flank pain, hematuria, and a palpable abdominal mass occurs in only approximately 9% of patients. Incidental identification of asymptomatic renal mass lesions has been occurring with increasing frequency owing to the large number of abdominal ultrasounds and CT scans done for other reasons.

Renal cell carcinoma has been associated with various paraneoplastic syndromes, including erythrocytosis, AA amyloidosis, polymyalgia rheumatica, and hepatic dysfunction. For patients with symptoms suggestive of renal cell carcinoma, radiographic evaluation with abdominal ultrasonography or CT is recommended. Identification of a solid mass or complex cyst requires further intervention. Small lesions should be biopsied if possible. Larger lesions can be removed without biopsy if imaging findings are consistent with malignancy. Additionally, CT to evaluate the local disease extent and assess for metastatic disease is also recommended.

Patients with nonmetastatic disease undergo radical or partial nephrectomy. For patients who are not surgical candidates, active surveillance or ablative treatment can be considered for those with small tumors. No established adjuvant therapy for renal cell carcinoma is available, although studies using targeted agents are ongoing; consequently, patients with localized renal cell carcinoma are observed following surgery regardless of the local extent of disease. Selected patients with metastatic disease at presentation undergo cytoreductive nephrectomy, which has been associated with improved survival in some studies. Patients with lung-only metastasis and good performance status benefit most. Common sites of metastasis in renal cell carcinoma are the lung, liver, bone, and renal fossa.

Previously, metastatic renal cell carcinoma treatment was disappointing because responses to cytotoxic chemotherapy were limited and survival was often short. Although interleukin-2 can result in long-term remission in about 10% of patients, this agent is expensive, not widely available, and is associated with significant toxicity. However, because of rapidly expanding knowledge about the molecular pathogenesis of renal cell carcinoma, multiple targeted therapies are now available, and many of these agents have been shown to have significant activity against renal cell carcinoma. These agents are categorized as vascular endothelial growth factor (VEGF) inhibitors and mammalian target of rapamycin (mTOR) inhibitors. VEGF inhibitors include bevacizumab and various VEGF tyrosine kinase inhibitors, such as sunitinib,

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sorafenib, pazopanib, and axitinib. The mTOR inhibitors include temsirolimus and everolimus. Unfortunately, no studies comparing any of these agents have been published to date. Most patients receive a VEGF tyrosine kinase inhibitor in the first-line setting. Those with high-risk disease, which is determined by performance status, elevated serum lactate dehydrogenase level, elevated serum calcium level, and anemia, are often treated with an mTOR inhibitor, although sunitinib is also active against high-risk disease. Agents with demonstrated activity in second-line treatment include axitinib, sorafenib, and everolimus. Bevacizumab, a monoclonal antibody directed against VEGF, can also be used with interferon alfa in first-line treatment or as a single agent in second-line or later treatment.

KEY POINTS

- The classic triad of flank pain, hematuria, and a palpable abdominal mass occurs only in approximately 9% of patients with renal cell carcinoma.
- For patients with suspected renal cell carcinoma, radiographic evaluation with abdominal ultrasonography or CT is recommended, with histologic sampling done on identification of a kidney lesion that is characterized by a mass or a complex cyst.
- Patients with nonmetastatic renal cell carcinoma undergo radical or partial nephrectomy.
- The response of metastatic renal cell carcinoma to traditional cytotoxic chemotherapy is limited and associated with short survival; however, multiple targeted therapies, including vascular endothelial growth factor inhibitors, have significant activity against renal cell carcinoma and may improve survival in select patients.

Bladder Cancer

Bladder cancer is the most commonly diagnosed cancer of the urinary tract. In the United States, almost all bladder cancer is transitional cell carcinoma, which will be the focus of this section. The incidence of bladder cancer has increased by more than 50% during the past 20 to 30 years. Risk factors include advanced age, white ethnicity, various occupational exposures, and cigarette smoking; smoking is the most important risk factor and encompasses current and former smokers and individuals exposed to second-hand smoke. Individuals at occupational risk include metal workers, painters, miners, textile workers, and leather workers, among others.

The most common presenting symptom is painless hematuria, although some patients experience other urinary symptoms, such as frequency, urgency, or dysuria. Identification of new-onset hematuria in patients older than 40 years mandates urologic evaluation with cystoscopy. Biopsy or resection can be performed during initial cystoscopy, depending on the status of the lesion. Most bladder cancer is superficial and does not invade into muscle. These lesions often can be treated locally with transurethral resection of the bladder tumor. Following resection, additional treatment with intravesical bacillus Calmette-Guérin or chemotherapy is usually given, with the amount of treatment determined by risk assessment. The risk of recurrence and of new primary tumors is high following a diagnosis of superficial bladder cancer; consequently, careful surveillance is essential following initial treatment.

Cystectomy is recommended only for patients with frequent, high-grade recurrences occurring within a short period. Conversely, patients with muscle-invasive disease often are treated with radical cystectomy, although bladder-sparing approaches can be considered in some patients. Neoadjuvant cisplatin-based chemotherapy is also recommended, as it can improve survival in patients with muscle-invasive disease; however, the role of adjuvant chemotherapy is much less clear.

Treatment outcomes for patients with metastatic bladder cancer are disappointing. Although cisplatin-based regimens have been shown to improve survival, cures are uncommon, and median survival is only about 15 months.

KEY POINTS

- Identification of new-onset hematuria in patients older than 40 years mandates urologic evaluation with cystoscopy.
- Most bladder cancer is superficial, does not invade into muscle, and can usually be treated locally with transurethral resection of the bladder tumor.
- Patients with muscle-invasive bladder cancer often are treated with radical cystectomy, although bladder-sparing approaches can be considered in some patients.

Lymphoid Malignancies

Epidemiology and Risk Factors

Transient palpable lymphadenopathy is a common physical finding, particularly among young patients, and is virtually always benign, with less than 1% of cases persisting and later found to be lymphoma. Local or systemic infection with bacteria or viruses, drug reactions, and autoimmune disease can all be characterized by transient lymphadenopathy.

Lymphoma is the most common subtype of the hematologic malignancies and is heralded by lymphadenopathy. The fifth most common malignancy, lymphoma constitutes 5% of all cancers and 3% of cancer-related deaths in the United States. In 2013, the American Cancer Society estimated there would be 79,030 new cases of lymphoma diagnosed in the Unites States, 88% of which would be non-Hodgkin lymphoma (NHL) and 12% of which would be Hodgkin lymphoma. The incidence of lymphoma has doubled over the past 30 years; however, Surveillance Epidemiology and End Result statistics (SEER) reported a drastic improvement in 5-year relative survival rates for both non-Hodgkin (47% in 1975-1977

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versus 71% in 2002-2008) and Hodgkin lymphoma (72% in 1975-1977 versus 87% in 2002-2008).

NHL occurs more often in men, and the incidence increases with age. Hodgkin lymphoma has a bimodal age distribution, occurring between ages 15 and 45 years and after age 55 years. The cause of some subtypes of lymphoma remains unknown. One exception is mucosa-associated lymphoid tissue (MALT) lymphoma, which is caused by an underlying infection with *Helicobacter pylori*. Other infections, including Epstein-Barr virus, HIV, human T-cell lymphotrophic virus type-1 (HTLV-1), and hepatitis B and C viruses, can also directly drive transformation of lymphoid tissue to lymphoma or contribute indirectly to transformation by causing immunodeficiency, which is also a risk factor for lymphoma. For example, patients who receive immunosuppressive drugs such as cyclosporine or tacrolimus following transplantation may develop lymphoproliferative disorders that evolve to high-grade B-cell NHL.

In addition to chronic inflammation caused by infectious agents, genetic factors and occupational risk factors predisposing to lymphoma include exposure to herbicides, chlorinated organic compounds, and other fertilizing material used in farming. Hodgkin lymphoma survivors have an increased lifetime risk of acquiring NHL, presumably because of the lifelong T-cell defect associated with Hodgkin lymphoma.

KEY POINTS

- The cause of some lymphoma subtypes is underlying infection, including *Helicobacter pylori,* Epstein-Barr virus, HIV, human T-cell lymphotrophic virus type-1, and hepatitis B and C virus infections.
- In addition to chronic inflammation caused by infectious agents, genetic factors and occupational risk factors predisposing to lymphoma include exposure to herbicides, chlorinated organic compounds, and other fertilizing material used in farming.

Evaluation and Diagnosis

Initial workup of patients with lymphadenopathy includes a detailed history of recent travel, insect bites, sexual encounters, injection drug use, blood product transfusions, and all new medications. Fever, night sweats, or unexpected weight loss should be documented. A comprehensive physical examination determines the number of sites, size (small versus large), and consistency (firm and fixed versus soft and moveable) of lymphadenopathy. In addition, careful assessment for enlarged Waldeyer tonsillar ring nodes and hepatic and splenic enlargement is warranted. Patients with soft, small, freely moveable lymph nodes that are limited to one or two adjacent sites and who have no other significant history or physical examination findings can be followed with serial examinations over 6 to 8 weeks and require no other laboratory studies or imaging. Persistent or enlarging lymphadenopathy, particularly when associated with systemic symptoms, may require further assessment, including a chest radiograph, complete blood count with differential, and a serum chemistry panel.

To establish a diagnosis of lymphoma, it is optimal to perform an excisional biopsy to preserve lymph node architecture. Core needle biopsy can be used for deep lymph nodes in place of excision, but fine-needle aspiration should be avoided. The biopsy specimen is used for histopathologic, cytogenetic, fluorescence in situ hybridization (FISH), and immunophenotypic analysis and gene expression profiling. Routine blood tests should include a complete blood count with differential, erythrocyte sedimentation rate, and chemistry panel, including serum urate levels. Serum levels of lactate dehydrogenase, β_2-microglobulin, and immune globulins should also be assessed to assist in diagnosis and establish prognosis. Screening for viral infections, including hepatitis B and C viruses, HIV, HTLV-1, human herpesvirus-8, Epstein-Barr virus, and when indicated in gastric lymphoma, *H. pylori* infection, is appropriate to identify possible causative drivers of lymphoma.

After a histologic diagnosis of lymphoma is made, a total-body PET/CT scan and an iliac crest bone marrow biopsy are done to complete staging. Patients with aggressive lymphoma with involvement of the testes, sinuses, bone marrow, and ocular sites require a lumbar puncture owing to an increased risk for central nervous system involvement.

KEY POINTS

- Patients with small, soft, freely moveable lymph nodes that are limited to one or two adjacent sites and who have no other significant history or physical examination findings can be followed with serial examinations and require no laboratory studies or imaging. HVC
- Persistent or enlarging lymphadenopathy, particularly when associated with systemic symptoms, may require further assessment, including a chest radiograph, a complete blood count with differential, a serum chemistry panel, and assessment for viral infections.
- Excisional biopsy and core biopsy for deep lymphadenopathy are appropriate for diagnosing lymphoma; however, fine-needle aspiration should not be used.

Classification, Staging, and Prognosis of Malignant Lymphoma

NHL consists of more than 20 lymphoma subtypes defined by cell surface antigen expression and other morphologic features, including unique molecular profiles. NHL falls into two categories based on a B-cell immunophenotype or a T-cell or natural killer (NK)–cell lineage immunophenotype. B-cell lymphomas account for 85% of all cases of NHL, with T-cell (13%) and NK-cell (2%) lymphomas constituting the remainder. Classification of NHL and Hodgkin lymphoma is summarized in the 2008 World Health Organization 2008 classification system.

Staging of lymphoma consists of structural disease assessment using physical examination, CT imaging, and biopsy of

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potential disease sites and disease activity assessment using PET scanning to quantify the standard uptake value (SUV). SUV activity is an indicator of glucose uptake and metabolism, with more aggressive, quickly growing lymphomas using more glucose and thus associated with a higher SUV score. The Ann Arbor staging criteria can be used for determining disease extent for most forms of lymphoma (**Figure 16**).

Lymphomas are classified into three prognostic groups: indolent, aggressive, and highly aggressive. Traditional methods of staging used for other cancers are inadequate for prognosis and treatment planning for NHL. Because of this, the International Prognostic Index (IPI) was developed which generates a score based on patient age, performance status, serum lactate dehydrogenase level, disease stage, and degree of extranodal involvement. The IPI score correlates with progression-free and overall survival after standard therapy, and separate IPI scoring systems have been developed for diffuse large B-cell lymphoma (DLBCL) (revised IPI), mantle cell lymphoma (MIPI), and follicular lymphoma (FLIPI); however, new therapies, plus treatment with rituximab, have lessened the predictive value of these indices.

Indolent lymphomas may not require therapy for decades but are difficult to cure. Conversely, aggressive lymphomas, and particularly, highly aggressive lymphomas such as Burkitt lymphoma, require immediate therapy and often can be cured. Newer modalities of prognostic testing are available, including next-generation sequencing that assesses major portions of tumor genomes to identify mutations predictive of outcome to available therapies. Consequently, classic staging and IPI scores will likely become less relevant over time.

KEY POINTS

- The Ann Arbor staging criteria can be used for determining extent of disease for most forms of lymphoma.
- Use of International Prognostic Index (IPI) scores can help determine the prognosis of patients with diffuse large B-cell lymphoma (revised IPI), mantle cell lymphoma (MIPI), and follicular lymphoma (FLIPI), although new therapies, in addition to treatment with rituximab, have lessened the predictive value of these indices.

Overview and Treatment of Indolent Lymphomas

Follicular Lymphoma

Follicular lymphoma constitutes 20% of all cases of NHL in the United States and Europe and 70% of all cases of indolent

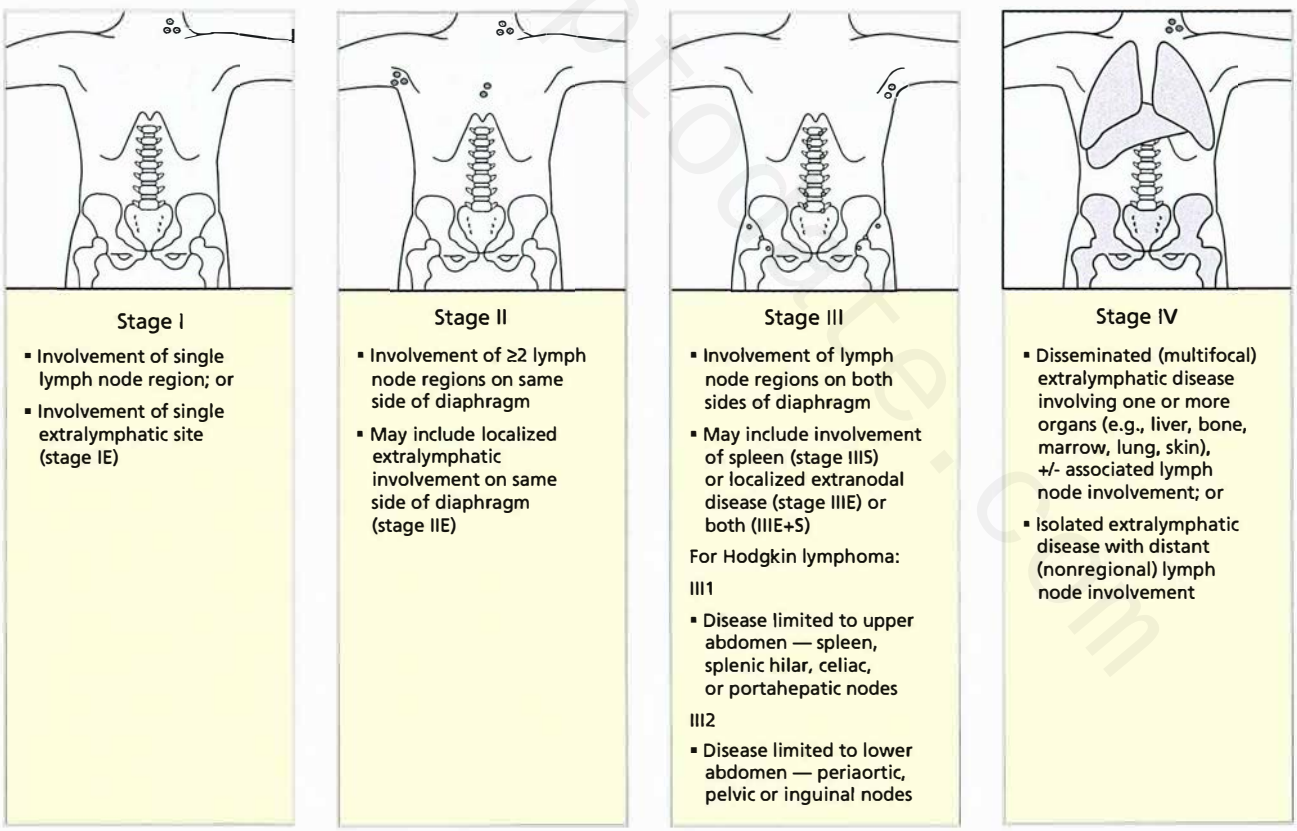

FIGURE 16. Ann Arbor Staging System for Hodgkin and non-Hodgkin lymphoma.

Reprinted with permission from DeVita, VT, Lawrence TS, Rosenberg SA. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology* 9th Ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

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NHL, ranking second in incidence to DLBCL (30%). Follicular lymphoma is characterized by the presence of surface B-cell markers (CD10, 19, 20, and 22) and small cells on morphologic analysis. Incidence increases with increasing age (median age at presentation, 60 years). Invariably, patients present with advanced-stage disease, including bone marrow involvement (stage IV). However, unlike patients with large cell lymphoma, patients with follicular lymphoma have an indolent clinical course (that is, disease is slow to progress), with most patients having lymphadenopathy but no other symptoms at presentation, and some patients not requiring therapy for decades. Diagnosis is confirmed by biopsy of a palpable lymph node and cytogenetic analysis identifying a translocation [t(14:18)] that causes an overexpression of the *BCL2* oncogene.

An international prognostic score specific for follicular lymphoma (FLIPI) has been created that provides prognostic information and helps to guide therapeutic choices. Routinely, therapy is withheld until patients become symptomatic because it is generally not curative, and early initiation of therapy does not change long-term prognosis. Disease causing localized symptoms can be treated effectively with involved-field radiation therapy combined with rituximab. Symptomatic systemic disease requires multiagent therapy that traditionally includes rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP); or rituximab and bendamustine. Radioimmunoconjugates that consist of an anti-CD20 antibody directed against CD20-expressing lymphoma and that deliver targeted cytotoxic radiation by being conjugated with a radioisotope (tositumomab and ibritumomab) have been used effectively to induce long-term remissions. Autologous and allogeneic hematopoietic stem cell transplantation (HSCT) is used in younger patients with advanced symptomatic follicular lymphoma whose disease is responsive to standard chemotherapy. Allogeneic transplantation remains the only curative therapy but is associated with a significant risk for morbidity and mortality. New therapeutic approaches include maintenance rituximab for 2 years after completion of rituximab and chemotherapy. Combining rituximab with immune modulators such as lenalidomide may also be effective and may eliminate the need for cytotoxic chemotherapy. Salvage therapy with ibrutinib, a Bruton tyrosine kinase inhibitor, has recently been shown to be highly effective.

KEY POINTS

- The clinical course of patients with follicular lymphoma is usually indolent, with most patients having lymphadenopathy but no symptoms at presentation, and some patients requiring no therapy for decades.
- Allogeneic hematopoietic stem cell transplantation remains the only curative therapy for follicular lymphoma but is associated with a significant risk for morbidity and mortality.

Mucosa-associated Lymphoid Tissue Lymphoma

MALT lines the entire gastrointestinal tract, providing for immune surveillance and initiating immunologic responses to pathogens. Chronic antigen stimulation can lead to clonal expansion of MALT and progress to malignant transformation manifesting as lymphoma. The lymphoma originates in B cells in the marginal zone of MALT and expresses the CD20 surface antigen. The clinical course of MALT lymphoma is usually indolent, and presentation is usually localized. Gastric MALT lymphoma occurs most commonly, but MALT lymphoma can occur throughout the gastrointestinal tract and can also be characterized as extranodal marginal-zone lymphoma when involving a tissue independent of a lymph node. Constituting 50% of all cases of gastric lymphomas, gastric MALT lymphomas usually are localized (stage I and II) and almost always (70% to 98%) are caused by chronic inflammation of an ulcer bed resulting from infection with *H. pylori* diagnosed by upper endoscopy and biopsy. Strikingly, complete remissions are achieved in greater than 70% of patients with limited disease without chemotherapy after completion of antimicrobial therapy directed against *H. pylori* infection and concomitant proton pump inhibitor treatment.

For MALT lymphoma that is not localized to the stomach, or rarely, that is localized to the stomach but does not respond to eradication of *H. pylori* infection, surgical removal, involved-field radiation therapy, and, when indicated, anti-CD20–directed therapy with R-CVP may be effective. Isolated splenic MALT lymphoma is characterized by asymptomatic splenomegaly, circulating lymphocytosis, and a low level of monoclonal serum proteins. Complete responses can occur following splenectomy.

Patients with chronic autoimmune disease, such as Sjögren syndrome or Hashimoto thyroiditis, can present with MALT lymphoma of the salivary glands and thyroid, respectively. Other less frequent sites of presentation include the orbits, lungs, and bladder, all usually associated with a form of chronic inflammation. The large cell variant of MALT lymphoma requires the aggressive chemotherapy used to treat DLBCL.

KEY POINTS

- In patients with mucosa-associated lymphoid tissue lymphoma, complete remission is achieved in most patients with limited disease without chemotherapy after completion of antimicrobial therapy directed against *Helicobacter pylori* infection and concomitant proton pump inhibitor therapy.
- For mucosa-associated lymphoid tissue lymphoma that is not localized to the stomach or is not responsive to *Helicobacter pylori* infection eradication, treatment includes surgical removal, involved-field radiation therapy, and, when indicated, anti-CD20–directed therapy with rituximab combined with multiagent chemotherapy.

HVC

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Chronic Lymphocytic Leukemia

B-cell chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia, accounting for 10% of hematologic malignancies. Patients with CLL present at a median age of 70 years, and, with newer therapies, median survival for affected patients is approaching that of age-matched controls. Patients are usually asymptomatic at presentation, with CLL identified by a relative lymphocytosis on a routine complete blood count. Although common in western countries, CLL occurs uncommonly in Japan and China and usually is characterized by a T-cell phenotype. Younger patients develop CLL less frequently, and, when they do, they usually have more aggressive disease. No definitive causative factors are associated with CLL, although it is more common among first-degree relatives.

Diagnosis is confirmed by flow cytometry indicating co-expression of cell surface antigens CD5 and CD23. Several staging criteria from the Rai or Binet staging systems are used. Early-stage disease (stage 0) is limited to patients with elevated lymphocyte counts, mid-stage disease (stage I and II) is associated with lymphadenopathy and splenomegaly, and late-stage disease (stage III and IV) is characterized by suppression of normal hematopoiesis (anemia and thrombocytopenia).

Prognosis is determined by gene mutation status (immune globulin variable heavy-chain mutation) and FISH or array-based karyotyping. In patients with CLL, a deletion of chromosome 17p is concerning because it is associated with a short median survival (<3 years). Whether to initiate therapy depends on several factors, including disease stage, patient age and comorbidities, lymphocyte doubling time, and other prognostic markers. Asymptomatic patients with low-stage disease (stage 0 to II) can be observed without therapy, often for decades. When therapy is indicated, the goal in most patients is palliation. Combination therapy with rituximab and multiagent chemotherapy (fludarabine, cyclophosphamide, and prednisone or rituximab and bendamustine) has been the most effective treatment regimen. Curative therapy (allogeneic HSCT) is reserved for younger patients with aggressive symptomatic disease.

Concomitant autoimmune disease, including immune thrombocytopenia and hemolytic anemia, is common among patients with CLL. Regardless of therapy, patients with CLL have a chronic immunodeficiency that may be characterized by recurrent sinus and pulmonary infections and low serum IgG levels requiring replacement therapy. Surveillance for viral infections and early initiation of antimicrobial agents for presumed bacterial infections are essential. Consideration for live virus vaccines including herpes zoster should be made early in the course of disease before a more profound immunodeficiency develops. Patients are at increased risk for second malignancies and transformation from CLL to a large cell lymphoma (Richter transformation) requiring aggressive multiagent chemotherapy with R-CHOP.

KEY POINTS

- Patients with chronic lymphocytic leukemia usually have no symptoms on presentation, with disease identified by incidentally discovered relative lymphocytosis.
- Diagnosis of chronic lymphocytic leukemia is confirmed by flow cytometry indicating co-expression of cell surface antigens CD5 and CD23, and prognosis is determined by gene mutation status (immune globulin variable heavy-chain mutation) and fluorescence in situ hybridization or array-based karyotyping.
- Asymptomatic patients with low-stage chronic lymphocytic leukemia (stage 0 to II) can be observed without therapy for decades.

HVC

Hairy Cell Leukemia

Hairy cell leukemia is a rare disorder with only 2000 new cases diagnosed annually in the United States and Europe. The incidence is higher in men (5 to 1) and older patients. This disorder is characterized by an accumulation of malignant B cells in the bone marrow and spleen that manifests as pancytopenia and progressive splenomegaly without lymphadenopathy. Typically, an attempt at bone marrow aspiration is unsuccessful (a "dry tap") owing to reticulin fibrosis and packing of the marrow with B cells that have the classic appearance of thread-like projections emanating from the cell surface ("hairy" cells) (Figure 17). Diagnosis is established by bone marrow biopsy results and confirmed by expression of specific cell surface antigens. Treatment with a purine analog such as cladribine plus rituximab for resistant disease results in complete and durable remission in most patients.

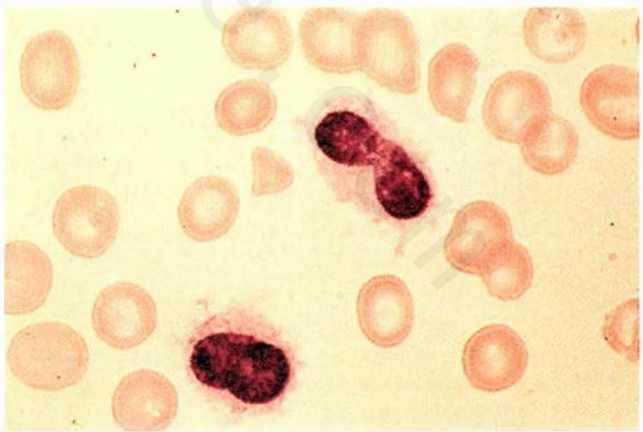

FIGURE 17. Hairy cell leukemia depicted by a peripheral blood smear showing atypical lymphocytes with thread-like cytoplasmic projections from the cell surface.

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KEY POINTS

- Hairy cell leukemia is characterized by an accumulation of malignant B cells in the bone marrow and spleen that manifests as pancytopenia and progressive splenomegaly without lymphadenopathy.
- Treatment of hairy cell leukemia with purine analogs plus rituximab for resistant disease results in complete and durable remission for most patients.

Overview and Treatment of Aggressive Lymphomas

Diffuse Large B-Cell Lymphoma

DLBCL is the most common form of lymphoma, and when considered together along with the other less common form, diffuse large T-cell lymphoma, represents 30% of all lymphoma cases. Most patients with DLBCL present with advanced (stage III and IV) disease, fever, night sweats, or weight loss (B symptoms), and experience rapid disease progression without therapy. The way in which the T-cell variant presents depends on the course and subtype of disease.

The IPI is used to assist in determining prognosis before therapy and considers age, serum lactate dehydrogenase level, number of extranodal sites, disease stage, and performance status. Standard therapy for all patients with DLBCL, regardless of stage or prognosis, is R-CHOP. Studies evaluating more aggressive initial therapy for advanced disease in patients with high IPI scores including rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyper-CVAD), as well as the addition of novel agents, including immune modulators such as lenalidomide, are ongoing. Involved-field radiation therapy is added for patients with bulky disease, with expected cure rates ranging from less than 20% for those with advanced disease and high IPI scores to more than 80% for those with localized disease and low IPI scores. Autologous HSCT is used as salvage therapy in patients with recurrent, chemotherapy-sensitive disease who experienced a disease-free interval of longer than 1 year from initial therapy. The use of allogeneic transplantation in patients with DLBCL remains investigational. Patients with the T-cell variant of large cell lymphoma are treated with CHOP, but outcomes for these patients vary significantly.

The most aggressive forms of large cell lymphoma are Burkitt lymphoma and lymphoblastic lymphoma. Onset of disease is acute, and patients usually present with life-threatening metabolic and structural abnormalities. Treatment is the same as that used to treat acute lymphoblastic leukemia (R-hyper-CVAD for CD20-positive disease), and it is associated with high response rates (80%) and is curative in nearly 50% of patients.

KEY POINTS

- Most patients with diffuse large B-cell lymphoma present with advanced (stage III and IV) disease, have B symptoms (fever, night sweats, or weight loss), and will experience rapid disease progression without therapy.
- Standard therapy for all patients with diffuse large B-cell lymphoma, regardless of stage or prognosis, is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

Mantle Cell Lymphoma

Overexpression of cyclin D1, a cell-cycle gene regulator, is associated with a chromosomal translocation [t(11:14)] and can result in mantle cell lymphoma, a rare form of NHL that has a varied clinical course depending on the extent of disease. Usually, patients present with advanced disease characterized by lymphadenopathy, weight loss, and sometimes fever, and have diffuse sites of involvement, including the gastrointestinal tract, bone marrow, and bloodstream. Previously, most patients with mantle cell lymphoma treated with R-CHOP experienced brief remissions and limited median survival (<3 years). Newer approaches using more intensive chemotherapy such as R-hyper-CVAD and including autologous HSCT have increased median survival rates and, occasionally, resulted in durable complete remissions. Allogeneic HSCT, although associated with a significant risk of morbidity and mortality, can produce long-term remissions, even in patients with relapsed disease. Newer FDA approved agents active against relapsed disease include bortezomib, a proteasome inhibitor; temsirolimus; and ibrutinib.

Fifteen percent of patients with mantle cell lymphoma present with localized and indolent disease. This group is younger (<65 years), has normal serum lactate dehydrogenase and serum β_2-microglobulin levels, and has no B symptoms. Median survival in these patients exceeds 6 years, and initiation of therapy can be delayed until symptoms develop. The variable course of mantle cell lymphoma led to the development of a graded prognostic score (MIPI) to guide therapy.

KEY POINTS

- Most patients with mantle cell lymphoma present with advanced disease characterized by lymphadenopathy, weight loss, and occasionally fever, and have diffuse sites of involvement, including the gastrointestinal tract, bone marrow, and bloodstream.
- Allogeneic hematopoietic stem cell transplantation, although associated with a significant risk of morbidity and mortality, can produce long-term remissions in patients with mantle cell lymphoma, even in those with relapsed disease.

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Hodgkin Lymphoma

Hodgkin lymphoma encompasses four classic histologic subtypes (nodular sclerosing, mixed cellularity, lymphocyte predominant, and lymphocyte depleted) and one nonclassic subtype (nodular lymphocyte-predominant subtype expressing the CD20 cell surface antigen). Hodgkin lymphoma is distinctive among lymphomas because it commonly presents locally, is associated with firm lymphadenopathy, and allows for therapy to be more readily limited in intensity and duration based on stage and risk factors compared with other types of lymphoma. The presentation is consistent among subtypes and is characterized by palpable, firm lymph nodes, and, in some patients, B symptoms. Other physical examination findings include splenomegaly (30%) and hepatomegaly (5%).

Hodgkin lymphoma is curable in most patients, even those with advanced disease. Therapy is not based on histology in classic Hodgkin lymphoma but rather on stage. The staging evaluation consists of PET scanning and a bone marrow biopsy after lymph node biopsy results confirm a diagnosis.

Stage I and II disease in patients without B symptoms (limited to lymph nodes and the same side of the diaphragm) can be treated effectively with radiation alone or radiation combined with a short course of chemotherapy. Patients with advanced disease (stage III and IV) or those with B symptoms, regardless of stage, usually require a full course of chemotherapy. The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine remains the standard of care for all stages of classic Hodgkin lymphoma when chemotherapy is indicated. Rituximab is added to this combination in patients with CD20-positive disease (nodular lymphocyte–predominant subtype).

The goal of treatment is to administer the least amount of chemotherapy sufficient to achieve a durable remission (cure) while avoiding early and late (chronic) therapy-related toxicity. Therapy-related toxicities include bleomycin-induced pneumonitis, doxorubicin-induced cardiac dysfunction, vincristine-induced neuropathy, and late second malignancies and myelodysplasia. Early repeat PET scanning provides important prognostic information in patients with Hodgkin lymphoma, but not in those with NHL. Patients with Hodgkin lymphoma who have a normal PET scan after two to three cycles of chemotherapy, regardless of residual lymphadenopathy, have more than a 90% likelihood of long-term disease response compared with those with residual PET activity, who have less than a 15% likelihood of being cured with standard therapy. Multiple prognostic risk scores are available to assist in determining long-term prognosis, but PET findings in response to two to three cycles of chemotherapy may be more predictive.

Multiple effective salvage therapies are available for patients with recurrent and resistant Hodgkin lymphoma. Patients with recurrent chemotherapy-sensitive disease are usually candidates for autologous HSCT, whereas those with disease resistant to salvage chemotherapy may achieve long-term remissions with allogeneic HSCT. Brentuximab, an anti-CD30 monoclonal antibody, is also effective as salvage therapy. Patients with Hodgkin lymphoma, including those cured by therapy, may have long-term deficits in T-cell function and should be monitored for late reactivation of viruses.

KEY POINTS

- Hodgkin lymphoma is curable in most patients, even those with advanced disease.
- Patients with stage I and II Hodgkin lymphoma without B symptoms can be treated effectively with radiation alone or radiation combined with a short course of chemotherapy, whereas those with stage III and IV disease or with B symptoms, regardless of stage, usually require a full course of chemotherapy.
- Patients with recurrent chemotherapy-sensitive Hodgkin lymphoma usually are candidates for autologous hematopoietic stem cell transplantation, whereas those with disease resistant to salvage chemotherapy may achieve long-term remissions with allogeneic hematopoietic stem cell transplantation.

Cutaneous T-Cell Non-Hodgkin Lymphoma

The more common forms of cutaneous T-cell NHL are lymphomas expressing T-cell surface antigens (CD4) that infiltrate skin and initially cause rash (mycosis fungoides), and occasionally, circulate in the blood (Sézary syndrome). The large CD4-expressing malignant T cells have classic cerebriform-appearing nuclei and clonal T-cell receptor gene rearrangements. Presentation begins with small areas of pruritic erythema. Disease progression manifests with raised plaques, diffuse skin erythema, and skin ulcers. In the final stages of disease progression, organ infiltration and evolving immunodeficiency cause recurrent bacterial infections, sepsis, and death.

Therapy is guided by disease stage. Early-stage disease (stages I and II) is limited to the skin only and is associated with a median survival of more than 20 years. Early-stage disease is treated effectively with topical glucocorticoids and, when needed, additional retinoids such as bexarotene as well as psoralen and ultraviolet A (PUVA) therapy that can be combined with interferon alfa. Advanced-stage disease (stages III and IV) is characterized by extensive skin and organ involvement and is associated with a median survival of 4 years. Advanced-stage disease requires more aggressive therapy, including electron-beam radiation therapy; photopheresis; chemotherapy including methotrexate, gemcitabine, and CHOP; purine analogs such as pentostatin; histone deacetylase inhibitors such as romidepsin and vorinostat; and monoclonal antibodies such as alemtuzumab. Allogeneic HSCT may be curative in young patients with an appropriate donor.

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KEY POINTS

- Early-stage cutaneous T-cell non-Hodgkin lymphoma is treated with topical glucocorticoids, retinoids (when needed), and psoralen and ultraviolet light with interferon alfa.
- Advanced-stage cutaneous T-cell non-Hodgkin lymphoma is treated with chemotherapy, purine analogs, histone deacetylase inhibitors, and monoclonal antibodies.
- Allogeneic hematopoietic stem cell transplantation may be curative in young patients with an appropriate donor.

Cancer of Unknown Primary Site

Introduction

In the United States, approximately 35,000 patients receive a diagnosis of cancer of unknown primary site (CUP) annually. Continued improvements in diagnostic imaging have resulted in decreased frequency of CUP diagnosis.

Diagnosis and Evaluation

CUP is a diagnosis of exclusion established in patients with a solid metastatic tumor after a detailed medical history and physical examination have been done and imaging studies or other diagnostic studies have not identified a primary tumor site.

Diagnostic efforts should focus on identifying whether a patient is among the approximately 20% of patients with CUP who have a more favorable prognosis and who can benefit from a specific treatment strategy. A biopsy obtained from the site that can be sampled in the safest, least invasive manner is performed, and specimens are evaluated by immunohistochemical stains consistent with the tumor's pattern of presentation to attempt to establish a diagnosis of a more treatable subtype of CUP. The clinical evaluation should not involve an exhaustive search for a primary site because detection of an asymptomatic and occult primary tumor does not improve outcome. Physicians should discuss with patients and their families that focusing on identification of the primary tumor can distract from the more important issue of managing the metastatic cancer. Efforts to identify primary tumors should focus only on those tumors that are suggested by the clinical presentation or could be managed with a specific, effective therapy. For example, upper endoscopy and colonoscopy are warranted in patients with evidence or symptoms of gastrointestinal bleeding but should not be done routinely. Men should undergo a testicular examination, a prostate examination, and serum prostate-specific antigen measurement. Women should undergo breast examination, mammography, and a full gynecologic examination.

Measurement of serum tumor marker levels, such as carcinoembryonic antigen, CA-19-9, CA-15-3, and CA-125, is rarely helpful and virtually never diagnostic. Although PET scans may sometimes suggest the location of a primary tumor, these findings are rarely definitive and do not improve long-term outcome.

Although several companies currently offer molecular analyses such as gene expression profiling or microRNA profiling to attempt to identify the site of tumor origin in patients with CUP, these approaches have yet to be validated in randomized prospective trials and are not considered standard practice.

KEY POINTS

- The clinical evaluation in patients with cancer of unknown primary site should not involve an exhaustive search for a primary tumor because finding an asymptomatic and occult primary site does not improve outcome. HVC
- In patients with cancer of unknown primary site, measurement of serum tumor marker levels, such as carcinoembryonic antigen, CA-19-9, CA-15-3, and CA-125, is rarely helpful and virtually never diagnostic. HVC
- Although PET scans may sometimes suggest the location of a primary tumor, these findings are rarely definitive and do not improve long-term outcome in patients with cancer of unknown primary site. HVC

Prognostic Subgroups of CUP

If a primary tumor site is identified, the patient no longer has CUP and should receive treatment that is appropriate for the new diagnosis. For those patients who retain a CUP diagnosis, evaluation is focused on identifying the prognostic subgroups into which their disease is categorized.

Favorable Subgroups

Isolated Regional Lymphadenopathy

Patients with CUP who have lymphadenopathy in a single lymph node or single lymph node region belong to a potentially more treatable subgroup of patients with CUP.

Women with adenocarcinoma limited to lymph nodes in one or both axillae have locoregional breast cancer until proved otherwise and should undergo MRI of the breasts. If a primary tumor is identified on MRI imaging, the patient should be managed as appropriate for her breast cancer. However, even patients with negative MRI findings should be treated for presumptive stage II breast cancer and undergo mastectomy and appropriate axillary lymph node management. Although a primary breast cancer tumor is identified on pathologic inspection of resected breast specimens in 50% women with CUP and axillary lymphadenopathy, the management and prognosis of these patients are similar to that of

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women with breast cancer whether or not a primary breast cancer tumor is identified.

Patients with isolated cervical lymphadenopathy should undergo triple endoscopic examination (upper endoscopy, bronchoscopy, and laryngoscopy) to identify a head and neck primary tumor site. However, even patients in whom a primary tumor site is not identified should receive chemotherapy and radiation therapy for head and neck cancer, which yields a high response rate and can be curative in some patients, especially those with squamous cell histology and nonbulky cervical lymphadenopathy. Patients with adenocarcinoma or supraclavicular lymphadenopathy have a worse prognosis; however, treatment recommendations for adenocarcinoma and squamous cell histology in these patients are similar in the absence of identification of other disease sites.

Patients with isolated inguinal lymphadenopathy should undergo a thorough anorectal, perineal, and genital examination. In the absence of identification of a primary site, resection or locoregional radiation therapy may result in a favorable outcome. Resection or localized radiotherapy may also be used to manage other isolated solitary or regional enlarged lymph nodes.

Peritoneal Carcinomatosis in Women

Women with CUP characterized by ascites and abdominal carcinomatosis are regarded as having ovarian cancer until proved otherwise and are managed with cytoreductive surgery and ovarian cancer chemotherapy regimens.

Poorly Differentiated Nonadenocarcinoma

Certain groups of patients with poorly differentiated CUP that cannot be identified as adenocarcinoma may benefit from specific chemotherapeutic approaches. Young men with poorly differentiated carcinoma that is relatively symmetrical around the midline and is characterized by bulky retroperitoneal or mediastinal lymphadenopathy may have an unrecognized germ cell tumor. These patients require measurement of serum α-fetoprotein and β-human chorionic gonadotropin levels, a testicular examination, and testicular ultrasonography. Management consists of platinum-containing germ cell tumor regimens and germ cell treatment paradigms.

Poorly differentiated neuroendocrine tumors constitute another nonadenocarcinoma CUP subgroup that may benefit from specific chemotherapeutic strategies. Metastases predominantly to the liver and to bone are common. Therapy with platinum-based chemotherapy using a regimen similar to that used to treat small cell lung cancer often results in responses, and occasionally, complete clinical responses. Note that only high-grade, poorly differentiated neuroendocrine tumors are sensitive to platinum-based regimens; well-differentiated neuroendocrine tumors do not respond to this approach.

KEY POINTS

- Patients with cancer of unknown primary site and isolated cervical lymphadenopathy should undergo triple endoscopic examination (upper endoscopy, bronchoscopy, and laryngoscopy) to identify a head and neck primary tumor site.
- Women with adenocarcinoma limited to lymph nodes in one or both axillae have locoregional breast cancer until proved otherwise and should undergo MRI of the breasts.
- Patients with cancer of unknown primary site and isolated inguinal lymphadenopathy should undergo a thorough anorectal, perineal, and genital examination.
- Young men with poorly differentiated carcinoma that is relatively symmetrical around the midline and characterized by bulky retroperitoneal or mediastinal lymphadenopathy may have an unrecognized germ cell tumor.

Nonfavorable Subgroups

There are no accepted standard treatment regimens for patients with nonfavorable CUP (those patients with CUP who do not fit into one of the favorable subgroups); therapy tends to be empiric, and the prognosis is often poor. The use of gastrointestinal cancer regimens for CUP that is mostly below the diaphragm and lung cancer regimens for CUP that is mostly above the diaphragm is reasonable. Accurate assessments of performance status, as well as liver, kidney, and bone marrow function, are important when developing treatment strategies. Patients who are medically fit (Eastern Cooperative Oncology Group performance status of 0 or 1; see Table 48) are most likely to benefit from and tolerate aggressive chemotherapy compared with those who are debilitated or have multiple comorbidities and for whom supportive therapy may be appropriate.

KEY POINT

- Gastrointestinal cancer regimens are used to treat cancer of unknown primary site (CUP) that is mostly below the diaphragm, and lung cancer regimens are used for CUP that is mostly above the diaphragm.

Melanoma

Epidemiology, diagnosis, and staging of melanoma are discussed in MKSAP 17 Dermatology.

Treatment

Wide local excision is the standard of care for patients with nonmetastatic melanoma. Recommended margins are 0.5 cm for in situ lesions, 1 cm for melanomas with less than 1 mm of invasion, and 2 cm for melanomas with deeper invasion.

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Sentinel lymph node biopsy should be done for melanomas 1 mm thick or greater and should be considered for thin melanomas less than 1 mm thick if high-risk features are present, such as tumor ulceration or a mitotic rate of 1/mm² or more. If the sentinel lymph node is positive or if lymph nodes are involved clinically, complete lymphadenectomy (removal of the remaining nodes in the involved nodal basin) is recommended.

Patients with melanomas that are 4 mm thick or greater or who have lymph node involvement have a 25% to 75% risk of dying from melanoma; adjuvant chemotherapy is not beneficial in these patients. Adjuvant immunotherapy with interferon alfa improves relapse-free survival, but its impact on overall survival is not clear. This agent is associated with significant toxicity, including fever, myalgia, fatigue, myelosuppression, depression, autoimmune disease, hepatotoxicity, cardiac ischemia, arrhythmias, and cardiomyopathy. Adjuvant interferon alfa is an option for patients with positive regional lymph nodes or skin metastases or for those with more advanced lymph node–negative melanoma (2-4 mm with ulceration or >4 mm) with no history of depression or autoimmune disease. Observation is also an acceptable option for these patients.

Patients with metastatic melanoma have a median survival of 11 months, and their disease is relatively chemotherapy resistant. In patients with metastatic disease limited to one or a few sites that is potentially resectable, surgical resection can result in prolonged survival. Immunotherapy or targeted therapy is preferred over chemotherapy. Chemotherapy can be used if patients are not candidates for these other therapies, or after their disease progresses while receiving other treatments. The most active chemotherapeutic agent for metastatic melanoma is dacarbazine, which results in a response rate of 19% to 25%.

Immunotherapy options for metastatic melanoma include interleukin-2 and ipilimumab. Immunotherapy is recommended as initial treatment in patients with metastatic disease that is considered lower-risk, typically defined as patients with minimal or no symptoms from their metastases; normal serum lactate dehydrogenase level; and metastases limited to skin, lymph nodes, or lung. Immunotherapy is also recommended in patients without a targetable mutation, even in the presence of more advanced or symptomatic disease. High-dose interleukin-2 is an option for patients with good performance status and is associated with a 15% response rate and a 5% to 6% rate of complete remission, with 50% of the responses lasting several years.

The monoclonal antibody ipilimumab is an immune check-point blocker that results in a 20% to 30% response rate with durable remissions; 60% of responders in clinical trials maintained a response for at least 2 years. Overall survival was improved to 10 months versus 6.4 months in the non-ipilimumab arm. This agent works by blocking cytotoxic T-lymphocyte antigen-4, leading to T-cell potentiation and an antitumor immune reaction. It is associated with clinically significant autoimmune toxicities, including colitis with risk of perforation, rash, hypophysitis, thyroiditis, hepatitis, and nephritis. These side effects are managed with vigilant follow-up and early use of glucocorticoids. Combined treatment with ipilimumab and nivolumab (an antibody against the programmed death 1 [PD-1] receptor) has led to rapid responses in a high percentage of patients with advanced melanoma in clinical trials. The anti–PD-1 monoclonal antibody pembrolizumab has shown substantial activity, including in patients previously treated with ipilimumab, and has been FDA approved for patients with metastatic melanoma whose disease progresses after other therapies.

All patients with metastatic melanoma should have their tumor assessed for the presence of a driver V600 *BRAF* mutation. For patients with V600 *BRAF* mutation, targeted therapy is recommended initially over immunotherapy for patients with poor performance status and/or more advanced disease. *BRAF* gene mutations are present in 50% to 70% of patients with melanoma. Vemurafenib is a selective *BRAF* inhibitor resulting in a response rate of more than 60% in patients with metastatic melanomas with a V600 *BRAF* mutation, with rapid tumor regression, a median response duration of 5 months, and overall survival of 13.6 months versus 9.7 months in patients receiving dacarbazine. Common side effects include rash, arthralgia, diarrhea, and secondary cutaneous squamous cell carcinoma.

KEY POINTS

- Wide local excision is the standard of care for patients with nonmetastatic melanoma.
- In a clinical trial for patients with metastatic melanoma, ipilimumab, a monoclonal antibody, resulted in a 20% to 30% response rate, with 60% of responders maintaining a response for at least 2 years and improved overall survival of 10 months versus 6.4 months in the non-ipilimumab arm.
- For patients with metastatic melanoma and a V600 *BRAF* mutation, targeted therapy is recommended initially over immunotherapy for patients with poor performance status and/or more advanced disease.

Prognosis and Follow-up

Patients with melanomas less than 1 mm thick with negative lymph nodes and no adverse risk factors have a 95% 5-year survival rate. Patients with 1-mm melanomas with negative lymph nodes have a 5-year survival rate between 50% and 85% (average rate, 70%). Melanomas in patients with positive lymph nodes are associated with a 5-year survival rate of 25% to 70% (average rate, 45%).

Patients with a history of melanoma should undergo annual skin examinations for life, perform monthly skin self-examinations, and undergo physical examination with complete history every 3 to 12 months for 5 years and then annually.

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The goal of surveillance is to identify potentially curable recurrences and to monitor for second primary melanomas. Routine blood tests are not recommended. Although guidelines suggest discussing screening chest radiography, CT scanning, or PET/CT scanning with patients who have had higher-risk melanomas (positive lymph nodes, size >4 mm or >2 mm with ulceration), the value of imaging studies in asymptomatic patients is questionable, and many studies therefore recommend against their use.

KEY POINTS

- Patients with a history of melanoma should undergo annual skin examinations for life, perform monthly skin self-examinations, and undergo physical examination with complete history every 3 to 12 months for 5 years and then annually.

HVC

- In the follow-up care of patients with melanoma, routine blood tests are not recommended, and the value of screening chest radiography, CT scanning, or PET/CT scanning is questionable.

Oncologic Urgencies and Emergencies

Structural Urgencies and Emergencies

Superior Vena Cava Syndrome

Superior vena cava (SVC) syndrome is caused by acute obstruction of blood flow to the right atrium from the upper torso, can result in symptoms of progressive dyspnea and cough, and may be associated with swelling of the face and neck. SVC syndrome is usually insidious in onset and may less frequently be characterized by swelling of the upper extremities, chest pain, and pain on swallowing. Other physical findings include venous distention in the neck and chest, cyanosis, and facial plethora.

The most common cause of SVC syndrome is lung cancer (both small cell and non-small cell lung cancer), accounting for 65% of all cases. Other malignancies less commonly associated with SVC syndrome include diffuse large B-cell lymphoma, lymphoblastic lymphoma, acute lymphoblastic leukemia, Hodgkin lymphoma, and germ cell tumors. Mediastinal widening and pleural effusions are common radiographic findings; however, up to 16% of patients have a normal chest radiograph. Tissue biopsy is essential for establishing a histologic diagnosis and guiding therapy for the specific cancer type. Mediastinoscopy is commonly used to obtain tissue in patients with SVC syndrome, and is associated with a procedure-related complication rate of 5%. Percutaneous transthoracic CT-guided needle biopsy is another acceptable approach.

Symptoms can be treated with diuretics and glucocorticoids, if needed, pending results of a tissue diagnosis. Cancer type–specific therapy, including chemotherapy, radiation therapy, or a combination of the two, is usually rapidly effective (typically within 2 weeks) in ameliorating SVC-related symptoms. Anticoagulation may be required if complete patency of the SVC is not established. Salvage approaches have included endovascular stent placement, thrombolytic therapy, and embolectomy, with limited reports of success.

KEY POINTS

- Superior vena cava syndrome can be caused by various malignancies, with small cell lung cancer and non–small cell lung cancer the most common.
- Symptomatic treatment of superior vena cava syndrome is appropriate until a tissue diagnosis is established to guide cancer type–specific therapy, which is usually rapidly effective.

Neoplastic Disease-Induced Acute Central Nervous System Emergencies

Increased Intracranial Pressure

Mass effect within the brain causes progressive increased intracranial pressure (ICP), which, if left untreated, can lead to diffuse brain injury, permanent disability, and death. Although some primary brain tumors (such as glial tumors or lymphoma) may cause increased ICP, metastatic disease is a more common cause. Tumors originating from lung cancer and cutaneous melanoma are the most common malignancy-related causes of increased ICP and are also associated with intracerebral hemorrhage, particularly melanoma. Other less common causes of malignancy-related increased ICP include lymphoma and germ cell tumors.

Headache is typically the first presenting symptom followed by vomiting, altered mental status, focal neurologic deficits, and loss of consciousness as ICP increases. Because progression can be rapid, emergent assessment with CT of the head or MRI of the brain is essential to avoid the late adverse consequences of ICP leading to permanent neurologic dysfunction and death. When increased ICP is suspected in association with an intracerebral mass, lumbar puncture is contraindicated because the procedure can precipitate brainstem herniation. Conversely, diffuse central nervous system (CNS) involvement by a malignancy such as leukemia or carcinomatosis without a defined mass is not a contraindication for a diagnostic lumbar puncture.

Immediate treatment is essential. Glucocorticoids are the initial therapy of choice. Oral administration may be appropriate for patients without severe symptoms or associated clinical findings, although patients with impaired mentation, uncontrolled seizures, or those in whom oral intake of medication cannot be assured should receive intravenous treatment. Dexamethasone, 8 to 10 mg every 6 hours, is recommended for both oral and intravenous administration. Higher-dose dexamethasone (100 mg/d) does not improve responses and is associated with more adverse effects than the recommended dose. In patients with severe symptoms

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CONT.

or complications associated with increased ICP, osmotic diuresis with mannitol in addition to glucocorticoids should be considered.

An isolated brain mass in a young patient, particularly in the setting of HIV infection, is suspicious for CNS lymphoma. When primary CNS lymphoma is suspected early in the course of increased ICP, it is appropriate to obtain a tissue biopsy before initiating glucocorticoids to preserve tumor cell viability for diagnostic purposes. In addition to tumor masses, malignant cells (leukemia, lymphoma, and melanoma) can cause obstructing hydrocephalus that usually requires surgical decompression. When ICP is controlled, elective surgical excision followed by focal stereotactic or whole-brain radiation therapy of isolated brain metastases should be considered. Multiple brain metastases are usually treated with radiation therapy and chemotherapy or tumor-specific targeted therapies such as ipilimumab for melanoma.

Cerebral syndrome, a consequence of capillary leakage from vascular beds, can cause edema and mimic brain metastasis. Cranial nerve palsy can be a consequence of viral infections or paraneoplastic syndrome or due to direct invasion of the cranial nerves in the subarachnoid space caused by leptomeningeal carcinomatosis. Other nonmalignant causes of pain and motor dysfunction include degenerative spine disease due to disk and bone spur impingement on nerve roots. Trauma or metastatic disease can cause cauda equina syndrome, which can be confused with spinal cord compression.

Spinal Cord Compression

Up to 10% of patients with cancer will experience neck or back pain followed by progressive neurologic dysfunction due to malignancy-induced compression of the spinal cord. The most common causes of spinal cord compression include cancer of the lung, breast, and prostate, and multiple myeloma. Because any malignancy can cause spinal cord compression, the symptoms of neck or back pain should be evaluated immediately in patients with cancer to avoid the potentially devastating consequences of progressive neurologic deterioration that can become permanent within hours to days.

Expansion of one or multiple vertebral body metastases with extension into the epidural space causes ischemic injury to the spinal cord and resultant neurologic dysfunction. Pain is uniformly the initial symptom followed by a sense of heaviness in the legs, progressing to leg muscle weakness manifesting as difficulty climbing stairs and rising from a sitting position. If untreated, bowel and bladder dysfunction and lower extremity paresis occur. Physical findings can vary, particularly early in the course of compression, with pain on palpation over the involved vertebral body, hyperreflexia, and diffuse lower extremity weakness being the most common findings.

Emergent MRI or CT of the entire spine should be performed to confirm the diagnosis and identify other potential asymptomatic metastatic sites. To avoid permanent neurologic deficits in patients with cancer and back pain, high-dose intravenous glucocorticoids (dexamethasone, 20 mg) should be administered immediately on presentation followed by maintenance glucocorticoids until definitive therapy is administered on confirmation of spinal cord compression. Early intervention can completely reverse the adverse consequences of spinal cord compression, with standard definitive therapy consisting of surgical decompression or radiation therapy supplemented by chemotherapy in chemotherapy-responsive malignancies such as lymphoma.

KEY POINTS

- Headache is typically the first presenting symptom of increased intracranial pressure (ICP) followed by vomiting, altered mental status, focal neurologic deficits, and loss of consciousness as ICP increases.
- Lumbar puncture is contraindicated when increased ICP is suspected to be caused by an intracerebral mass because the procedure may precipitate brainstem herniation leading to permanent neurologic dysfunction and death.
- Patients with cancer with unremitting neck or back pain should receive immediate medical evaluation, spinal imaging, and intravenous glucocorticoid therapy.

Malignant Pleural and Pericardial Effusions

The initial presentation in patients with cancer can include pleural or pericardial fluid, but more often this finding reflects advancing and incurable disease. Lung cancer, breast cancer, melanoma, and lymphoma are among the more common causes of malignant pleural and pericardial effusions, but any malignancy can cause these findings.

The usual presentation of pleural effusion is dyspnea on exertion, but chest pain, cough, and dyspnea at rest are also common. Patients with cancer and dyspnea should have a chest radiograph or chest CT to confirm the presence and extent of the effusion. Initial thoracentesis may be both diagnostic (with cytologic examination of the pleural fluid) and therapeutic. Thoracoscopy can be useful both for drainage and to allow for pleural biopsy which may be helpful in diagnosis.

In patients with pleural effusion, up to 20 mL/kg of body weight of fluid can be drained from a pleural cavity for symptomatic relief, but to avoid re-expansion pulmonary edema, no more than 1500 mL should be drained at one time. Unfortunately, malignancy-induced pleural effusions recur in 70% of patients. Periodic repeated thoracenteses may be effective with slowly recurring effusions whereas more rapidly recurring effusions may be managed with traditional thoracostomy tube placement or placement of an indwelling pleural catheter, which is a smaller drainage tube that can be managed as an outpatient. If spontaneous obliteration of the pleural space does not occur following prolonged drainage, infusion of agents to cause pleurodesis, including tetracycline, bleomycin, or talc, is effective in treating recurrent malignant effusions.

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CONT.

Unlike pleural effusion, pericardial effusion may cause little to no symptoms initially and is usually identified as an enlarged heart on chest radiograph or low voltages on electrocardiogram. Patients with significant accumulation of pericardial fluid may present initially with dyspnea, orthopnea, and chest pain, and later with hemodynamic instability if cardiac tamponade develops. Prompt echocardiography is essential for confirming a diagnosis and facilitating intervention in patients with suspected malignant pericardial effusion.

Immediate subxiphoid cardiocentesis allows for drainage and enables proper cardiac chamber filling. Drainage is usually followed by surgical creation of a pericardial window or partial pericardiectomy. Chemotherapy, cancer-specific targeted therapies, or radiation therapy may be appropriate for patients with responsive disease.

KEY POINTS

- The usual presentation of pleural effusion is dyspnea on exertion, but chest pain, cough, and dyspnea at rest are also common; conversely, pericardial effusion initially presents asymptomatically and is usually identified as an enlarged heart on chest radiograph or low voltages on electrocardiogram.
- In patients with pleural effusion, no more than 1500 mL of fluid should be drained at one time to prevent re-expansion pulmonary edema.
- Recurrent malignant pleural effusions after prolonged drainage should be treated with agents that cause pleurodesis such as tetracycline, bleomycin, or talc.
- Echocardiography is essential to establish an early diagnosis of pericardial effusion to avoid progression to cardiac tamponade.

Metabolic Urgencies and Emergencies

Tumor Lysis Syndrome

Malignancies associated with rapid cell turnover can release large quantities of electrolytes and procoagulants into the circulation, causing the potentially life-threatening complication of tumor lysis syndrome. Spontaneous tumor lysis syndrome occurs commonly in patients with leukemia and Burkitt lymphoma and after treatment of bulky large B-cell lymphoma or advanced chronic lymphocytic leukemia. Rapid cell breakdown results in hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and disseminated intravascular coagulation. Hyperuricemia can lead to urate nephropathy and acute kidney injury.

Prevention of tumor lysis syndrome is optimal. Large-volume intravenous hydration with normal saline plus administration of allopurinol to limit hyperuricemia is usually effective. Because of its rapid onset of action and ability to lower urate levels quickly that may be renoprotective, rasburicase should be administered before initiation of chemotherapy in patients with underlying kidney disease or those with signs of kidney disease, including an elevated serum creatinine level and a low urine output. Hemodialysis may be needed to address fluid overload, uremia, severe hyperkalemia, or hyperphosphatemia.

KEY POINTS

- Spontaneous tumor lysis syndrome occurs commonly in patients with leukemia and Burkitt lymphoma and after treatment of bulky large B-cell lymphoma or advanced chronic lymphocytic leukemia.
- Prevention and treatment of tumor lysis syndrome include large-volume intravenous hydration with normal saline and treatment with allopurinol or rasburicase when kidney disease is present.

Hypercalcemia

Hypercalcemia is usually a manifestation of advanced disease, is associated with poor prognosis, and occurs in up to 10% of patients with cancer. Hypercalcemia is most common among patients with multiple myeloma, breast cancer, renal cell carcinoma, and lung cancer (particularly squamous cell lung cancer). Patients initially present with nausea, vomiting, constipation, and polyuria. Polydipsia, diffuse muscle weakness, and confusion follow and can lead to acute and chronic kidney injury. Release of parathyroid hormone–related protein by malignant cells causes hypercalcemia in 80% of patients, whereas direct bone destruction causes hypercalcemia in 20%. Parathyroid hormone–related protein can be a diagnostic aid in patients with hypercalcemia and can be used as a tumor marker.

Immediate hydration with large-volume normal saline infusion followed by forced diuresis using furosemide restores intravascular volume and decreases serum calcium levels. In patients with malignancies that initially responded to glucocorticoids, including multiple myeloma, additional glucocorticoid therapy is warranted. Bisphosphonates are the most common medications used to maintain normal serum calcium levels, but can result in hypocalcemia. Osteonecrosis of the jaw and kidney disease can occur with repeated administration of these agents. Receptor activator of nuclear factor κB ligand (RANKL) inhibitors, such as denosumab, are also effective for achieving normocalcemia, are not associated with kidney injury, and are easier to administer and monitor than bisphosphonates. However, there is less clinical experience with these agents and they are significantly more expensive than bisphosphonates. Treatment with chemotherapy or disease-specific targeted agents is appropriate for long-term control of hypercalcemia.

KEY POINTS

- Hypercalcemia is most common among patients with multiple myeloma, breast cancer, renal cell carcinoma, and lung cancer, and can include nausea, vomiting, constipation, and polyuria on presentation followed by polydipsia, diffuse muscle weakness, and confusion.

(Continued)

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KEY POINTS *(continued)*

- Aggressive intravenous hydration followed by forced diuresis is the initial management of patients with hypercalcemia followed by infusion of bisphosphonates or receptor activator of nuclear factor κB ligand (RANKL) inhibitors for long-term control.

Effects of Cancer Therapy and Survivorship

Introduction

Adverse events are common with administration of all forms of antineoplastic therapy; these effects can be acute and chronic and can negatively affect treatment efficacy, quality of life, and survivorship. Transient suppression of hematopoiesis is among the most common acute toxicities, manifesting with anemia, neutropenia, and thrombocytopenia. Newer agents, particularly cancer-specific targeted therapies, cause unique, and sometimes profound, toxicities, requiring expertise and vigilance to avoid vital organ dysfunction. Cardiac, pulmonary, neurocognitive, and reproductive late adverse effects, as well as secondary malignancies, are becoming more common as the number of cancer survivors increases (**Table 61**).

Acute Effects of Cancer Therapy

Hematopoietic Toxicity

Varying degrees of suppression of erythrocyte, leukocyte, and platelet production is common with most forms of antineoplastic therapy. Mild suppression usually reverses spontaneously or after temporary dose reduction or treatment discontinuation. Profound suppression can be life threatening and specific to the hematopoietic lineage.

TABLE 61. Cancer Treatment-Related Toxicities

Chemotherapy Toxicities	Representative Chemotherapeutic Agents
Myelosuppression	Most cytotoxic drugs
Emesis	Cisplatin, doxorubicin, cyclophosphamide
Diarrhea	5-FU, capecitabine, irinotecan
Alopecia	Doxorubicin, paclitaxel, cyclophosphamide
Stomatitis	Doxorubicin, methotrexate
Vesicant (blistering)	Doxorubicin, mitomycin
Peripheral neuropathy	Paclitaxel, docetaxel, cisplatin, vincristine
Pulmonary toxicity	Bleomycin, mitomycin
Kidney toxicity	Cisplatin, ifosfamide
Cardiac toxicity	Doxorubicin
Gonadal toxicity	Alkylating agents (e.g., cyclophosphamide)
Carcinogenicity	Alkylating agents, etoposide, and doxorubicin (AML), cyclophosphamide (bladder cancer), tamoxifen (endometrial cancer)
Hormonal Agent Toxicities	
Osteopenia	Anastrozole, letrozole, exemestane
Thrombosis	Tamoxifen
Biologicals and Targeted Therapy Toxicities	
Infusion reactions	Rituximab, trastuzumab, bevacizumab
Rash	Cetuximab, erlotinib
Fatigue	Sorafenib, sunitinib
Thrombosis/bleeding	Bevacizumab
Reactivation of viral diseases	Rituximab (hepatitis B), alemtuzumab (cytomegalovirus)
Reversible posterior leukoencephalopathy	Rituximab
Immune-related enterocolitis	Ipilimumab
Cardiac toxicity	Trastuzumab
Skin cancers	Vemurafenib

5-FU = 5-fluorouracil; AML = acute myeloid leukemia.

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Neutropenia and Fever

Patients with a neutrophil count below 1000/μL (1×10^9/L) are at significantly increased risk of infection. However, antibiotic prophylaxis for prevention of infection during chemotherapy-induced neutropenia is not routinely given except in selected patients with profound neutropenia (defined as ≤100/μL [0.1×10^9/L] neutrophils) expected to last 7 days or longer.

In patients with neutropenia who develop fever or other clinical signs of infection, immediate treatment is necessary to prevent a potentially life-threatening infection as rapid deterioration can occur over 12 to 24 hours, potentially resulting in sepsis, shock, and death. Empiric broad-spectrum antimicrobial treatment is therefore provided before a diagnostic evaluation is completed, even if a likely source of infection is not obvious.

Patients with neutropenic fever are often classified as low- or high-risk. Individuals without significant comorbidities and in whom the duration of neutropenia is expected to be brief (<7 days) are usually considered to be at low risk for complications from neutropenia. Selected low-risk patients with stable vital signs and an unremarkable physical examination may be eligible for outpatient oral therapy at experienced centers with close monitoring capability. Treatment is usually with a fluoroquinolone in combination with an oral β-lactam antibiotic until the neutrophil count recovers. High-risk patients are those with an expected long duration (≥7 days) of neutropenia or the presence of advanced malignant disease or other comorbidities. These individuals are usually treated as inpatients with empiric parenteral broad-spectrum antimicrobial agents selected to also cover any suspected source of infection while further diagnostic evaluation is pursued. Appropriate antibiotic regimens include monotherapy with an antipseudomonal β-lactam agent (ceftazidime, cefepime, meropenem, imipenem, or piperacillin-tazobactam) or combination therapy with activity against both gram-positive and gram-negative organisms. Antifungal agents are usually used initially only in patients who are hemodynamically unstable, or are added in patients who are persistently febrile on broad-spectrum antibiotic treatment without an identifiable source of infection.

Hematopoietic growth factors, including granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, can decrease the severity and duration of neutropenia. They are FDA approved for prophylactic use with administration of myelosuppressive chemotherapy, although due to expense and modest effect on clinical outcomes, they are not used routinely. Their use is typically limited to patients receiving regimens expected to cause neutropenia in more than 20% of treated patients and/or profound neutropenia, and in selected patients at high risk of neutropenia-associated infection. The effectiveness of hematopoietic growth factors when used therapeutically to shorten the duration of established neutropenia or in combination with antibiotics in patients with neutropenic fever has not been established; therefore, they are usually used only in patients with profound neutropenia (≤100/μL [0.1×10^9/L] neutrophils) expected to be of long duration or associated with severe sepsis and hemodynamic instability.

KEY POINTS

- Patients presenting with fever and neutropenia (absolute neutrophil count less than 1000/μL [1×10^9/L]) require immediate medical attention and prompt initiation of antimicrobial agents.
- Hematopoietic growth factors, including granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, can decrease the severity and duration of neutropenia but due to expense and only modest effect on outcomes, they should be reserved for patients at high risk for neutropenia-associated infection. HVC

Thrombocytopenia and Anemia

Thrombocytopenia can be life threatening when platelet levels fall below 10,000/μL (10×10^9/L), which is the usual threshold for transfusion. Use of platelet growth factors such as thrombopoietin is not considered standard practice for patients with chemotherapy-induced thrombocytopenia.

Anemia in symptomatic patients is treated with transfusions. General use of erythropoietin is discouraged owing to adverse events such as thrombosis and a decrease in overall survival.

KEY POINT

- Platelet growth factors such as thrombopoietin are not considered standard therapeutic practice for patients with chemotherapy-induced thrombocytopenia and are reserved for those with immune-mediated thrombocytopenia. HVC

Disorders of Pulmonary Function

Acute and debilitating chronic pulmonary dysfunction can occur after chemotherapy and radiation therapy involving the lung fields. Bleomycin is the most common cause of pulmonary dysfunction associated with cytotoxic chemotherapy and can cause the most severe side effects. Usually, bleomycin pulmonary toxicity occurs after a patient has exceeded a cumulative dose threshold (400 U); however, acute presentations after one dose have also been reported. Onset of bleomycin toxicity can be insidious and is characterized initially by a dry cough. Serial pulmonary function tests can be helpful to monitor for decreases in DLCO or forced expiratory volumes, but these tests are not always predictive. Early discontinuation of bleomycin is essential to avoid progressive dyspnea from evolving into bleomycin-induced pneumonitis, pulmonary fibrosis, and even death. Treatment of bleomycin-induced pneumonitis with glucocorticoids can limit its progression, but permanent residual pulmonary dysfunction usually occurs. High fractions of inspired oxygen should be avoided in all patients who received bleomycin previously to avoid late toxicity.

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Involved-field radiation therapy, particularly when combined with chemotherapy, can cause pneumonitis that is effectively treated with glucocorticoids. A slow taper of the glucocorticoid dose is essential to avoid glucocorticoid-withdrawal exacerbations of pneumonitis.

KEY POINT

- In patients receiving cytotoxic chemotherapy, early discontinuation of bleomycin is essential to avoid progressive dyspnea due to evolving bleomycin-induced pneumonitis, pulmonary fibrosis, and death.

Disorders of Genitourinary and Kidney Function

Kidney failure due to renal tubular dysfunction can occur following administration of cisplatin and ifosfamide; consequently, serum electrolyte levels and kidney function must be carefully monitored. High-dose methotrexate used to treat osteosarcoma and lymphoma can also cause renal tubular injury, which can be avoided with aggressive intravenous hydration, forced diuresis, urine alkalization, and administration of leucovorin. Transient kidney disease caused by newer targeted therapies, such as sunitinib and vemurafenib, can be reversed with drug dosage reductions or cessation. Radiation therapy to the kidneys can cause acute and chronic kidney dysfunction.

Hemorrhagic cystitis can occur after any dose of cyclophosphamide or ifosfamide. Aggressive intravenous hydration with forced diuresis can limit renal tubular and bladder damage. The uroprotective agent, mesna, has greatly reduced the incidence of hemorrhagic cystitis.

KEY POINT

- In patients with cancer undergoing treatment with potentially nephrotoxic drugs, serial assessments of serum electrolyte levels and kidney function are required to avoid permanent kidney damage.

Immune-Related Toxicities

A new class of antineoplastic therapeutic agents directed against T-cell checkpoint receptors, such as ipilimumab or PD-1 and PD-L1 inhibitors, can cause numerous, potentially permanent and life-threatening, immune-related organ toxicities. These agents have caused autoimmune, hepatic, gastrointestinal, pulmonary, endocrine (hypothalamus, thyroid, and adrenal), and neurologic T-cell–induced damage that usually reverses with glucocorticoids.

Effects on Bone Health

Aromatase inhibitors, commonly used to treat breast cancer, can cause debilitating osteopenia resulting in pathologic fractures that can be avoided with calcium and vitamin D supplements and, when indicated, by use of serial bone density scans and bisphosphonate therapy.

KEY POINT

- Aromatase inhibitors can cause debilitating osteopenia resulting in pathologic fractures that can be avoided with calcium and vitamin D supplements and, when indicated, by use of serial bone density scans and bisphosphonate therapy.

Late Effects of Cancer Therapy

Secondary Malignancies

Patients with a history of cancer may have an increased lifetime risk for development of secondary malignancies owing to exposure to chemotherapy and radiation (treatment-related neoplasms), genetic susceptibilities (cancer genetic syndromes), shared causative exposures, and the cancerization field effect (for example, an increased risk for a second aerodigestive tract cancer in smokers with a previous cancer of this type). Hematopoietic clonal disorders, including myelodysplasia, leukemia, and lymphoma, can occur decades after completion of therapy. Typical agents associated with therapy-related myelodysplasia include alkylators, anthracyclines, and topoisomerase II inhibitors. Likewise, leukemia and lymphoma can develop as a late consequence of exposure to chemotherapy and radiation. Similarly, radiation-induced solid tumors, such as breast cancer after mantle radiation for Hodgkin lymphoma, are not uncommon, especially in women treated early in life. Thus, the overall cancer rate in cancer survivors is higher than that in the general population.

KEY POINTS

- Myelodysplasia can occur years to decades after patients with cancer receive chemotherapy.
- Radiation-induced solid tumors, such as breast cancer, are not uncommon in women treated early in life with mantle radiation therapy for Hodgkin lymphoma.

Disorders of Cardiac Function

Various antineoplastic agents can cause acute and chronic cardiac dysfunction. Anthracyclines such as doxorubicin are the most common cause of chemotherapy dose-dependent–induced cardiomyocyte damage, leading to late and irreversible chronic heart failure. Cardiac dysfunction can be avoided by limiting the cumulative dose and discontinuing anthracyclines in patients in whom a decrement of left ventricular function is observed during therapy. However despite these precautions, a 1.5% late risk of cardiac dysfunction after exposure to anthracyclines still exists. Cessation of therapy and aggressive medical management with diuresis and afterload reduction may lead to complete recovery of cardiac function, but sometimes, heart failure is permanent. Acute and reversible cardiac dysfunction can occur after treatment with trastuzumab, a monoclonal antibody directed against

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CONT. the *HER2/neu* receptor, the effects of which are not dose dependent. Involved-field radiation therapy encompassing the heart can cause premature coronary artery stenosis and left ventricular dysfunction.

KEY POINT

- Cardiac dysfunction can often be avoided by limiting the cumulative dose and discontinuing anthracyclines in patients in whom a decrement of left ventricular function is observed during cancer therapy; however, even with precautions, a late risk of heart failure in cancer survivors still exists.

Sexual Function

Sexual dysfunction is common and underreported among patients receiving cancer therapy. Hormonal therapy and radiation of pelvic structures can impair sexual function in both sexes. Anxiety and depression may also play a role. Women may experience vaginal dryness leading to dyspareunia, and hormonal changes can result in loss of libido, arousal, and orgasm. Men develop erectile dysfunction but may also have loss of libido and ability to ejaculate. Physicians should directly inquire to determine if sexual dysfunction is ongoing during and after therapy. Social, emotional, hormonal, and anatomic causes can all be involved in sexual dysfunction. Phosphodiesterase-5 enzyme inhibitors such as sildenafil for erectile dysfunction and topical low-dose estrogen or nonhormonal lubricants for vaginal dryness and discomfort are effective treatments and, when given, should be combined with counseling.

KEY POINT

- Along with counseling, phosphodiesterase-5 enzyme inhibitors such as sildenafil for erectile dysfunction and low-dose estrogen or nonhormonal lubricants for vaginal dryness and discomfort can effectively treat cancer treatment–related sexual dysfunction.

Survivorship

General Principles

More than 14 million cancer survivors are dealing with the toll of treatment and its aftermath in the United States. Consequently, interest in developing guidelines and strategies to care for the immediate and late adverse consequences of cancer has recently increased. The process of both living with cancer as well as living beyond cancer is termed survivorship, and recommendations for survivorship care from the Institute of Medicine include the following:

1. prevention of new and recurrent cancer and of other late effects;
2. surveillance for cancer spread, recurrence, or second malignancies, including screening recommendations for new cancers;
3. intervention for consequences of cancer and its treatment, including medical problems such as lymphedema; neurocognitive changes; sexual dysfunction; symptoms such as pain and fatigue; psychological distress; and financial concerns about employment, insurance, and disability; and
4. coordination of care between specialists and internists to ensure that survivors' health needs are met.

Survivorship Care Plan

A "Survivorship Care Plan" (SCP) should be generated by a patient's oncologist and provided to the patient and the patient's internist when active cancer management is being transitioned to posttreatment care. The objective of the SCP is to summarize critical information needed for the patient's long-term care, including cancer type; treatments received, and their potential consequences; results of diagnostic tests; recommendations for timing and type of follow-up evaluation; and recommendations for preventive practices and health maintenance and well-being. Although several different models for survivorship health care delivery have been developed, it is important for the care providers to establish a clear plan to definitively delineate management responsibility among providers.

For more information on survivorship planning, see the Institute of Medicine's Web site at http://iom.edu/Reports/2005/From-Cancer-Patient-to-Cancer-Survivor-Lost-in-Transition.aspx.

Screening for Second Cancers and Lifestyle Modifications

Because cancer risk is higher among cancer survivors, with a risk as high as 30%, for example, in patients who have had head and neck cancer or lung cancer, diligent adherence to screening guidelines is imperative. Additionally, an emphasis on lifestyle modifications to reduce cancer risk is extremely important and includes smoking cessation, exercise, and weight loss.

Cognitive Function after Cancer Therapy

Cancer survivors often report cognitive dysfunction, particularly impairment of multitasking and executive functions. These problems occur most frequently after chemotherapy ("chemo brain"), endocrine therapy, and brain radiation. Recent studies support patients' reports of impairment in verbal ability, memory, and visuospatial and executive functions. A recent study showed that such symptoms occurred in about 20% of breast cancer survivors. Symptoms seem to improve with time.

Validation of patients' concerns and reassurance that symptoms usually improve over time may be beneficial. Interventions include management of contributing factors such as pain, anxiety, depression, and fatigue, and discontinuation

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of medications that might contribute to cognitive impairment. Nonpharmacologic interventions may include coping behaviors such as use of reminder notes and avoidance of multitasking. Pharmacologic interventions, such as modafinil, are under study.

Other Issues for Survivors

Fear of recurrence, sleep disorders, anxiety and depression, fatigue, and chronic pain may be part of the survivor experience and require medical management. Vaccination recommendations may differ for cancer survivors. Patients who are immunosuppressed from leukemia or lymphoma or from treatment such as allogeneic hematopoietic stem cell transplantation should not receive live herpes zoster; oral polio; attenuated live influenza; or measles, mumps, and rubella vaccines.

KEY POINTS

- A survivorship care plan and clear delineation of responsibility for follow-up care should be formulated at the completion of cancer therapy and provided to the patient and internist.
- Patients reporting impaired cognitive function after cancer treatment can benefit from validation of their symptoms and being told that their symptoms will likely improve with time.
- Patients with immunosuppression caused by their malignancy or its treatment should not receive live vaccines.

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Hematology Questions

Item 1

A 45-year-old woman is evaluated in the emergency department for a 1-day history of abdominal pain and fever. She also reports unexpected, heavy menstrual bleeding of 1 day's duration and easy bruising of 2 days' duration. Medical and family histories are unremarkable, and she takes no medications.

On physical examination, the patient is oriented to person and place, but not time. Temperature is 38.1 °C (100.6 °F), blood pressure is 170/98 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. Other than confusion, neurologic examination is normal. Subconjunctival hemorrhages are present. Cardiopulmonary examination is normal. Abdominal examination reveals tenderness to palpation without guarding or rebound. Pelvic examination shows blood in the vaginal vault with no cervical motion tenderness or adnexal masses.

Laboratory studies:

Hematocrit	26%
Leukocyte count	10,300/μL (10.3×10^9/L)
Platelet count	24,000/μL (24×10^9/L)
Reticulocyte count	8.3% of erythrocytes
Bilirubin, total	2.3 mg/dL (39.3 μmol/L)
Creatinine	3.2 mg/dL (283 μmol/L)
Lactate dehydrogenase	1500 U/L

Which of the following is the most appropriate diagnostic test to perform next?

(A) ADAMTS-13 activity level
(B) Osmotic fragility test
(C) Peripheral blood smear
(D) Stool Shiga toxin assay

Item 2

A 75-year-old man arrives at the emergency department after passing three large-volume, melenic stools over a 2-hour period. Medical history is significant for atrial fibrillation and hypertension. Medications are warfarin, metoprolol, and lisinopril.

On physical examination, he is diaphoretic and the skin is cool to the touch. Temperature is 36.8 °C (98.2 °F), blood pressure is 82/64 mm Hg, pulse rate is 142/min and irregular, and respiration rate is 20/min. Oxygen saturation is 95% breathing ambient air. Cardiac examination reveals tachycardia. Pulmonary examination is normal. Peripheral pulses are thready. Rectal examination reveals melenic stool that is guaiac positive.

Laboratory studies:

Hemoglobin	8.2 g/dL (82 g/L); 12.8 g/dL (128 g/L) 3 months ago
Leukocyte count	8600/μL (8.6×10^9/L)
Platelet count	183,000/μL (183×10^9/L)
INR	7.4

In addition to intravenous vitamin K and fluid resuscitation, which of the following is the most appropriate treatment?

(A) 4-Factor prothrombin complex concentrate
(B) Activated factor VII
(C) Cryoprecipitate
(D) Fresh frozen plasma

Item 3

A 37-year-old woman is evaluated for a 6-month history of progressive shortness of breath. Although she remains physically active, she becomes dyspneic when walking up multiple flights of stairs or running to catch a bus. Medical history is significant for a diagnosis of a pulmonary embolism 2 years ago, which was associated with oral contraceptive use. She was initially treated with low-molecular-weight heparin followed by therapeutic warfarin for 3 months. She is a nonsmoker. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, she is afebrile, blood pressure is 128/76 mm Hg at rest, pulse rate is 72/min, and respiration rate is 15/min. Oxygen saturation is 98% breathing ambient air. Pulmonary examination reveals clear lungs. Cardiac examination is significant for a fixed, split S_2, a holosystolic murmur at the left sternal border that increases on inspiration, and a heave. Trace lower extremity bilateral edema is present. The remainder of the examination is noncontributory.

Walking up stairs at the office at a moderate pace, she becomes short of breath after two flights of stairs, oxygen saturation decreases to 92%, and pulse rate increases to 145/min.

A chest radiograph is normal, showing no parenchymal abnormalities. Transthoracic echocardiography shows right atrial and ventricular dilation and moderate tricuspid regurgitation but no other valvular abnormalities.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Pulmonary CT angiography
(B) Serum D-dimer test
(C) Venous Doppler ultrasonography of the legs
(D) Ventilation-perfusion (V/Q) lung scan

Item 4

A 48-year-old woman is evaluated for fatigue and intermittent abdominal discomfort of 2 months' duration and occasional dark urine. Medical and family histories are unremarkable. Her only medication is an oral contraceptive pill.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 125/74 mm Hg, pulse rate is 68/min, and respiration rate is 13/min. Pallor is observed, and abdominal tenderness is present on palpation. No icterus, bruising, or splenomegaly is noted.

Laboratory studies:

Hemoglobin	7.2 g/dL (72 g/L)
Leukocyte count	3000/μL (3×10^9/L) with a normal differential
Platelet count	125,000/μL (125×10^9/L)
Reticulocyte count	8% of erythrocytes
Bilirubin, total	Normal
Direct antiglobulin (Coombs) test	Negative

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A bone marrow biopsy shows 20% cellularity. Flow cytometry reveals erythrocytes lacking CD55 and CD59. Abdominal ultrasonography shows portal vein thrombosis.

Which of the following is the most likely diagnosis?

(A) Aplastic anemia
(B) Myelodysplastic syndrome
(C) Myeloproliferative neoplasm
(D) Paroxysmal nocturnal hemoglobinuria

Item 5

A 36-year-old woman is evaluated in the emergency department for a 1-month history of intermittent abdominal pain, a 1-week history of abdominal swelling, and a 4.5-kg (10 lb) weight gain. She rarely drinks alcohol. Her only medication is an oral combination contraceptive pill.

On physical examination, temperature is 36.4 °C (97.5 °F), blood pressure is 115/76 mm Hg, pulse rate is 92/min, and respiration rate is 16/min. Tender hepatomegaly and tense ascites are noted on abdominal palpation. No jaundice or spider telangiectasias are observed.

Laboratory studies show a hemoglobin level of 11.5 g/dL (115 g/L), leukocyte count of 12,000/μL (12×10^9/L), and platelet count of 335,000/μL (335×10^9/L). A viral hepatitis screening panel and pregnancy test are both negative.

Abdominal Doppler flow ultrasonography shows hepatic vein thrombosis and elevated estimated portal pressures.

Which of the following diagnostic tests is most likely to explain the cause of this patient's condition?

(A) Antiphospholipid antibody
(B) Factor V Leiden
(C) *JAK2 V617F* activating mutation
(D) Prothrombin gene mutation (G20210A)

Item 6

A 24-year-old man is evaluated in the emergency department for prolonged and severe bleeding 3 days after undergoing hemorrhoidectomy. He reports continually bleeding and soaking through four bath towels. Medical history is significant for prolonged bleeding following wisdom tooth removal. Family history is notable for a brother who experienced heavy bleeding with tooth extraction and a maternal grandfather who died of an intracerebral hemorrhage at age 32 years. He takes no medications.

On physical examination, the patient appears pale. Temperature is 36.7 °C (98.1 °F), blood pressure is 90/55 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. Continued rectal bleeding is observed, with no clear source on anoscopy.

Laboratory studies:

Hematocrit	17%
Leukocyte count	12,000/μL (12×10^9/L)
Platelet count	380,000/μL (380×10^9/L)
Activated partial thromboplastin time (aPTT)	45 s
Prothrombin time	12.2 s
aPTT following 1:1 mixing study with normal plasma	32 s

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bleeding time
(B) Factor VIII level
(C) Factor XI level
(D) Lupus anticoagulant

Item 7

A 52-year-old man is evaluated for orthopnea and dyspnea on exertion of 4 weeks' duration. Twelve weeks ago, he developed chronic abdominal pain, diarrhea, and weight loss. Two weeks ago, he developed new-onset eczema and nonhealing, painful sores inside his mouth. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, the patient appears ill and uncomfortable. Temperature is 36.4 °C (97.5 °F), blood pressure is 138/88 mm Hg, pulse rate is 88/min, and respiration rate is 18/min. He has diffuse erythroderma and multiple oral aphthous ulcers. On cardiac examination, prominent jugular venous distention, an S_4 gallop, and a grade 2/6 holosystolic murmur are noted. On pulmonary examination, crackles are auscultated. Palpation of the abdomen elicits generalized tenderness without guarding. Lower extremity edema is present to the knee.

Laboratory studies:

Hemoglobin	13.5 g/dL (135 g/L)
Leukocyte count	18,000/μL (18×10^9/L) with 50% lymphocytes, 10% eosinophils, and 40% neutrophils
Platelet count	155,000/μL (155×10^9/L)
Troponin I	Negative

Electrocardiography shows low QRS voltage in all leads without evidence of ischemic changes. Echocardiography shows restrictive left ventricular filling, increased echogenicity of the endomyocardium, and moderate mitral regurgitation.

A peripheral blood smear demonstrates mature eosinophils. Secondary causes of eosinophilia have been excluded.

Which of the following is the most likely diagnosis?

(A) Acute eosinophilic leukemia
(B) Chronic myeloid leukemia
(C) Hypereosinophilic syndrome
(D) Systemic mastocytosis

Item 8

A 35-year-old woman is evaluated for worsening thrombocytopenia; she is pregnant at 36 weeks' gestation. Medical history is significant for immune thrombocytopenic purpura. Previous platelet counts during this pregnancy have been 80,000 to 100,000/μL (80-100 × 10^9/L). Her only medication is a prenatal vitamin.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 165/110 mm Hg, pulse rate is 95/min, and respiration rate is 18/min. Abdominal examination reveals mild right upper quadrant discomfort on palpation. Reflexes are normal, and no clonus is observed. She has lower extremity edema to the level of the knees bilaterally.

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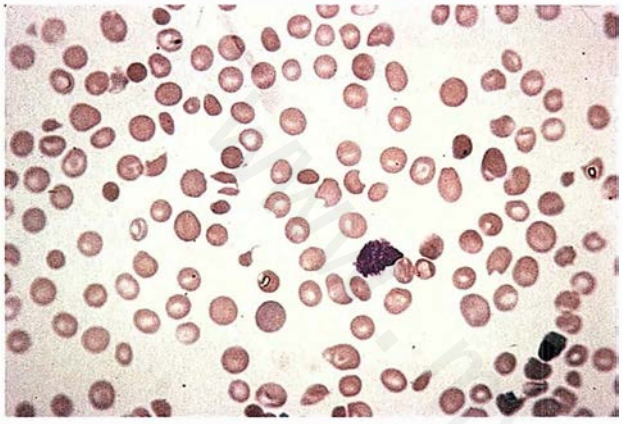
Laboratory studies:

Hemoglobin	10.5 g/dL (105 g/L)
Platelet count	21,000/μL (21×10^9/L)
Alanine aminotransferase	480 U/L
Aspartate aminotransferase	600 U/L
Creatinine	1.2 mg/dL (106.1 μmol/L)
Urinalysis	3+ protein

A peripheral blood smear is shown.



Which of the following is the most appropriate management of this patient's thrombocytopenia?

(A) Emergent delivery
(B) Intravenous immune globulin
(C) Plasma exchange
(D) Prednisone

Item 9

A 44-year-old man is evaluated in follow-up for an episode of unprovoked left proximal leg deep venous thrombosis 3 months ago. Following initial anticoagulation with low-molecular-weight heparin, he began treatment with warfarin. INR testing done every 3 to 4 weeks has shown a stable therapeutic INR. He has mild left leg discomfort after a long day of standing, but it does not limit his activity level. He tolerates warfarin well. Family history is unremarkable, and he takes no other medications.

On physical examination, vital signs are normal. He has mild edema of the left leg below the knee, with post-thrombotic pigmentation. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Continue anticoagulation indefinitely
(B) Discontinue warfarin in another 3 months
(C) Discontinue warfarin now
(D) Discontinue warfarin and perform thrombophilia testing

Item 10

A 28-year-old woman is evaluated for a 1-week history of progressive dyspnea and fatigue. She was diagnosed with Hodgkin lymphoma 2 months ago and is receiving chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). She takes no other medications.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 134/82 mm Hg, pulse rate is 105/min, and respiration rate is 16/min. Oxygen saturation is 98% breathing ambient air. Conjunctival pallor is noted but no scleral icterus. The lungs are clear to auscultation, and the cardiac examination is normal. The remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	6.8 g/dL (68 g/L)
Leukocyte count	1300/μL (1.3×10^9/L)
Platelet count	83,000/μL (83×10^9/L)
Cytomegalovirus IgG antibody	Positive

A peripheral blood smear shows pancytopenia but is otherwise unremarkable.

Which of the following is the most appropriate erythrocyte transfusion product for this patient?

(A) Leukoreduced
(B) Leukoreduced, cytomegalovirus-negative
(C) Leukoreduced, irradiated
(D) Leukoreduced, washed

Item 11

H

A 70-year-old man is admitted to the hospital for fatigue and malaise of 3 weeks' duration and easy bruising and fever of 1 week's duration. Medical and family histories are unremarkable. He takes no medications.

On physical examination, temperature is 38.1 °C (100.5 °F), blood pressure is 128/83 mm Hg, pulse rate is 115/min, and respiration rate is 13/min; BMI is 28. Conjunctivae are pale. Splenomegaly is noted and lower extremity petechiae are observed.

Laboratory studies show a hemoglobin level of 7.3 g/dL (73 g/L), a leukocyte count of 20,000/μL (20×10^9/L), and a platelet count of 14,000/μL (14×10^9/L). Bone marrow examination reveals 35% lymphoblasts. A peripheral blood smear demonstrates immature cells identified as lymphoid blasts by flow cytometry. Cytogenetic testing using fluorescence in situ hybridization is positive for t(9;22).

In addition to dexamethasone, which of the following is the most appropriate treatment?

(A) Asparaginase
(B) Dasatinib
(C) Daunorubicin
(D) Vincristine

Item 12

H

A 38-year-old man is evaluated in the hospital for increasing right leg pain and swelling. He experienced a right femur fracture 2 days ago and underwent surgical repair. Medical history is unremarkable, but family history reveals his mother experienced a pulmonary embolism at age 66 years while receiving breast cancer treatment, and

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CONT.

a maternal uncle had a "leg clot" at age 82 years. Medications are as-needed oxycodone and prophylactic-dose enoxaparin.

On physical examination, vital signs are normal. The right leg shows increased circumference of 2 cm at the midcalf compared with the left. The surgical site is clean and dry.

Laboratory studies show normal activated partial thromboplastin and prothrombin times.

Doppler ultrasonography shows a right proximal leg deep venous thrombosis.

Which of the following is the most appropriate thrombophilia testing for this patient?

(A) Antiphospholipid antibodies
(B) Factor V Leiden
(C) Prothromhin gene mutation
(D) No thrombophilia testing

Item 13

A 23-year-old man is admitted to the hospital with an acute vaso-occlusive pain episode. He reports pain in his back and legs with no respiratory or abdominal symptoms and rates his pain 10/10. Medical history is significant for homozygous sickle cell anemia (Hb SS). He has vaso-occlusive pain episodes approximately every 2 months. He typically receives erythrocyte transfusions for symptomatic anemia one to three times per year. Medications are folic acid and hydroxyurea.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 115/70 mm Hg, pulse rate is 96/min, and respiration rate is 20/min. Oxygen saturation is 96% breathing ambient air. Scleral icterus is observed. A grade 2/6 early systolic murmur is heard at the base of the heart. Lungs are clear. No hepatosplenomegaly or tenderness is noted on abdominal examination.

Laboratory studies show a hemoglobin level of 7 g/dL (70 g/L), a mean corpuscular volume of 110 fL, and a serum creatinine level of 0.4 mg/dL (35.4 µmol/L).

A chest radiograph is normal.

Hydration and incentive spirometry are initiated.

Which of the following analgesic regimens is most appropriate for this patient?

(A) As-needed ketoprofen and morphine
(B) As-needed morphine
(C) Scheduled meperidine
(D) Scheduled morphine

Item 14

A 25-year-old woman is evaluated for a 3-hour history of pleuritic chest pain and mild shortness of breath. She is pregnant at 16 weeks' gestation. Her symptoms began acutely; she reports no other symptoms or previous problems during the pregnancy. Medical and family history is unremarkable. Her only medication is a prenatal vitamin.

On physical examination, she is afebrile, blood pressure is 125/88 mm Hg, heart rate is 80/min, and respiration rate is 15/min. Oxygen saturation is 97% breathing ambient air. Lungs are clear, and cardiac examination is normal. She has a distended, pregnant abdomen. Trace bipedal edema is noted, and the left midcalf circumference is 1.5 cm larger than the right. The remainder of the physical examination is unremarkable.

A chest radiograph is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT pulmonary angiography
(B) D-dimer test
(C) Lower extremity venous duplex ultrasonography
(D) Ventilation-perfusion lung scan

Item 15

A 42-year-old woman is evaluated for thrombocytopenia. She was admitted to the hospital 1 week ago for newly diagnosed acute myeloid leukemia. She has been receiving leukoreduced, irradiated erythrocyte and platelet transfusions since admission. Yesterday, her platelet count was 8000/µL (8×10^9/L). A platelet count checked 30 minutes after a random, donor-pooled platelet transfusion was 11,000/µL (11×10^9/L). This morning, her platelet count was 6000/µL (6×10^9/L). Thirty minutes after a random, donor-pooled platelet transfusion, the platelet count is 9000/µL (9×10^9/L). She has had four uncomplicated pregnancies and deliveries. Medications are daunorubicin, cytarabine, cefepime, posaconazole, valacyclovir, and ondansetron.

On physical examination, vital signs are normal. No splenomegaly is present. Ecchymoses are seen at previous venipuncture sites. She has scattered petechiae over the lower extremities. The remainder of the examination is normal.

Peripheral blood smear reveals no schistocytes or platelet clumps.

Which of the following is the most appropriate management?

(A) Transfuse ABO-matched platelets
(B) Transfuse HLA-matched platelets
(C) Transfuse washed platelets
(D) Observation

Item 16

A 56-year-old man is evaluated in the hospital for acute onset right lower extremity pain and swelling. He was admitted to the hospital 2 days ago with hematemesis and underwent emergent upper endoscopy with band ligation of extensive esophageal varices. He received 2 units of packed red blood cells. Medical history is significant for alcoholic cirrhosis. He stopped drinking alcohol 18 months ago. His only outpatient medication is propranolol.

On physical examination, he is alert and oriented. He is afebrile, blood pressure is 128/76 mm Hg, pulse rate is 82/min, and respiration rate is 16/min. Splenomegaly is present. The right calf is 4 cm in circumference larger than the left. The remainder of the physical examination is noncontributory.

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H CONT.

Laboratory studies:

Activated partial thromboplastin time	39.3 s
Hemoglobin	10.3 g/dL (103 g/L)
Platelet count	78,000/μL (78×10^9/L)
Prothrombin time	16.3 s

A lower extremity Doppler ultrasonography reveals a right leg proximal deep venous thrombosis (DVT).

Which of the following is the most appropriate management of this patient's DVT?

(A) Argatroban
(B) Inferior vena cava filter placement
(C) Intravenous heparin
(D) Rivaroxaban

Item 17

A 30-year-old woman is evaluated in follow-up for anemia diagnosed during a recent evaluation for symptoms of fatigue. She reports no shortness of breath, dizziness, or chest pain. Medical history is notable only for heavy menses. Family history is remarkable for anemia in her mother. Her only medication is an iron supplement. She is white.

On physical examination, the patient appears well. Temperature is 36.9 °C (98.4 °F), blood pressure is 100/60 mm Hg, pulse rate is 80/min, and respiration rate is 12/min. BMI is 25. No lymphadenopathy or organomegaly is identified, and the remainder of her physical examination is unremarkable.

Laboratory studies:

Hemoglobin	8.5 g/dL (85 g/L)
Mean corpuscular volume	68 fL
Platelet count	400,000/μL (400×10^9/L)
Reticulocyte count	6% of erythrocytes
Bilirubin, total	2.0 mg/dL (34.2 μmol/L)
Lactate dehydrogenase	300 U/L
Iron studies	
Ferritin	450 ng/mL (450 μg/L)
Iron	60 μg/dL (11 μmol/L)
Total iron-binding capacity	300 μg/dL (54 μmol/L)
Hemoglobin electrophoresis	
Hemoglobin A	94% (slightly low)
Hemoglobin A_2	4% (increased)
Hemoglobin F	2% (increased)
Hemoglobin S	0% (normal)

Numerous target cells are seen on a peripheral blood smear.

Which of the following is the most likely diagnosis?

(A) Anemia of chronic disease
(B) Iron malabsorption
(C) α-Thalassemia
(D) β-Thalassemia

Item 18

A 68-year-old man is evaluated for a 3-year history of dyspnea on exertion. He experiences no headaches or blurred vision. Medical history is notable for a stroke 2 years ago. He is a smoker with an 80-pack-year smoking history. Medications are hydrochlorothiazide, lisinopril, aspirin, and simvastatin.

On physical examination temperature is 36.7 °C (98.0 °F), blood pressure is 145/84 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. Oxygen saturation breathing ambient air is 88%. He has facial plethora. He has no carotid bruits. Cardiac sounds are distant. Pulmonary examination reveals distant breath sounds with scattered wheezing. No hepatosplenomegaly is palpated. No digital clubbing is observed.

Laboratory studies show a hemoglobin level of 18.2 g/dL (182 g/L), leukocyte count of 8000/μL (8×10^9/L) with a normal differential, and platelet count of 225,000/μL (225×10^9/L). Erythropoietin level is 30 mU/mL (30 U/L).

The patient is advised to quit smoking.

Which of the following is the most appropriate next step in management?

(A) Bone marrow biopsy
(B) *JAK2 V617F* testing
(C) Phlebotomy
(D) Supplemental oxygen

Item 19

A 73-year-old woman is evaluated for increasing dyspnea on exertion and left buttock pain of 1 week's duration. She reports pain with standing straight or sitting down. She has no history of trauma. Family history is unremarkable, and she takes no medications.

On physical examination, the patient is pale and displays significant distress by bending over and grasping the back of the chair. Temperature is 36.6 °C (98.1 °F), blood pressure is 140/80 mm Hg, pulse rate is 108/min, and respiration rate is 19/min. A 10-cm hematoma is noted on the left buttock with tracking down the back of the thigh, with smaller ecchymoses scattered over her arms and shins. She has no bleeding of the gums or nose. A stool sample is guaiac negative.

Laboratory studies:

Hematocrit	35%
Leukocyte count	9100/μL (9.1×10^9/L)
Mean corpuscular volume	89 fL
Platelet count	310,000/μL (310×10^9/L)
Activated partial thromboplastin time (aPTT)	90 seconds
Prothrombin time	10.3 seconds
aPTT following 1:1 mixing study with normal plasma	45 seconds
Factor VIII activity	3% (normal, 50%-150%)
Factor VIII inhibitor	Markedly elevated

Which of the following is the most appropriate management?

(A) Administer desmopressin
(B) Administer factor VIII
(C) Administer recombinant activated factor VII
(D) Measure lupus anticoagulant

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Item 20

A 52-year-old man is evaluated in follow-up. He was admitted to the hospital 2 weeks ago with a new diagnosis of acute myeloid leukemia. He has received induction chemotherapy with daunorubicin and cytarabine. Medical history is remarkable for an urticarial reaction to a platelet transfusion that resolved promptly with diphenhydramine. Other medications are posaconazole, valacyclovir, and cefepime.

On physical examination, temperature is 37.4 °C (99.3 °F), blood pressure is 132/72 mm Hg, pulse rate is 84/min, and respiration rate is 18/min. Oxygen saturation is 94% breathing ambient air. Oropharyngeal examination is unremarkable. He has scattered petechiae over both ankles and an ecchymosis at the insertion site of his central venous catheter.

Laboratory studies show he is neutropenic and has a platelet count of 12,000/μL (12×10^9/L).

Which of the following is the most appropriate management of this patient's thrombocytopenia?

(A) Transfuse leukoreduced, irradiated platelets
(B) Transfuse leukoreduced, irradiated, HLA-matched platelets
(C) Transfuse leukoreduced, irradiated, washed platelets
(D) Recheck platelet count in 24 hours

Item 21

A 77-year-old woman is evaluated for frequently fluctuating INRs (<1.8 to >3.5) while taking warfarin therapy. She has undergone INR testing every 1 to 2 weeks and frequent warfarin dose adjustments. She reports a consistent dietary intake. Medical history is notable only for recurrent deep venous thrombosis. She takes no other medications.

On physical examination, vital signs are normal, as is the remainder of the examination.

Which of the following is the most appropriate next step in management?

(A) Daily low-dose vitamin K supplementation
(B) Genetic testing for cytochrome P-450 2C9 and vitamin K epoxide reductase complex-1 polymorphisms
(C) Genetic testing for factor V Leiden
(D) Warfarin cessation and aspirin initiation

Item 22

A 24-year-old woman is evaluated in the emergency department for dyspnea on exertion and severe fatigue. Medical history is significant for sickle cell anemia, with a hospital admission for acute chest syndrome last year. She reports that her 4-year-old son had a high fever 1 week ago. She takes stable doses of hydroxyurea and a folic acid supplement.

On physical examination, she appears breathless and pale. Temperature is 38.4 °C (101.1 °F), blood pressure is 95/61 mm Hg, pulse rate is 104/min, and respiration rate is 14/min. Scleral icterus is observed. Lungs are clear. Cardiac examination reveals tachycardia with a prominent flow murmur.

Laboratory studies:

Hemoglobin	3.4 g/dL (34 g/L)
Leukocyte count	14,000/μL (14×10^9/L)
Platelet count	222,000/μL (222×10^9/L)
Reticulocyte count	0.1% of erythrocytes

Which of the following is the most likely cause of this patient's findings?

(A) Cytomegalovirus
(B) Epstein-Barr virus
(C) Influenza A virus
(D) Parvovirus B19

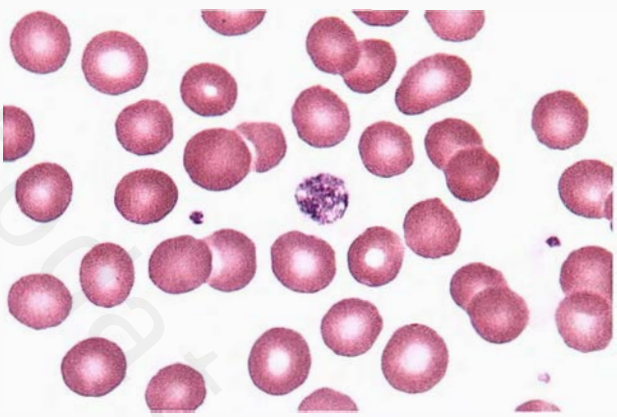
Item 23

A 35-year-old woman is evaluated for the recent onset of a rash on her legs. She has no other symptoms. She does not drink alcohol. Medications are an oral contraceptive and a multivitamin.

On physical examination, vital signs are normal. Nonpruritic, nonblanching red macules are noted on the lower extremities. Abdominal examination reveals no splenomegaly.

Laboratory study results show a hematocrit of 38%, leukocyte count of 7000/μL (7×10^9/L), and platelet count of 78,000/μL (78×10^9/L).

The peripheral blood smear is shown.



Which of the following is the most appropriate management?

(A) Anti-D immune globulin
(B) Prednisone
(C) Repeat complete blood count in 1 week
(D) Rituximab
(E) Splenectomy

Item 24

A 43-year-old man is evaluated for a 2-day history of painful swelling of the left thigh just below the groin. He reports no preceding trauma, immobility, surgery, hospital stay, or long-distance airline travel. Medical history is notable for well-controlled hypertension. His only medication is losartan.

On physical examination, vital signs are normal. BMI is 28. An approximately 6-cm area of erythema and tenderness with a palpable cord is present overlying the greater saphenous vein on the proximal medial aspect of

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the left thigh up to the inguinal crease, consistent with superficial thrombophlebitis. Examination of the distal extremities is normal, without swelling or asymmetry. The remainder of the examination is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Low-dose aspirin
(B) Serum D-dimer testing
(C) Venous duplex ultrasonography of the left thigh
(D) Warm compresses and NSAIDs

Item 25

A 79-year-old woman is diagnosed with new-onset anemia during a routine examination. Medical history is significant for an ischemic stroke 8 weeks ago, which resulted in residual right-sided weakness and admission to a rehabilitation facility. At that time, her complete blood count was normal. She has been eating poorly while in the facility. Her medications are aspirin, lisinopril, and simvastatin.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 120/70 mm Hg, pulse rate is 82/min, and respiration rate is 12/min; BMI is 27. Right-sided motor strength is 3/4 and sensation is normal.

Laboratory studies:

Hemoglobin	10.1 g/dL (101 g/L)
Mean corpuscular volume	102 fL
Folate	2.5 ng/mL (5.7 nmol/L)
Homocysteine	10.2 mg/L (75.4 µmol/L)
Methylmalonic acid	Normal

Which of the following is the most likely diagnosis?

(A) Folate deficiency
(B) Iron deficiency
(C) α-Thalassemia trait
(D) Vitamin B_{12} deficiency

Item 26

A 67-year-old man is evaluated during follow-up consultation after a diagnosis of essential thrombocythemia discovered incidentally on a routine health maintenance examination. His medical history is otherwise unremarkable, and he takes no medications.

On physical examination, he is afebrile, blood pressure is 115/72 mm Hg, pulse rate is 72/min, and respiration rate is 18/min. Cardiac evaluation reveals a regular rate and rhythm with no murmurs.

Results of laboratory studies show a hemoglobin level of 15 g/dL (150 g/L), leukocyte count of 5600/µL (5.6×10^9/L), and platelet count of 770,000/µL (770×10^9/L). Follow-up testing confirms a diagnosis of essential thrombocythemia.

Which of the following is the most appropriate treatment?

(A) Anagrelide plus low-dose aspirin
(B) Hydroxyurea plus low-dose aspirin
(C) Ruxolitinib
(D) Warfarin
(E) Observation

Item 27

A 78-year-old woman is evaluated for progressive fatigue and dyspnea with exertion over the past 6 months. She has otherwise felt well with no nausea, vomiting, or changes in stool. Medical history is significant for hypertension and an aortic valve replacement at age 67 years. Medications are metoprolol and warfarin.

On physical examination, the patient appears well. Temperature is 37.0 °C (98.6 °F), blood pressure is 135/55 mm Hg, pulse rate is 65/min, and respiration rate is 14/min. BMI is 28. She has mild scleral icterus. The lungs are clear to auscultation. Examination of the heart reveals a mechanical S_2, a grade 3/6 systolic murmur at the right upper sternal border radiating to the carotid arteries, and a soft diastolic murmur heard at the left sternal border. The spleen is not palpable, and no pedal edema is present. Stool guaiac testing is negative.

Laboratory studies:

Haptoglobin	32 mg/dL (320 mg/L)
Hemoglobin	6.5 g/dL (65 g/L)
Leukocyte count	5500/µL (5.5×10^9/L)
Mean corpuscular volume	71 fL
Platelet count	290,000/µL (290×10^9/L)
Reticulocyte count	2.9% of erythrocytes
Bilirubin, total	2.7 mg/dL (46.2 µmol/L)
Bilirubin, direct	1.0 mg/dL (17.1 µmol/L)
Ferritin	3.6 ng/mL (3.6 µg/L)
Lactate dehydrogenase	1200 U/L

Peripheral blood smear shows 3+ schistocytes and microcytic, hypochromic cells.

Which of the following is the most appropriate diagnostic test to perform next?

(A) ADAMTS-13 assay
(B) D-dimer measurement
(C) Direct antiglobulin (Coombs) test
(D) Echocardiography

Item 28

A 42-year-old man arrives for follow-up consultation. Three months ago he developed a proximal right leg deep venous thrombosis following a skiing-related fracture of the right tibia. Although not recommended by guidelines, a thrombophilia evaluation was performed, which revealed an elevated plasma homocysteine level, and subsequent genetic testing revealed that he is homozygous for the C677T methylene tetrahydrofolate reductase (*MTHFR*) polymorphism. He is otherwise healthy, and his medical history is unremarkable. He has a 12-year-old son. There is no family history of thrombotic disorders. His only medication is warfarin.

Which of the following is the most appropriate next step in management?

(A) Folic acid and vitamin B_{12} administration
(B) Indefinite continuation of warfarin
(C) *MTHFR* polymorphism testing of first-degree relatives
(D) Warfarin discontinuation

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Item 29

A 45-year-old man is evaluated following a recent diagnosis of hereditary hemochromatosis. He was screened after a relative was diagnosed with hereditary hemochromatosis. He is asymptomatic and has no clinical or laboratory evidence of liver disease, diabetes mellitus, or cardiomyopathy. Medical history is otherwise negative, and he takes no medications.

On physical examination, vital signs are normal. The examination is unremarkable.

Weekly phlebotomy is planned.

Which of the following dietary constituents should this patient be advised to avoid?

(A) Calcium supplements
(B) Raw or undercooked seafood
(C) Red meat
(D) Vitamin C–containing fruits and vegetables

Item 30

A 26-year-old woman is evaluated during consultation for concerns about a possible hypercoagulable state. Her mother was recently diagnosed with heterozygous factor V Leiden mutation following multiple episodes of venous thromboembolic disease. The patient is concerned with her own risk of thrombosis. Medical history is unremarkable, with no venous thromboembolism or abnormal bleeding. She takes no medications.

The physical examination is unremarkable.

Which of the following is the most appropriate diagnostic test?

(A) Activated protein C resistance assay
(B) Factor V activity level
(C) Factor V Leiden genetic test
(D) No testing

Item 31

A 43-year-old woman is admitted to the hospital for fatigue of 4 weeks' duration, easy bruising and bleeding gums of 1 week's duration, and a 1-day fever of 38.9 °C (102.0 °F).

On physical examination, the patient appears ill. Temperature is 39.4 °C (103.0 °F), blood pressure is 105/62 mm Hg, pulse rate is 115/min, and respiration rate is 22/min. She has gingival bleeding, bleeding around her intravenous insertion site, and multiple ecchymoses and petechiae. Hepatomegaly is also noted.

Laboratory studies:

Activated partial thromboplastin time	65 s
Hemoglobin	7.6 g/dL (76 g/L)
Leukocyte count	32,000/μL (32×10^9/L)
Platelet count	25,000/μL (25×10^9/L)
Prothrombin time	24 s
Fibrinogen	97 mg/dL (0.97 g/L)

A peripheral blood smear shows 80% immature blasts with prominent Auer rods phenotypically consistent with promyelocytes.

Which of the following is the most appropriate initial management?

(A) All-*trans* retinoic acid
(B) Chemotherapy
(C) t(9:22) testing
(D) t(15:17) testing

Item 32

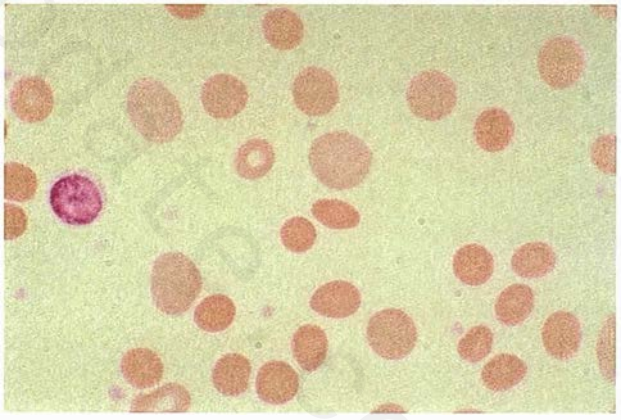
A 25-year-old woman is evaluated for worsening shortness of breath that began 2 to 3 days ago. A week before the onset of these symptoms, she developed a flulike syndrome of fever, myalgia, arthralgia, and transient facial rash. Medical history is significant for anemia. Her father also has anemia. She takes no medications.

On physical examination, the patient appears pale. Temperature is 36.9 °C (98.5 °F), blood pressure is 100/60 mm Hg, pulse rate is 100/min, and respiration rate is 24/min. BMI is 24. Scleral icterus is noted. On palpation, her spleen is enlarged. Cardiopulmonary examination reveals tachycardia.

Laboratory studies:

Hematocrit	18%
Leukocyte count	8300/μL (8.3×10^9/L)
Platelet count	200,000/μL (200×10^9/L)
Lactate dehydrogenase	500 U/L
Direct antiglobulin (Coombs) test	Negative

A peripheral blood smear is shown.



Which of the following is the most appropriate diagnostic test?

(A) Diagnostic trial of prednisone
(B) Flow cytometry
(C) Glucose-6-phosphate dehydrogenase activity
(D) Osmotic fragility test

Item 33

A 45-year-old man is evaluated in follow-up for iron deficiency anemia discovered during routine evaluation 1 week

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ago. His complete blood count was normal when he was last evaluated 1 year ago. He feels well, his medical history is unremarkable, and he takes no medications.

The physical examination performed 1 week ago was normal.

A fecal occult blood test is negative.

Iron replacement is initiated.

Which of the following is the most appropriate management?

(A) Colonoscopy and upper endoscopy
(B) Repeat iron studies in 1 month
(C) Tissue transglutaminase IgA antibody assay
(D) Wireless capsule endoscopy

Item 34

A 24-year-old woman undergoes routine evaluation. She is pregnant at 12 weeks' gestation. Medical history is notable for homozygous sickle cell anemia (Hb SS). She has had multiple uncomplicated painful crises treated at home with hydration, nonopioid analgesia, and incentive spirometry. She requires hospital management for these episodes approximately twice per year. She has declined the use of hydroxyurea. Her only other medication is folic acid.

On physical examination, vital signs are normal. Mild scleral icterus is noted. A grade 2/6 early systolic flow murmur is heard at the cardiac base. The examination is otherwise normal.

Laboratory results show a hemoglobin level of 7.5 g/dL (75 g/L).

Which of the following is the most appropriate management?

(A) Erythrocyte transfusion to maintain hemoglobin level at 10 g/dL (100 g/L)
(B) Erythropoiesis-stimulating agent
(C) Exchange transfusion
(D) No transfusion at this time

Item 35

A 73-year-old woman is evaluated in the emergency department following a fall in her home. She tripped and fell over a rug. She did not lose consciousness but is experiencing left hip pain. Medical history is remarkable for atrial fibrillation. Her only medication is warfarin.

On physical examination, the patient is afebrile, blood pressure is 137/88 mm Hg, pulse rate is 105/min and irregular, and respiration rate is 14/min. The lungs are clear to auscultation, and the cardiac examination is significant only for an irregular rate. She has mild tenderness to palpation over the left hip. No hematoma or other bleeding is evident. The remainder of the examination is unremarkable.

Laboratory studies show a normal hemoglobin level and an INR of 10.2.

Radiographs of the left hip are negative for fracture.

In addition to withholding warfarin, which of the following is the most appropriate management of this patient's anticoagulation?

(A) 4-Factor prothrombin complex concentrate
(B) Fresh frozen plasma
(C) Oral vitamin K
(D) No additional therapy

Item 36

A 52-year-old man is evaluated for low back pain of 3 months' duration that is nonradiating, progressive, and worse with ambulation. He reports no preceding injury. Medical history is notable for smoldering multiple myeloma diagnosed 1 year ago; he has been stable since that time. His only medication is as-needed acetaminophen.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 132/82 mm Hg, pulse rate is 70/min, and respiration rate is 14/min. No focal neurologic findings are noted. He has pain to palpation of the lower lumbar spine. The remainder of the examination is unremarkable.

Laboratory studies show a hemoglobin level of 13 g/dL (130 g/L), serum creatinine level of 1.0 mg/dL (88.4 µmol/L), and serum calcium level of 9.8 mg/dL (2.5 mmol/L).

Plain radiographs of the lumbosacral spine demonstrate degenerative disk changes in the lumbar spine but no lytic lesions or fractures.

Which of the following is the most appropriate management?

(A) Chemotherapy
(B) MRI of the lumbar spine
(C) Symptomatic treatment and routine follow-up
(D) Zoledronic acid

Item 37

A 19-year-old woman is evaluated for progressive weakness and dyspnea during exercise. Medical history is notable for heavy menses since menarche that last approximately 8 days. She had abnormal bleeding with wisdom tooth extraction 5 years ago. Her mother and sister have heavy menses. Her only medication is a multivitamin.

On physical examination, she appears pale. Temperature is 36.8 °C (98.2 °F), blood pressure is 110/65 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. Pale conjunctivae are noted. A grade 2/6 systolic murmur is heard at the cardiac base. The lung fields are clear. The remainder of the examination is normal.

Laboratory studies:

Hematocrit	25%
Leukocyte count	5700/µL (5.7×10^9/L)
Mean corpuscular volume	71 fL
Platelet count	490,000/µL (490×10^9/L)
Activated partial thromboplastin time	25 s
Prothrombin time	10 s

Which of the following is the most likely diagnosis?

(A) Factor VII deficiency
(B) Factor XI deficiency
(C) Factor XII deficiency
(D) Hemophilia A
(E) von Willebrand disease

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Item 38

A 73-year-old woman undergoes follow-up warfarin monitoring. She takes warfarin for atrial fibrillation and her INRs have previously been stable. Five days ago, she was prescribed a 3-day course of trimethoprim-sulfamethoxazole for an uncomplicated urinary tract infection. Three weeks ago, her INR was 2.9; this morning, her INR is 8.2. She has no history of major bleeding.

On physical examination, vital signs are normal. No bruising or bleeding is evident. The cardiac examination reveals an irregular rhythm but is otherwise unremarkable.

Laboratory studies show a hemoglobin level of 13.6 g/dL (136 g/L) and platelet count of 178,000/μL (178 × 10^9/L).

Which of the following is the most appropriate management?

(A) Fresh frozen plasma infusion
(B) Oral vitamin K and repeat INR in 24 hours
(C) Prothrombin complex concentrate administration
(D) Warfarin interruption

Item 39

A 58-year-old man is evaluated in the hospital for thrombocytopenia. He recently underwent multiple orthopedic procedures for repair of traumatic injuries experienced 3 days ago. He received 12 units of packed red blood cells throughout trauma resuscitation and surgical procedures. Except for postoperative pain, the patient reports no focal symptoms. Medical history is otherwise unremarkable. Medications are as-needed acetaminophen and oxycodone for pain relief and subcutaneous unfractionated heparin for venous thromboembolism prophylaxis.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 135/85 mm Hg, pulse rate is 89/min, and respiration rate is 18/min. Multiple healing surgical incisions are clean and dry, without evidence of infection. No lower extremity edema is present. The remainder of the examination is unremarkable.

Laboratory studies show a hemoglobin level of 11.5 g/dL (115 g/L), leukocyte count of 9800/μL (9.8 × 10^9/L), and platelet count of 115,000/μL (115 × 10^9/L) (previously 160,000/μL [160 × 10^9/L]).

Which of the following is the most appropriate next step in management?

(A) 4T pretest probability scoring
(B) Heparin-induced platelet aggregation assay
(C) Platelet factor 4 enzyme-linked immunosorbent assay
(D) Serotonin release assay

Item 40

A 65-year-old man was admitted to the hospital 10 days ago with community-acquired pneumonia requiring intubation, mechanical ventilation, and fluids and vasopressors for persistent hypotension. He has since been extubated and his blood pressure has stabilized; he no longer requires vasopressor therapy. Oxygen saturation is 90% with 3 L/min oxygen via nasal cannula. He has a resolving cough and improving fatigue. Medical history is otherwise unremarkable. Medications in the hospital are levofloxacin, heparin, and omeprazole.

Laboratory studies:

Hemoglobin	7.4 g/dL (74 g/L) (10.6 g/dL [106 g/L] on admission)
Reticulocyte count	2.0% of erythrocytes; absolute: 58,000/μL (58 × 10^9/L)
Creatinine	2.8 mg/dL (248 μmol/L) (4.5 mg/dL [398 μmol/L] on admission)
Iron studies	
Ferritin	410 ng/mL (410 μg/L)
Iron, serum	30 μg/dL (5.4 μmol/L)
Total iron-binding capacity	144 μg/dL (26 μmol/L)

Electrocardiography reveals no ST- or T-wave changes.

Which of the following is the most appropriate management of this patient's anemia?

(A) Erythrocyte transfusion
(B) Erythropoiesis-stimulating agent
(C) Intravenous iron
(D) Continue current management

Item 41

A 45-year-old man presents to the emergency department with a 1-week history of fever, chills, hypotension, cough, progressive dyspnea, and lethargy. Medical history is remarkable for hepatitis C virus infection with cirrhosis. Medications are omeprazole and propranolol.

On physical examination, the patient is in moderate respiratory distress. Temperature is 39.2 °C (102.6 °F), blood pressure is 74/42 mm Hg, pulse rate is 144/min, and respiration rate is 26/min. Oxygen saturation is 76% breathing ambient air. He has no jugular venous distention. Chest examination reveals decreased breath sounds over the lower left lung field. Mild abdominal distention is present without a fluid wave. The spleen tip is palpable below the left costal margin.

Laboratory studies:

Activated partial thromboplastin time	42.4 s
Hemoglobin	11.8 g/dL (118 g/L)
Leukocyte count	10,500/μL (10.5 × 10^9/L)
Platelet count	63,000/μL (63 × 10^9/L)
Prothrombin time	16.6 s
INR	1.4
Fibrinogen	154 mg/dL (1.5 g/L)

A chest radiograph shows opacity of the left lower lobe and a moderate left-sided pleural effusion.

The patient is admitted to the ICU. Placement of an internal jugular central venous catheter is planned for medication administration.

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Which of the following is the most appropriate next step in management before catheter placement?

(A) Cryoprecipitate transfusion
(B) Fresh frozen plasma transfusion
(C) Platelet transfusion
(D) No transfusion

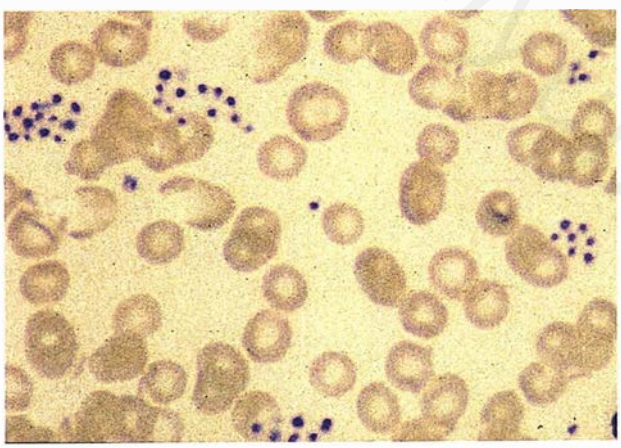
Item 42

A 35-year-old woman is evaluated following a recent diagnosis of iron deficiency anemia secondary to menorrhagia. She began an oral contraceptive to control bleeding and oral iron sulfate 6 weeks ago. She has no other medical conditions and takes no additional medications.

On physical examination, vital signs are normal. The conjunctivae are pink. No petechiae or purpura is evident. The remainder of the examination is normal.

Laboratory studies show a hematocrit level of 39%, leukocyte count of 5800/μL (5.8×10^9/L), and platelet count of 35,000/μL (35×10^9/L).

The peripheral blood smear is shown.



Which of the following is the most appropriate management?

(A) Antinuclear antibody and HIV testing
(B) Plasma exchange
(C) Prednisone
(D) Repeat complete blood count with a citrated tube

Item 43

A 45-year-old woman is evaluated before surgery; she is scheduled to undergo elective hysterectomy for fibroid tumors. Her medical history is significant for type 1 von Willebrand disease (vWD), long-standing iron deficiency anemia, and heavy menstrual bleeding. Family history is notable for vWD in the patient's father, sister, and two sons. Her only medication is iron sulfate.

On physical examination, vital signs are normal. The patient has palpable lower abdominal masses along the midline consistent with fibroids.

Which of the following is the most appropriate perioperative treatment?

(A) Cryoprecipitate
(B) Fresh frozen plasma
(C) Recombinant factor VIII
(D) Tranexamic acid
(E) von Willebrand factor–containing factor VIII concentrates

Item 44

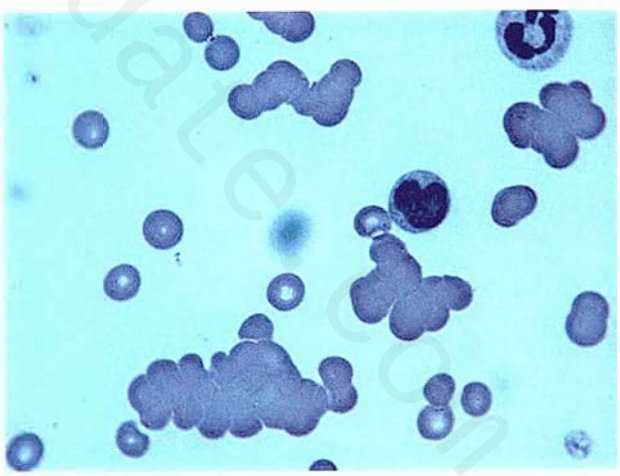
A 55-year-old man is evaluated for fatigue and gradually increasing dyspnea of 1 month's duration. He has otherwise felt well and has no other symptoms, although he reports an occasional bluish tint to his fingers while at work. He is employed as a frozen food handler in a grocery store. Medical history is unremarkable, and he takes no medications.

On physical examination, the patient appears pale. Temperature is 37.0 °C (98.6 °F), blood pressure is 130/65 mm Hg, pulse rate is 98/min, and respiration rate is 18/min. BMI is 26. Mild scleral icterus is noted. A grade 2/6 systolic murmur is heard at the left costal margin without radiation. The lungs are clear to auscultation. No lymphadenopathy is noted, but the spleen tip is palpable below the left costal margin.

Laboratory studies:

Hematocrit	23%
Leukocyte count	13,200/μL (13.2×10^9/L) with normal differential
Platelet count	355,000/μL (355×10^9/L)
Reticulocyte count	14% of erythrocytes
Lactate dehydrogenase	978 U/L

Peripheral blood smear is shown.



Which of the following is the most appropriate diagnostic test to perform next?

(A) Direct antiglobulin (Coombs) test
(B) Flow cytometry for CD55 or CD59
(C) Hemoglobin electrophoresis
(D) Indirect antiglobulin (Coombs) test

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Item 45

A 50-year-old man is evaluated for anemia following a diagnosis of osteomyelitis of the right foot. Complete blood counts before the osteomyelitis diagnosis have been normal. Medical history is notable for type 2 diabetes mellitus. His only medication is metformin.

On physical examination, vital signs are normal; BMI is 30. No cardiopulmonary findings attributable to the anemia are noted. The right foot has a small, deep open wound through which bone can be detected with a metal probe.

Laboratory studies:

Erythrocyte sedimentation rate	60 mm/h
Hemoglobin	8.5 g/dL (85 g/L)
Leukocyte count	15,000/μL (15×10^9/L)
Mean corpuscular volume	80 fL
Reticulocyte count	0.5% of erythrocytes
Iron studies	
Ferritin	500 ng/mL (500 μg/L)
Iron	50 μg/dL (9 μmol/L)
Total iron-binding capacity	225 μg/dL (40 μmol/L)
Transferrin saturation	30%

Appropriate antibiotics are initiated.

Which of the following is the most appropriate management of this patient's anemia?

(A) Bone marrow aspiration
(B) Erythropoiesis-stimulating agent therapy
(C) Oral iron supplementation
(D) Continue current management

Item 46

A 24-year-old man is evaluated for a 2-month history of frequent upper respiratory tract infections, easy bruising, and worsening endurance. Medical and family histories are unremarkable. He takes no medications.

On physical examination, the patient appears fatigued, but not acutely ill. Temperature is 36.7 °C (98.0 °F), blood pressure is 105/62 mm Hg, pulse rate is 108/min, and respiration rate is 14/min. Pallor and several 3- to 4-cm ecchymoses on the lower extremities are noted. He has no hepatosplenomegaly.

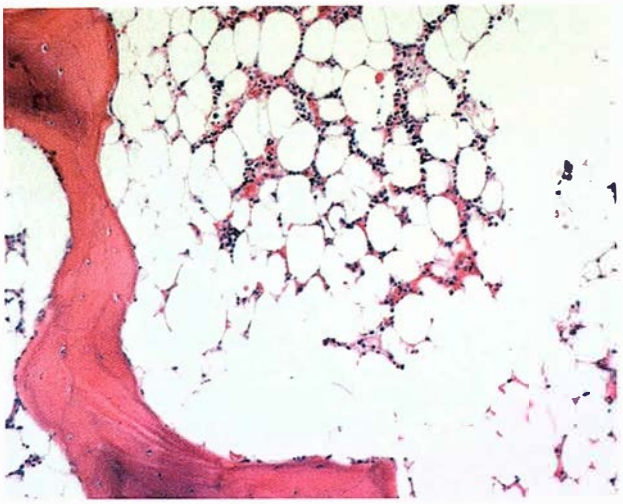
Laboratory studies:

Haptoglobin	40 mg/dL (400 mg/L)
Hemoglobin	7.2 g/dL (72 g/L)
Leukocyte count	1000/μL (1×10^9/L) with 5% neutrophils
Platelet count	7000/μL (7×10^9/L)
Lactate dehydrogenase	150 U/L

Bone marrow aspirate demonstrates less than 5% blasts and no dysplastic changes. Results of a bone marrow biopsy are shown (see top of next column).

Which of the following is the most likely diagnosis?

(A) Acute lymphoblastic leukemia
(B) Acute myeloid leukemia
(C) Aplastic anemia
(D) Myelodysplastic syndrome
(E) Paroxysmal nocturnal hemoglobinuria



ITEM 46

Item 47

A 56-year-old woman is evaluated for an elevated serum protein level discovered during a routine examination for a life insurance policy. She is asymptomatic. Medical and family histories are unremarkable, and she takes no medications.

On physical examination, vital signs are normal, and the remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	13.4 g/dL (134 g/L)
Leukocyte count	6400/μL (6.4×10^9/L)
Platelet count	224,000/μL (224×10^9/L)
Calcium	9.6 mg/dL (2.4 mmol/L)
Creatinine	0.7 mg/dL (61.9 μmol/L)
IgA	2080 mg/dL (20.8 g/L)

Serum protein electrophoresis and immunofixation reveal a monoclonal IgA κ band measuring 1.8 g/dL. A 24-hour urine protein electrophoresis reveals 80 mg of total protein and trace monoclonal free κ light chains that are too low to quantify.

A bone marrow aspirate and biopsy reveals clonal plasma cells representing 8% of the overall marrow cellularity. A skeletal survey demonstrates no lytic lesions, osteopenia, or fractures.

Which of the following is the most appropriate diagnostic test to perform next?

(A) MRI of the cervical, thoracic, and lumbar spine
(B) Serum β_2-microglobulin measurement
(C) Serum free light chain testing
(D) Serum lactate dehydrogenase measurement

Item 48

A 63-year-old man is evaluated for severe mid-upper back pain following a minor fall 1 day ago. He also notes progressive fatigue of 6 months' duration and a 6.8-kg (15 lb) weight loss. Medical history is notable for an 80-pack-year smoking history, although he is currently a nonsmoker.

On physical examination, temperature is 37.3 °C (99.1 °F), blood pressure is 112/74 mm Hg, pulse rate

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is 98/min, and respiration rate is 18/min. BMI is 22. The cardiopulmonary examination is unremarkable. He has no lymphadenopathy or hepatosplenomegaly. Point tenderness to palpation is noted over the mid thoracic spine. No skin changes or peripheral edema are observed.

Laboratory studies:

Hemoglobin	11 g/dL (110 g/L)
Leukocyte count	4800/μL (4.8×10^9/L) with a normal differential
Platelet count	155,000/μL (155×10^9/L)
Albumin	2.8 g/dL (28 g/L)
Calcium	11.8 mg/dL (3.0 mmol/L)
Creatinine	3.1 mg/dL (274 μmol/L)
Total protein	6.3 g/dL (63 g/L)
Urinalysis	Trace protein, no blood, 0 erythrocytes/hpf, no casts
Urine protein-creatinine ratio	2300 mg/g

A chest radiograph shows no infiltrates and a normal cardiac silhouette. Radiographs of the thoracic spine reveal osteopenia with a compression fracture of T6.

Which of the following is the most appropriate diagnostic test to perform next?

(A) 1,25-Dihydroxyvitamin D (calcitriol) measurement
(B) Intact parathyroid hormone measurement
(C) Parathyroid hormone-related protein measurement
(D) Serum protein electrophoresis and free light chain test

Item 49

A 48-year-old man is evaluated in the emergency department for fever and cough of 7 days' duration. Medical history is notable for an aortic valve replacement. His only regular medication is warfarin, although he reports taking acetaminophen every 2 to 3 hours to relieve his fever and chest pain as a result of coughing.

On physical examination, the patient appears ill and slightly jaundiced. Temperature is 38.9 °C (102.0 °F), blood pressure is 90/45 mm Hg, pulse rate is 120/min, and respiration rate is 24/min. Oxygen saturation is 91% breathing ambient air. Coarse breath sounds with rhonchi in the right lung base are heard on auscultation. Cardiac examination reveals regular tachycardia and a mechanical S_2 but no other findings. Right upper quadrant tenderness and multiple ecchymoses are noted.

Laboratory studies:

D-dimer	5800 μg/mL (5800 mg/L)
Leukocyte count	22,000/μL (22×10^9/L)
Platelet count	95,000/μL (95×10^9/L)
Prothrombin time	58 s
Fibrinogen	110 mg/dL (1.1 g/L)
INR	8.8 (6 weeks ago, 2.5)
Factor V	20% (normal, 50%-150%)
Factor VII	5% (normal, 50%-150%)
Factor VIII	200% (normal, 50%-150%)

Chest radiograph shows a right lower lobe infiltrate.

Which of the following is the most likely cause of the patient's coagulation abnormality?

(A) Disseminated intravascular coagulation
(B) Liver failure
(C) Vitamin K deficiency
(D) Warfarin overdose

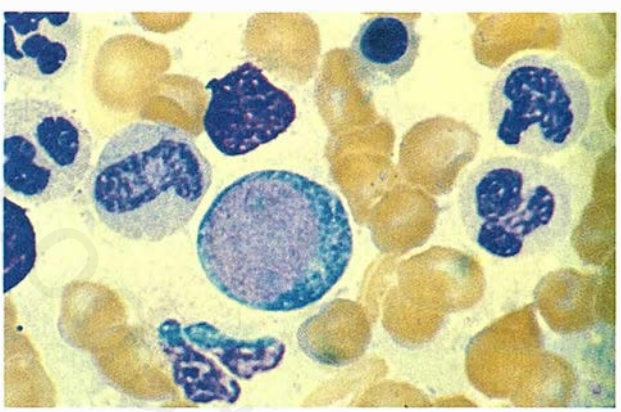
Item 50

A 34-year-old man is evaluated for a 3-month history of fatigue, early satiety, and a 10-kg (22 lb) weight loss. Medical history is notable for hypertension, which is well controlled with hydrochlorothiazide.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 135/81 mm Hg, pulse rate is 114/min, and respiration rate is 13/min. Cardiac and pulmonary examinations are normal, and no lymphadenopathy is noted. The spleen is palpable 10 cm below the costal margin.

Laboratory studies show a hemoglobin level of 8.4 g/dL (84 g/L), leukocyte count of 314,000/μL (314×10^9/L), and platelet count of 622,000/μL (622×10^9/L).

A peripheral blood smear is shown.



Which of the following is the most likely genetic mutation to explain this patient's findings?

(A) *BCR-ABL*
(B) IGH/CD1
(C) *JAK2 V617F*
(D) PML-RAR

Item 51

A 30-year-old man with acute lymphoblastic leukemia is evaluated for fever, chills, rigors, and dyspnea, which started toward the end of a platelet transfusion given for chemotherapy-induced thrombocytopenia.

On physical examination, the patient is lethargic, flushed, and clammy. Temperature is 39.4 °C (102.9 °F), blood pressure is 90/42 mm Hg, pulse rate is 150/min, and respiration rate is 24/min (before transfusion, temperature was 37.2 °C [99.0 °F], blood pressure was 140/76 mm Hg, and pulse rate was 90/min). Oxygen saturation is 94% breathing ambient air. Rigors are noted, and skin is warm

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H CONT. to the touch without skin changes. Head, neck, and pulmonary examinations are unremarkable. Cardiac examination reveals tachycardia but no murmurs.

In addition to stopping the transfusion and administering intravenous fluids, which of the following is the most appropriate treatment?

(A) Diphenhydramine, acetaminophen, and meperidine
(B) Epinephrine
(C) Vancomycin and cefepime
(D) No additional treatment

Item 52

A 61-year-old man is evaluated in the emergency department for diffuse, mild, left calf pain without swelling of 10 days' duration, which has worsened in the past 2 days. The patient reports no provoking injury or incident. He feels well otherwise. Medical and family histories are unremarkable. He takes no medications.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 132/82 mm Hg, pulse rate is 75/min, and respiration rate is 16/min. BMI is 32. He is in no acute distress, but he scores his leg pain as 3/10 in intensity. Mild to moderately deep palpation of the calf muscles provokes diffuse discomfort. The left leg is not discolored, and no edema is present, but it feels slightly fuller than the right and is 1 cm in circumference larger than the right at the midcalf level.

Which of the following is the most appropriate management?

(A) Anticoagulant therapy for 3 months
(B) Blood D-dimer test
(C) Duplex ultrasonography of the leg
(D) Magnetic resonance venography of the leg

Item 53

H

A 23-year-old man is admitted to the hospital for severe right upper quadrant pain of 2 days' duration. Medical history is significant for homozygous sickle cell anemia (Hb SS). His only medication is folic acid.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 115/70 mm Hg, pulse rate is 100/min, and respiration rate is 24/min. Oxygen saturation is 98% breathing ambient air. Palpation confirms a tender right upper quadrant. The remainder of the examination is normal.

Laboratory studies reveal a hemoglobin level of 7.5 g/dL (75 g/L) and a platelet count of 415,000/μL (415×10^9/L).

Abdominal ultrasonography confirms a diagnosis of cholecystitis, and a laparoscopic cholecystectomy is planned before hospital discharge.

In addition to antibiotics, which of the following is the most appropriate preoperative management?

(A) Erythrocyte exchange transfusion to a target hemoglobin S of less than 30%
(B) Erythrocyte transfusion to a hemoglobin level of 10 g/dL (100 g/L)
(C) Erythrocyte transfusion to a hemoglobin level of 12 g/dL (120 g/L)
(D) Erythrocyte transfusion for symptomatic anemia

Item 54

H

A 65-year-old woman is evaluated in the emergency department for a 1-day history of pain and swelling in her left leg. Medical history is significant for coronary artery bypass graft surgery 8 days ago with vein harvesting from the right leg. She also has hypertension and hyperlipidemia. Medications are atorvastatin, atenolol, clopidogrel, and aspirin.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 115/68 mm Hg, pulse rate is 65/min, and respiration rate is 18/min. Oxygen saturation breathing ambient air is 96%. Her sternotomy incision is healing well. The cardiopulmonary examination is normal. The left leg is swollen to the mid-thigh.

Laboratory studies reveal a hematocrit of 33%, leukocyte count of 12,000/μL (12×10^9/L), and platelet count of 55,000/μL (55×10^9/L).

Duplex ultrasonography of the left leg shows acute thrombus in the common femoral vein.

Which of the following is the most appropriate next step in management?

(A) Await platelet factor 4 immunoassay before initiating anticoagulation
(B) Await serotonin release assay before initiating anticoagulation
(C) Initiate argatroban
(D) Initiate heparin
(E) Initiate warfarin

Item 55

A 32-year-old woman is evaluated for anticoagulation management after an uncomplicated vaginal delivery of a healthy newborn. She was diagnosed with a bilateral pulmonary embolism at 25 weeks' gestation and was treated with therapeutic low-molecular-weight heparin (LMWH). The LMWH was discontinued at the onset of labor and was restarted 6 hours after delivery. Medical history is otherwise unremarkable, and her only medication is full-dose LMWH.

Anticoagulation for 3 months is planned. The patient wishes to breastfeed her newborn.

Which of the following is the most appropriate anticoagulation option for this patient?

(A) Apixaban
(B) Dabigatran
(C) Fondaparinux
(D) Rivaroxaban
(E) Warfarin

Item 56

A 72-year-old woman is evaluated in follow-up for a recent diagnosis of multiple myeloma. She presented with an

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8-month history of progressive fatigue and dyspnea with exertion, but has had no other symptoms. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 142/86 mm Hg, pulse rate is 90/min, and respiration rate is 14/min. No focal neurologic deficits are observed. Cardiopulmonary examination is normal, and the remainder of the physical examination is unremarkable.

Initial laboratory studies showed a hemoglobin level of 9.2 g/dL (92 g/L), serum calcium level of 10.2 mg/dL (2.6 mmol/L), and serum creatinine level of 1.3 mg/dL (115 µmol/L).

A monoclonal IgG κ band of 4.2 g/dL was seen on serum protein electrophoresis and immunofixation, and myeloma was confirmed with a bone marrow aspirate and biopsy showing clonal plasma cells representing 70% of the overall cellularity.

A skeletal survey demonstrates diffuse osteopenia and a T12 compression fracture with 50% height loss. No lytic lesions are seen.

In addition to starting chemotherapy, which of the following is the most appropriate treatment?

(A) Balloon kyphoplasty to the T12 vertebra
(B) Radiation therapy to the thoracic spine
(C) Zoledronic acid
(D) No additional treatment

Item 57

A 22-year-old woman is evaluated for a 2-month history of increasing fatigue and dyspnea, which is most noticeable with exercise. She otherwise feels well. She notes no gastrointestinal symptoms, although she believes that her urine sometimes appears darker than usual. She eats a normal diet, menstruation is of usual duration and flow, and she is physically active as a distance runner. Medical and family histories are otherwise unremarkable; her only medication is ibuprofen as needed.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 100/55 mm Hg, pulse rate is 65/min, and respiration rate is 16/min. She has no muscle tenderness or weakness. The remainder of the physical examination is normal. A stool sample is guaiac negative.

Laboratory studies:

Haptoglobin	Undetectable
Hematocrit	25%
Leukocyte count	5500/µL (5.5×10^9/L)
Mean corpuscular volume	72 fL
Platelet count	430,000/µL (430×10^9/L)
Reticulocyte count	1.2% of erythrocytes
Creatine kinase	165 U/L
Ferritin	3 ng/mL (3 µg/L)
Lactate dehydrogenase	1400 U/L
Urinalysis	Dipstick positive for 4+ blood; 0-1 leukocytes/hpf, and 0 erythrocytes/hpf

Peripheral blood smear shows hypochromic microcytic erythrocytes without schistocytes or spherocytes.

Which of the following is the most likely cause of this patient's anemia?

(A) Exercise-induced hematuria
(B) Exercise-induced hemolysis
(C) Inflammatory myopathy
(D) Rhabdomyolysis

Item 58

A 27-year-old woman is evaluated during a follow-up visit. She was evaluated 3 months previously for symptoms of fatigue of 9 months' duration and a craving for ice. She experiences heavy, irregular menstrual cycles, but has no history of other bleeding. Medications are oral contraceptive pills and daily iron, which were initiated 3 months ago.

On physical examination, vital signs are normal; BMI is 31. No splenomegaly is noted.

Laboratory studies:

	3 Months Ago	2 Months Ago	Current
Ferritin	6 ng/mL (6 µg/L)	16 ng/mL (16 µg/L)	45 ng/mL (45 µg/L)
Hemoglobin	8.7 g/dL (87 g/L)	10.1 g/dL (101 g/L)	13 g/dL (130 g/L)
Mean corpuscular volume	71 fL	77 fL	88 fL
Platelet count	800,000/µL (800×10^9/L)	790,000/µL (790×10^9/L)	775,000/µL (775×10^9/L)

Which of the following is the most appropriate diagnostic test to perform next?

(A) *BCR-ABL* genetic analysis
(B) *JAK2 V617F* analysis
(C) Prothrombin time and activated partial thromboplastin time
(D) von Willebrand factor antigen

Item 59

An 18-year-old woman is evaluated in follow-up after routine evaluation 3 months ago revealed iron deficiency thought to be related to menorrhagia. She is African and emigrated from the Ivory Coast 6 months ago. Medical history is remarkable for a 2-year history of chronic dyspepsia treated occasionally with a liquid antacid. Her other medications are an oral contraceptive pill and oral ferrous sulfate three times daily.

On physical examination, vital signs are normal. She appears healthy.

Laboratory studies:

	3 Months Ago	Current
Hematocrit	30%	33%
Mean corpuscular volume	70 fL	70 fL
Platelet count	525,000/µL (525×10^9/L)	500,000/µL (500×10^9/L)

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Reticulocyte count	–	0.4% of erythrocytes
Red cell distribution width	17.5% (normal, 14.6%-16.5%)	17%
Iron studies		
Ferritin	10 ng/mL (10 µg/L)	10 ng/mL (10 µg/L)
Iron	15 µg/dL (2.7 µmol/L)	15 µg/dL (2.7 µmol/L)
Total iron-binding capacity	425 µg/dL (76 µmol/L)	400 µg/dL (71.6 µmol/L)
Transferrin saturation	12%	13%

Which of the following is the most appropriate management?

(A) Add ascorbic acid
(B) Perform *Helicobacter pylori* stool antigen assay
(C) Perform IgG antigliadin assay
(D) Switch to ferrous gluconate

Item 60

A 63-year-old man is scheduled for recommended repeat colonoscopy in follow-up of adenomatous polyps detected on screening 3 years ago. Medical history is significant for an unprovoked pulmonary embolism 5 years ago. He was initially treated with warfarin but switched to rivaroxaban 1 year ago because of fluctuating INR values with warfarin. He is otherwise healthy and has had no bleeding.

Laboratory studies show a normal complete blood count and a serum creatinine level of 0.8 mg/dL (70.7 µmol/L).

Which of the following is the most appropriate management of this patient's anticoagulation for undergoing colonoscopy?

(A) Continue rivaroxaban without interruption
(B) Stop rivaroxaban 1 day before colonoscopy without bridging
(C) Stop rivaroxaban 1 day before colonoscopy and bridge with low-molecular-weight heparin
(D) Stop rivaroxaban 5 days before colonoscopy without bridging
(E) Stop rivaroxaban 5 days before colonoscopy and bridge with low-molecular-weight heparin

Item 61

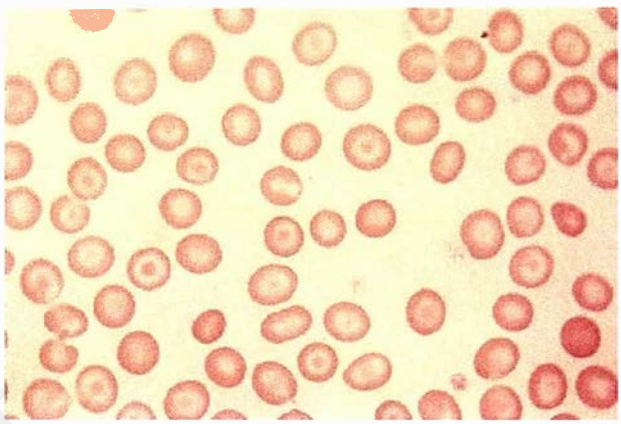
An 18-year-old woman is evaluated following the discovery of anemia on a precollege physical examination. She is asymptomatic. She has regular menstrual cycles every 28 days, which last 5 to 6 days with heavy bleeding on the first 2 days. Medical history is otherwise unremarkable; however, her mother has anemia that is refractory to oral iron therapy. Her only medication is oral iron, which she began taking independently after her anemia diagnosis.

The physical examination is unremarkable.

Laboratory studies:

Erythrocyte count	6.0×10^6/µL (6.0×10^{12}/L)
Hematocrit	33%
Hemoglobin	11 g/dL (110 g/L)
Leukocyte count	6000/µL (6×10^9/L)
Mean corpuscular volume	70 fL
Platelet count	150,000/µL (150×10^9/L)
Reticulocyte count	2.3% of erythrocytes
Red cell distribution width	15 (normal range, 14.6-16.5)
Iron studies	
Ferritin	100 ng/mL (100 µg/L)
Iron	60 µg/dL (11 µmol/L)
Total iron-binding capacity	250 µg/dL (45 µmol/L)

A peripheral blood smear is shown.



Which of the following is the most appropriate management?

(A) Discontinuation of oral iron supplementation
(B) Fecal occult blood test
(C) Oral contraceptive pill
(D) Parenteral iron supplementation

Item 62

A 19-year-old woman is seen for counseling regarding contraceptives. Medical history is unremarkable; she is nulliparous and has never taken prescription contraceptives. Her father had a pulmonary embolism at age 47 years, which was associated with arthroscopic knee surgery, and her 23-year-old sister experienced a deep venous thrombosis 3 weeks after delivering her first child. The patient does not smoke and takes no medications.

On physical examination, she appears well. Vital signs are normal; BMI is 31. The remainder of the examination is unremarkable.

She states that she does not want to use a copper intrauterine device (IUD).

Which of the following contraceptive methods would be most appropriate for this patient?

(A) Estrogen-progestin vaginal ring
(B) Low-dose combination estrogen-progestin pill
(C) Progestin-releasing IUD
(D) Transdermal estrogen-progestin patch

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Item 63

A 63-year-old man is evaluated in the emergency department for significant shortness of breath and pleuritic anterior chest pain of 48 hours' duration. Three days ago, he completed a 12-hour flight from Asia to the United States. Medical history is otherwise unremarkable and he takes no medications.

On physical examination, he is in mild respiratory distress. He is afebrile, blood pressure is 135/87 mm Hg, pulse rate is 108/min, and respiration rate is 18/min. Oxygen saturation breathing ambient air is 94%. The remainder of the physical examination is unremarkable.

Electrocardiography shows nonspecific ST- and T-wave changes. Echocardiography shows normal right ventricular function. CT angiography of the chest demonstrates multiple pulmonary artery filling defects in the distal branches of the right pulmonary artery consistent with pulmonary embolism.

Which of the following is the most appropriate next step in management?

(A) Catheter-directed thrombolysis
(B) Inpatient anticoagulation
(C) Outpatient anticoagulation
(D) Systemic thrombolysis

Item 64

A 67-year-old man is evaluated for progressive lower extremity swelling and dyspnea with exertion of 12 months' duration and orthopnea of 2 months' duration. He is black. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 118/64 mm Hg, pulse rate is 84/min, and respiration rate is 18/min. He has jugular venous distention, a summation gallop, and dullness to percussion and decreased breath sounds at the lung bases. Bilateral lower extremity pitting edema extends to the mid-calf level. The remainder of the physical examination is normal.

On laboratory testing, complete blood count is normal. Comprehensive metabolic profile reveals only an elevated total serum protein level. Serum protein electrophoresis and immunofixation reveal a monoclonal IgG κ band measuring 0.9 g/dL. A 24-hour urine protein electrophoresis and immunofixation reveal no monoclonal protein and no albuminuria.

Chest radiograph shows cardiomegaly and bilateral pleural effusions. Transthoracic echocardiography reveals severe symmetric left ventricular and septal thickening with a small ventricular cavity and reduced systolic function. Bone marrow aspirate and biopsy shows clonal plasma cells representing 8% of the total cellularity. Although a bone marrow biopsy is negative, a Congo red stain of a fat pad aspirate is positive for amyloid deposits.

Which of the following is the most appropriate management?

(A) Amyloid typing
(B) Autologous hematopoietic stem cell transplantation
(C) Chemotherapy
(D) Transmyocardial biopsy

Item 65

A 24-year-old woman with hemoglobin SS sickle cell disease is evaluated in the emergency department for extremity and chest pain of 24 hours' duration. She is 24 weeks pregnant. She reports the pain is similar to her usual vasoocclusive pain located in her legs and low back but is not sufficiently relieved by morphine taken at home. She experiences pain episodes approximately two to three times per year, which she often manages at home. Medical history is otherwise unremarkable. Her only other medication is a folic acid supplement.

On physical examination, the patient appears uncomfortable and pale, with slight scleral icterus. She is afebrile, blood pressure is 120/70 mm Hg, pulse rate is 110/min, and respiration rate is 24/min and unlabored. Oxygen saturation is 94% breathing ambient air. Cardiac examination reveals regular heart sounds with a grade 2/6 systolic murmur. The lungs are clear to auscultation.

Laboratory studies:

Hemoglobin	5.9 g/dL (59 g/L) (prepregnancy baseline: 7-8 g/dL [70-80 g/L]; during pregnancy: 6-7 g/dL [60-70 g/L])
Alanine aminotransferase	35 U/L
Aspartate aminotransferase	32 U/L
Creatinine	0.7 mg/dL (35.4 μmol/L)

Fetal examination reveals no fetal distress.

Which of the following is the most appropriate treatment?

(A) Erythrocyte transfusion
(B) Exchange transfusion
(C) Hydroxyurea
(D) Intravenous fluids and narcotic analgesics

Item 66

A 65-year-old man is evaluated in the emergency department for a 3-day history of abdominal pain. The pain began acutely and is constant. Medical history is remarkable only for a 4-month history of generalized progressive pruritus without a skin rash. He does not drink alcohol or smoke cigarettes and has no risk factors for chronic hepatitis. He takes no medications.

On physical examination, vital signs are normal. He has a plethoric complexion. Cardiopulmonary examination is normal. Tender hepatomegaly and splenomegaly are present.

Laboratory evaluation discloses erythrocytosis, leukocytosis, thrombocytosis, and markedly elevated serum aminotransferase levels.

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Abdominal ultrasonography reveals hepatomegaly, splenomegaly, ascites, and a lack of blood flow in two of the hepatic veins, compatible with Budd-Chiari syndrome.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bone marrow biopsy
(B) Factor V Leiden genetic test
(C) Flow cytometry for CD55 and CD59
(D) *JAK2 V617F* mutation analysis

Item 67

A 58-year-old woman is diagnosed with acute deep venous thrombosis (DVT) of the proximal left leg. Low-molecular-weight heparin (LMWH) and warfarin are initiated. Medical history is otherwise nonsignificant, and she takes no other medications.

When should LMWH be discontinued?

(A) In 3 days if the INR is therapeutic
(B) In 3 days if the INR is therapeutic for 24 hours
(C) In 5 days if the INR is therapeutic
(D) In 5 days if the INR is therapeutic for 24 hours

Item 68

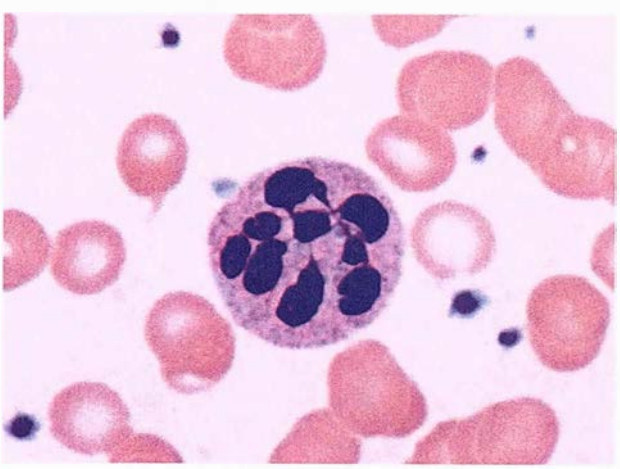
A 30-year-old woman is evaluated for progressive difficulty walking and numbness in both feet of 1 to 2 months' duration. She is otherwise healthy. She has followed a vegan diet for the past several years. Her only medication is an oral contraceptive pill.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 120/66 mm Hg, pulse rate is 76/min, and respiration rate is 12/min; BMI is 25. She has decreased sensation and vibratory sense in both legs below the knees. No other neurologic deficits are observed.

Laboratory studies:

Hemoglobin	10.4 g/dL (104 g/L)
Leukocyte count	2800/μL (2.8×10^9/L)
Mean corpuscular volume	105 fL
Vitamin B_{12}	210 pg/mL (155 pmol/L)

A peripheral blood smear is shown.



Which of the following is the most appropriate diagnostic test to perform next?

(A) Bone marrow biopsy
(B) Folate level measurement
(C) Homocysteine level measurement
(D) Methylmalonic acid level measurement

Item 69

A 72-year-old man is evaluated for a 6-month history of progressive fatigue, dyspnea with exertion, intermittent drenching night sweats, and a 6.8-kg (15 lb) weight loss. Medical history is unremarkable, and he takes no medications.

On physical examination, the patient appears fatigued. Temperature is 37.0 °C (98.6 °F), blood pressure is 148/86 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. BMI is 24. Neurologic and funduscopic examinations are normal. Lungs are clear to auscultation. Rubbery, 1.5- to 2.5-cm lymph nodes are palpable in the bilateral anterior cervical lymph node chains, right axilla, and bilateral inguinal regions. The spleen is palpable 2 cm below the mid left costal margin.

Laboratory studies:

Hemoglobin	9.4 g/dL (94 g/L)
Leukocyte count	5400/μL (5.4×10^9/L)
Platelet count	184,000/μL (184×10^9/L)
Reticulocyte count	1.5% of erythrocytes
Blood urea nitrogen	20 mg/dL (7.1 mmol/L)
Creatinine	1.1 mg/dL (97.2 μmol/L)
Immunoglobulins	
IgG	540 mg/dL (5.4 g/L)
IgA	80 mg/dL (0.8 g/L)
IgM	3882 mg/dL (38.8 g/L)
Lactate dehydrogenase	120 U/L
Protein, total	9.3 g/dL (93 g/L)

A blood smear is unremarkable with the exception of a reduced number of erythrocytes. A direct antiglobulin (Coombs) test is negative. Serum protein electrophoresis and immunofixation reveal a monoclonal IgM κ band measuring 3.2 g/dL.

A bone marrow aspirate and biopsy reveals clonal plasma cells, plasmacytoid lymphocytes, and mature B cells, representing 50% of the overall marrow cellularity without erythroid hyperplasia. CT of the neck, chest, abdomen, and pelvis demonstrates splenomegaly and cervical, axillary, mesenteric, and inguinal lymphadenopathy with lymph nodes measuring up to 3 cm. The lung fields are clear.

Which of the following is the most appropriate management?

(A) Cold agglutinin titer
(B) Plasma exchange
(C) Rituximab plus chemotherapy
(D) Serum viscosity testing

Item 70

A 25-year-old man is evaluated in the emergency department for a 1-day history of brown urine, fatigue, and

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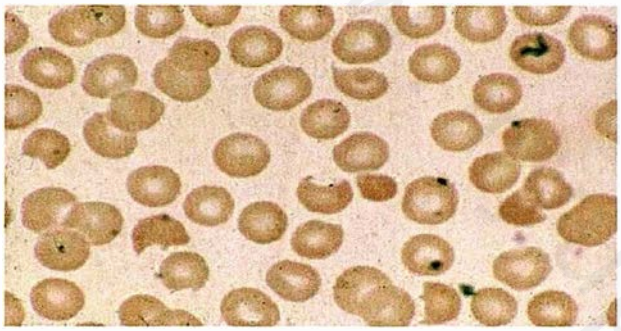
shortness of breath. He was diagnosed with a urinary tract infection 4 days ago, for which he was prescribed trimethoprim-sulfamethoxazole. Medical history is otherwise unremarkable. He is black.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 110/75 mm Hg, pulse rate is 90/min, and respiration rate is 24/min. BMI is 23. Scleral icterus is apparent. Abdominal examination is normal with no indication of hepatosplenomegaly.

Laboratory studies:

Hematocrit	21%
Platelet count	215,000/μL (215 × 10^9/L)
Reticulocytes	10% of erythrocytes
Bilirubin, total	5.0 mg/dL (85.5 μmol/L)
Lactate dehydrogenase	350 U/L

A peripheral blood smear is shown.



Trimethoprim-sulfamethoxazole is discontinued.

Which of the following is the most appropriate diagnostic test to perform next?

(A) ADAMTS-13 activity assay
(B) Direct antiglobulin (Coombs) test
(C) Glucose-6-phosphate dehydrogenase activity
(D) Osmotic fragility test

Item 71

A 35-year-old woman is evaluated in the emergency department for a 3-day history of worsening dyspnea on exertion. She reports no chest pain. Medical history is notable for systemic lupus erythematosus, which is well controlled with hydroxychloroquine. She takes no other medications.

On physical examination, the patient appears pale and fatigued. Temperature is 37.0 °C (98.6 °F), blood pressure is 110/72 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. Oxygen saturation is 97% breathing ambient air. Neurologic examination is normal. Scleral icterus is noted. She has no lymphadenopathy. A grade 2/6 crescendo-decrescendo systolic murmur is auscultated at the upper right sternal border, and the lung fields are clear bilaterally. Abdominal examination reveals no hepatosplenomegaly or tenderness. Rectal examination shows no masses, and a stool sample is guaiac negative.

Laboratory studies:

Hemoglobin	6.2 g/dL (62 g/L)
Leukocyte count	15,000/μL (15 × 10^9/L)
Mean corpuscular volume	101 fL
Platelet count	280,000/μL (280 × 10^9/L)
Reticulocyte count	18% of erythrocytes
Bilirubin, total	2.3 mg/dL (39.3 μmol/L)
Creatinine	Normal
Lactate dehydrogenase	980 U/L
Direct antiglobulin (Coombs) test	Positive for C3 and IgG

Peripheral blood smear shows spherocytes and polychromatophilic erythrocytes but is otherwise normal.

Which of the following is the most appropriate management?

(A) Erythrocyte transfusion
(B) Prednisone
(C) Rituximab
(D) Splenectomy
(E) Vitamin B_{12}

Item 72

A 54-year-old man is evaluated during follow-up consultation regarding laboratory studies completed for a life insurance policy. He reports no symptoms.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 131/76 mm Hg, pulse rate is 88/min, and respiration rate is 15/min. No splenomegaly is noted.

Laboratory studies:

Hemoglobin	8.9 g/dL (89 g/L)
Leukocyte count	3000/μL (3.0 × 10^9/L) with 30% neutrophils, 10% monocytes, and 60% lymphocytes
Mean corpuscular volume	105 fL
Platelet count	75,000/μL (75 × 10^9/L)
Folate	Normal
Vitamin B_{12}	Normal

A bone marrow biopsy shows trilineage dysplasia with 1% blasts. Results of cytogenetic testing show loss of the Y chromosome (-Y).

These findings are compatible with low-risk disease by the International Prognostic Scoring System – Revised criteria.

Which of the following is the most appropriate management?

(A) 5-Azacytidine
(B) Allogeneic hematopoietic stem cell transplantation
(C) Erythropoietin
(D) Observation

Item 73

A 73-year-old man develops acute respiratory distress near the completion of a transfusion of 1 unit of erythrocytes following a total hip arthroplasty. Medical history is significant for hypertension, type 2 diabetes mellitus complicated by

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nephropathy, and hyperlipidemia. Medications are amlodipine, insulin, atorvastatin, and subcutaneous unfractionated heparin.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 184/72 mm Hg, pulse rate is 114/min, and respiration rate is 24/min. Oxygen saturation is 86% breathing ambient air. Jugular venous pressure is 8 cm H_2O. Crackles are heard halfway up both lung fields. Cardiac examination reveals tachycardia but no murmurs. Trace bilateral pedal edema is noted.

Laboratory studies:

Hemoglobin	7.7 g/dL (77 g/L) (6.8 g/dL [68 g/L] before transfusion)
Bilirubin, total	1.2 mg/dL (20.5 µmol/L)
Creatinine	2.8 mg/dL (248 µmol/L) (2.7 mg/dL [239 µmol/L] before transfusion)
Lactate dehydrogenase	90 U/L
Urinalysis	Negative for protein or blood

Electrocardiography demonstrates sinus tachycardia but shows no evidence of ST-segment or T-wave abnormalities. A chest radiograph reveals bibasilar airspace opacities.

Which of the following is the most likely diagnosis?

(A) Acute hemolytic transfusion reaction
(B) Transfusion-associated circulatory overload
(C) Transfusion-related acute lung injury
(D) Transfusion-transmitted sepsis

Item 74

A 47-year-old woman is evaluated for fatigue and easy bruising of 6 weeks' duration. Medical and family histories are unremarkable, and she takes no medications.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 131/76 mm Hg, pulse rate is 95/min, and respiration rate is 15/min. Pallor and scattered lower extremity bruising are noted.

Laboratory studies:

Hemoglobin	7.6 g/dL (76 g/L)
Leukocyte count	2000/µL (2×10^9/L) with 30% neutrophils, 20% monocytes, and 50% lymphocytes
Mean corpuscular volume	103 fL
Platelet count	35,000/µL (35×10^9/L)
Folate	Normal
Vitamin B_{12}	Normal

A bone marrow aspirate and biopsy show trilineage dysplasia with 7% blasts. Cytogenetic testing results indicate a complex karyotype.

These findings define high-risk disease by the International Prognostic Scoring System – Revised criteria.

Which of the following is the most appropriate management?

(A) 5-Azacytidine
(B) Allogeneic hematopoietic stem cell transplantation
(C) Erythropoietin
(D) Observation

Item 75

A 65-year-old man is evaluated for shortness of breath with light activity. Medical history is significant for type 2 diabetes mellitus with associated chronic kidney disease; progressive anemia has also been noted. He has no evidence of gastrointestinal bleeding. His only medication is glipizide.

On physical examination, temperature is 37.1 °C (98.7 °F), blood pressure is 140/80 mm Hg, pulse rate is 86/min, and respiration rate is 20/min; BMI is 30.

Laboratory studies:

Hemoglobin	8 g/dL (80 g/L)
Mean corpuscular volume	90 fL
Reticulocyte count	1% of erythrocytes
Creatinine	2.3 mg/dL (203 µmol/L)
Folate	Normal
Ferritin	550 ng/mL (550 µg/L)
Transferrin saturation	40%
Vitamin B_{12}	Normal
Glomerular filtration rate	25 mL/min/1.73 m^2

Which of the following is the most appropriate management?

(A) Erythrocyte transfusion
(B) Erythropoiesis-stimulating agent therapy
(C) Erythropoietin level measurement
(D) Iron replacement

Item 76

A 23-year-old woman is evaluated in the emergency department for profound shortness of breath, which developed earlier in the day. She reports no chest pain but feels very weak. Medical history is significant for homozygous sickle cell anemia (Hb SS). She was evaluated in the emergency department 1 week ago for symptomatic anemia; she received a transfusion of 2 units of packed red blood cells, her hemoglobin level increased to 8.5 g/dL (85 g/L), and she was sent home. Her only medication is folic acid.

On physical examination, she appears pale and weak. Temperature is 37.1 °C (98.8 °F), blood pressure is 100/60 mm Hg, pulse rate is 110/min, and respiration rate is 32/min. Oxygen saturation is 96% breathing ambient air. Scleral icterus is noted. Cardiac examination reveals a grade 3/6 early systolic murmur at the base of the heart. Lungs are clear. Abdominal palpation reveals no hepatosplenomegaly.

Laboratory studies:

Hemoglobin	3.5 g/dL (35 g/L)
Platelet count	415,000/µL (415×10^9/L)
Reticulocyte count	8% of erythrocytes
Bilirubin, total	7.7 mg/dL (132 µmol/L)
Lactate dehydrogenase	650 U/L

Which of the following is the most likely diagnosis?

(A) Aplastic crisis
(B) Delayed hyperhemolytic transfusion reaction
(C) Hepatic sequestration crisis
(D) Splenic sequestration crisis

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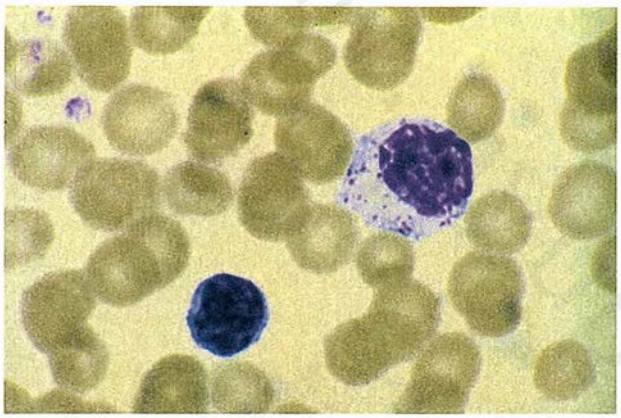
Item 77

A 46-year-old woman is evaluated for a 3-week history of increasing fatigue and new lymphadenopathy. Medical history is remarkable for a 3-year history of rheumatoid arthritis. Medications are methotrexate and ibuprofen as needed.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 128/78 mm Hg, pulse rate is 92/min, and respiration rate is 18/min. Bilateral axillary lymph nodes are palpable. The spleen is palpable 1 cm below the left costal margin. Other than changes of rheumatoid arthritis apparent in the hands and feet, the remainder of the physical examination is normal.

Laboratory studies show a hemoglobin level of 12.5 g/dL (125 g/L); a leukocyte count of 2000/μL (2×10^9/L) with 70% lymphocytes, 10% monocytes, and 20% neutrophils; and a platelet count of 155,000/μL (155×10^9/L).

A peripheral blood smear is shown.



Which of the following is the most likely diagnosis?

(A) Aplastic anemia
(B) Autoimmune neutropenia
(C) Felty syndrome
(D) Paroxysmal nocturnal hemoglobinuria

Oncology Questions

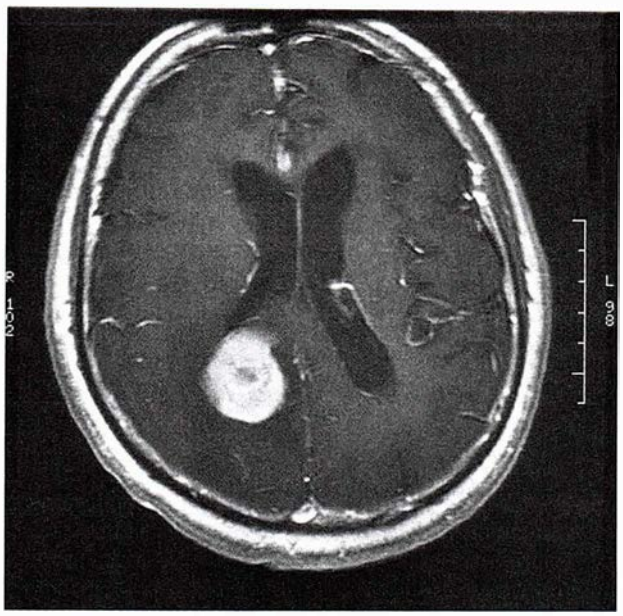
Item 78

A 28-year-old woman is evaluated in the emergency department for a 1-week history of progressive headache associated with nausea and vomiting. Medical history is significant for HIV infection. She is nonadherent to her antiretroviral therapy regimen and takes no other medications.

On physical examination, she is awake and oriented. The patient is afebrile, blood pressure is 130/80 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. No enlarged lymph nodes are palpated. The liver and spleen are not enlarged. The remainder of her physical examination is unremarkable, and her neurologic examination shows papilledema but no other focal findings.

Results of a complete blood count and serum chemistry panel, including toxoplasmosis titer measured at the time of HIV diagnosis, are normal.

CT scan of the head is shown (see top of next column).



Which of the following is the most appropriate next step in management?

(A) Combination chemotherapy
(B) High-dose intravenous glucocorticoids
(C) Intracranial pressure monitoring
(D) Stereotactic radiation therapy

Item 79

A 68-year-old woman is evaluated in the emergency department for a 1-week history of polyuria, polydipsia, and progressive confusion. She has a 2-year history of multiple myeloma that was treated 1 year ago with chemotherapy. Her medical history is otherwise noncontributory, and she takes no medications.

On physical examination, the patient is afebrile, blood pressure is 100/60 mm Hg, pulse rate is 100/min, and respiration rate is 14/min. The patient's skin and mucous membranes are dry. She appears confused, and her reflexes are hyporeactive. The remainder of her examination is unremarkable.

Laboratory studies:

Blood urea nitrogen	60 mg/dL (21.4 mmol/L)
Calcium	14.5 mg/dL (3.6 mmol/L)
Creatinine	3.5 mg/dL (309.4 μmol/L) (baseline 1.2 mg/dL [106.1 μmol/L])

Intravenous high-volume normal saline and high-dose glucocorticoids are started.

Which of the following is the most appropriate next step in treatment?

(A) Cinacalcet
(B) Hemodialysis
(C) Intravenous bisphosphonate
(D) Multiagent chemotherapy

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Item 80

A 58-year-old man undergoes follow-up evaluation for cancer of the ascending colon diagnosed 3 weeks ago. Colonoscopy at that time revealed a fungating mass in the ascending colon. Biopsy revealed adenocarcinoma, and additional studies showed no evidence of metastatic disease. Right hemicolectomy was performed. The pathology report showed a 4-cm primary adenocarcinoma with clear margins at resection, full-thickness penetration through the colonic wall into pericolonic fat, and 4/21 lymph nodes involved (stage III). Medical history is otherwise unremarkable, and the patient takes no medications.

On physical examination, vital signs are normal. Examination of the abdomen shows well-healed surgical scars but is otherwise normal.

Which of the following is the most appropriate management at this time?

(A) Leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX)
(B) Radiation therapy
(C) Radiation therapy and capecitabine followed by capecitabine plus oxaliplatin (CAPOX)
(D) Observation

Item 81

A 70-year-old man is hospitalized for new-onset abdominal pain and nausea. He has had little to eat or drink for the past 24 hours. The patient had a cerebrovascular accident 1 year ago and since then has resided in a nursing home. He has long-standing congestive cardiomyopathy, hypertension, type 1 diabetes mellitus with peripheral neuropathy, and chronic kidney disease. He is mostly bedbound but is able to sit in a chair with assistance for several hours each day. Medications are amlodipine, enalapril, furosemide, insulin, and metoprolol.

On physical examination, the patient appears chronically ill. Temperature is 37.7 °C (99.9 °F), blood pressure is 150/85 mm Hg, pulse rate is 80/min, and respiration rate is 12/min. BMI is 21. The sclerae are icteric, and mucous membranes are dry. There are crackles at the bilateral lung bases. Heart examination is significant for an S_3 heart sound. The abdomen is moderately distended with diffuse mild tenderness but without rebound or guarding. The liver edge is palpable. There is bilateral pitting edema of the extremities.

The patient's Eastern Cooperative Oncology Group/World Health Organization performance status level is assessed to be 4 (completely disabled, totally confined to a bed or chair, and unable to do any self-care).

The serum albumin level is 2.8 g/dL (28 g/L), the serum total bilirubin level is 2.3 mg/dL (39.3 μmol/L), and the serum creatinine level is 2.6 mg/dL (229.8 μmol/L).

A CT scan of the abdomen without contrast shows hepatomegaly with multiple metastatic lesions, enlarged retroperitoneal lymph nodes, abdominal carcinomatosis, moderate ascites, and a nonobstructing mass lesion in the cecum. A diagnostic paracentesis is performed, and 2 liters of bloody ascitic fluid are removed; cytology samples are positive for adenocarcinoma.

Gentle intravenous hydration is begun, and the patient is given parenteral morphine, which provides adequate relief of pain.

Which of the following is the most appropriate management?

(A) Leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX)
(B) Single-agent, low-dose 5-fluorouracil
(C) Surgical resection of the cecal mass
(D) Supportive, comfort-oriented care

Item 82

A 55-year-old man is evaluated for a 3-month history of cough and unexplained weight loss and a 2-week history of shortness of breath. He has never smoked cigarettes.

On physical examination, vital signs are normal. Breath sounds are decreased, and there is dullness to percussion over the right lung field. Examination findings are otherwise unremarkable.

Chest radiograph shows a right pleural effusion and right hilar mass. CT scan of the chest reveals a large right pleural effusion, a right upper lobe mass with associated consolidation, hilar and mediastinal lymphadenopathy, and an irregular right adrenal mass. A CT-guided transthoracic biopsy of the right upper lobe mass shows adenocarcinoma.

Which of the following is the most appropriate management?

(A) EGFR mutation testing
(B) K-*ras* mutation testing
(C) PET scanning
(D) Surgical resection

Item 83

A 68-year-old woman is evaluated for a 1-month history of a painful lump underneath the tongue. She has a 45-pack-year smoking history and continues to smoke.

On physical examination, vital signs are normal. An ulcerated lesion measuring approximately 1 cm is seen on the anterior floor of the mouth.

The lesion is resected. Pathology specimens identify poorly differentiated squamous cell carcinoma with negative margins.

The patient is encouraged to stop smoking. Following discussion of the benefits and risks, she is enrolled in a lung cancer screening program utilizing low-dose CT scanning.

Which of the following surveillance tests should also be recommended for this patient?

(A) CT scans
(B) PET/CT scan
(C) Oral examinations and direct laryngoscopy
(D) No additional follow-up

Item 84

A 55-year-old woman is evaluated in the emergency department for a 3-day history of diarrhea. She reports

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seven to eight stools daily without vomiting. She also notes abdominal cramping without vomiting and has been able to maintain adequate fluid intake. Medical history is significant for metastatic malignant melanoma, for which she recently completed the third of four planned doses of ipilimumab therapy. She has no history of inflammatory bowel disease, recent antibiotic use, recent travel, or consumption of uncooked foods. The remainder of the medical history is noncontributory, and she takes no other medications.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 125/85 mm Hg, pulse rate is 90/min without orthostatic changes, and respiration rate is 14/min. The abdomen is soft and nontender with increased bowel sounds. The remainder of the physical examination is normal.

Laboratory studies:

Hemoglobin	12.2 g/dL (122 g/L)
Leukocyte count	9300/μL (9.3×10^9/L) with normal differential
Alanine aminotransferase	120 U/L
Aspartate aminotransferase	160 U/L
Creatinine	1.2 mg/dL (106.1 μmol/L)
Fecal occult blood test	Negative

A chest radiograph is normal and abdominal films show nondilated bowel loops with no free air.

In addition to discontinuing the ipilimumab and providing supportive care, which of the following is the most appropriate next step in treatment?

(A) Broad-spectrum intravenous antibiotics
(B) Granulocyte-macrophage colony-stimulating factor
(C) High-dose intravenous glucocorticoids
(D) Observation

Item 85

A 33-year-old woman was diagnosed with *BRCA1* mutation 2 months ago. Her paternal aunt was diagnosed with breast cancer at age 45 years and was found to have a deleterious *BRCA1* mutation. She has no family history of ovarian cancer. She has one child and would like to have another child in the next year. She seeks advice on when to have prophylactic bilateral salpingo-oophorectomies (BSO). She is in good health and has no active medical problems.

Physical examination shows no worrisome breast masses. Pelvic examination is normal. The remainder of the physical examination is normal.

Laboratory studies are normal. Results of a mammogram 1 month ago, a transvaginal ultrasound 2 weeks ago, and a breast MRI 1 week ago are normal.

Which of the following is the most appropriate management?

(A) Recommend immediate BSO
(B) Recommend prophylactic BSO by age 35 years
(C) Defer prophylactic BSO until age 40 years
(D) Semi-annual pelvic ultrasound until age 50 years

Item 86

A 68-year-old man is evaluated for a 4-month history of fatigue, weight loss, and night sweats. He is a farmer and has been unable to work since his symptoms developed. Medical history is significant for hypertension, type 2 diabetes mellitus, and an anterior ST-elevation myocardial infarction. Medications are ramipril, glipizide, metoprolol, and low-dose aspirin.

On physical examination, the patient is afebrile, blood pressure is 140/88 mm Hg, pulse rate is 60/min, and respiration rate is 16/min. BMI is 30. Enlarged axillary lymph nodes are palpated.

Laboratory studies:

Hemoglobin	10.5 g/dL (105 g/L)
Lactate dehydrogenase	Elevated
HIV	Negative
Epstein-Barr virus	Negative
Hepatitis B virus	Negative
Hepatitis C virus	Negative

CT scans show axillary, mediastinal, and pelvic lymphadenopathy. Echocardiogram shows a left ventricular ejection fraction of 30%.

Lymph node and bone marrow biopsies reveal diffuse large B-cell lymphoma.

Which of the following factors most strongly correlates with overall survival in this patient after treatment?

(A) Revised International Prognostic Index score
(B) Presence of anemia
(C) Presence of B symptoms
(D) Presence of type 2 diabetes mellitus

Item 87

A 42-year-old woman is evaluated for postcoital bleeding and intermittent pelvic pain. She otherwise feels well. The patient is premenopausal and has two children.

On physical examination, vital signs are normal. General examination is normal. An ulcerating 2-cm cervical mass is visible on speculum examination. Bimanual pelvic examination shows a bulky mass in the cervix that is fixed to the left pelvic side wall and is not mobile.

Results of complete blood count and serum chemistry panel are normal.

CT scan of the abdomen and pelvis shows a 4.5-cm mass involving the lower uterus and extending to the left pelvic side wall. Left hydronephrosis and hydroureter are present. No disease is detected outside the pelvis. Biopsy of the cervical mass shows poorly differentiated invasive squamous cell carcinoma. Chest CT is normal.

Which of the following is the most appropriate treatment?

(A) Radiation therapy
(B) Radiation therapy with concurrent chemotherapy
(C) Radical hysterectomy
(D) Radical hysterectomy followed by chemotherapy
(E) Simple hysterectomy with ovarian preservation

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Item 88

A 70-year-old man is evaluated for a 3-month history of fatigue, weight loss, fever, and night sweats. He has a long-standing history of Crohn disease treated with infliximab.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 110/60 mm Hg, pulse rate is 105/min, and respiration rate is 16/min. Fixed cervical, axillary, and inguinal lymphadenopathy is present on palpation. There is no splenomegaly. The remainder of the examination is unremarkable.

Chest radiograph is normal. CT scans show extensive cervical, axillary, abdominal, and pelvic lymphadenopathy; there is no mediastinal lymphadenopathy.

Which of the following is the most likely diagnosis?

(A) Non-Hodgkin lymphoma
(B) Sarcoidosis
(C) Testicular cancer
(D) Tuberculosis

Item 89

A 78-year-old man is hospitalized for a 1-week history of progressive and severe back pain and weakness in both legs. He describes a sense of "heaviness" in his legs and has had increasing difficulty climbing stairs and getting out of a chair. Medical history is significant for asymptomatic multiple myeloma that has been followed with periodic examinations and laboratory studies; his last assessment was 3 months ago and was stable.

On physical examination, vital signs are normal. He has point tenderness over the T10 and T11 vertebral bodies, decreased lower extremity muscle strength ($3^+/5$), increased reflexes isolated to both lower extremities, and bilateral extensor plantar responses. The remainder of the physical examination is unremarkable.

Laboratory studies are significant for a serum hemoglobin level of 6.5 g/dL (65 g/L) and a serum calcium level of 13 mg/dL (3.2 mmol/L).

MRI of the thoracic and lumbar spine shows a vertebral body mass with extension into the epidural space at T12 and compression of the spinal cord.

Which of the following is the most appropriate initial step in treatment?

(A) Biopsy of the epidural mass
(B) Decompressive surgery
(C) Intravenous glucocorticoids
(D) Multiagent chemotherapy
(E) Radiation therapy

Item 90

A 55-year-old woman is evaluated for a mass in her left breast. She otherwise feels well. She is postmenopausal. Medical and family histories are otherwise negative and she takes no medications.

On physical examination, vital signs are normal. A firm, mobile mass measuring 2.5 × 2.0 cm is palpated in the upper outer quadrant of the left breast, adjacent to the areola. There is no right breast mass. The remainder of the examination is unremarkable.

Mammogram of the left breast shows a 2.9-cm spiculated mass at the site of the palpable lesion. Ultrasound examination shows a 3.5-cm mass. Ultrasound-guided biopsy specimens reveal grade 3 invasive ductal carcinoma that is estrogen receptor negative, progesterone receptor negative, and *HER2* positive. No lymphovascular invasion is noted.

A preoperative echocardiogram is normal; the left ventricular ejection fraction is 65%.

The patient desires breast-conserving surgery, but the surgeon believes that the mass is too large to resect with a lumpectomy because of her small breast size, the moderately large size of the cancer, and its central location.

Which of the following is the most appropriate management?

(A) Mastectomy with postoperative chemotherapy
(B) Neoadjuvant anastrozole
(C) Neoadjuvant trastuzumab-based chemotherapy
(D) Staging CT and bone scans

Item 91

An 80-year-old woman is hospitalized after a mechanical fall. She has a history of stage I estrogen receptor–positive and progesterone receptor–positive left breast cancer diagnosed 13 years ago; *HER2* testing was not done at that time. She was treated with breast-conserving surgery, primary breast radiation, and adjuvant tamoxifen for 5 years. She is not having any current bone pain or headaches.

On physical examination, vital signs are normal. A large palpable lesion is present over the left frontal skull. There is no lymphadenopathy. Examination of the left breast shows a healed incision with no masses. There are no right breast masses. The remainder of the examination is unremarkable.

Serum alkaline phosphatase level is elevated at 264 U/L (normal 36-92 U/L) and serum CA 15-3 level is 100.2 U/mL (normal <30 U/mL). Remaining laboratory studies, including serum calcium level, are normal.

CT scan of the head done in the emergency room shows a 3-cm lytic lesion in the left frontal skull. MRI of the brain confirms the presence of a large frontal skull lesion but shows no brain metastases. Bone and CT scans show lesions in the spine, skull, sternum, and bilateral ilium bones consistent with metastases. No visceral disease is present.

Biopsy of a lytic lesion in the right ilium shows metastatic adenocarcinoma consistent with primary breast cancer (estrogen receptor positive, progesterone receptor positive, and *HER2* negative).

Which of the following is the most appropriate treatment?

(A) Anastrozole
(B) Chemotherapy
(C) Radiation to areas of bone involvement
(D) Radium-223 isotope

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Item 92

A 57-year-old woman undergoes follow-up evaluation. The patient underwent bilateral breast reduction surgery 3 months ago. The initial pathology report noted bilateral atypical ductal hyperplasia. Examination of additional pathology specimens showed no evidence of carcinoma. A mammogram obtained 2 months prior to the breast reduction surgery was normal.

The patient has been taking continuous conjugated estrogen and medroxyprogesterone hormone replacement therapy (HRT) since menopause at age 50 years. HRT has been tapered since the diagnosis of atypical ductal hyperplasia, and plans are to discontinue therapy in 1 month. There is no family history of breast or ovarian cancer.

On physical examination, vital signs are normal. Well-healed mastopexy incisions with mild induration are present. There are no breast masses. The remainder of the examination is unremarkable.

Which of the following is the most appropriate breast cancer prevention strategy?

(A) Begin antiestrogen chemoprevention therapy
(B) Begin vitamin D supplementation
(C) Bilateral prophylactic mastectomy
(D) Continue hormone replacement therapy

Item 93

A 70-year-old man undergoes follow-up evaluation for a recent diagnosis of colorectal cancer. He underwent left hemicolectomy and a bulky 8-cm tumor of the sigmoid colon was removed. Pathology reports revealed a poorly differentiated adenocarcinoma penetrating into pericolonic fat, with 1/22 resected lymph nodes involved with cancer (T3N1; stage III). The patient recovered well from surgery and completed 6 months of adjuvant chemotherapy.

Findings on physical examination today, including vital signs, are unremarkable.

The patient is scheduled to have physical examination and carcinoembryonic antigen monitoring every 3 to 6 months. Colonoscopy could not be performed preoperatively because of obstruction and is therefore scheduled to be done 6 months after surgery and repeated at 3- to 5-year intervals.

Which of the following surveillance imaging studies should also be done?

(A) Chest/abdomen CT scans annually for 3 to 5 years
(B) Chest/abdomen CT scans annually for 10 years
(C) PET/CT scans annually for 5 years
(D) No additional imaging studies

Item 94

A 35-year-old man undergoes follow-up evaluation. The patient is asymptomatic. Testicular cancer was diagnosed recently and was treated with radical inguinal orchiectomy and adjuvant bleomycin/etoposide/cisplatin chemotherapy. Treatment was completed 3 months ago. Medical history is otherwise noncontributory, and the patient takes no medications.

On physical examination, vital signs are normal. The remainder of the examination is unremarkable.

Which of the following treatment-related conditions is this patient most likely to develop?

(A) Gastric ulcer
(B) Metabolic syndrome
(C) Obstructive uropathy
(D) Soft-tissue sarcoma

Item 95

A 48-year-old woman is evaluated for a 6-week history of fatigue and an enlarged right cervical lymph node. She has no significant medical history and takes no medications.

On physical examination, vital signs are normal. A 4-cm firm, enlarged right cervical lymph node is palpated. There is no other lymphadenopathy and no splenomegaly. The remainder of the examination is unremarkable.

Laboratory studies, including complete blood count, erythrocyte sedimentation rate, serum lactate dehydrogenase level, and serum β_2-microglobulin level, are normal.

Lymph node biopsy reveals effacement of the normal architecture by sheets of atypical lymphoid cells. Flow cytometry results are positive for B antigens CD19, CD20, CD22, and CD79a, consistent with diffuse large B-cell lymphoma. CT scans of the chest, abdomen, and pelvis show an isolated enlarged right cervical lymph node but are otherwise normal.

Which of the following is the most appropriate treatment?

(A) Allogeneic hematopoietic stem cell transplantation
(B) Autologous hematopoietic stem cell transplantation
(C) Involved-field radiation therapy
(D) Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)

Item 96

A 62-year-old man is evaluated for a 1-month history of nausea, anorexia, right upper quadrant abdominal pain, and a 4.5-kg (10-lb) weight loss. A superficial spreading melanoma of the left thigh, 2.2 mm deep, with one positive sentinel lymph node was diagnosed 1 year ago. The patient declined adjuvant interferon alfa therapy.

On physical examination, vital signs are normal. There is a well-healed 4-cm incision on the upper left anterior thigh and a healed incision in the left inguinal area. Abdominal examination reveals mild right upper quadrant tenderness to palpation, and the liver is palpable 4 cm below the costochondral margin with a nodular, firm edge. The remainder of the examination is normal.

Laboratory studies are significant for alanine aminotransferase of 211 U/L, aspartate aminotransferase of 156 U/L, and serum bilirubin of 1.6 mg/dL (27.4 µmol/L).

CT scan of the abdomen and pelvis shows an enlarged liver with five hypodense lesions in both lobes measuring up to 2.5 cm that are consistent with metastases. There are no ascites, abdominal lymphadenopathy, or splenomegaly.

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Ultrasound-guided liver biopsy specimens show metastatic melanoma. CT scan of the chest is normal.

Which of the following is the most appropriate next step in management?

(A) *BRAF* V600 mutation analysis
(B) Dacarbazine-based chemotherapy
(C) High-dose interferon alfa
(D) Immunotherapy with ipilimumab

Item 97

A 61-year-old woman undergoes routine follow-up evaluation. Stage II colon cancer was diagnosed 3 years ago and was treated with surgical resection. The patient now feels well. She works full time and exercises regularly. Medical history is otherwise unremarkable, and she takes no medications.

Findings on physical examination, including vital signs, are normal.

Routine surveillance CT scans of the chest and abdomen show three new hypodense lesions in the right lobe of the liver, ranging in size from 1 to 3 cm. No other abnormalities are seen.

Which of the following is the most appropriate management?

(A) CT-guided needle biopsy of a liver lesion
(B) Hepatic artery embolization
(C) Palliative systemic chemotherapy
(D) Radiation therapy to the liver
(E) Right hepatectomy

Item 98

A 62-year-old man is evaluated for a 4- to 6-week history of passing bright red blood stool. He has no other symptoms. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Abdominal examination is normal; the liver and spleen are not enlarged. Digital rectal examination reveals brown stool that is positive for occult blood.

Colonoscopy reveals a nonobstructing polypoid mass in the sigmoid colon. The remainder of the colon, from the ileocecal valve to the anus, is normal. Biopsy of the mass shows adenocarcinoma.

Which of the following diagnostic studies should be performed next?

(A) Bone scan
(B) CT colonography
(C) CT of the chest, abdomen, and pelvis
(D) PET/CT

Item 99

A 27-year-old man is evaluated in the emergency department for a 1-week history of bruising and gingival bleeding with flossing. He has no significant medical history and takes no medications.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 110/80 mm Hg, pulse rate is 80/min, and respiration rate is 14/min. Scattered ecchymoses and cutaneous petechiae are present. There is no lymphadenopathy or splenomegaly.

Laboratory studies:

Leukocyte count	150,000/μL (150×10^9/L)
Platelet count	20,000/μL (20×10^9/L)
Creatinine	4 mg/dL (353.6 μmol/L)
Fibrinogen	Normal
Phosphorus	8 mg/dL (2.58 mmol/L)
Urate	12 mg/dL (0.71 mmol/L)

Peripheral blood smear shows 70% circulating myeloblasts.

Which of the following is the most appropriate treatment?

(A) Fresh frozen plasma
(B) High-volume normal saline hydration and rasburicase
(C) Multiagent chemotherapy
(D) Platelet transfusion

Item 100

A 32-year-old woman undergoes postoperative follow-up evaluation. The patient was diagnosed with a 1.9-cm, stage II, estrogen receptor–positive, progesterone receptor–positive, *HER2*-positive grade 3 invasive ductal carcinoma of the left breast, with 2/6 positive lymph nodes. She underwent breast excision 2 weeks ago. Medical history is otherwise noncontributory. She and her husband have one child and wish to have additional children.

On physical examination, vital signs are normal. There is a healing left breast incision. There is no lymphadenopathy. The remainder of the examination is unremarkable.

Laboratory studies are normal.

Which of the following is the most appropriate next step in the management of this patient?

(A) Begin adjuvant chemotherapy without trastuzumab
(B) Delay chemotherapy until after further childbearing
(C) Recommend embryo cryopreservation before chemotherapy
(D) Advise against further pregnancies

Item 101

A 64-year-old man is evaluated for a 2-month history of increasing abdominal discomfort, right upper quadrant abdominal pain, and decreased appetite. He has lost 2.5 kg (5.5 lb) during this time. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. BMI is 29. A 3-cm left supraclavicular lymph node is palpated. The abdomen is moderately distended, soft, and nontender. The liver is enlarged on palpation. Testicular examination is unremarkable. A digital rectal examination shows a normal rectum and moderately enlarged prostate without nodularity. A stool sample is negative for occult blood.

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Laboratory studies are significant for a serum alkaline phosphatase level of 340 U/L, serum total bilirubin level of 1.3 mg/dL (22.2 µmol/L), and serum creatinine level of 0.7 mg/dL (61.9 µmol/L).

CT scans of the chest, abdomen, and pelvis show extensive metastases scattered throughout the liver, with enlarged periportal and retroperitoneal lymph nodes measuring up to 4 cm in diameter and no bony metastases. CT-guided needle biopsy of the liver shows moderately differentiated adenocarcinoma. Upper endoscopy and colonoscopy are normal.

Treatment for which of the following malignancies would be most appropriate?

(A) Gastrointestinal
(B) Germ cell (testicular)
(C) Lung
(D) Neuroendocrine
(E) Prostate

Item 102

A 60-year-old woman is evaluated for a 5-year history of asymptomatic, intermittently enlarged lymph nodes. She has no other significant medical history and takes no medications.

On physical examination, the patient is afebrile, blood pressure is 140/85 mm Hg, pulse rate is 76/min, and respiration rate is 12/min. Enlarged cervical, axillary, and epitrochlear lymph nodes are palpated. There is no splenomegaly. The remainder of the examination is unremarkable.

Complete blood count and peripheral blood smear are normal. Chest radiograph is normal. CT scans show no evidence of mediastinal, abdominal, or pelvic lymphadenopathy.

A lymph node biopsy reveals a CD20-positive grade II follicular lymphoma, and a bone marrow biopsy shows infiltration with small CD20-positive lymphocytes representing 20% of the cellular elements. Fluorescence in situ hybridization analysis shows the presence of the *BCL2* oncogene.

Which of the following is the most appropriate treatment?

(A) Lenalidomide
(B) Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
(C) Rituximab
(D) Rituximab plus involved-field radiation therapy
(E) Observation

Item 103

A 44-year-old woman is evaluated for a 2-month history of a painless right neck mass. Medical history is unremarkable, and she takes no medications. She is a lifelong nonsmoker.

On physical examination, vital signs are normal. A 5-cm right anterior neck mass is palpated. The remainder of the examination is unremarkable.

An initial CT scan of the neck shows a 4.5-cm, partially necrotic, right-sided lymph node. Asymmetric thickening of the right base of the tongue is also seen. Subsequent laryngoscopy shows an ulcerated mass involving the right base of the tongue. Biopsy of the tongue mass identifies poorly differentiated invasive squamous cell carcinoma. PET/CT scans show no evidence of distant metastases.

Which of the following studies should be performed next?

(A) Bone scan
(B) Human papillomavirus immunohistochemistry testing
(C) MRI of the brain
(D) Right cervical lymph node biopsy

Item 104

H

A 72-year-old man is evaluated in the emergency department for a 3-week history of headache and facial swelling and a 2-week history of shortness of breath.

On physical examination, the patient is afebrile, blood pressure is normal, pulse rate is 104/min, and respiration rate is 22/min. Oxygen saturation is 90% on ambient air. Diffuse facial erythema is present, and neck veins are dilated bilaterally.

CT scan of the chest shows a 7-cm medial left lung mass and bulky mediastinal lymphadenopathy. Superior vena cava compression with associated collateral vessels is also identified. MRI of the brain is negative.

Which of the following is the most appropriate management?

(A) Biopsy of the lung mass
(B) Immediate radiation therapy
(C) Placement of a superior vena cava stent
(D) Venography

Item 105

A 65-year-old woman is evaluated for aching pain in the bilateral hips, knees, and ankles.

Two years ago she was diagnosed with estrogen and progesterone receptor-positive, *HER2*-negative, stage IIIA cancer of the left breast, with 4 positive lymph nodes. She received adjuvant chemotherapy, breast radiation, and anastrozole. After eight months of anastrozole, she experienced severe arthralgia in her knees, hips, and ankles, worse in the morning and after sitting. Anastrozole was stopped for 3 weeks, and her symptoms markedly improved. Letrozole was then started. Now 4 months after beginning letrozole, her joint pains have recurred and are again debilitating. NSAIDs do not provide relief.

On physical examination, vital signs are normal. Well-healed bilateral mastectomy incisions are present without nodularity. There is no lymphadenopathy. The remainder of the physical examination is unremarkable.

In addition to discontinuing the letrozole, which of the following is the most appropriate management?

(A) Obtain PET scan
(B) Prednisone
(C) Restart anastrozole
(D) Start tamoxifen

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Item 106

A 76-year-old woman is evaluated for a 3-month history of abdominal pain and weight loss. She has also had a nonproductive cough for several weeks. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. BMI is 22. A firm 3-cm left supraclavicular lymph node is palpated. Abdominal examination reveals a liver edge that is palpable 3 cm below the right costal margin. On digital rectal examination, a stool sample is positive for trace occult blood.

Contrast-enhanced CT scans of the chest and abdomen show multiple lung and liver metastases and a mass in the transverse colon. Biopsy of the mass obtained during colonoscopy reveals adenocarcinoma.

Which of the following diagnostic studies should be performed next?

(A) K-*ras* and N-*ras* genotyping of the tumor
(B) Measurement of serum dihydropyrimidine dehydrogenase (DPD) level
(C) Measurement of serum *UGT1A1* level
(D) Multigene array analysis of the tumor for prognostic markers

Item 107

A 68-year-old man requests evaluation for prostate cancer. He is asymptomatic. Following a discussion of the risks and benefits of prostate cancer screening, the patient decides to be screened.

Physical examination findings are normal. Digital rectal examination is normal.

Serum prostate-specific antigen level is 5.8 ng/mL (5.8 µg/L).

Transrectal ultrasound–guided prostate biopsy is done and shows adenocarcinoma in 2/12 cores, confined to the right lobe (Gleason score: 3 + 3 = 6).

Which of the following diagnostic imaging studies should be done next?

(A) Bone scan
(B) CT of the chest, abdomen, and pelvis
(C) Immunoscintigraphy
(D) PET/CT
(E) No imaging studies are needed

Item 108

A 38-year-old man is evaluated for a pigmented lesion on his upper left back. The lesion has been increasing in size over the past 2 months. He is otherwise asymptomatic. Medical history is unremarkable.

On physical examination, vital signs are normal. A 1.8-cm, irregular, dark, pigmented, slightly raised papule with irregular borders is present on his upper back. There are no adjacent lesions and no associated lymphadenopathy. The remainder of the examination is unremarkable.

Skin biopsy shows malignant melanoma, superficial spreading type, and measuring 1.4 mm in thickness, with invasion into the reticular dermis but not into the subcutaneous tissue. Dermal mitotic figures are not identified, and there is no lymphovascular invasion. Tumor extends to the lateral and deep margins of the excision. There is evidence of a vertical growth phase.

In addition to complete excision with a 2-cm margin, which of the following is the most appropriate treatment?

(A) Adjuvant chemotherapy
(B) Adjuvant interferon alfa
(C) Sentinel lymph node biopsy
(D) No further therapy

Item 109

A 69-year-old man undergoes follow-up evaluation. He was diagnosed with stage II colon cancer 3 years ago, and surgical resection was performed. The patient has been followed since then without additional treatment. He has no other medical problems and takes no medications.

Physical examination findings, including vital signs, are normal.

Follow-up contrast-enhanced CT scans of the chest and abdomen show two new hypodense lesions (6 cm and 4 cm) confined to the right lobe of the liver, with the larger lesion located close to hilum but without evidence of vascular invasion. No other metastases or additional abnormalities are identified.

The patient is evaluated by an experienced liver surgeon who believes that the larger lesion is unresectable due to its close proximity to the middle hepatic vein.

Laboratory studies, including measures of liver and kidney function, are normal.

Which of the following is the most appropriate approach to providing chemotherapy in this patient?

(A) Adjuvant chemotherapy
(B) Conversion chemotherapy
(C) Neoadjuvant chemotherapy
(D) Palliative chemotherapy
(E) No chemotherapy

Item 110

A 49-year-old woman is evaluated for a 3-month history of abdominal discomfort and fatigue. She has recently noted increasing abdominal girth despite a decreased appetite. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. BMI is 29. Cardiopulmonary examination is normal. The abdomen is moderately distended, soft, and nontender with shifting dullness consistent with ascites.

CT scans of the chest, abdomen, and pelvis are consistent with abdominal carcinomatosis with omental masses and ascites. No adnexal masses are seen.

Which of the following is the most appropriate management?

(A) Cytoreductive surgery followed by systemic chemotherapy
(B) Intraperitoneal chemotherapy

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(C) Omental mass biopsy followed by pelvic radiation therapy and chemotherapy
(D) Ovarian biopsy followed by systemic chemotherapy
(E) Supportive comfort-oriented care

Item 111

A 70-year-old man undergoes follow-up evaluation to determine treatment options following a third occurrence of bladder cancer. High-grade transitional cell carcinoma of the bladder was initially diagnosed 7 months ago following cystoscopy to evaluate painless hematuria. Transurethral resection of the bladder tumor (TURBT) was performed followed by administration of intravesical bacillus Calmette-Guérin (BCG). Three months later, surveillance cystoscopy identified recurrent superficial high-grade transitional cell carcinoma in the same location that was again treated with TURBT and BCG. Now, 4 months following the second episode, high-grade transitional cell carcinoma is again diagnosed. This time, the cancer is in the same location with an additional focus near the trigone. No evidence of invasion into the muscle layer of the bladder has ever been identified.

Physical examination findings, including vital signs, are normal.

CT scans of the abdomen and pelvis (done at the time of the second recurrence) identified no evidence of significant bladder wall thickening, regional lymphadenopathy, or evidence of metastatic disease.

Which of the following is the most appropriate treatment at this time?

(A) Chemotherapy
(B) Cystectomy
(C) External-beam radiation therapy
(D) TURBT followed by intravesical BCG

Item 112

A 48-year-old man is evaluated for a 3-month history of dyspepsia, increasing episodes of nausea, and fatigue. He is maintaining adequate caloric intake and is continuing to work and participate in all routine daily activities, albeit with some increased fatigue.

On physical examination, the patient is afebrile, blood pressure is 115/70 mm Hg, pulse rate is 72/min, and respiration rate is 10/min. BMI is 26. A firm liver edge is palpated 5 cm below the right costal margin. The remainder of the examination is unremarkable.

Upper endoscopy reveals a mass arising in the wall of the proximal stomach just below the gastroesophageal junction. Biopsy of the mass reveals adenocarcinoma. CT scans of the chest and abdomen show multiple liver metastases and evidence of peritoneal carcinomatosis.

Before selecting a systemic chemotherapy regimen, which of the following information about the tumor biopsy specimen would be most helpful?

(A) *BRAF* mutational status
(B) Estrogen and progesterone receptor status
(C) *HER2* expression status
(D) K-*ras* mutational status

Item 113

A 34-year-old woman is evaluated for a 4-week history of tenderness in her left lower breast. Her paternal grandmother died of ovarian cancer at age 54 years. There is no family history of breast cancer. She has a 2-cm palpable left lower outer breast mass on exam. The remainder of the examination is unremarkable.

Results of complete blood count and serum chemistry panel are normal. A mammogram shows increased density and calcifications at the site of the palpable mass. Ultrasound examination reveals a 1.9-cm hypoechoic mass. Ultrasound-guided needle biopsy specimens show a high-grade invasive ductal carcinoma, estrogen receptor–negative, progesterone receptor–negative, and negative for *HER2* amplification.

Which of the following is the most appropriate initial management?

(A) Bilateral mastectomy
(B) *BRCA1/2* testing
(C) Left mastectomy
(D) Lumpectomy with sentinel lymph node biopsy

Item 114

A 54-year-old woman undergoes an examination. She feels well and is asymptomatic. The patient asks to be screened for ovarian cancer. She is postmenopausal and has two children. She used oral contraceptives from age 20 to 35 years. There is no family history of breast, ovarian, colon, endometrial, or gastric cancer.

On physical examination, vital signs are normal. Other findings on physical examination, including pelvic and rectal examinations, are normal.

Which of the following is the most appropriate ovarian cancer screening option for this patient?

(A) Serum CA-125 testing
(B) Transvaginal ultrasound
(C) Transvaginal ultrasound and serum CA-125 testing
(D) No screening studies are indicated

Item 115

A 60-year-old woman is evaluated for right-sided flank pain. Medical history is unremarkable.

Findings on physical examination, including vital signs, are normal.

CT scan of the abdomen and pelvis identifies a 6-cm right upper pole kidney mass. The lesion is resected with negative margins. Pathology specimens show clear cell carcinoma with evidence of renal vein involvement.

Which of the following is the most appropriate management after surgery?

(A) Adjuvant sunitinib
(B) Adjuvant temsirolimus
(C) Radiation therapy
(D) Observation

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Item 116

A 52-year-old woman is evaluated for a 3-month history of enlarged bilateral axillary lymph nodes. She has also recently developed fever, weight loss, and night sweats. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 100/60 mm Hg, pulse rate is 90/min, and respiration rate is 14/min. Firm bilateral axillary lymph nodes are palpated. Splenomegaly is present. The remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	9.0 g/dL (90 g/L)
Leukocyte count	18,000/μL (18×10^9/L)
Platelet count	70,000/μL (70×10^9/L)
Lactate dehydrogenase	Elevated
β_2-microglobulin	Elevated

CT scans of the chest, abdomen, and pelvis show bilateral enlarged axillary and intra-abdominal lymph nodes and an enlarged spleen. Axillary lymph node excisional biopsy reveals diffuse infiltration with small monoclonal lymphoid cells with CD20+ and cyclin D1 overexpression. Subsequent colonoscopy is performed, and biopsy indicates mucosal infiltration with lymphoid cells expressing B-cell markers.

Which of the following is the most likely diagnosis?

(A) Diffuse large B-cell lymphoma
(B) Follicular lymphoma
(C) Hodgkin lymphoma
(D) Mantle cell lymphoma

Item 117

A 62-year-old woman undergoes follow-up evaluation. Stage II ovarian cancer was diagnosed 5 months ago. No residual cancer was identified after debulking surgery. Postoperative chemotherapy was given and resulted in complete remission. The patient currently reports feeling well.

Medical history includes stage I endometrial cancer diagnosed at age 42 years for which the patient underwent hysterectomy without bilateral salpingo-oophorectomy. Family history is significant for endometrial cancer in her maternal grandmother and colon cancer in her mother and maternal uncle.

On physical examination, vital signs are normal. A well-healed abdominal midline incision is present. Remaining examination findings are unremarkable.

Results of complete blood count, serum chemistry panel, and serum CA-125 level are normal.

Which of the following studies should be done next?

(A) *BRCA1/2* testing
(B) Serial CT scans of abdomen and pelvis
(C) Serum CA-125 monitoring
(D) Testing for Lynch syndrome

Item 118

A 48-year-old man is evaluated for a 7-year history of spreading plaques associated with dry, itchy skin. He has no other significant medical history and takes no medications.

On physical examination, vital signs are normal. Skin lesions are present on the arms, back, and legs. Representative skin findings on the back are shown.



There is no lymphadenopathy or hepatosplenomegaly. The remainder of the examination is unremarkable. Results of complete blood count and serum chemistry panel are normal.

Chest radiograph is normal. Skin biopsy reveals infiltration with CD4-positive T cells with cerebriform-appearing nuclei consistent with mycosis fungoides.

Which of the following is the most appropriate management?

(A) Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy
(B) Psoralen plus ultraviolet A (PUVA) therapy
(C) Topical glucocorticoids
(D) Rituximab

Item 119

A 69-year-old woman is evaluated for a 3-month history of intermittent rectal bleeding and increasing fatigue. Medical history is unremarkable, and she takes no medications. Her father died of metastatic colon cancer at age 78 years.

On physical examination, vital signs are normal. The abdomen is soft and nontender. Bowel sounds are normal, and the liver and spleen are not enlarged. Digital rectal examination discloses blood-streaked stool.

Colonoscopy reveals a nonobstructing 4-cm mass in the mid rectum, approximately 8 cm from the anal verge. Biopsy findings show adenocarcinoma. Pelvic MRI shows tumor penetration into, but not through, the rectal wall (TNM stage T2); no abnormal lymph nodes are seen (TNM stage N0). Contrast-enhanced CT scans of the chest and abdomen are normal.

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Which of the following is the most appropriate treatment at this time?

(A) Chemotherapy
(B) Radiation plus chemotherapy
(C) Radiation plus chemotherapy followed by surgical resection
(D) Surgical resection

Item 120

A 58-year-old woman is undergoes a routine cervical cancer screening examination. She is asymptomatic. The patient is postmenopausal and has two children. Medical history is unremarkable. Her mother was diagnosed with breast cancer at age 72 years.

On physical examination, vital signs are normal. An ovarian mass, measuring approximately 8 cm, is palpated on pelvic examination. Remaining examination findings are unremarkable.

Laboratory studies show a normal complete blood count, chemistry panel, and serum CA-125 level.

Transvaginal ultrasound shows a 12.8-cm complex mass in the cul de sac extending to both adnexa. No ascites are present. CT scan of the pelvis shows a 13.4-cm complex left pelvic mass and a 5.8-cm right pelvic mass but no liver lesions, ascites, peritoneal masses, or pleural effusions. Chest radiograph and chest CT scans are normal.

Which of the following is the most appropriate management?

(A) CT-guided biopsy of the mass
(B) Exploratory surgery
(C) MRI of the abdomen and pelvis
(D) *BRCA1/2* testing

Item 121

A 54-year-old man is evaluated for a 3-month history of worsening dyspepsia, gastric bloating, and abdominal discomfort. His dyspepsia has so far been treated with ranitidine. The patient is allergic to penicillin.

On physical examination, the patient is afebrile, blood pressure is 112/70 mm Hg, pulse rate is 83/min, and respiration rate is 14/min. BMI is 25. No palpable lymphadenopathy is present. Abdominal examination reveals mild epigastric tenderness. The remainder of the examination is unremarkable.

The hemoglobin level is 11.5 g/dL (115 g/L). Complete blood count and differential are otherwise normal. Results of fecal occult blood testing are positive.

Upper endoscopy shows several small gastric ulcers. Histopathologic studies reveal evidence of *Helicobacter pylori* infection and small clonal mucosa-associated B cells expressing the CD20 antigen consistent with mucosa-associated lymphoid tissue lymphoma. A CT scan of the abdomen shows no evidence of lymphadenopathy.

Ranitidine is discontinued.

Which of the following is the most appropriate management?

(A) Begin omeprazole, metronidazole, and clarithromycin
(B) Begin rituximab
(C) Obtain bone marrow biopsy
(D) Obtain PET/CT scan

Item 122

A 61-year-old man is evaluated in follow-up after surgical resection of a tongue base tumor.

A neck CT showed asymmetric thickening of the left tongue base and a 2-cm lymph node on the left. Biopsy identified moderately differentiated invasive squamous cell carcinoma. Preoperative PET/CT showed no distant metastatic disease. At surgery, the mass was resected with one positive margin; left modified radical neck dissection identified 3/31 positive lymph nodes, with one lymph node with extracapsular extension.

On physical examination, vital signs are normal. The tongue base resection is well healed and the oral cavity is otherwise normal. The neck incisions are clean and dry, and no lymphadenopathy is detected.

Which of the following is the most appropriate postsurgical management?

(A) Cetuximab alone
(B) Chemotherapy alone
(C) Chemotherapy and radiation therapy
(D) Radiation therapy followed by chemotherapy
(E) Observation

Item 123

A 24-year-old man is evaluated after he felt a mass in his right testicle. The patient is asymptomatic and is otherwise healthy.

On physical examination, vital signs are normal. A 2- to 3-cm solid mass is palpated in the right testicle. The remainder of the examination is unremarkable.

Serum α-fetoprotein level is normal, serum lactate dehydrogenase (LDH) level is 450 U/L, and serum β-human chorionic gonadotropin level is less than 5 U/L.

Testicular ultrasound confirms the presence of a hypoechoic solid right testicular mass.

Right radical inguinal orchiectomy is performed, and pathological examination reveals seminoma. Subsequent CT scan of the abdomen and pelvis shows no lymphadenopathy or evidence of metastatic disease. The tumor is stage I based on surgical and radiographic findings and tumor marker studies. LDH is normal following orchiectomy.

Which of the following is the most appropriate management for this patient?

(A) Active surveillance
(B) Hematopoietic stem cell transplantation
(C) Platinum-based chemotherapy
(D) Retroperitoneal lymph node dissection

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Item 124

A 59-year-old woman undergoes follow-up evaluation for management of limited-stage small cell lung cancer diagnosed during care for an episode of pneumonia.

The patient was treated with a course of chemotherapy and radiation therapy. CT scan of the chest following treatment showed near-complete resolution of the lung mass and lymphadenopathy.

On physical examination, vital signs are normal. Auscultation of the chest is unremarkable, and the remainder of her examination is normal.

Which of the following is the most appropriate next step in the management of this patient?

(A) Maintenance chemotherapy
(B) PET/CT scan
(C) Prophylactic cranial irradiation
(D) Surgical removal of the residual lung mass

Item 125

A 68-year-old man undergoes follow-up evaluation. The patient has stage IIIB nodular sclerosing Hodgkin lymphoma that was initially diagnosed 3 years ago. Complete remission was achieved following administration of six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy. Two months ago, stage IIIB Hodgkin lymphoma was again diagnosed. Salvage chemotherapy was initiated with dexamethasone, ifosfamide, cisplatin, and etoposide (DICE). The patient has now completed two cycles of DICE chemotherapy.

On physical examination, the patient is afebrile, blood pressure is 142/80 mm Hg, pulse rate is 80/min, and respiration rate is 12/min. There is no palpable lymphadenopathy. The remainder of the examination is unremarkable. Results of a complete blood count and serum chemistry panel are normal.

PET/CT imaging shows no residual disease.

Which of the following is the most appropriate treatment at this time?

(A) Allogeneic hematopoietic stem cell transplantation
(B) Autologous hematopoietic stem cell transplantation
(C) Continued salvage DICE chemotherapy
(D) Involved-field radiation therapy

Item 126

A 44-year-old woman undergoes follow-up evaluation. Stage I cancer of the left breast was diagnosed 3 years ago (1.4-cm, grade 2 invasive ductal carcinoma, estrogen receptor positive, progesterone receptor positive, *HER2* negative, 0/2 positive sentinel lymph nodes, and a low score on 21-gene recurrence score testing). *BRCA1/2* testing results were negative. She underwent breast-conserving surgery and radiation therapy and then started tamoxifen. The patient is concerned about her risk of recurrence. Menses are irregular. She has occasional hot flushes and night sweats on tamoxifen but otherwise feels well. There is no family history of breast or ovarian cancer.

On physical examination, vital signs are normal. BMI has remained stable at 22.4. Well-healed left breast and left axilla incisions are present. There are no breast masses or lymphadenopathy. The remainder of the examination is unremarkable.

Results of a bilateral mammogram obtained 1 month ago were normal.

Which of the following is the most appropriate next step in the management of this patient?

(A) Bilateral breast MRI
(B) Complete blood count, liver chemistry studies, and CEA and CA 15-3 measurement
(C) CT of the chest, abdomen, and pelvis and bone scan
(D) No diagnostic studies at this time

Item 127

A 72-year-old man undergoes follow-up examination for prostate cancer. The patient was diagnosed with prostate cancer 2 years ago and was treated with external-beam radiation therapy. Six months ago, androgen deprivation therapy was added in response to a rising prostate-specific antigen level in the absence of local disease progression.

More recently, the patient developed worsening back and chest pain. A bone scan showed multifocal osseous metastases in the thoracic spine, lumbar spine, and ribs. CT scans of the chest, abdomen, and pelvis did not show enlarged lymph nodes or visceral metastases. His symptoms remain poorly controlled on opioid medications. Medications are extended-release morphine, oxycodone-acetaminophen, leuprolide, and flutamide.

On physical examination, blood pressure is 140/82 mm Hg, pulse rate is 97/min, and respiratory rate is 20/min. Physical examination reveals multiple tender areas involving the thoracic and lumbar spine. The remainder of the physical examination, including neurological examination, is normal.

In addition to a bisphosphonate, which of the following is the most appropriate treatment?

(A) Bilateral orchiectomy
(B) Estrogen therapy
(C) External-beam radiation to the lumbar spine
(D) Radium-223

Item 128

A 51-year-old woman undergoes a follow-up evaluation. The patient recently required surgery for stage I cancer of the right breast confirmed as a grade 3 invasive ductal carcinoma that was estrogen receptor negative, progesterone receptor negative, and *HER2* negative. Sentinel lymph nodes were negative. The patient currently states that she feels well. Medical history is otherwise unremarkable, and she is perimenopausal.

On physical examination, vital signs are normal. Healed incisions of the right breast and right axilla are present. There are no masses in either breast and no lymphadenopathy. The remainder of the examination is unremarkable.

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Which of the following is the most appropriate next step in management?

(A) Anastrozole
(B) Anthracycline-based chemotherapy
(C) Autologous hematopoietic stem cell transplantation
(D) Bevacizumab

Item 129

A 38-year-old woman undergoes routine follow-up evaluation. The patient was treated with mantle irradiation for stage IIA Hodgkin lymphoma at age 19 years. She has done well and has no evidence of recurrence. Personal and family medical histories are noncontributory.

On physical examination, vital signs are normal. A healed incision from a previous lymph node biopsy is present in the right supraclavicular area. There is no lymphadenopathy, and breast examination is normal. The remainder of the examination is unremarkable.

No recent imaging studies have been obtained.

Which of the following is the recommended cancer screening program for this patient?

(A) Begin annual mammograms now
(B) Begin annual mammogram and breast MRIs now
(C) Begin annual mammograms at age 40 years
(D) Begin monthly breast self-examination now

Item 130

A 55-year-old woman undergoes follow-up evaluation for a recent diagnosis of lung cancer. Initial evaluation included a plain chest radiograph that showed a right middle lobe mass confirmed as a 3-cm spiculated mass on chest CT. PET/CT identified hypermetabolic uptake in the mass but was otherwise normal.

On surgical resection, the tumor was identified as an intermediate-grade adenocarcinoma with clear margins and was negative for molecular genetic abnormalities. One hilar lymph node was positive, and 10/10 mediastinal lymph nodes were negative for tumor.

She has never smoked. Medical history is otherwise negative, and she takes no medications.

On physical examination, vital signs are normal. Her right thoracic surgical incisions are clean and dry. The lung fields are clear. The remainder of her examination is unremarkable.

Which of the following is the most appropriate next step in this patient's management?

(A) Chemotherapy
(B) Erlotinib
(C) Radiation therapy
(D) Observation

Item 131

A 58-year-old woman is evaluated for a 6-month history of progressive lymphadenopathy. She is otherwise asymptomatic. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Cervical and axillary lymphadenopathy is palpated. Abdominal examination reveals splenomegaly; the liver is not enlarged. The remainder of the examination is unremarkable.

Laboratory studies indicate a leukocyte count of 12,000/μL (12.0×10^9/L), with 65% lymphocytes.

CT scans show diffuse cervical, axillary, abdominal, and pelvic lymphadenopathy and splenomegaly.

Which of the following diagnostic studies should be performed next?

(A) Bone marrow biopsy
(B) Excisional biopsy of an enlarged lymph node
(C) Fine-needle lymph node biopsy
(D) Lumbar puncture
(E) PET/CT scan

Item 132

A 79-year-old man is evaluated for a recent diagnosis of prostate cancer following detection of a left-sided prostate nodule during evaluation for worsening prostatic hyperplasia symptoms. Biopsy of the prostate nodule showed adenocarcinoma with a Gleason score of 3 + 4 = 7; additional core samples were negative for cancer. Medical history is also significant for myocardial infarction and heart failure. The patient has been hospitalized three times in the past 12 months because of exacerbations of heart failure. Medications are carvedilol, lisinopril, metoprolol, aspirin, furosemide, tamsulosin, and finasteride.

On physical examination, vital signs are normal. Mild bibasilar crackles are auscultated and there is trace lower extremity edema. The remainder of the physical examination is unremarkable.

Serum prostate-specific antigen level prior to biopsy was 4.9 ng/mL (4.9 μg/L).

Which of the following is the most appropriate management?

(A) Active surveillance
(B) Cryotherapy
(C) External-beam radiation therapy
(D) Radical prostatectomy
(E) Observation

Item 133

A 77-year-old woman is evaluated for new-onset fatigue and anemia. She otherwise feels well. Medical history is unremarkable, and she takes no medications.

Physical examination findings, including vital signs, are normal. BMI is 22.

Colonoscopy identifies a 7-cm mass in the transverse colon. Biopsy of the mass shows poorly differentiated adenocarcinoma. Contrast-enhanced CT scans of the chest, abdomen, and pelvis show the mass, but no other abnormalities are identified.

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Which of the following is likely to be the most important factor in determining this patient's prognosis?

(A) Degree of differentiation of the tumor
(B) Patient's performance status
(C) Size of the tumor
(D) Stage of the tumor

Item 134

A 48-year-old woman is evaluated for a 6-month history of rectal pain and bright red blood per rectum upon defecation. She has a long-standing history of genital warts. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Abdominal examination reveals no masses. Bowel sounds are normal, and the liver and spleen are not enlarged. Digital rectal examination reveals a hard, tender mass in the anal canal measuring approximately 2.5 cm in diameter. There is no inguinal lymphadenopathy.

Laboratory studies are unremarkable.

Contrast-enhanced CT scan of the pelvis confirms the anal mass and shows no associated lymphadenopathy or other abnormalities. Contrast-enhanced CT scans of the chest and abdomen are normal. Biopsy of the anal mass shows invasive squamous cell carcinoma.

Which of the following is the most appropriate treatment?

(A) Radiation therapy
(B) Radiation therapy with concurrent chemotherapy
(C) Radiation therapy with concurrent chemotherapy followed by surgical resection
(D) Surgical resection

Item 135

A 62-year-old man undergoes follow-up evaluation. The patient received an examination 2 weeks ago following a minor bicycle accident during which a firm, nontender, palpable liver edge 2 cm below the right costal margin was found incidentally. Examination findings were otherwise unremarkable.

A contrast-enhanced CT scan of the abdomen showed a slightly enlarged liver with numerous (>10) hypodense lesions ranging in size from 0.5 to 1.5 cm. Needle biopsy of a liver lesion showed a low-grade, well-differentiated neuroendocrine tumor with fewer than 2 mitoses per 50/hpf. An indium-111 pentetreotide scan (radiolabeled octreotide scan) confirmed the presence of multiple small-volume liver lesions, as well as an approximately 1-cm area of increased avidity in the mesentery consistent with a small bowel carcinoid primary tumor.

Medical history is otherwise unremarkable. He has not had diarrhea, constipation, flushing of the skin, or wheezing. He takes no medications.

On physical examination, vital signs are normal. The remainder of the examination is unremarkable except for the palpable liver edge.

Laboratory studies:

Alkaline phosphatase	115 U/L
Alanine aminotransferase	Normal
Aspartate aminotransferase	Normal
Total bilirubin	Normal
Serotonin	Normal

Which of the following is the most appropriate management?

(A) Hepatic artery embolization
(B) Octreotide therapy
(C) Radiofrequency ablation of the liver lesions
(D) Repeat abdominal imaging in 3 to 4 months
(E) Systemic chemotherapy

Item 136

A 55-year-old man is evaluated for a 1-year history of postprandial indigestion. Associated symptoms are nausea, oily stools, and a 4.5-kg (10.0-lb) weight loss over the past 6 months. His medical history is significant for a recent diagnosis of prediabetes. His current medications are ibuprofen, acetaminophen, and omeprazole.

On physical examination, vital signs are normal; BMI is 25. Scleral icterus is present. Abdominal examination reveals epigastric abdominal pain without guarding or rebound. The remainder of the examination is normal.

Upper endoscopy is normal. Contrast-enhanced CT scan shows a solid 2.5-cm hypoattenuating lesion suspicious for pancreatic adenocarcinoma confined to the head of the pancreas. Dilation of the upstream pancreatic duct and common bile duct is noted. There is no regional lymphadenopathy. The liver parenchyma appears normal.

Which of the following is the most appropriate management?

(A) Endoscopic ultrasound-guided fine needle aspiration
(B) Measurement of CA 19-9
(C) Percutaneous needle biopsy
(D) Surgical resection of the pancreatic mass

Item 137

A 63-year-old woman is evaluated for a 2-month history of pain in her right chest and right ribs as well as right upper abdominal discomfort. Medical history is significant for stage II cancer of the right breast diagnosed 4 years ago and identified as an estrogen receptor–positive, progesterone receptor–negative, *HER2*-negative invasive ductal carcinoma with negative sentinel lymph nodes. She was treated with breast-conserving therapy, primary breast radiation therapy, and adjuvant chemotherapy and has been receiving adjuvant anastrozole since completing radiation.

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On physical examination, vital signs are normal. There is tenderness over the anterior lower right ribs, but no mass or bone defects are present. There are no breast masses or lymphadenopathy. Abdominal examination shows no epigastric mass or tenderness. The liver and spleen are not palpable.

Chest and rib radiographs are normal. CT scans of the abdomen and pelvis show two liver lesions and lytic bone lesions in the spine and pelvis consistent with metastases.

Which of the following is the most appropriate management?

(A) Anthracycline-based chemotherapy
(B) Biopsy of a liver lesion
(C) Exemestane combined with everolimus
(D) PET/CT scan

Item 138

A 70-year-old woman is hospitalized for worsening generalized weakness, anorexia for several days associated with weight loss, and back pain responsive to NSAID administration. The patient recently completed chemotherapy for poorly differentiated adenocarcinoma of the right lung and metastasis-related pathologic compression of the L3 vertebral body without cord compression. Her Eastern Cooperative Oncology Group/World Health Organization performance status is 3 (confined to bed or chair more than 50% of waking hours).

At the time of diagnosis, the patient was treated with four cycles of carboplatin/paclitaxel chemotherapy. CT scans after completing chemotherapy showed an increase in the right lung mass, a new right pleural effusion, increased size of hilar and mediastinal lymph nodes, and new lesions in the liver, consistent with metastases.

On physical examination, the patient is afebrile, blood pressure is 95/57 mm Hg, pulse rate is 90/min, and respiration rate is 20/min. Oxygen saturation is 94% on ambient air. Decreased breath sounds are auscultated over the right lower lung field. There is tenderness over the lumbosacral area. Neurological examination is normal.

Which of the following is the most appropriate next step in management?

(A) Comprehensive palliative care assessment
(B) Initiation of a different chemotherapy regimen
(C) Initiation of artificial nutrition support
(D) Placement of a thoracostomy tube
(E) Radiation therapy to the L3 vertebral body

Item 139

A 78-year-old man is evaluated for headaches, blurred vision, facial flushing, and mild right midback discomfort. The patient is a lifelong nonsmoker.

On physical examination, blood pressure is 150/95 mm Hg; other vital signs are normal. Oxygen saturation is 99% on ambient air. Facial plethora is present. There is no hepatosplenomegaly. The remainder of the examination is unremarkable.

Laboratory studies:

Erythropoietin	150 mU/mL (150 U/L)
Hematocrit	55.2%
Hemoglobin	18.2 g/dL (182 g/L)
Leukocyte count	8200/μL (8.2×10^9/L)
Platelet count	312,000/μL (312×10^9/L)

Urinalysis reveals microscopic hematuria.

Which of the following diagnostic studies should be performed next?

(A) Bone marrow biopsy
(B) CT of the abdomen and pelvis
(C) *JAK2* mutation testing
(D) Peripheral blood flow cytometry

Item 140

A 42-year-old man is evaluated for a 3-month history of dyspepsia and increasing episodes of nausea. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Examination of the abdomen is normal.

Upper endoscopy discloses a large (6-cm) mass in the wall of the proximal duodenum. Biopsy reveals a gastrointestinal stromal tumor staining positive for KIT protein (CD117). Contrast-enhanced CT scans of the chest and abdomen show no other abnormalities.

The patient undergoes complete resection of the mass with clear margins. The final pathology report confirms the original diagnosis and notes a high mitotic rate of 5 to 10 mitoses per 50/hpf. The tumor is classified as being at higher risk for recurrence on the basis of its mitotic rate, large size, and location in the small intestine.

Which of the following is the most appropriate adjuvant treatment?

(A) Epirubicin, cisplatin, and 5-fluorouracil
(B) Imatinib
(C) Radiation therapy
(D) Observation

Item 141

A 37-year-old woman is evaluated in the emergency department for fever and rigors of 4 hours' duration. Medical history is significant for acute lymphoblastic leukemia for which she completed multiagent chemotherapy 10 days ago. Her medical history is otherwise noncontributory, and she takes no other medications.

On physical examination, temperature is 38.8 °C (101.8 °F), blood pressure is 110/60 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. On pulmonary

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examination, the lungs are clear. The remainder of the physical examination is unremarkable.

Laboratory studies indicate a leukocyte count of 0.3/μL (0.0003×10^9/L) with 0 neutrophils. The remaining laboratory studies are normal.

A chest radiograph is normal. Blood and urine cultures are obtained.

Which of the following is the most appropriate next step in management?

(A) Administer granulocyte-macrophage colony-stimulating factor
(B) Await culture results before starting antimicrobial therapy
(C) Begin piperacillin-tazobactam
(D) Begin vancomycin

Item 142

A 61-year-old man undergoes follow-up evaluation for prostate cancer diagnosed 6 months ago that was treated with radical prostatectomy. CT scans of the chest, abdomen, and pelvis at the time of diagnosis were normal. Bone scan at that time showed no evidence of metastatic disease. The serum prostate-specific antigen (PSA) level at the time of surgery was 12 ng/mL (12 μg/L), decreasing to 0.6 ng/mL (0.6 μg/L) 6 weeks after surgery.

Physical examination findings are unremarkable.

Serum PSA measurement obtained at the time of this visit is 10 ng/mL (10 μg/L). Repeat imaging studies were obtained, and no evidence of metastatic disease was identified.

Which of the following is the most appropriate management?

(A) Androgen deprivation therapy
(B) Chemotherapy
(C) Continued monitoring of the serum PSA level
(D) Salvage radiotherapy

Item 143

A 72-year-old man is evaluated for a 4-month history of pain in the left side of his throat. He also has pain when swallowing and a 2-month history of dysphagia. The patient has a 15-pack-year smoking history but stopped smoking 5 years ago. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. There is no palpable cervical adenopathy and there are no abnormalities on inspection or palpation of the oral pharynx and tongue.

Laryngoscopy identifies a mass centered in the left tongue base. Biopsy of the mass identifies moderately differentiated invasive squamous cell carcinoma. PET/CT scans show hypermetabolic uptake in the tongue base mass without any evidence of cervical lymph node involvement or distant metastasis. On PET/CT the tongue base mass measures 2.1 cm.

Which of the following is the most appropriate treatment approach for this patient?

(A) Concurrent cisplatin-based chemotherapy followed by radiation
(B) Radiation followed by adjuvant chemotherapy
(C) Radiation therapy plus cetuximab
(D) Radiation therapy or surgery alone

Item 144

A 55-year-old man undergoes follow-up evaluation for pancreatic cancer. He underwent a pancreaticoduodenectomy (Whipple procedure), with the pathology report showing stage II pancreatic cancer. Because of postoperative complications and a slow recuperation period, he did not receive postoperative therapy. Nine months postoperatively, the patient was able to resume all activities, including full-time work and regular exercise. Three months later, however, he developed right upper quadrant pain. A CT scan showed postsurgical changes in the pancreatic bed and multiple liver metastases. The patient remains medically fit, has good oral intake, and maintains all activities. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. BMI is 27. The abdomen is soft and nontender with normal bowel sounds. The liver is enlarged. The remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	12.8 g/dL (128 g/L)
Leukocyte count	7200/μL (7.2×10^9/L)
Platelet count	302,000/μL (302×10^9/L)
Albumin	Normal
Total bilirubin	Normal
Creatinine	Normal

Which of the following is the most appropriate management?

(A) Multiagent systemic chemotherapy
(B) Single-agent systemic chemotherapy
(C) Radiation therapy to the liver
(D) Transarterial chemoembolization of liver lesions

Item 145

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A 32-year-old man is evaluated in the emergency department for fever, neck pain, and a rapidly enlarging right cervical lymph node. The patient first noticed the lymph node 3 weeks ago. He has no significant medical history and takes no medications.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 120/70 mm Hg, pulse rate is 110/min, and respiration rate is 17/min. A 16-cm firm, enlarged right cervical lymph node is palpated. There is no other lymphadenopathy and no splenomegaly. The remainder of the examination is unremarkable.

Laboratory studies:

Complete blood count	Normal
Creatinine	1.2 mg/dL (106.1 μmol/L)
Lactate dehydrogenase	830 U/L
Phosphorus	5.4 mg/dL (1.74 mmol/L)
Potassium	5.0 mEq/L (5.0 mmol/L)
Urate	8.0 mg/dL (0.47 mmol/L)

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CT scans of the chest, abdomen, and pelvis reveal a 20-cm enlarged right cervical lymph node that is displacing the trachea to the left. Biopsy of the node shows CD20-positive Burkitt lymphoma. Treatment with hydration, furosemide, and allopurinol are initiated.

Which of the following is the most appropriate additional treatment?

(A) Involved-field radiation therapy
(B) Clarithromycin, amoxicillin, plus omeprazole
(C) Rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyper-CVAD)
(D) Surgical debulking followed by radiation therapy

Item 146

A 45-year-old man undergoes follow-up evaluation for chronic lymphocytic leukemia. He was diagnosed 1 year ago after presenting with profound fatigue, decreased performance status, diffuse lymphadenopathy, and splenomegaly. He has been treated with rituximab, fludarabine, cyclophosphamide, and prednisone since the time of diagnosis without significant improvement in his symptoms or blood counts. He continues to complain of marked fatigue but minimal symptoms associated with lymphadenopathy or splenic enlargement. He reports no abnormal bleeding. Current medications are alemtuzumab and gamma globulin. Family history is significant for a mother with transfusion-dependent myelodysplastic syndrome and a sister and brother who are well.

On physical examination, vital signs are normal. Enlarged cervical, axillary, and inguinal lymph nodes are palpated. Splenomegaly extending 15 cm below the costal margin at the anterior axillary line is present. The remainder of the examination is unremarkable.

Laboratory studies show a hemoglobin level of 9.5 g/dL (95 g/L), a leukocyte count of 30,000/μL (30×10^9/L) with 70% small mature lymphocytes, and a platelet count of 40,000/μL (40×10^9/L).

Flow cytometry studies show small mature B cells co-expressing CD5 and CD23. Fluorescence in situ hybridization indicates a chromosome 17p deletion.

Chest radiograph is normal. CT scans show extensive cervical, axillary, abdominal, and pelvic lymphadenopathy and splenomegaly.

Which of the following is the most appropriate next step in treatment?

(A) Hematopoietic stem cell transplantation
(B) Leukapheresis
(C) Lymph node radiation
(D) Splenectomy

Item 147

A 76-year-old man is evaluated for a 1-month history of increasing fatigue, abdominal pain, decreased appetite, and a 4.5-kg (10-lb) weight loss. He does not have cough, dyspnea, or chest pain. Medical history is unremarkable, and he takes no medications. The patient is a lifelong nonsmoker.

On physical examination, the patient is afebrile, blood pressure is 130/80 mm Hg, pulse rate is 84/min, and respiration rate is 12/min. Abdominal examination reveals hepatomegaly. The remainder of the examination is unremarkable.

The serum alkaline phosphatase level is 225 U/L, the serum total bilirubin level is 2.0 mg/dL (34.2 μmol/L), and the serum creatinine level is 0.9 mg/dL (79.6 μmol/L).

Contrast-enhanced CT scans of the abdomen and pelvis show multiple liver metastases with 50% liver replacement and several metastases in the ribs and pelvic bones. CT-guided needle biopsy of the liver reveals high-grade poorly differentiated neuroendocrine cancer. A subsequent chest CT scan shows no evidence of tumor.

Which of the following is the most appropriate treatment?

(A) Hepatic artery embolization
(B) Octreotide
(C) Platinum-based systemic chemotherapy
(D) Radiation therapy for bone metastases
(E) Radiofrequency ablation of liver metastases

Item 148

A 43-year-old woman undergoes follow-up evaluation following a recent diagnosis of estrogen receptor–positive, progesterone receptor–positive, *HER2*-negative, grade 2 invasive ductal carcinoma of the left breast. The patient was treated with surgery, adjuvant chemotherapy, and radiation therapy. This is her first postradiation visit. She currently takes no medications. She is premenopausal.

On physical examination, vital signs are normal. Well-healed incisions of the left breast and left axilla are present. There is no lymphadenopathy and no right breast masses. The remainder of the examination is unremarkable.

Results of a complete blood count and serum chemistry panel are normal.

Which of the following is the most appropriate therapy?

(A) Exemestane alone
(B) Tamoxifen alone
(C) Maintenance chemotherapy with oral capecitabine
(D) No additional adjuvant therapy

Item 149

A 65-year-old man is seen in follow-up for a recent diagnosis of non–small cell lung cancer. He presented 2 weeks ago with a 3-month history of worsening shortness of breath, fatigue, and reduced appetite with a 35-pound weight loss. Medical history is notable for COPD with baseline shortness of breath with exertion, but no supplemental oxygen

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requirement. Medications are tiotropium and as-needed albuterol metered dose inhalers.

Physical examination at the time of diagnosis revealed decreased breath sounds in the left lung field. Chest radiograph showed near complete obliteration of the left lung field. CT scan of the chest confirmed the presence of a large left-sided pleural effusion and showed evidence of multiple hepatic and osseous metastatic lesions. He underwent left-sided large volume thoracentesis, and cytology confirmed squamous cell carcinoma.

He currently notes that despite fluid drainage, his breathing has not improved significantly and he is now using home oxygen. He remains weak, spending significant time in bed and requiring assistance in performing many of his daily self-care activities.

Chest auscultation reveals a clear improvement in left-sided breath sounds, and a chest radiograph shows a small amount of residual pleural fluid on the left.

Which of the following is the most appropriate management?

(A) Palliative care assessment
(B) Platinum-based chemotherapy
(C) Pleurodesis
(D) Radiation to bone metastases

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Answers and Critiques

Hematology Answers

Item 1 Answer: C

Educational Objective: Diagnose thrombotic thrombocytopenic purpura.

The most appropriate diagnostic test to perform at this time is a peripheral blood smear. This patient likely has thrombotic thrombocytopenic purpura (TTP). TTP should be suspected in patients who have microangiopathic hemolytic anemia, characterized by schistocytes on the peripheral blood smear and increased serum lactate dehydrogenase levels, and thrombocytopenia. A peripheral blood smear is essential to determine whether the anemia is caused by a microangiopathic hemolytic process as indicated by the presence of schistocytes. Patients may also have fever; kidney manifestations such as hematuria, elevated creatinine level, and proteinuria; and fluctuating neurologic manifestations, but the absence of these symptoms does not exclude the diagnosis.

Assays for ADAMTS-13 activity and inhibitor titer are available but are best used for prognosis rather than to guide therapy, because TTP requires immediate treatment that cannot be delayed until laboratory test results are available. Low activity levels and a positive inhibitor titer confer a higher risk for relapse.

An osmotic fragility test is used to evaluate for hereditary spherocytosis, which can produce hemolysis in the setting of an acute infection. However, hereditary spherocytosis does not cause thrombocytopenia, kidney injury, or mental status changes.

TTP can overlap with hemolytic uremic syndrome (HUS), which usually occurs in children. HUS may be precipitated by an infectious diarrheal illness, especially *Escherichia coli* O157:H7 or *Shigella* species. These bacteria elaborate a toxin that resembles antigens on renal endothelial cells and bind and cause renal cell death. It is not clinically helpful to attempt to distinguish between TTP and HUS, because many patients with HUS respond to plasma exchange, the treatment for TTP.

KEY POINT

- Thrombotic thrombocytopenic purpura is a clinical diagnosis that requires the presence of thrombocytopenia and microangiopathic hemolytic anemia, which is confirmed by schistocytes on the peripheral blood smear.

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Item 2 Answer: A

Educational Objective: Treat a patient for major bleeding who is taking warfarin.

The patient should be given 4-factor prothrombin complex concentrate (4f-PCC) in addition to intravenous vitamin K and fluids. He is experiencing major bleeding complicated by warfarin therapy and requires immediate anticoagulation reversal. 4f-PCC is a plasma-derived product that contains all four vitamin K–dependent coagulation factors (factors II, VII, IX, and X). Unlike fresh frozen plasma (FFP), 4f-PCC is stored at room temperature, does not require ABO typing, and can be infused quickly because of its small volume, thus reducing the time to delivery of therapy. Compared with FFP, 4f-PCC has been shown to more rapidly achieve hemostasis in patients with visible or musculoskeletal bleeding with less risk of fluid overload and no difference in thromboembolic events. This agent has therefore been approved by the FDA for urgent reversal of coagulation factor deficiencies related to vitamin K antagonist therapy for adult patients with acute major bleeding, as well as for adult patients in need of urgent surgery or an invasive procedure.

Activated factor VII (factor VIIa) has been evaluated in case series for the treatment of vitamin K antagonist–related bleeding. Although factor VIIa can correct the INR quickly in most instances, it is unclear if this is associated with achievement of optimal hemostasis considering factors II, IX, and X are not replaced with this agent. A low dose of factor VIIa may be used in conjunction with 3-factor PCCs (which contain very little factor VII) for treatment of major vitamin K antagonist–associated bleeding in situations when 4f-PCCs are not available and the patient has a contraindication to the use of FFP (for example, uncompensated heart failure).

Cryoprecipitate is rich in fibrinogen and is used to treat inherited or acquired fibrinogen deficiency or dysfibrinogenemia. It has no role in the management of vitamin K antagonist–related bleeding.

FFP can be used when 4f-PCC is not readily available. However, 4f-PCC is also less likely than FFP to induce transfusion-associated circulatory overload, an important consideration in patients with heart failure or transfusion-related acute lung injury. Furthermore, 4f-PCC goes through viral inactivation, which reduces the incidence of transfusion-transmitted infectious diseases.

KEY POINT

- Major bleeding associated with vitamin K antagonists should be treated by reversing anticoagulation with 4-factor prothrombin complex concentrate in addition to intravenous vitamin K.

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Item 3 Answer: D

Educational Objective: Diagnose chronic thromboembolic pulmonary hypertension in a patient with a previous pulmonary embolism.

A radionuclide ventilation-perfusion (V/Q) lung scan is the preferred and recommended initial study to evaluate for possible chronic thromboembolic pulmonary hypertension (CTEPH), which is likely in this patient. CTEPH is defined as a mean pulmonary artery pressure of greater than 25 mm Hg, with normal pulmonary capillary wedge pressure, left atrial pressure, and left ventricular end-diastolic pressure. It typically occurs within 2 years following a pulmonary embolism (PE), affecting 3.8% of patients, although only about 50% of these have a history of clinically detected PE. Patients with CTEPH often present with persistent shortness of breath or progressively worsening dyspnea, especially on exertion. For a patient in whom pulmonary hypertension is suspected, a V/Q scan can help determine if the patient's pulmonary hypertension is due to obstruction of medium-sized or larger pulmonary arteries (as is characteristic of CTEPH), because V/Q mismatches would be seen. In nonthromboembolic pulmonary hypertension, a V/Q scan would be normal. If the V/Q scan suggests CTEPH, confirmatory right heart catheterization with pulmonary artery pressure measurements and pulmonary arteriography is indicated.

Pulmonary CT angiography (CTA) is not sensitive for diagnosing chronic PE and often appears normal despite chronic perfusion defects, primarily because CTEPH involves chronic changes in the pulmonary vasculature owing to organization of thrombus and recanalization and is not associated with distinct intraluminal filling defects. V/Q scanning is more sensitive for detecting these changes, with a reported sensitivity of CTEPH detection of more than 96% compared with 51% with CTA.

Serum D-dimer testing is not a sensitive marker to detect CTEPH. The pulmonary changes associated with CTEPH involve organization of clots and are not clearly associated with active thrombosis. Therefore, D-dimer levels are unable to provide diagnostic information.

Similarly, venous Doppler ultrasonography would be helpful in evaluating for active thrombosis in the legs but would not provide helpful diagnostic information for evaluation of pulmonary hypertension.

KEY POINT

- Ventilation-perfusion lung scanning is appropriate for determining chronic thromboembolic pulmonary hypertension in patients with a history of pulmonary embolism and persistent or progressive dyspnea.

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Item 4 Answer: D

Educational Objective: Diagnose paroxysmal nocturnal hemoglobinuria.

The most likely diagnosis is paroxysmal nocturnal hemoglobinuria (PNH). PNH is an acquired clonal stem cell disorder that should be considered in patients presenting with hemolytic anemia, pancytopenia, or unprovoked atypical thrombosis. Mutations in the *PIG-A* gene lead to the reduction or absence of glycosylphosphatidylinositol, an important erythrocyte-anchoring protein. Hemolysis is caused by the absence of decay-accelerating factor (CD55) and the membrane inhibitor of reactive lysis (CD59), which are glycosylphosphatidylinositol-dependent complement regulatory proteins. Diagnosis of PNH is based on flow cytometry results, which can detect CD55 and CD59 deficiency on the surface of peripheral erythrocytes or leukocytes.

The patient does not have aplastic anemia (AA). Although AA often has small PNH clones present, thrombosis and hemolysis are not features of this disease. In patients with AA, however, annual screening for the presence of PNH clones by flow cytometry is recommended.

The myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis. Although MDS may present with a hypocellular bone marrow approximately 10% of the time, thrombosis and hemolysis are not typical symptoms. MDS usually presents with anemia or pancytopenia and a hypercellular marrow with dysplastic changes in cell precursors.

Myeloproliferative neoplasms (MPNs) can present with splanchnic thrombosis and should be considered in the differential diagnosis of unusual blood clots. However, the peripheral blood counts do not suggest MPN (no cell lines are elevated), and hemolysis is not a prominent clinical feature. Additionally, the marrow in MPNs is typically hypercellular or fibrotic.

KEY POINT

- Findings diagnostic of paroxysmal nocturnal hemoglobinuria include hemolytic anemia, hypocellular bone marrow, and lack of CD55 and CD59.

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Item 5 Answer: C

Educational Objective: Diagnose Budd-Chiari syndrome associated with *JAK2 V617F* activating mutation.

Testing for the *JAK2 V617F* activating mutation is the most appropriate next step. This patient presents with acute portal

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hypertension caused by thrombosis of the hepatic veins, or Budd-Chiari syndrome (BCS), which is one of the few noncirrhotic causes of portal hypertension. Clinically, this syndrome can present acutely as fulminant hepatic failure or subacutely with tender hepatomegaly and rapid-onset ascites, as in this patient. Upon discovery of the *JAK2* activating mutation in 2005, it became apparent that up to half of patients with idiopathic BCS had an acquired mutation in *JAK2*, without overt suggestion of a myeloproliferative neoplasm. Therefore, testing for *JAK2* is part of the diagnostic testing protocol that includes consideration of paroxysmal nocturnal hemoglobinuria in the differential diagnosis of splanchnic vein thrombosis.

Antiphospholipid antibodies have been associated with BCS, but they are notoriously nonspecific, and much of the literature concerning antiphospholipid antibodies was written before more specific acquired causes were discerned. Diagnosis of antiphospholipid antibody syndrome requires persistent elevation of antibodies in association with a clinically consistent clot. Because deep venous thrombosis (DVT) and pulmonary embolism (PE), arterial thrombosis, and placental clots are more commonly associated with antiphospholipid antibody syndrome than splanchnic vein thrombosis, testing for this disorder is not indicated until other more likely diagnoses are excluded.

Factor V Leiden most characteristically presents as DVT, with or without PE. Less commonly, patients may experience cerebral, mesenteric, and portal vein thrombosis.

Patients with the prothrombin gene mutation (G20210A) are at increased risk for DVT and, less commonly, cerebral vein thrombosis. In patients with splanchnic vein thrombosis, testing for the more common *JAK2* mutation is the most appropriate initial step.

KEY POINT

- A *JAK2* activating mutation occurs in approximately half of patients with idiopathic Budd-Chiari syndrome.

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Item 6 Answer: B

Educational Objective: Diagnose hemophilia A.

The patient should undergo factor VIII testing. He has had abnormal bleeding following a surgical procedure and dental extractions. The activated partial thromboplastin time (aPTT) is prolonged but corrects fully in a 1:1 mixing study. This could occur with clotting factor deficiencies VIII, IX, and XI; however, this patient's bleeding disorder appears to be familial. Because his maternal grandfather may have had a bleeding disorder resulting in intracerebral bleeding at a young age, and his brother had abnormal bleeding, the likely inheritance pattern is X-linked recessive; only hemophilia A and B are inherited in this fashion. Hemophilia A results from factor VIII deficiency and hemophilia B from factor IX deficiency; both produce a prolongation of the aPTT that fully corrects in a mixing study. Persons with severe hemophilia have less than 1% factor VIII or IX activity; they will have severe recurrent hemarthroses as well as retroperitoneal and intramuscular bleeding. Central nervous system hemorrhage is especially hazardous and is a leading cause of death. Mild hemophilia may present in adulthood and is characterized by posttraumatic or surgical bleeding.

The bleeding time test is performed by blotting away excess blood, which tests primary hemostasis rather than fibrin formation. The bleeding time is prolonged in patients with platelet dysfunction, von Willebrand disease (vWD), thrombocytopenia, and anemia. The bleeding time will be abnormal in this patient because of his anemia and will not assist in establishing the diagnosis.

Patients with factor XI deficiency will have a prolonged aPTT, as in this patient, but the inheritance pattern is autosomal recessive, not X-linked. Additionally, bleeding is not spontaneous, tends to be milder in degree, and typically affects mucocutaneous surfaces. It is highly unlikely to cause an intracerebral hemorrhage in a younger person, such as this patient's grandfather.

The antiphospholipid syndrome is defined by the presence of antiphospholipid antibodies and typical clinical manifestations. This disorder may occur as an independent syndrome (primary antiphospholipid syndrome) or secondary to underlying systemic lupus erythematosus. Antiphospholipid antibodies include anticardiolipin, anti-β_2-glycoprotein I, and the lupus anticoagulant. The lupus anticoagulant does prolong the aPTT, but the aPTT will not correct in a 1:1 mixing study. Lupus anticoagulant is also more likely to lead to abnormal thrombosis rather than bleeding.

KEY POINT

- Hemophilia A results from factor VIII deficiency and hemophilia B from factor IX deficiency; both produce a prolongation of the activated partial thromboplastin time that fully corrects in a mixing study.

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Item 7 Answer: C

Educational Objective: Diagnose hypereosinophilic syndrome.

The most likely diagnosis is hypereosinophilic syndrome (HES). This patient presents with cardiac complications of HES, an elevated eosinophil count (>1500/μL [1.5 × 10^9/L]) without a secondary cause, and evidence of organ involvement. The causes of eosinophilia are described in the CHINA mnemonic (connective tissue diseases, helminthic infection, idiopathic [HES], neoplasia, allergy). The most common organs affected by HES include the skin, lungs,

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gastrointestinal tract, and heart. HES may or may not be associated with mutations in the tyrosine kinase receptor gene, but such involvement is important to identify, because treatment with imatinib is effective in such cases.

Acute eosinophilic leukemia is characterized by increases in immature eosinophils in blood and bone marrow and infiltration of tissues with immature eosinophils. Like HES, cardiac dysfunction can develop, but findings of an acute leukemic syndrome are pronounced and include anemia, thrombocytopenia, and infection.

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder characterized by myeloid proliferation. In chronic-phase CML, the leukocyte count is high, the hemoglobin level is low or normal, and the platelet count is normal or high. CML may be associated with an absolute eosinophilia, but tissue or organ dysfunction is not common. Detection of the (9;22) translocation by routine cytogenetics or fluorescence in situ hybridization or of the *BCR-ABL* fusion transcript by reverse transcriptase-polymerase chain reaction is diagnostic.

Systemic mastocytosis with eosinophilia is characterized by urticaria pigmentosa, a unique identifying clinical finding. Urticaria pigmentosa findings include pruritic yellow to red or brown macules, papules, plaques, and nodules. The most common noncutaneous findings are gastrointestinal and include symptoms such as abdominal pain, diarrhea, nausea, and vomiting.

KEY POINT

- An elevated eosinophil count (>1500/μL [1.5×10^9/L]) without a secondary cause and evidence of organ involvement are diagnostic of hypereosinophilic syndrome.

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Item 8 Answer: A

Educational Objective: Manage thrombocytopenia in pregnancy.

The most appropriate management for this patient's thrombocytopenia is immediate delivery of the fetus, because she has HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome. Although she has a history of immune thrombocytopenic purpura (ITP), and her platelet counts have been low throughout the pregnancy, her markedly decreased platelet count is worrisome and could indicate development of another condition. Worsening anemia, right upper quadrant pain, hypertension, proteinuria, and elevated liver enzymes are more consistent with a microangiopathy of pregnancy (HELLP syndrome, preeclampsia, thrombotic thrombocytopenic purpura [TTP]) rather than worsening ITP. Her clinical picture is more consistent with preeclampsia (new-onset hypertension at >20 weeks' gestation) with proteinuria or the HELLP syndrome. The relationship between preeclampsia and HELLP syndrome is unclear; HELLP syndrome occurs in 10% to 20% of women with preeclampsia but occasionally in some patients without hypertension or proteinuria. The primary treatment for both conditions, particularly in advanced pregnancy, is urgent delivery. Platelet counts tend to recover quickly after delivery; persistent thrombocytopenia several days after delivery should raise concern for another diagnosis, such as thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS).

Administering intravenous immune globulin is not indicated as a treatment for thrombocytopenia associated with preeclampsia and HELLP syndrome.

Plasma exchange can be undertaken if TTP is present earlier in the pregnancy before delivery is a viable option, but would not be a preferred treatment strategy in a patient in whom delivery is appropriate. Plasma exchange would be indicated if thrombocytopenia persisted after delivery and TTP-HUS were diagnosed.

Glucocorticoids such as prednisone are not indicated for microangiopathy of pregnancy. Additionally, if used as a treatment for ITP, prednisone typically takes 48 to 72 hours for effectiveness. Therefore, treatment with prednisone would not be appropriate in this patient.

KEY POINT

- Immediate delivery of the fetus is the best management approach for pregnant women experiencing thrombotic microangiopathy of pregnancy.

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Item 9 Answer: A

Educational Objective: Determine duration of anticoagulation in a patient with venous thromboembolism.

This patient should continue anticoagulation therapy indefinitely. Because his venous thromboembolism (VTE) was unprovoked, he is at relatively high risk for recurrence if he stops anticoagulation. Based on his history, stable INR values, absence of comorbidities, and age, his bleeding risk is low. He also does not have a strong preference to discontinue anticoagulation. The decision to treat him for an extended period of time is consistent with the American College of Chest Physicians guidelines, which suggest extended anticoagulant therapy in patients with unprovoked proximal leg deep venous thrombosis (DVT) or pulmonary embolism who have low or moderate bleeding risk. Re-evaluation of this indication based on periodic risk/benefit assessments, new clinical study data, and new anticoagulation drug availability is appropriate.

Short-term anticoagulant therapy (3 months) is suggested for patients with VTE associated with a major transient risk factor, such as major surgery, trauma, or immobility; patients with unprovoked distal leg DVT; and patients with unprovoked proximal leg DVT who are at high

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risk for bleeding. Therefore, 3 months of therapy, or extending treatment to 6 months, would not be optimal treatment for this patient with an unprovoked proximal DVT.

Because identification of an inherited thrombophilia often does not change treatment decisions in a patient with VTE (does not reliably predict risk of recurrence or influence duration of recommended anticoagulation), evidence-based guidelines recommend against routine thrombophilia testing. In this patient with an unprovoked proximal DVT, the recommendation for long-term anticoagulation would not be altered by the results of such testing, thus, it would not be helpful. Testing may be indicated, however, in patients with VTE at intermediate risk for recurrence by traditional predictors in whom finding a strong thrombophilic risk might alter therapeutic decisions.

KEY POINT

- Long-term anticoagulation therapy is recommended for patients with unprovoked proximal leg deep venous thrombosis or pulmonary embolism who have low or moderate bleeding risk.

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Item 10 Answer: C

Educational Objective: Treat anemia in a patient with Hodgkin lymphoma.

The patient should receive leukoreduced, irradiated erythrocytes. She has pancytopenia with symptomatic anemia likely because of her chemotherapy. Her bone marrow erythrocyte production cannot be efficiently increased because of her cancer treatment, so an erythrocyte transfusion is clinically indicated. However, immunocompromised patients (those with severe, inherited T-cell immunodeficiency syndromes or Hodgkin lymphoma or recipients of allogeneic or autologous hematopoietic stem cell transplantation, purine analog–based chemotherapy [fludarabine, cladribine, deoxycoformycin], alemtuzumab, or rabbit antithymocyte globulin therapy) are at increased risk of developing transfusion-associated graft-versus-host disease (ta-GVHD). ta-GVHD occurs when the recipient's immune system is unable to eradicate contaminating donor lymphocytes in the transfused erythrocyte or platelet product; the transfused lymphocytes mount an immune response toward the recipient that may result in a maculopapular skin rash, gastrointestinal symptoms, cough and dyspnea, and pancytopenia due to marrow aplasia. Irradiation of the cellular product inactivates contaminating lymphocytes and prevents this complication. ta-GVHD may also occur when partial HLA matching occurs, in which the recipient is heterozygous for an HLA haplotype for which the donor is homozygous. In such a situation, the recipient's immune system will not recognize the donor lymphocytes as foreign and will fail to mount an immune response. As such, all HLA-matched products require irradiation (that is, HLA-matched platelets for patients with platelet transfusion refractoriness owing to alloimmunization), regardless of the competency of the recipient's immune system.

The patient would benefit from leukoreduced erythrocytes, thus minimizing the risk of febrile nonhemolytic transfusion reactions, as well as HLA alloimmunization and subsequent platelet transfusion refractoriness. Although leukoreduction alone likely reduces the risk of ta-GVHD, it does not eliminate the risk of this complication.

This patient has a positive cytomegalovirus (CMV) IgG antibody and thus has already been exposed to this infectious agent. Therefore, a CMV-negative product is not required. Furthermore, the current generation of prestorage leukocyte filters has significantly decreased the risk of CMV transmission as a result of erythrocyte and platelet transfusion. As such, not all transfusion centers use CMV-negative products for recipients who are CMV seronegative.

Washed erythrocytes are considered for patients with a history of severe allergic reactions to transfusions, which this patient does not have.

KEY POINT

- Leukoreduced and irradiated erythrocytes should be used when transfusing select patients who are immunocompromised to reduce the risk of transfusion-associated graft-versus-host disease and febrile nonhemolytic transfusion reaction.

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Item 11 Answer: B

Educational Objective: Manage Philadelphia chromosome–positive acute lymphoblastic leukemia in an older patient.

This patient has acute lymphoblastic leukemia (ALL), and the most appropriate treatment is dasatinib with dexamethasone. Diagnosis requires the presence of 25% or more lymphoblasts on bone marrow examination. Cytochemical stains and flow cytometry can help distinguish ALL from acute myeloid leukemia (AML) and B-cell from T-cell ALL. The prognosis for an older patient with ALL has traditionally been poor, with Philadelphia chromosome [t(9;22)] positivity indicating worse outcomes. Twenty-five percent of all adults with ALL and up to 50% of those older than 70 years are positive for t(9;22). With the advent of tyrosine kinase inhibitor (TKI) therapy, medications like imatinib and dasatinib have become the backbone of therapy for Philadelphia chromosome–positive ALL and can be used alone or with chemotherapy. The most significant advance in the treatment of older patients with

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CONT.

Philadelphia chromosome–positive disease is TKI therapy. The results of dasatinib and dexamethasone therapy are better than those for traditional chemotherapy, with less toxicity. For older patients who have Philadelphia chromosome–negative ALL, no clear standard cytotoxic chemotherapy regimen exists. However, TKI therapy can provide disease control for greater than 1 year with much less toxicity.

Based on encouraging progress in intensive pediatric regimens, asparaginase has been incorporated into care for adolescents and young adults with ALL. However, use in older adult patients does not improve outcomes and multiplies toxicity.

Anthracyclines (such as daunorubicin), vincristine, and dexamethasone are part of traditional chemotherapy for pediatric and adult patients with ALL; however, results in older patients are disappointing. Therefore, none of these medications would be the best treatment option for this older patient. Combination regimens such as hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) can cure adults with ALL, but are too toxic for use in elderly populations. The paradox of ALL in older adults is that although less aggressive regimens are less toxic, they compromise the ability to control the leukemia.

KEY POINT

- Tyrosine kinase inhibitor therapy, such as dasatinib, provides a significant advance in the treatment of older patients with Philadelphia chromosome–positive acute lymphoblastic leukemia.

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Item 12 Answer: D

Educational Objective: Determine indications for thrombophilia testing in a patient with a first thromboembolic event.

No thrombophilia testing is indicated in this patient. No evidence indicates that identification of a thrombophilia in this patient would influence the duration or intensity of anticoagulant therapy. Consequently, the American Society of Hematology recommends against thrombophilia testing in patients who develop a venous thromboembolism (VTE) in the setting of a major transient risk factor (surgery, trauma, or prolonged immobility). The appropriate duration of anticoagulation for this patient with VTE due to recent trauma and major surgery is 3 months, regardless of identification of a thrombophilia. It is unclear which patients benefit from thrombophilia testing. It may be appropriate to consider evaluation for a strong thrombophilia in a patient with VTE who is at intermediate risk for recurrent VTE by traditional recurrence risk factors. These are patients with a thromboembolism associated with minor VTE risk factors, such as women with hormone- or pregnancy-associated VTE or men or women with VTE associated with minor immobility or minor surgery. Finding a strong thrombophilia in these patients may be one of the indications for long-term anticoagulation.

Antiphospholipid antibodies (APLAs) impart a greater risk of arterial and venous thromboembolism. Although the prothrombin time (PT) and activated partial thromboplastin time (aPTT) may be elevated in patients with APLAs, they are not adequately sensitive or specific to indicate the presence or absence of this cause of thrombophilia. If antiphospholipid syndrome is suspected, APLA tests (lupus anticoagulant, anticardiolipin antibodies, and anti-β_2-glycoprotein I antibodies) should be ordered, independent of whether the PT and aPTT are normal or prolonged. Testing for any of these conditions is not indicated in this patient.

If thrombophilia testing is indicated, evaluation should be based on the circumstances, location, and extent of the thrombosis, possibly with input from a coagulation subspecialist. Factor V Leiden and the prothrombin G20210A mutation are the most common inherited thrombophilias and are associated with a mildly increased risk for VTE.

KEY POINT

- Thrombophilia testing is not indicated in patients who develop a venous thromboembolism in the setting of a major transient risk factor (major surgery or trauma or prolonged immobility), because results would not influence duration or intensity of anticoagulation therapy.

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Item 13 Answer: D

Educational Objective: Manage an acute, uncomplicated vaso-occlusive pain episode with opioids.

The most appropriate pain regimen for this patient is scheduled morphine. Pain is the most common complication of sickle cell disease (SCD) and may be the initial presenting symptom in patients who subsequently develop more severe complications, such as acute chest syndrome (ACS) or multiorgan failure. Patients commonly have musculoskeletal symptoms, but vaso-occlusion can occur in any organ system. No reliable physical or laboratory findings serve as useful surrogate markers for excluding vaso-occlusion; therefore, managing a painful episode in SCD is based on symptoms. Management of an uncomplicated painful episode includes hydration, nonopioid and opioid analgesia, and incentive spirometry to avoid ACS. Morphine and hydromorphone are the opioid analgesics of choice. During hospitalization, opioid analgesia is most effectively delivered by regularly scheduled opioid administration or by patient-controlled analgesia pumps that include a basal rate and a demand option.

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Meperidine is generally avoided because of its short half-life and lowered seizure threshold.

NSAIDs such as ketoprofen may be useful in the outpatient management of a painful vaso-occlusive crisis in patients with stable kidney function, but are probably inadequate as single agents for patients with severe pain requiring hospitalization. In addition, randomized studies have demonstrated no benefit of adding an NSAID to an opioid for the treatment of acute vaso-occlusive crisis in hospitalized patients.

KEY POINT

- During hospitalization, opioid analgesia is most effectively delivered by regularly scheduled opioid administration or by patient-controlled analgesia pumps.

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Item 14 Answer: C

Educational Objective: Diagnose suspected pulmonary embolism in a pregnant woman.

This patient, who is pregnant and has a clinical suspicion for pulmonary embolism (PE), should undergo lower extremity venous duplex ultrasonography. Because anticoagulant therapy for PE and deep venous thrombosis (DVT) is similar, diagnosing a DVT noninvasively through ultrasonography would allow immediate initiation of therapy and avoid fetal exposure to radiation and contrast, which are involved in other studies for diagnosing PE. However, a normal lower extremity study for DVT does not exclude the presence of a PE in a patient with a reasonable pretest probability based on clinical features, such as this woman. If her ultrasound is normal, a ventilation-perfusion (V/Q) lung scan is the next preferred modality. If a V/Q scan is unavailable, CT pulmonary angiography is the next diagnostic choice.

Unfortunately, no validated clinical prediction rules exist for assessing pretest probability of PE in pregnant women. Additionally, D-dimer levels are normally elevated during pregnancy. Therefore, D-dimer testing has minimal clinical utility in evaluating for the presence of PE or DVT.

KEY POINT

- The preferred initial diagnostic test to perform in a pregnant patient with possible pulmonary embolism is lower extremity venous duplex ultrasonography to assess for the presence of deep venous thrombosis, which, if present, would obviate the need for radiation and contrast exposure associated with other diagnostic studies.

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Item 15 Answer: B

Educational Objective: Treat platelet transfusion refractoriness.

This patient should receive HLA-matched platelets. She meets criteria for platelet transfusion refractoriness, defined as an increase in the platelet count less than 10,000/μL (10×10^9/L) measured 10 to 60 minutes after transfusion on at least two separate occasions. Nonimmune causes include sepsis, fever, disseminated intravascular coagulation, splenomegaly, and medications that decrease platelet half-life. This patient has no features suggesting a nonimmune cause. She is most likely alloimmunized from her previous pregnancies. Such patients are ideally treated with HLA-matched platelets. A systematic review demonstrated improved 1-hour posttransfusion platelet counts with HLA typing. However, the effects on 24-hour platelet counts were more varied, and the impact of this practice on bleeding and mortality is unclear. If HLA-matched platelets are not available, other strategies can be used, including transfusion of HLA-compatible platelets, in which the transfused platelets are missing the antigen to which the patient's alloantibodies are directed, or platelet crossmatching, in which the patient's serum is incubated with donor platelets.

ABO-matched platelets lead to a slightly higher platelet increment in patients who are not alloimmunized but are not likely to have a significant impact on someone who is truly alloimmunized.

Washed platelets are typically reserved for patients who have had severe allergic reactions to platelet transfusion (such as patients who are IgA deficient).

Studies have shown that prophylactic platelet transfusion for a platelet count less than 10,000/μL (10×10^9/L) is superior to platelet transfusions administered at the onset of clinical bleeding, thus decreasing the incidence of clinically significant bleeding. As such, observation without platelet transfusion is inappropriate.

KEY POINT

- Patients experiencing platelet transfusion refractoriness because of alloimmunization should receive HLA-matched platelets.

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Item 16 Answer: B

Educational Objective: Manage a patient with acute venous thromboembolism who experienced a major bleeding episode.

Inferior vena cava (IVC) filter placement is indicated; this patient cannot safely undergo anticoagulation because of his

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CONT.

recent major gastrointestinal bleed. He is at increased risk for bleeding owing to the presence of a coagulopathy, likely secondary to his liver disease, and thrombocytopenia, likely due to hypersplenism from an enlarged spleen resulting from portal hypertension. Despite having prolonged coagulation parameters, patients with liver disease are not "autoanticoagulated" and may experience venous thromboembolism (VTE), because procoagulant and anticoagulant protein production is deficient in unpredictable ratios, making it nearly impossible to predict if the patient is most at risk for bleeding or thrombosis. Because of this, anticoagulation in patients with liver disease should be undertaken with caution because of the risk for bleeding. This patient's bleeding risk is very high because of the recent episode of bleeding varices. When IVC filters are necessary, retrievable filters are strongly recommended rather than permanent filters. Whether IVC filters are beneficial for patients with pulmonary embolism (PE) despite appropriate therapeutic anticoagulation is unclear; a possible indication is massive PE with poor cardiopulmonary reserve. No evidence supports the use of IVC filters in the primary prophylaxis of VTE. If the bleeding risk resolves, a conventional course of anticoagulant therapy is recommended with consideration of filter removal.

Considering this patient's risk for bleeding, no anticoagulant (such as heparin, argatroban, rivaroxaban) can safely be given. Additionally, rivaroxaban and argatroban are partially cleared by the liver and are contraindicated in severe liver disease.

KEY POINT

- In patients who cannot safely undergo anticoagulation therapy for venous thromboembolism, such as those with recent bleeding, an inferior vena cava filter should be used until the bleeding risk resolves.

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Item 17 Answer: D

Educational Objective: Diagnose β-thalassemia.

This patient's most likely diagnosis is β-thalassemia intermedia. She has erythrocyte parameters typical for thalassemia (hemolytic anemia, microcytosis, target cells), a common genetic disorder caused by a mutation in one or more α-globin or β-globin genes leading to a quantitative deficiency in the synthesis of that globin chain. The imbalance in globin-chain synthesis leads to impaired production of hemoglobin and ineffective erythropoiesis, with intramedullary hemolysis and often chronic anemia. α-Thalassemia and β-thalassemia are usually differentiated by hemoglobin electrophoresis, with β-thalassemia associated with a slightly increased hemoglobin A_2 and some residual hemoglobin F. Because of this patient's increased hemoglobin A_2 level, she most likely has β-thalassemia. Because of the low-level hemolysis associated with either type of thalassemia, patients with thalassemia (and other chronic hemolytic anemias) can commonly have low folate levels even if dietary intake is inadequate, leading to worsening of chronic anemia.

Although most patients with β-thalassemia intermedia are anemic at baseline, most are physiologically adjusted to a hemoglobin level between 7 and 10 g/dL (70-100 g/L). This is not an anemia associated with chronic inflammation.

The patient's iron studies do not indicate iron deficiency; in fact, her ferritin level is elevated, which is often seen in thalassemia. Therefore, she is unlikely to be experiencing iron malabsorption.

KEY POINT

- Hemolytic anemia, microcytosis, and target cells are typical of β-thalassemia, which is associated with slightly increased hemoglobin A_2 and some residual hemoglobin F.

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Item 18 Answer: D

Educational Objective: Evaluate erythrocytosis.

The patient should receive supplemental oxygen. He probably has secondary erythrocytosis due to hypoxic lung disease and may benefit from oxygen therapy based on his documented hypoxemia (arterial P_{O_2} ≤55 mm Hg [7.3 kPa] or arterial oxygen saturation ≤88%). The erythropoietin level is elevated owing to hypoxemia, causing an erythrocyte mass. No splenomegaly is present on physical examination, and the lung examination suggests COPD.

Because of the patient's elevated erythropoietin level and hypoxemia, a bone marrow biopsy is not required to exclude polycythemia vera (PV). No leukocytosis, basophilia, or thrombocytosis is seen on laboratory studies, all of which are common in PV.

The *JAK2 V617F* activating mutation defines PV, and 95% of PV harbors this mutation, with the other 5% presenting with variations of the mutation. No *JAK2*-negative PV exists. However, *JAK2* testing is expensive and is not required when a clear cause of secondary erythrocytosis is apparent.

The appropriate management of secondary erythrocytosis is control of the underlying cause. In most circumstances, therapeutic phlebotomy is not recommended for secondary erythrocytosis, because the increased erythrocyte mass is compensating for an unmet tissue oxygenation need.

KEY POINT

- Secondary erythrocytosis can be caused by hypoxemia, so patients may benefit from oxygen supplementation.

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Item 19 Answer: C

Educational Objective: Manage acquired hemophilia.

The patient should be given recombinant activated factor VII (VIIa). She is an older adult with no bleeding history and no family history of bleeding disorders who now has intramuscular and cutaneous bleeding, which suggests an acquired bleeding disorder. Acquired hemophilia (acquired factor VIII deficiency) causes bleeding with an isolated prolongation of the activated partial thromboplastin time (aPTT). It is associated with the postpartum state, malignancy, or autoimmune conditions, but 50% of cases are idiopathic. Patients have no history of bleeding, but bleeding at presentation can be severe. Unlike congenital hemophilia, bleeding in acquired hemophilia tends to be mucocutaneous and intramuscular. Factor VIII levels are reduced, and mixing study results show unsuccessful correction consistent with an inhibitor. Test results for the lupus anticoagulant are negative.

Patients with low titers of inhibitor (measured in Bethesda units) may be treated with factor VIII concentrates. Patients with high inhibitor titers (>5 Bethesda units) require treatment with recombinant factor VIIa or prothrombin complex concentrates designed to activate factor X and secure hemostasis independent of factor VIII and the intrinsic pathway. Patients may require immunosuppression for inhibitor eradication.

Mild bleeding associated with low inhibitor titers may be treated with desmopressin. However, this patient's hematocrit is low, she has tachycardia possibly related to volume depletion, and her inhibitor level is elevated, making desmopressin a less suitable treatment than recombinant factor VIIa.

Lupus anticoagulants can interfere with the coagulation cascade, causing a prolongation of the aPTT or prothrombin time not corrected by a mixing study. Although they prolong in vitro coagulation tests, they are associated with an increased risk for venous and arterial thromboembolism, not a bleeding tendency. This patient's cutaneous and intramuscular bleeding is inconsistent with the presence of a lupus anticoagulant.

KEY POINT

- Recombinant activated factor VII is used to treat the bleeding episodes of acquired hemophilia associated with high titers of inhibitor.

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Item 20 Answer: D

Educational Objective: Manage thrombocytopenia in a patient with acute myeloid leukemia.

The platelet count should be rechecked in 24 hours. Although this patient is significantly thrombocytopenic, phase III clinical trial data do not support the use of prophylactic platelet transfusions for patients with acute myeloid leukemia (AML) whose platelet count is 10,000/μL (10×10^9/L) or higher. Randomized studies have been published comparing a platelet transfusion threshold of 10,000/μL (10×10^9/L) to 20,000/μL (20×10^9/L) in stable patients with AML undergoing induction or consolidation chemotherapy; all have demonstrated equivalent outcomes with respect to clinically significant bleeding, need for erythrocyte transfusions, and mortality during induction chemotherapy. Therefore, these data support and guidelines recommend a threshold of 10,000/μL (10×10^9/L) for prophylactic platelet transfusion in hospitalized patients with thrombocytopenia due to decreased bone marrow production. Patients with acute promyelocytic leukemia (APL), fever, clinically significant bleeding, or a need for invasive procedures were not evaluated in these studies and are typically transfused at a threshold of 20,000/μL (20×10^9/L).

Transfusion of leukoreduced, irradiated platelets would be appropriate if the patient's platelet count decreases to less than 10,000/μL (10×10^9/L). HLA-matched platelets would only be used if the patient had a history of platelet transfusion refractoriness attributed to platelet alloantibodies. Washing of platelets leads to loss of platelet numbers and function and is reserved for patients with a history of a severe allergic reaction to a transfused blood product (such as anaphylaxis in a patient with IgA deficiency).

KEY POINT

- Clinically stable patients with chemotherapy-induced thrombocytopenia who are not bleeding do not benefit from platelet transfusion when the platelet count is 10,000/μL (10×10^9/L) or greater.

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Item 21 Answer: A

Educational Objective: Manage warfarin therapy with vitamin K supplementation.

The patient should begin daily low-dose vitamin K supplementation. In 2007, a double-blind randomized trial compared the effects of low-dose vitamin K (100-150 μg/d) and placebo on INR stability in 70 patients receiving chronic warfarin therapy. Vitamin K supplementation resulted in 19 of 35 patients achieving the predefined criteria for stable control of anticoagulation compared with only 7 of 35 patients receiving placebo. It was hypothesized that low-dose vitamin K reduced the day-to-day variation in dietary vitamin K intake in patients with unexplained INR fluctuations.

Polymorphisms in the genes transcribing enzymes involved in the metabolism of vitamin K antagonists, such

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as cytochrome P-450 2C9 and vitamin K epoxide reductase complex-1, contribute to the variability in dose requirements among patients but do not explain day-to-day or week-to-week INR fluctuations in individual patients. Therefore, genetic testing would not be helpful in this situation.

A factor V Leiden mutation would not explain INR fluctuations. The only thrombophilia that might cause INR fluctuations over time is the presence of a lupus anticoagulant; however, such frequent fluctuations as this patient is experiencing would not be expected with any thrombophilia. Thus, a thrombophilia evaluation would not be indicated.

Aspirin alone will not provide the same protective benefit as warfarin for this patient with recurrent deep venous thrombosis.

KEY POINT

- In some patients with fluctuating INRs while taking warfarin, daily supplementation with low-dose vitamin K (100-150 µg/d) can stabilize the INR.

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Item 22 Answer: D

Educational Objective: Diagnose the cause of an aplastic crisis.

The patient has parvovirus B19 infection. She has chronic hemolytic anemia due to sickle cell anemia and presents with severe anemia and a completely inadequate reticulocyte response 1 week after being exposed to a child with a febrile illness, which was likely caused by parvovirus B19. Hydroxyurea could lead to worsening anemia in a patient with sickle cell anemia but would not cause the acute signs or symptoms found in this patient. A subsequent bone marrow examination would demonstrate pure red cell aplasia (PRCA). Parvovirus has a tropism for erythrocyte precursors and is a known cause of aplastic crisis in patients with underlying sickle cell disease (SCD). Immune competent patients and those without chronic hemolysis have a milder hematologic response to parvovirus infection and are more likely to recover spontaneously.

Cytomegalovirus could cause constitutional symptoms and could trigger a painful crisis, but it is not associated with direct destruction of erythrocyte precursors. Cytomegalovirus may cause retinitis, gastroenteritis, or hepatitis in an immunocompromised patient, none of which are seen in this patient. Adults with SCD are functionally asplenic.

Epstein-Barr virus is unlikely owing to its lack of association with PRCA. However, viral illnesses are the frequent underlying causes that precipitate vaso-occlusive crises or acute chest syndrome in patients with SCD.

Influenza A virus is an unlikely diagnosis because the patient has no typical symptoms. Although influenza A could cause severe viral pneumonia and could lead to acute chest syndrome, its association with PRCA is not strong.

KEY POINT

- Parvovirus B19 infection can cause acquired pure red cell aplasia in an otherwise functionally asplenic patient with sickle cell disease.

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Young NS, Brown KE. Parvovirus B19. N Engl J Med. 2004 Feb;350(6):586-97. [PMID: 14762186]

Item 23 Answer: C

Educational Objective: Manage asymptomatic immune thrombocytopenic purpura.

The patient most likely has immune thrombocytopenic purpura (ITP) and should have another complete blood count performed in 1 week. Although ITP is a diagnosis of exclusion, supportive clinical findings include an otherwise normal blood count and the absence of additional organ dysfunction. Platelets on the peripheral blood smear are large because they typically have been recently released from the marrow, and the enhanced hemostatic function of these young platelets may account for less severe bleeding symptoms than those associated with other diseases with a similar platelet count. Not all patients with ITP require therapy, and monitoring for signs of bleeding or further declines in platelet counts may be appropriate. Asymptomatic patients without evidence of bleeding and platelet counts greater than 30,000 to 40,000/µL (30-40 $\times 10^9$/L) have less than a 15% chance of developing more severe thrombocytopenia requiring treatment. In such patients, the most appropriate course of action is to provide counseling on potential bleeding symptoms and repeat the complete blood count at a designated interval, generally 1 to 2 weeks, until the course of the illness is determined.

In adults with ITP, therapy may be required for patients with platelet counts lower than 30,000 to 40,000/µL (30-40 $\times 10^9$/L) or with bleeding. Initial therapy consists of glucocorticoids. Patients who do not respond to glucocorticoid therapy should be treated with an additional agent such as intravenous immune globulin or anti-D immune globulin or rituximab.

Splenectomy leads to a sustained remission in 75% of patients. Because of this patient's lack of symptoms and platelet count greater than 30,000/µL (30×10^9/L), therapy is unnecessary at this time, and the patient may be safely observed.

KEY POINT

- Patients with immune thrombocytopenic purpura without evidence of bleeding and platelet counts greater than 30,000 to 40,000/µL (30-40 $\times 10^9$/L) have less than a 15% chance of developing more severe thrombocytopenia requiring treatment and can be managed with careful observation.

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Item 24 Answer: C

Educational Objective: Manage unprovoked proximal leg superficial thrombophlebitis.

This patient should undergo venous duplex ultrasonography of the left thigh to evaluate for deep venous thrombosis (DVT) associated with his superficial venous thrombophlebitis (SVT). DVT or pulmonary embolism (PE) develops in up to 3.3% of patients with isolated SVT. The risk increases in patients with SVT of the great or small saphenous vein, with extremity swelling more pronounced than would be expected from the SVT alone, and with progressive symptoms. In these situations, such as with this patient, duplex ultrasonography is indicated to assess for the possibility of an associated DVT.

The effectiveness of low-dose aspirin to treat or prevent propagation of clots in SVT has not been established. Additionally, the use of other anticoagulants for treatment of SVT is controversial. Some evidence indicates that patients with extensive SVT may benefit from a short course of anticoagulant therapy. However, because of a lack of additional data, the specific patients for whom treatment is indicated, the optimal duration of anticoagulation, and the appropriate drug dose and choice are unknown.

D-dimer testing has no utility for differentiating superficial from deep venous thrombosis because levels may be elevated in both conditions. It would, therefore, not be useful in this patient.

Nonextensive SVT, defined as less than 5 cm in length and not near the deep venous system, may be treated with only symptomatic therapy consisting of analgesics, anti-inflammatory medications, and warm or cold compresses for symptom relief, because the risk of progression into the deep venous system and of PE is low.

KEY POINT

- Duplex ultrasonography is indicated to assess for the possibility of an associated deep venous thrombosis (DVT) in patients with isolated superficial venous thrombophlebitis (SVT), because DVT or pulmonary embolism risk increases in patients with SVT of the great or small saphenous vein, with extremity swelling more pronounced than would be expected from the SVT alone, and with progressive symptoms.

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Item 25 Answer: A

Educational Objective: Diagnose folate deficiency.

This patient has folate deficiency. Folate deficiency caused by decreased folate consumption occurs infrequently, because normal diets are replete with folate. However, patients with folate-deficient diets, especially those with generalized malnutrition or poor nutrition, can become folate deficient in weeks to months because of relatively limited stores of folate in the body. Other less common causes of folate deficiency include conditions such as hemolytic anemia (for example, sickle cell disease), desquamating skin disorders (for example, psoriasis), and other conditions associated with increased cellular turnover. Measuring serum folate levels is typically unreliable in diagnosing folate deficiency, because folate levels increase rapidly after a single folate-containing meal. Plasma homocysteine levels increase in folate deficiency, whereas homocysteine and methylmalonic acid levels are increased in cobalamin deficiency. An elevated homocysteine level has a sensitivity of greater than 90% in the diagnosis of folate deficiency, making homocysteine measurement a reasonable test when the disorder is suspected but the serum folate level is normal.

In addition to peripheral blood smear findings of microcytosis and anisopoikilocytosis (abnormalities in erythrocyte size and shape), patients with iron deficiency have reduced serum iron and ferritin levels, increased total iron-binding capacity, and reduced transferrin saturation (iron/total iron-binding capacity). The patient's macrocytosis and high homocysteine level make iron deficiency an unlikely cause of her anemia.

α-Thalassemia trait (or α-thalassemia minor) is associated with mild anemia, microcytosis, hypochromia, target cells on the peripheral blood smear, and, in adults, normal hemoglobin electrophoresis results. The (-α/-α) variant is found in 2% to 3% of all black persons and is often mistaken for iron deficiency. The patient's new-onset macrocytic anemia is not consistent with an inherited hemoglobinopathy associated with microcytosis.

Vitamin B_{12} deficiency usually develops over several months, not weeks. Furthermore, homocysteine and methylmalonic acid levels are elevated in vitamin B_{12} deficiency, but this patient's methylmalonic acid level is normal.

KEY POINT

- An elevated homocysteine level is 90% sensitive for folate deficiency, making this measurement the most sensitive diagnostic marker in suspected folate deficiency when the serum folate level is normal.

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Kaferle J, Strzoda CE. Evaluation of macrocytosis. Am Fam Physician. 2009 Feb 1;79(3):203-8. [PMID: 19202968]

Item 26 Answer: B

Educational Objective: Treat essential thrombocythemia based on risk stratification.

Hydroxyurea plus low-dose aspirin is the most appropriate treatment for patients with essential thrombocythemia (ET) in whom treatment is indicated. Treatment of ET requires

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reduction of the platelet count; however, when and whom to treat remain controversial. Although the exact platelet count does not determine the risk for thrombosis, lowering the platelet count in patients at risk for thrombosis will decrease this risk and, possibly, the risk for secondary myelofibrosis. Patients do not require treatment if they are younger than 60 years, have a platelet count less than 1 million/μL (1000×10^9/L), and have no history of thrombosis. Hydroxyurea plus low-dose aspirin is the best treatment option for ET when treatment is required in patients older than 60 years, those with a platelet count greater than 1 million/μL (1000×10^9/L), or those with a history of thrombosis or an increased risk for thrombosis because of cardiovascular risk factors such as hypertension and diabetes mellitus. Hydroxyurea plus low-dose aspirin reduces the risk for arterial thrombosis and bleeding (regardless of the platelet count achieved) in patients with ET.

Anagrelide is another platelet-lowering agent used to manage ET, but in a randomized trial comparing anagrelide with hydroxyurea, anagrelide was found to have a less favorable side effect profile. Likewise, hydroxyurea, but not anagrelide, decreases thrombotic risk independent of platelet-count lowering.

Ruxolitinib is an inhibitor of constitutively active *JAK2 V617F*. Although 50% of patients with ET demonstrate this mutation, ruxolitinib has a therapeutic role only in alleviating the splenomegaly and systemic symptoms of primary myelofibrosis.

Warfarin has not been studied for primary prophylaxis of ET; therefore, it would not be an appropriate treatment choice for this patient.

The patient's age is an important factor in initiating therapy, making observation an inappropriate choice.

KEY POINT

- Hydroxyurea plus low-dose aspirin is the best treatment option for essential thrombocythemia when treatment is required in patients older than 60 years, those with a platelet count greater than 1 million/μL (1000×10^9/L), or those with a history of thrombosis.

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Item 27 Answer: D

Educational Objective: Diagnose macroangiopathic hemolytic anemia caused by a mechanical heart valve.

This patient should be further evaluated with echocardiography; she likely has hemolysis due to her mechanical aortic valve. She has evidence of hemolytic anemia based on her low serum haptoglobin and high lactate dehydrogenase levels. The peripheral blood smear shows schistocytes, which are often found in clinical conditions in which erythrocytes are damaged in small blood vessels (microangiopathic hemolytic anemia), but schistocytes may also occur from trauma in larger blood vessels (macroangiopathic hemolytic anemia). The patient has a mechanical heart valve with a significant murmur, suggesting possible valve dysfunction, and, in the absence of other likely causes of a microangiopathic hemolytic anemia, this is likely the cause of her hemolysis. Therefore, echocardiography to identify a regurgitant jet or paravalvular leak, suggested by the murmur present in this patient, would be the most appropriate next diagnostic study. In patients with suspected valve-associated hemolysis, transesophageal echocardiography is the preferred study because of its ability to effectively visualize the aortic valve structures for this potential complication. Patients with chronic intravascular hemolysis may ultimately develop iron deficiency anemia as the heme iron released from the hemolysis passes through the kidneys and is lost in the urine.

Thrombotic thrombocytopenic purpura (TTP) is a cause of microangiopathic hemolytic anemia and should be considered in this patient. However, her normal platelet count and the slowly progressive onset of her symptoms make this diagnosis unlikely. In patients with TTP, an ADAMTS-13 assay may be helpful in estimating prognosis, but would not be an appropriate study in this patient.

Disseminated intravascular coagulation (DIC) is an acquired form of microangiopathic hemolytic anemia. Acute DIC is associated with evidence of accelerated fibrinolysis, including increased fibrin degradation products and D-dimer. However, this patient has no other clinical findings consistent with DIC (such as bleeding or thrombocytopenia), making this an unlikely diagnosis and a D-dimer measurement unnecessary.

The direct antiglobulin (Coombs) test is used to determine an autoimmune cause of hemolytic anemia. However, neither warm nor cold autoimmune hemolytic anemia causes schistocytes as seen in this patient's blood smear, making this diagnosis unlikely. Therefore, this test would be of low diagnostic yield.

KEY POINT

- Patients with suspected macroangiopathic hemolytic anemia caused by a mechanical heart valve should be diagnosed using transesophageal echocardiography.

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Item 28 Answer: D

Educational Objective: Manage anticoagulation in a patient with an elevated plasma homocysteine level and methylene tetrahydrofolate reductase polymorphism.

This patient's warfarin should be discontinued. Patients who have experienced a single venous thromboembolism (VTE) due to a major transient risk factor only require short-term anticoagulation for 3 months. This patient experienced a deep

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venous thrombosis following a traumatic tibia fracture. Generally, the clinical setting of a thrombotic event (unprovoked versus provoked) provides greater prognostic information regarding recurrence risk than the results of thrombophilia testing. Therefore, in most instances, thrombophilia testing results will not influence treatment duration and testing is not indicated. If thrombophilia testing is considered, it should be targeted to persons in whom finding a strong thrombophilia may influence length of anticoagulant treatment or have an impact on other family members if they also tested positive for the higher risk thrombophilia. However, consensus is limited on what defines higher risk thrombophilias.

Elevated plasma homocysteine levels are associated with an increased risk for a first venous or arterial thromboembolic event. Homocysteine levels can be lowered with folic acid, vitamin B_6, and vitamin B_{12}. However, this does not change the risk of a first thromboembolic event, which this patient has already experienced, nor of recurrent VTE.

Homozygosity for the methylene tetrahydrofolate reductase (*MTHFR*) C677T polymorphism can be associated with elevated homocysteine levels but alone is not a risk factor for VTE. Thus, no clinical indication exists for testing for the *MTHFR* polymorphism in patients or first-degree relatives.

KEY POINT

- Thrombophilia test results typically do not influence treatment duration, so testing is not indicated, especially for patients with only a single venous thromboembolism resulting from a major transient risk factor.

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Item 29 Answer: B

Educational Objective: Diagnose infectious complications of iron overload syndromes.

This patient should be advised to avoid eating raw or undercooked seafood. Patients with iron overload syndromes, including those with hereditary hemochromatosis, are at risk for a number of infections with organisms whose virulence is increased in the presence of excess iron. Although the exact mechanisms of increased susceptibility to specific infections are not known, pathogens require mobilization of tissue iron from the host, which is increased in iron overload syndromes. Additionally, excess iron appears to impair host defenses against certain infections, such as decreasing the chemotactic response and compromising the ability of phagocytic cells. The result is increased virulence among specific infectious organisms in patients with iron overload, including *Vibrio* species (*vulnificus*, *cholerae*), *Escherichia coli*, *Yersinia enterocolitica*, *Listeria monocytogenes*, cytomegalovirus, hepatitis B and C viruses, and HIV. Fungi include *Aspergillus fumigatus* and mucor. *V. vulnificus* infection is associated with ingestion of raw seafood, especially oysters, and the risk of sepsis and death is significantly increased in persons with hemochromatosis; therefore, these foods should be specifically avoided by these patients.

Oral calcium supplements may bind iron in the gut and inhibit iron absorption and are acceptable to take if needed for another indication. However, this inhibitory effect is small relative to the removal of iron by phlebotomy. Therefore, supplementation for treatment of hemochromatosis in those undergoing phlebotomy is not usually required.

Although red meat contains iron, and excessive meat intake should be avoided, consumption of moderate amounts of meat by those being treated with phlebotomy is reasonable for nutritional purposes. The amount of iron removed by phlebotomy far exceeds the iron content of a moderate intake of meat.

Vitamin C (ascorbic acid) may interact with tissue iron and lead to generation of oxidative radicals with the potential for tissue damage. However, the amount of vitamin C contained in fruits and vegetables is relatively low, and their consumption as part of a normal diet should not be discouraged.

KEY POINT

- *Vibrio vulnificus* infection is associated with ingestion of raw seafood, especially oysters, and the risk of sepsis and death is increased in persons with hereditary hemochromatosis.

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Item 30 Answer: D

Educational Objective: Manage testing of family members for factor V Leiden mutation.

This patient should not undergo further testing for a factor V Leiden (FVL) mutation. FVL is the most common inherited thrombophilia, resulting from a point mutation in the factor V gene that causes it to be resistant to inactivation by activated protein C (APC). FVL prevalence in the United States is 3% to 8% in whites and 1.2% in blacks, but it rarely occurs in African and Asian populations. Homozygous FVL carries an 18-fold increased risk of first-time venous thromboembolism (VTE), whereas FVL heterozygosity only carries a 2.7-fold increased risk. Although this patient's mother has a known inherited thrombophilia with recurrent episodes of VTE, no evidence indicates testing for inherited thrombophilia is beneficial in an asymptomatic child, particularly with heterozygous FVL, which is not considered a strong thrombophilia.

In patients in whom testing for FVL is indicated, the presence of FVL can be detected by an APC resistance assay that assesses the ability of protein C to inactivate factor Va. This is a very sensitive study that effectively excludes FVL if normal and is the preferred initial screening test, mainly because it is typically less expensive than the FVL

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genetic test. An abnormal result suggests heterozygous or homozygous FVL, depending on the degree of abnormality, but should be followed by confirmatory genetic polymerase chain reaction testing of the FVL gene that assesses for the point mutation in genetic material from leukocytes from the peripheral blood.

Factor V deficiency is an extremely rare inherited disorder that causes abnormal bleeding as a result of failure of thrombin generation because of inadequate amounts of factor V. This patient has no evidence of a bleeding disorder, so testing factor levels is not indicated.

KEY POINT

- Routine testing for factor V Leiden (FVL) mutation in offspring of a patient with FVL is not indicated.

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Item 31 Answer: A

Educational Objective: Treat acute promyelocytic leukemia.

All-*trans* retinoic acid (ATRA) should be administered as soon as possible, followed by chemotherapy, for this patient with acute promyelocytic leukemia (APL). APL is a clinically and biologically distinct variant of acute myelocytic leukemia characterized by the presence of a (15;17) gene translocation, which gives rise to the promyelocytic leukemia–retinoic acid receptor-α fusion transcript and arrest of leukemic cells at the promyelocyte stage. Adding ATRA to standard induction and consolidation chemotherapy releases the block in promyelocyte maturation and produces cure in up to 80% of patients. If APL is suspected, ATRA should be initiated without waiting for confirmation. This patient's symptoms and laboratory studies strongly suggest APL, with prominent Auer rods on the peripheral blood smear and bleeding out of proportion to thrombocytopenia. She also has biochemical evidence of disseminated intravascular coagulation, which is a defining clinical clue to APL. In addition to appropriate blood product transfusion support, early ATRA administration is required to help patients survive induction chemotherapy. The greatest mortality risk from APL accrues in the first 2 weeks, with delay in ATRA administration being one of several root causes.

Testing for the t(9;22) would not be helpful in this patient, because it would identify the Philadelphia chromosome, which only has relevance in chronic myeloid leukemia or acute lymphoblastic leukemia.

Testing for the t(15;17) would confirm a diagnosis of APL and can be accomplished in less than 24 hours using fluorescence in situ hybridization. However, enough clinical clues are already provided to strongly suspect the diagnosis, and ATRA should be initiated at the point of clinical suspicion to improve early survival.

KEY POINT

- Immediate administration of all-*trans* retinoic acid is important in preventing early mortality in suspected acute promyelocytic leukemia.

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Item 32 Answer: D

Educational Objective: Diagnose hereditary spherocytosis.

This patient should undergo an osmotic fragility test. She most likely has hereditary spherocytosis. Inheritance is usually autosomal dominant with variable penetrance but may occasionally be sporadic. Alternations in membrane structure destabilize the erythrocyte, leading to a spherocytic shape, reduced deformability, trapping, and subsequent destruction in the spleen. Hereditary spherocytosis should be suspected in patients with a personal or family history of anemia, jaundice, splenomegaly, or gallstones. Some patients, such as this patient, may come to medical attention because of an aplastic crisis precipitated by an acute parvovirus B19 infection. Spherocytes are present on the peripheral blood smear, and the direct antiglobulin (Coombs) test (DAT) is negative. The osmotic fragility test with 24-hour incubation is a key step in diagnosis, demonstrating increased erythrocyte fragility in hypotonic saline compared with control erythrocytes.

Patients with warm autoimmune hemolytic anemia (WAIHA) may present with rapid or insidious symptoms of anemia or jaundice; mild splenomegaly is often present. Spherocytes are seen on the peripheral blood smear. The DAT is used to diagnose WAIHA. In less than 10% of patients, the DAT may be normal, in which case more sensitive diagnostic testing through a reference laboratory or blood center is required. First-line therapy for WAIHA is glucocorticoids; however, a trial period of prednisone is not indicated in this patient with a negative DAT and a family history of anemia.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal progenitor cell disorder characterized by hemolytic anemia, pancytopenia, or unprovoked thrombosis. Diagnosis is based on flow cytometry results, which can detect CD55 and CD59 deficiency on the surface of peripheral erythrocytes or leukocytes. In the absence of pancytopenia and a history of thrombosis, flow cytometry is not indicated in this patient

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is caused by various mutations on the X chromosome and occurs more commonly in men, often in blacks. During an acute hemolytic episode, bite cells may be seen on the peripheral blood smear, and a brilliant cresyl blue stain may reveal Heinz bodies (denatured oxidized hemoglobin). These

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findings are not present in the patient's peripheral blood smear, so measuring the G6PD activity is not indicated.

KEY POINT

- The osmotic fragility test with 24-hour incubation is a key step in diagnosing hereditary spherocytosis.

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Item 33 Answer: A

Educational Objective: Evaluate the cause of iron deficiency anemia with colonoscopy and upper endoscopy.

This patient should undergo evaluation by colonoscopy and upper endoscopy. Iron deficiency can result from blood loss or malabsorption. In men and nonmenstruating women, gastrointestinal blood loss is always the presumed cause of iron deficiency unless proven otherwise and may develop secondary to an undiagnosed colonic neoplasm. Colon cancer is the most commonly detected cancer causing iron deficiency anemia.

Remeasuring iron stores in 1 month will not be helpful and is not an appropriate choice without assessing the cause of the iron deficiency. In patients who receive adequate treatment for iron deficiency anemia, reticulocytosis can be expected within 7 to 10 days, and the hemoglobin level can be expected to increase in 1 to 2 days. Iron stores are not expected to normalize for 6 months.

Iron malabsorption can result from celiac disease, inflammatory bowel disease, or surgical resection (affecting the duodenum, as in gastric bypass). Some malabsorption syndromes, such as celiac disease, are not accompanied by diarrhea, steatorrhea, or weight loss. In developed nations, gastrointestinal bleeding is the most common cause of iron deficiency; iron malabsorption is much less common. Considering this patient's complete blood count was normal 1 year ago, celiac disease is an unlikely cause of iron deficiency, and screening for celiac disease with tissue transglutaminase IgA antibody is not appropriate at this time.

Wireless capsule endoscopy is an effective technology that provides visualization of the small bowel. Unlike angiography or technetium scans, wireless capsule endoscopy is effective even in the absence of active bleeding. It detects the source of occult bleeding in 50% to 75% of patients. In those with iron deficiency anemia, in whom bleeding can be episodic, capsule endoscopy is another way to investigate potential sources of blood loss after other investigations have been unrevealing. Wireless capsule endoscopy should not precede colonoscopy and upper endoscopy as the first diagnostic tests for adult patients with iron deficiency anemia and presumed gastrointestinal blood loss.

KEY POINT

- In men and nonmenstruating women, gastrointestinal blood loss is the presumed cause of iron deficiency unless proven otherwise; because it may develop secondary to an undiagnosed colonic neoplasm, colonoscopy and upper endoscopy are recommended.

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Item 34 Answer: D

Educational Objective: Manage transfusion in an asymptomatic pregnant patient with sickle cell anemia.

The patient should not receive an erythrocyte transfusion at this time. Erythrocyte transfusion in sickle cell disease (SCD) is appropriate only for specific indications, including stroke, symptomatic anemia, acute chest syndrome (ACS), surgical interventions, secondary prevention of stroke or ACS, and, possibly, prevention of priapism, pulmonary hypertension, and nonhealing ulcers. Transfusion is not indicated for uncomplicated pregnancy, routine painful episodes, minor surgery not requiring anesthesia, or asymptomatic anemia. Erythrocyte exchange transfusion is indicated for acute ischemic stroke, ACS with significant hypoxia, and multiorgan failure/hepatopathy as well as in persons in whom simple transfusion would increase the hemoglobin level to greater than 10 g/dL (100 g/L). Chronic transfusion can lead to iron overload, alloimmunization, and an increased risk for a delayed hemolytic transfusion reaction. Erythrocytes used in transfusion should be leukoreduced, hemoglobin S negative, and phenotypically matched for the E, C, and K antigens as well as for any known alloantibodies. Hemoglobin targets should remain less than 10 g/dL (100 g/L) to avoid hyperviscosity.

In a randomized trial, transfusion reduced the risk of pain crisis in pregnant women with SCD but showed no clear improvement in maternal mortality, perinatal mortality, or severe maternal morbidity (pulmonary embolism, chronic heart failure, ACS). Transfusion should be provided based on symptoms of anemia and not hemoglobin levels.

Erythropoiesis-stimulating agents (ESAs) are used to treat anemia in conditions in which bone marrow stimulation of erythrocyte production is inadequate, such as chronic kidney disease. However, in SCD, erythropoietin levels are typically high to augment bone marrow erythrocyte production in response to chronic hemolysis. Therefore, ESAs are not indicated for treatment of the anemia associated with SCD.

KEY POINT

- In patients with sickle cell disease, including pregnant patients, transfusion is not indicated for uncomplicated pregnancy, routine painful episodes, minor surgery not requiring anesthesia, or asymptomatic anemia.

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Item 35 Answer: C

Educational Objective: Manage a supratherapeutic INR in a patient receiving vitamin K antagonist therapy.

This patient should be treated with oral vitamin K for a supratherapeutic INR without evidence of active bleeding. Elevation of the INR beyond the desired therapeutic range is common in patients taking vitamin K antagonists. Recommended management depends on the level of INR elevation and whether active bleeding or bleeding risk factors are present. In patients without bleeding, management involves withholding warfarin and possibly administering oral vitamin K, depending on the level of INR elevation. For a supratherapeutic INR less than 5.0, withholding warfarin and restarting at a lower dose are usually adequate. For an INR of 5.0 to 9.0, a similar management strategy is appropriate, although administration of 1 to 2.5 mg of oral vitamin K is reasonable in patients at risk for bleeding. In patients with an INR greater than 9.0, such as this patient, administration of 2.5 to 5 mg of oral vitamin K is indicated to more rapidly reduce the INR to the desired range.

In patients with serious bleeding, active reversal of anticoagulation is indicated regardless of the INR level. Use of intravenous vitamin K and 4-factor prothrombin complex concentrate (PCC) (or 3-factor PCC and fresh frozen plasma [FFP] or recombinant activated factor VII) is preferred. FFP alone is an option if factor concentrates are unavailable. These treatments are not indicated in this patient who does not have evidence of active bleeding.

Because the risk of bleeding increases with the level of INR elevation, not providing additional treatment for this patient with a significantly supratherapeutic INR would be inappropriate.

KEY POINT

- In patients taking a vitamin K antagonist who have an INR greater than 9 and no evidence of bleeding, oral vitamin K and withholding warfarin are indicated to rapidly reduce the INR.

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Item 36 Answer: B

Educational Objective: Manage low back pain in a patient with smoldering multiple myeloma.

This patient should undergo MRI of the lumbar spine. He has a diagnosis of smoldering (asymptomatic) multiple myeloma, which is defined as an M protein level of 3 g/dL or more or clonal plasma cells representing 10% or more of the total marrow cellularity on bone marrow biopsy but the absence of disease-specific signs or symptoms. Most patients with smoldering myeloma eventually develop symptomatic disease, with a median time to progression of 4.8 years. Therefore, surveillance in these patients is necessary. The CRAB (hyperCalcemia, Renal failure, Anemia, Bone disease) criteria for a diagnosis of multiple myeloma requiring therapy are commonly used to determine the need to start chemotherapy. Although this patient does not have hypercalcemia, kidney disease (renal failure), or anemia, he is experiencing unexplained lower back pain with nonspecific findings on plain radiographic imaging. Therefore, additional imaging is warranted to better determine the cause of the pain. Although plain radiography remains an important component of the initial evaluation of patients with multiple myeloma, more than 30% of trabecular bone must be lost before lytic lesions are evident by plain radiographs. MRI is a more sensitive imaging modality for detecting lytic bone lesions of myeloma, and would be the preferred next imaging study in this patient. Additional imaging techniques that may be used in multiple myeloma include CT or PET/CT.

The role of chemotherapy in patients with smoldering myeloma is unclear. Although lenalidomide and dexamethasone have been shown to delay disease progression, the optimal patient population for these agents has not been identified, and early initiation of chemotherapy for smoldering myeloma is not routinely utilized.

Although most patients with acute low-back pain may be treated conservatively without imaging, symptomatic treatment of this patient's low back pain with routine follow-up would not be appropriate because of his diagnosis of multiple myeloma and the possibility that his back pain is secondary to disease progression.

Bisphosphonates are a key component of therapy for patients with multiple myeloma requiring therapy. Zoledronic acid has been shown to reduce the risk of skeletal-related events and improve progression-free survival. However, the patient has yet to be diagnosed with symptomatic myeloma. No role exists for the routine use of bisphosphonates for patients with smoldering myeloma.

KEY POINT

- An MRI or CT is more sensitive at detecting lytic bone lesions than plain radiographs in patients with multiple myeloma and should be considered when bone pain is present and plain radiographs are unrevealing.

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Item 37 Answer: E

Educational Objective: Diagnose von Willebrand disease.

The patient most likely has von Willebrand disease (vWD). vWD is an autosomal codominant disorder. Von Willebrand factor (vWF) protects factor VIII from degradation, and factor VIII levels can be low enough in vWD to cause slight prolongation of the activated partial thromboplastin time (aPTT), although typically the prothrombin time (PT) and aPTT are normal. Hemorrhagic manifestations of vWD are characterized by mucocutaneous bleeding, not hemarthroses as in hemophilia. Many women with vWD have significant menorrhagia, endometriosis, and postpartum hemorrhage. Mild vWD may not be detected by the Platelet Function Analyzer-100 (PFA-100®) assay, necessitating measurement of vWF antigen and activity levels for diagnosis. Additionally, levels of vWF fluctuate in response to estrogens, stress, exercise, inflammation, and bleeding, and repeated assays may be required to make the diagnosis.

Factor VII deficiency may be inherited or acquired as a result of vitamin K deficiency or warfarin therapy. Patients with factor VII deficiency will have an abnormal prolongation of the PT but a normal aPTT, which is incompatible with this patient's findings.

Factor XI deficiency is an autosomal recessive bleeding disorder and may be associated with a prolonged aPTT and significant bleeding with surgery or trauma. Severe factor XI deficiency is much more frequent in persons of European Jewish descent. Severe factor XI deficiency will prolong the aPTT and is not associated with spontaneous bleeding or with the classic bleeding manifestations of hemophilia, such as hemarthrosis or soft-tissue bleeding, making this diagnosis unlikely.

Factor XII deficiency also produces a normal PT and markedly prolonged aPTT but is not associated with bleeding manifestations and, therefore, is not a likely diagnosis for this patient.

Factor VIII deficiency is responsible for hemophilia A, an X-linked recessive disorder. Severe hemophilia A is characterized by recurrent hemarthroses resulting in chronic, crippling degenerative joint disease unless treated prophylactically with factor replacement. Mild hemophilia may present in adulthood, characterized by posttraumatic or surgical bleeding and a prolonged aPTT. This patient's clinical presentation of mucocutaneous bleeding, normal aPTT, and apparent inheritance pattern of bleeding are not compatible with hemophilia.

KEY POINT

- Symptoms of von Willebrand disease typically include easy bruising, postsurgical bleeding, and heavy menstrual bleeding in women in conjunction with normal prothrombin and normal to minimally prolonged activated partial thromboplastin times.

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Item 38 Answer: D

Educational Objective: Manage an elevated INR in a patient taking warfarin.

Because the patient is not bleeding and is not at high risk for bleeding, interruption of warfarin therapy is appropriate. Concomitant antibiotic and warfarin use can result in INR elevation. A population-based study revealed that the over-anticoagulation risk was most strongly increased by amoxicillin, clarithromycin, norfloxacin, and trimethoprim-sulfamethoxazole. Changes in the INR were often noted in the first 3 days of antibiotic use. This patient's elevated INR is most likely related to her concomitant use of warfarin and trimethoprim-sulfamethoxazole. The appropriate treatment for patients taking warfarin whose INR is supratherapeutic depends on the absolute INR value, the absence or presence of bleeding risk factors or active bleeding, and the seriousness of bleeding, if present. Increased age, actively bleeding lesions, coagulation disorders, and use of antiplatelet drugs increase the bleeding risk while taking warfarin. If the INR is less than 5.0 and no bleeding is apparent, the next dose of warfarin is withheld and the subsequent maintenance dose is reduced. If the INR is 9.0 or less and the risk of bleeding is low, the next one or two doses of warfarin are withheld and the INR is repeated in 48 hours; in these patients who have no evidence of bleeding, the American College of Chest Physicians (ACCP) recommends against the routine use of vitamin K. If the INR is greater than 9.0, warfarin is withheld and 2.5 to 5 mg of oral vitamin K is administered.

Patients with an elevated INR and serious bleeding (or those requiring rapid anticoagulation reversal) are treated by withholding warfarin and administering 10 mg of vitamin K intravenously. For patients with critical need of anticoagulation reversal (for example, intracerebral bleeding), the ACCP recommends administration of 4-factor prothrombin complex concentrate rather than fresh frozen plasma.

KEY POINT

- In patients without evidence of bleeding whose INR is 9.0 or less while taking warfarin, the next one or two dose(s) should be withheld, but the American College of Chest Physicians recommends against the routine use of vitamin K.

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Item 39 Answer: A

Educational Objective: Evaluate a patient for heparin-induced thrombocytopenia.

Performing 4T pretest probability scoring for the possibility of heparin-induced thrombocytopenia (HIT) is the most appropriate next step in management. This patient's platelet count decreased following a recent exposure to heparin, raising concern for the possibility of HIT. The 4T score is used to estimate the pretest probability of HIT based on clinical factors, including degree of thrombocytopenia, timing of the decrease in platelet count, presence of any potential sequelae of HIT (such as thrombosis), and whether another potential cause for thrombocytopenia exists. Possible point values range from 0 to 8; scores of 0 to 3 indicate low probability, 4 or 5 indicate intermediate probability, and 6 to 8 represent high pretest probability. The 4T score has been validated in a study of more than 3000 patients with a negative predictive value of 99.8% in those with low probability scores. Although specific decisions must be made for individual patients based on their clinical status, many physicians reserve further evaluation for patients with intermediate or high pretest probability scores, with close clinical observation in those with low probability scores. This patient has a 4T score of 1 based on a possible alternative explanation for his thrombocytopenia (blood transfusion), indicating a low pretest probability of HIT; therefore, observation without additional testing for HIT would be reasonable.

Confirmatory testing for antiplatelet antibodies may be done by direct antibody testing or by functional assays that test the ability of serum from patients with HIT to activate test platelets. Direct antibody testing is typically performed by enzyme-linked immunosorbent assay (ELISA) that detects antibodies directed toward heparin-platelet factor 4 complexes. The two commonly used functional assays are the serotonin release assay (SRA) and the heparin-induced platelet aggregation (HIPA) assay. SRA is considered the gold standard study for HIT with a sensitivity and specificity of more than 95%; HIPA is also very specific but has a lower sensitivity than SRA. However, no clear indication exists for confirmatory testing for HIT considering this patient's low pretest probability.

KEY POINT

- Assessing the pretest probability of heparin-induced thrombocytopenia by using a risk scoring system, such as the 4T score, is helpful in guiding therapy in patients at low risk for it.

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Item 40 Answer: D

Educational Objective: Manage anemia in a critically ill hospitalized patient.

Continuing current management is appropriate. The patient is asymptomatic and displays no end-organ compromise as a result of reduced oxygen-carrying capacity. A randomized phase III study was performed in euvolemic patients whose hemoglobin level decreased to less than 9 g/dL (90 g/L) within 72 hours of admission to an ICU. Patients were assigned to a liberal transfusion strategy targeting a hemoglobin level of 10 to 12 g/dL (100-120 g/L), in which they were transfused when their hemoglobin level decreased to less than 10 g/dL (100 g/L), or a restrictive approach, in which they were transfused for a hemoglobin level less than 7 g/dL (70 g/L) (target 7-9 g/dL [70-90 g/L]). Mortality rates were at least as good for those assigned to the restrictive transfusion approach. However, a subset analysis revealed that patients with ischemic heart disease had a trend toward higher mortality with a restrictive transfusion practice that was not statistically significant, suggesting that patients with ischemic heart disease should be evaluated on a case-by-case basis until further phase III data dictate otherwise.

Although the patient has an elevated creatinine level, this is likely the result of sepsis and appears to be improving with volume repletion and correction of hypotension. As such, there is no role for an erythropoiesis-stimulating agent (ESA). Furthermore, ESAs have not been studied for this indication.

The patient has iron indices typical of an inflammatory anemia (low serum iron, low total iron-binding capacity, normal transferrin saturation, elevated ferritin), likely due to sepsis and not iron deficiency anemia (low serum iron, high-normal to high total iron-binding capacity, low transferrin saturation, low ferritin). Therefore, intravenous iron is not indicated.

KEY POINT

- In hospitalized patients without symptoms or end-organ damage, a restrictive treatment strategy for hemoglobin levels less than 7 g/dL (70 g/L) and targeting 7 to 9 g/dL (70-90 g/L) is appropriate.

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Item 41 Answer: D

Educational Objective: Manage mild coagulopathy in a patient undergoing central venous catheter placement.

No transfusion is needed before central venous catheter insertion. This patient has modest coagulopathy and thrombocytopenia resulting from hepatitis C–related liver disease. Previous retrospective studies have shown that central venous catheter insertion is safe in patients with a prolonged prothrombin time and INR, including those with liver disease. In a prospective audit of 580 internal jugular and subclavian vein cannulations in patients with chronic liver

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disease and an INR of 1.5 or greater, only one major vascular complication was noted.

Although his fibrinogen level is slightly low, cryoprecipitate is typically reserved for patients with clinically significant bleeding and a fibrinogen level less than 100 mg/dL (1.0 g/L). Cryprecipitate in the prophylaxis of bleeding for patients with low fibrinogen levels undergoing procedures has not been evaluated.

Numerous studies have shown that fresh frozen plasma (FFP) is overutilized in nonbleeding patients with mild coagulopathies, which is a significant problem given the risks associated with FFP use, including transfusion-related acute lung injury, transfusion-transmitted infection, transfusion-associated circulatory overload, allergic reactions, and hemolysis. The role of FFP in the prevention of bleeding complications for nonbleeding patients undergoing procedures is unclear. However, it is known that FFP is ineffective at correcting a minimally elevated INR (<1.85).

Most procedures and surgeries can be safely performed with a platelet count of at least 50,000/μL (50×10^9/L), although a platelet count of at least 100,000/μL (100×10^9/L) is recommended for neurosurgical intervention. Thus, a platelet transfusion is not indicated for this patient.

KEY POINT

- Patients with mild coagulopathy requiring central venous catheter insertion do not need to receive fresh frozen plasma or other transfusions before the procedure.

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Item 42 Answer: D

Educational Objective: Manage pseudothrombocytopenia.

The patient's blood should be redrawn using a citrated tube. She has pseudothrombocytopenia as shown on the peripheral blood smear, a condition that leads to the formation of platelet clumps in vitro. This in vitro occurrence is caused by the presence of ethylenediaminetetra-acetic acid (EDTA) agglutinins, which naturally occur in approximately 0.1% of the population and lead to platelet clumping. The automated platelet counter does not recognize the clumps as masses of platelets, and the platelet count is, therefore, spuriously low. Drawing a complete blood sample into a citrate- or heparin-anticoagulated tube may resolve the clumping.

Prednisone and methylprednisolone are first-line agents for treating adults with immune (or idiopathic) thrombocytopenic purpura (ITP) who require therapy. ITP is an acquired autoimmune condition in which autoantibodies are directed against platelet surface proteins, leading to platelet destruction that may be only partially counteracted by increased bone marrow platelet production. Variants of ITP may be drug induced or part of a broader illness of abnormal immune regulation, as with systemic lupus erythematosus, HIV infection, or lymphoproliferative malignancies. Therapy may be required for patients with platelet counts lower than 30,000 to 40,000/μL ($30\text{-}40 \times 10^9$/L) or with bleeding. Because this patient most likely does not have ITP, diagnostic testing for systemic lupus erythematosus with antinuclear antibody or HIV testing is not indicated.

Plasma exchange would not benefit this patient. Thrombotic thrombocytopenic purpura (TTP) is a process characterized by abnormal activation of platelets and endothelial cells, deposition of fibrin in the microvasculature, and peripheral destruction of erythrocytes and platelets. Most patients with the typical sporadic form of TTP have developed autoantibodies directed against the protease that cleaves the high-molecular-weight multimers of von Willebrand factor. Initial treatment consists of plasma exchange. Because this patient has platelet clumping on the peripheral blood smear and no evidence of schistocytes characteristic of TTP-associated microangiopathic hemolysis, the diagnosis of TTP is unlikely and plasma exchange is unnecessary.

KEY POINT

- Platelet clumping signifies pseudothrombocytopenia, which will resolve if blood is redrawn using a citrated or heparinized tube.

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Item 43 Answer: E

Educational Objective: Manage von Willebrand disease perioperatively.

The most appropriate perioperative treatment for this patient is von Willebrand factor (vWF)–containing factor VIII concentrates. She has type 1 von Willebrand disease (vWD) and is scheduled for abdominal surgery. The best products to give are the vWF-containing factor VIII concentrates. These so-called "intermediate purity," plasma-derived products have undergone viral inactivation (of viruses such as HIV and hepatitis B and C), and their use has not led to transmission of any serious illness. Desmopressin, which leads to release of vWF and factor VIII from endothelial cells and thus provides hemostasis, can be used for less invasive procedures. However, unless a trial of desmopressin shows a robust, sustained response, it should not be used for a major surgery.

Cryoprecipitate contains a concentrated source of factor VIII, vWF, factor XIII, fibronectin, and fibrinogen and is the treatment of choice in bleeding patients with hypofibrinogenemia from liver disease, thrombolytic therapy, or disseminated intravascular coagulation (DIC). Cryoprecipitate is not virally inactivated and is therefore not a first-line agent for this patient with vWD.

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Fresh frozen plasma (FFP) contains all the blood clotting factors and is indicated for warfarin reversal in actively bleeding patients (alone or concomitantly with a 3-factor prothrombin complex concentrate), treatment of thrombotic thrombocytopenic purpura, dilutional coagulopathy during massive transfusion, and in bleeding patients with several factor deficiencies such as in DIC or liver disease. However, the concentration of vWF in FFP is too low to correct the patient's vWF levels without producing volume overload. Other risks include viral transmission, transfusion-related acute lung injury, and febrile, allergic, and anaphylactic reactions.

Recombinant factor VIII is used to treat patients with hemophilia A. Recombinant factor VIII is devoid of any vWF and would not improve hemostasis in this patient with vWD.

Fibrinolytic agents such as ε-aminocaproic acid and tranexamic acid can be used in patients with mild vWD to prevent dissolution of the hemostatic plug, particularly those associated with mucocutaneous bleeding. Prolonged use of these agents is associated with the potential for thrombosis, especially in patients with an underlying thrombophilia. Used as a single agent, tranexamic acid is unlikely to provide sufficient hemostasis for a patient undergoing abdominal surgery.

KEY POINT

- Patients with von Willebrand disease scheduled to undergo major surgery should be treated with factor VIII concentrates containing von Willebrand factor.

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Item 44 Answer: A

Educational Objective: Diagnose cold agglutinin disease.

A direct antiglobulin (Coombs) test is the most appropriate next diagnostic step for this patient with cold agglutinin disease. Autoimmune hemolytic anemias are characterized by the presence of antibodies directed toward antigens on the surface of erythrocytes; they are further classified by the type of immunoglobulin involved and the resulting tendency of hemolysis to occur in warm or cold environments. Direct IgG optimally binds erythrocytes at temperatures of 37.0 °C (98.6 °F), causing warm autoimmune hemolytic anemia. The immune response to the bound IgG causes erythrocytes to become spherocytic, resulting in hemolysis. Direct IgM binds more effectively at temperatures colder than 32.0 °C (89.6 °F), typically in the fingers, toes, and nose, causing cold agglutinin disease. IgM-coated erythrocytes agglutinate in the microvasculature, leading to cyanosis and ischemia in the cold extremities. The IgM antibodies fix complement and then detach from erythrocytes when they return to the warmer body core. This patient likely has cold agglutinin disease because he has an acquired hemolytic anemia associated with cold exposure and supported by his peripheral blood smear, showing agglutinated erythrocytes that disappear when warmed. Cold agglutinin disease may occur as a primary disorder or may be associated with a lymphoproliferative disorder or certain infections, such as *Mycoplasma pneumoniae* or Epstein-Barr virus. The primary treatment for cold agglutinin disease is avoidance of cold exposure.

Flow cytometry to detect the absence of specific cell surface antigens (CD55 and CD59) is useful in diagnosing paroxysmal nocturnal hemoglobinuria, which is another potential cause of hemolytic anemia. However, testing for this disorder is indicated only in patients without evidence of an autoimmune cause of hemolysis. Therefore, such testing would be inappropriate for this patient.

Multiple congenital hemoglobinopathies are associated with hemolysis, although this patient's clinical picture is consistent with an acquired hemolytic anemia. Therefore, hemoglobin electrophoresis would not likely be helpful in establishing the cause of his hemolysis.

The indirect antiglobulin test detects antierythrocyte antibodies in the serum and is used primarily before blood transfusion and in prenatal testing of pregnant women. It would not provide significant diagnostic information in this patient.

KEY POINT

- Cold agglutinin disease, identified by characteristic erythrocyte clumping that disappears when a peripheral blood sample is warmed, can be confirmed by direct antiglobulin (Coombs) testing.

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Item 45 Answer: D

Educational Objective: Manage inflammatory anemia.

The only management the patient requires at this time is observation. He has inflammatory anemia (previously anemia of chronic disease), which does not usually require treatment. Chronic infections such as tuberculosis or osteomyelitis, malignancies, and collagen vascular diseases are associated with anemia. In response to inflammatory states, erythropoietin production is inhibited and the erythroid precursor response to erythropoietin is blunted. Inflammation leads to increased levels of inflammatory cytokines, including tumor necrosis factor-α, interleukin (IL)-6, IL-1, and interferon, which lead to altered erythropoietin responsiveness. In particular, IL-6 causes hepatic synthesis of the small peptide hepcidin, which is pivotal in regulating iron absorption. Hepcidin causes decreased iron absorption from the gastrointestinal tract and decreased iron release by macrophages by inducing internalization and proteolysis of the transporter protein ferroportin. No laboratory test is commercially available for measuring hepcidin levels.

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A peripheral blood smear may be normal in patients with inflammatory anemia, or, over time, may show microcytic hypochromic erythrocytes such as in iron deficiency. Typically, inflammatory anemia is characterized by a hemoglobin level greater than 8 g/dL (80 g/L). Because of erythrocyte underproduction, the reticulocyte count is typically low for the degree of anemia. The serum iron level is initially normal but decreases over time, the total iron-binding capacity is low, and the ferritin level is typically elevated.

Although bone marrow evaluation is seldom necessary, ample stainable iron would be present. However, it is not indicated for diagnosis in classic cases of inflammatory anemia.

Erythropoiesis-stimulating agents may improve inflammatory anemia but are associated with thrombosis and other effects that impede safe use.

Iron replacement is unlikely to alleviate the patient's symptoms, because he is not iron deficient. Iron deficiency would present with a low ferritin level of less than 100 ng/mL (100 µg/L) even in the setting of chronic inflammation. Additionally, total iron-binding capacity in iron deficiency tends to be elevated and not decreased. However, the transferrin saturation is normal in inflammatory anemia.

KEY POINT

- Inflammatory anemia typically requires no treatment other than for the underlying condition.

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Item 46 Answer: C

Educational Objective: Diagnose aplastic anemia.

The patient has aplastic anemia (AA). He presents with an insidious clinical course and has severe pancytopenia. The absolute neutrophil count is only 50/µL (0.05×10^9/L). Despite severe neutropenia, AA may present with clinically unimpressive infections. This contrasts with the acute leukemias. The bone marrow biopsy demonstrating less than 10% cellularity confirms the diagnosis of aplasia. AA may occur secondary to infections or toxins. However, it usually presents without preceding insult. Such patients respond to immunosuppressive therapy, and allogeneic hematopoietic stem cell (HSC) transplantation can be curative in young otherwise healthy patients.

Acute lymphoblastic leukemia (ALL) is a reasonable consideration in this patient, because ALL is more common in adolescents and young adults. It can present with pancytopenia rather than hyperleukocytosis. However, the bone marrow biopsy excludes ALL, because leukemic blasts more typically cause marrow hypercellularity; very few blood-making cells are present on this patient's biopsy. For the same reason, acute myeloid leukemia can be excluded.

The myelodysplastic syndromes (MDS) are clonal HSC disorders characterized by ineffective hematopoiesis and a variable rate of transformation to acute myeloid leukemia. MDS can present with pancytopenia, although it occurs less commonly in younger patients. However, the bone marrow in MDS is classically hypercellular. Although hypocellular MDS exists, crossover with AA is considerable, and the decrease in marrow cellularity is not this striking.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired HSC disorder that should be considered in patients presenting with hemolytic anemia, pancytopenia, or unprovoked atypical thrombosis. The bone marrow is usually hypocellular with PNH, but other features such as hemolysis and thrombosis are present, distinguishing it from AA. Likewise, the degree of hypocellularity is not as severe as that of AA.

KEY POINT

- Aplastic anemia is characterized by severe hypocellularity of the bone marrow and pancytopenia.

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Item 47 Answer: C

Educational Objective: Diagnose monoclonal gammopathy of undetermined significance.

Serum free light chain (FLC) testing should be performed. This patient meets criteria for a diagnosis of monoclonal gammopathy of undetermined significance (MGUS), because clonal plasma cells represent less than 10% of the total marrow cellularity, and she does not meet CRAB (hyperCalcemia, Renal failure, Anemia, Bone disease) criteria for a diagnosis of multiple myeloma requiring therapy. MGUS is common, affecting 3.2% of persons 50 years or older and 5.3% of persons 70 years or older. The risk of progression to a clinically symptomatic disease is approximately 1% per year. Risk factors for progression include a non-IgG M protein, an M protein level of at least 1.5 g/dL, and an abnormal serum FLC ratio. A few FLCs (not bound to immunoglobulin) circulate normally and can be measured in serum. The FLC ratio measures the κ and λ FLCs, expressed as the κ/λ FLC ratio. Persons without a plasma cell dyscrasia have normal ratios; abnormal ratios suggest a disproportionate production of a monoclonal κ or λ chain. An abnormal FLC ratio is prognostically helpful, because it suggests a more virulent plasma cell clone that may be at higher risk of transforming into overt multiple myeloma. This patient has two risk factors identified thus far (M protein level ≥1.5 g/dL and an IgA M protein). Serum free κ and λ light chain level measurement and κ/λ FLC ratio determination are essential parts of the evaluation of MGUS; they help delineate the risk of progression to clinically symptomatic disease and dictate the frequency of follow-up. Patients with zero, one, two, or three risk factors have a risk of progression to clinically

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symptomatic disease over 20 years of 5%, 21%, 37%, and 58%, respectively.

MRI imaging of the spine and whole spine MRI have not been shown to further risk stratify patients with MGUS. However, in patients with smoldering (asymptomatic) multiple myeloma, more than one focal bone lesion on MRI is associated with a greater risk of progression to multiple myeloma requiring therapy.

The β_2-microglobulin and lactate dehydrogenase levels are useful tools for determining the prognosis of multiple myeloma requiring therapy but are not routinely performed in MGUS.

KEY POINT

- Risk factors for progression of monoclonal gammopathy of undetermined significance to multiple myeloma include a non-IgG M protein, an M protein level of at least 1.5 g/dL, and an abnormal serum free light chain ratio.

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Item 48 Answer: D

Educational Objective: Diagnose multiple myeloma requiring therapy.

Serum protein electrophoresis and serum free light chain (FLC) testing should be performed in this patient with likely multiple myeloma; together, these have a diagnostic sensitivity approaching 100% for multiple myeloma requiring therapy. This patient has several findings suspicious for this disease as the cause of his hypercalcemia, including osteopenia with a thoracic compression fracture, anemia, and kidney dysfunction. However, kidney dysfunction can occur as a direct result of hypercalcemia, regardless of its underlying cause. An important clue in this patient is the discordance between the degree of proteinuria assessed by the urinalysis compared with the urine protein-creatinine ratio. A routine dipstick urinalysis will detect albuminuria but is relatively insensitive at detecting other urine proteins. However, a urine protein-creatinine ratio measures all proteins in the urine, including immunoglobulins, if present. This discrepancy should raise suspicion for monoclonal FLCs in the urine (Bence-Jones proteinuria) and potential cast nephropathy. Similarly, a sulfosalicylic acid test will detect all urine proteins, including light chains, and can be performed for suspected myeloma cast nephropathy. In FLC myeloma, the serum protein electrophoresis may only reveal hypogammaglobulinemia and no monoclonal band or a low-level monoclonal band because of its insensitivity at detecting monoclonal FLCs. However, the serum FLC test, an antibody-based assay that can detect low levels of FLCs, will demonstrate an elevated level of the affected monoclonal FLC and an abnormal serum κ/λ FLC ratio.

Increased 1,25-dihydroxyvitamin D (calcitriol) levels may result from ingestion of calcitriol or increased 25-hydroxyvitamin D (calcidiol) activation to calcitriol as a result of underlying granulomatous disease (for example, sarcoidosis) or lymphoma, thus leading to hypercalcemia. This patient has no history of calcitriol ingestion and no physical examination or radiographic features of granulomatous disease or lymphoma. Increased calcitriol levels do not explain his anemia, osteopenia and thoracic compression fracture, or kidney dysfunction with nonalbumin proteinuria.

Primary hyperparathyroidism can present with hypercalcemia, bone mineral density loss with increased compression fracture risk, and, when hypercalcemia is severe enough or long-standing, kidney dysfunction. However, primary hyperparathyroidism is uncommonly associated with anemia and does not explain the proteinuria, so measuring the intact parathyroid hormone level is not indicated.

Hypercalcemia associated with myeloma results from osteoclast activation, not secretion of parathyroid hormone-related protein (PTHrP). PTHrP is produced more commonly in solid tumors, such as squamous cell (head and neck, lung); renal cell; and bladder, breast, and ovarian carcinomas. Although the patient has an extensive smoking history, no findings on physical examination or chest radiograph suggest the presence of a solid tumor. Additionally, PTHrP-mediated hypercalcemia from an occult solid tumor would not explain this patient's proteinuria.

KEY POINT

- Combination serum protein electrophoresis and free light chain testing has a sensitivity approaching 100% for diagnosing multiple myeloma requiring therapy.

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Item 49 Answer: B

Educational Objective: Diagnose coagulopathy of liver disease.

The patient most likely has liver failure resulting from excessive acetaminophen use as the cause of his coagulopathy. He takes chronic warfarin therapy but presents with a significant coagulopathy of unclear cause. Specific factor level measurement is useful when it is clinically helpful to understand the basis of a coagulation disorder to guide therapy. A panel of factors, including factor V, factor VII, and factor VIII, may be checked when it is important to distinguish between liver failure, disseminated intravascular coagulation, or vitamin K deficiency/warfarin overdose. In liver failure, all clotting factor activity levels are low except for factor VIII, which is synthesized in all endothelial cells rather than only

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hepatic endothelial cells. Additionally, good hepatic function is required for factor VIII clearance, thus factor VIII levels increase in liver disease. Patients with severe liver failure (and on occasion those with acute liver failure) will have prolonged prothrombin and activated partial thromboplastin times because of decreased levels of coagulation factors. This is called the coagulopathy of liver disease. The elevated D-dimer level is also consistent with liver disease, because D-dimers are cleared by the liver; a high D-dimer level does not automatically indicate disseminated intravascular coagulation (DIC).

DIC begins with abnormal thrombin generation, rapid consumption of clotting factors and platelets, and accelerated fibrinolysis. Although hemorrhage may result from low levels of clotting factors and platelets, histopathologic examination of affected tissues shows a fibrin clot in the microvasculature. A thrombotic microangiopathy may ensue, and schistocytes develop in 30% of patients. An elevated factor VIII level, as seen in this patient, rules out DIC.

Factor V levels can be used to distinguish between liver disease and vitamin K deficiency, because factor V is synthesized in the liver but is not a vitamin K–dependent factor. Thus, someone with vitamin K deficiency will have normal levels of factor V, whereas a patient with liver failure will have low factor V levels. This patient's low factor V level rules out warfarin overdose as well as vitamin K deficiency, because normal levels would be expected in vitamin K deficiency.

KEY POINT

- Coagulopathy of liver disease is characterized by prolonged prothrombin and activated partial thromboplastin times and increased factor VIII level.

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Item 50 Answer: A

Educational Objective: Diagnose chronic myeloid leukemia.

This patient is most likely to have a *BCR-ABL* genetic mutation predisposing him to chronic myeloid leukemia (CML). He has the classic presentation for CML with the insidious onset of fatigue; early satiety and progressive weight loss associated with splenomegaly; and a peripheral blood smear demonstrating myelocytes, metamyelocytes, and basophils. The peripheral blood smear of CML is commonly described as mimicking a bone marrow aspirate. Basophilia is a general clue to the presence of a myeloproliferative neoplasm (MPN).

IGH/CD1 is the mutation associated with mantle cell lymphoma (MCL). MCL can present with hyperleukocytosis and massive splenomegaly, but myeloid precursors and basophilia would not be seen on peripheral blood smear.

The *JAK2* gene mutation is associated with polycythemia vera, essential thrombocytosis (ET), and primary myelofibrosis but not CML. Because CML is a more likely diagnosis, especially because of the prominence and degree of leukocytosis, *BCR-ABL* mutation should be excluded first in this patient.

PML-RAR protein mutation is associated with acute promyelocytic leukemia (APL). APL does not demonstrate basophilia or transitional myeloid precursors on the peripheral blood smear. Additionally, it is clinically associated with disseminated intravascular coagulation and thrombocytopenia rather than thrombocytosis, and splenomegaly is uncommon in APL.

KEY POINT

- Patients with suspected chronic myeloid leukemia should be tested for an underlying *BCR-ABL* mutation.

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Item 51 Answer: C

Educational Objective: Treat a patient with transfusion-transmitted bacterial infection.

In addition to stopping the transfusion and resuscitating the patient, broad-spectrum antibiotics such as vancomycin and cefepime should be started, and blood cultures should be drawn to determine the infecting organism. The patient is most likely experiencing sepsis as a result of transfusion-transmitted bacterial infection. Clinical criteria for a possible septic transfusion reaction include any of the following within 5 hours of completion of a transfusion: temperature greater than 39.0 °C (102.2 °F) or temperature two degrees higher than pretransfusion, rigors, pulse rate greater than 120/min or more than 40/min higher than pretransfusion, or a decrease or increase in blood pressure of greater than 30 mm Hg. Transfusion-transmitted bacterial infection remains an important cause of transfusion-related morbidity and mortality with rates of all septic reactions and fatal septic reactions reaching 1:74,807 and 1:498,711 per distributed platelet component. The majority of infections are due to staphylococcal species, although gram-negative organisms are also implicated. The blood product bag should be sealed and sent to the microbiology laboratory for culture.

Acetaminophen, diphenhydramine, and meperidine may be used as symptomatic treatment of a febrile nonhemolytic transfusion reaction. However, febrile nonhemolytic transfusion reactions are not typically associated with hypotension.

Epinephrine should only be used to treat anaphylaxis, which is less likely than sepsis in this patient. Anaphylaxis is associated with hypotension and respiratory distress,

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but this patient has no dermatologic (pruritus, urticaria, angioedema), pulmonary (wheezing, cough), or gastrointestinal (nausea, vomiting, abdominal cramping, diarrhea) manifestations suggesting anaphylaxis. Additionally, anaphylaxis is not associated with fever.

Considering the high morbidity and mortality associated with a septic transfusion reaction, stopping the transfusion and volume resuscitation alone are insufficient. This patient needs broad spectrum antibiotics to treat his transfusion-associated infection.

KEY POINT

- Transfusion should be stopped immediately and intravenous fluids and antibiotics should be given to patients experiencing transfusion-transmitted bacterial infection.

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Item 52 Answer: B

Educational Objective: Choose the appropriate diagnostic test for a patient with a low pretest probability of deep venous thrombosis.

A blood D-dimer test should be performed. American College of Chest Physicians guidelines suggest that a clinical pretest probability assessment of deep venous thrombosis (DVT) should be the first part of the diagnostic process for a first lower extremity DVT, rather than performing an imaging study in all patients. The pretest probability that this patient has a DVT is low. Applying the Wells criteria for DVT, this patient's score is 0, making DVT an unlikely diagnosis. The criteria include a medical history indicating increased risk for venous thromboembolism (VTE) (such as previously documented DVT; paralysis, paresis, recent cast immobilization of legs; recent bedridden state for ≥3 days; major surgery) and leg symptoms highly suggestive of DVT (calf swelling ≥3 cm; swelling of the entire leg; unilateral pitting edema; localized tenderness along the deep venous system). Because this patient has none of these factors and no alternative explanation for his leg symptoms, obtaining a D-dimer test is an appropriate next step. If the test is negative, no further testing is needed, because a VTE has been ruled out. However, if the D-dimer is positive, an imaging study is then indicated. The imaging test of choice is duplex ultrasonography of the leg. When using the D-dimer test for pretest probability assessments, a moderately or highly sensitive assay should be used. Physicians must be aware of the sensitivity of the test used in local laboratories. Lower sensitivity assays have not been validated as useful for predicting pretest probability.

Long-term anticoagulants should not be prescribed without a confirmed diagnosis of VTE. However, in a patient with high or intermediate clinical suspicion of DVT, beginning anticoagulation while awaiting diagnostic test results is appropriate. In a patient with low clinical suspicion of acute DVT, such as this patient, withholding anticoagulant therapy while awaiting the test result is suggested.

If a D-dimer test is not available or is positive, performing duplex ultrasonography would be the appropriate next step.

Magnetic resonance venography is a noninvasive diagnostic method that is as accurate as contrast venography for DVT diagnosis. However, it is not the study of choice for DVT diagnosis because of the complexities of performing the test and its high cost relative to duplex ultrasonography. Additionally, initial imaging is not indicated in this patient with a low risk of DVT before further assessment with D-dimer testing.

KEY POINT

- A blood D-dimer test using a moderately or highly sensitive assay should be the first step in the diagnosis of deep venous thrombosis in a patient with low pretest probability.

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Item 53 Answer: B

Educational Objective: Manage transfusion in a patient with sickle cell disease who requires cholecystectomy.

This patient should receive an erythrocyte transfusion to a target hemoglobin level of 10 g/dL (100 g/L). He has homozygous sickle cell anemia (Hb SS) and must undergo laparoscopic cholecystectomy, a surgical procedure of low to moderate risk. Patients requiring surgery should undergo transfusion before their procedure to avoid complications. Transfusion to a hemoglobin level of 10 g/dL (100 g/L) has been shown to be equivalent to exchange transfusion for low- to medium-risk surgeries. The recent TAPS study showed that, for this surgical risk group, significantly more clinically important complications occurred in the group that did not receive preoperative transfusion (39%) than the group that did receive transfusion (15%). Significantly more serious events were also recorded in the nontransfusion group (30%) than in the transfusion group (3%), most of which were acute chest syndrome (ACS). Erythrocyte transfusions must be given with care in patients with sickle cell disease, because these transfusions are associated with iron overload. In some patients, "hyperhemolysis" occurs because of alloimmune responses to erythrocyte antigens, which leads to a delayed transfusion reaction characterized by hyperbilirubinemia and anemia. Additionally, erythrocyte transfusions that result

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in hemoglobin levels greater than 10 g/dL (100 g/L) can increase blood viscosity and potentially cause thrombotic complications.

Several multicenter studies have documented the clinical efficacy of transfusion to 10 g/dL (100 g/dL) compared with the more aggressive strategy of exchange transfusion targeting a hemoglobin S level of 30%. Transfusion and exchange transfusion are associated with similar serious surgery-related complications and ACS, but transfusion is associated with fewer transfusion-related complications and exposure to less blood.

KEY POINT

- Patients with sickle cell disease undergoing low- to moderate-risk surgery should receive erythrocyte transfusion, which has been shown to be equivalent to exchange transfusion, targeting a hemoglobin level of 10 g/dL (100 g/L) before the procedure to avoid complications.

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Item 54 Answer: C

Educational Objective: Manage heparin-induced thrombocytopenia.

This patient most likely has heparin-induced thrombocytopenia (HIT) with thrombosis after being exposed to heparin during coronary artery bypass graft surgery, so the most appropriate next step is to initiate argatroban, a direct thrombin inhibitor used for anticoagulation in HIT. Patients who receive heparin during cardiothoracic surgery or after orthopedic surgery are more likely to develop HIT than are patients who receive heparin for dialysis or deep venous thrombosis prophylaxis. HIT develops 5 to 10 days after exposure to heparin, with a decrease in platelet counts of 50% or more and, in a subset of patients, paradoxical arterial or venous thrombotic events despite the presence of thrombocytopenia. The "4T score" has been devised to help clinicians decide the pretest probability for diagnosing HIT based on clinical factors, including degree of thrombocytopenia, timing of the decrease in platelet count, presence of potential sequelae of HIT (such as thrombosis), and whether another potential cause for thrombocytopenia exists. Possible point values range from 0 to 8; scores of 0 to 3 indicate low probability, 4 or 5 indicate intermediate probability, and 6 to 8 represent high probability. The patient's 4T score is 8 (2 points each for timing of platelet count decrease, presence of thrombosis, timing of thrombocytopenia, and no other cause of the thrombocytopenia), indicating a high pretest probability of HIT. In patients with a high pretest probability, immediate cessation of any heparin-containing products is indicated, with initiation of a nonheparin anticoagulant; the only anticoagulant approved for the treatment of HIT is argatroban.

Confirmatory testing for presumed HIT is performed by HIT antibody testing. Immunoassays detect the presence of a HIT antibody (such as those directed toward platelet factor 4) in a patient's serum. Functional assays measure the ability of a HIT antibody from a patient's serum to activate test platelets (such as by measuring the release of serotonin). Because of the high risk of thrombosis associated with HIT and the possible delay associated with obtaining these studies, anticoagulation with a heparin alternative should be started before performing confirmatory testing.

Heparin cessation and treatment with a nonheparin anticoagulant are mandatory when a high pretest probability of HIT exists, because 30% to 50% of patients experience thromboses with heparin withdrawal alone. This patient already has evidence of thrombosis and must start treatment immediately to prevent extension and embolization.

Warfarin initiation alone is inadequate, because it may take 3 to 5 days to achieve a therapeutic anticoagulation effect. Additionally, starting warfarin before the platelet count has normalized in patients with HIT or starting warfarin without a bridging anticoagulant has been associated with development of warfarin skin necrosis and clot progression.

KEY POINT

- Heparin cessation and immediate treatment with a nonheparin alternative anticoagulant (lepirudin, argatroban, danaparoid) are mandatory when a high pretest probability of heparin-induced thrombocytopenia is present.

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Item 55 Answer: E

Educational Objective: Treat a patient with venous thromboembolism who wishes to breastfeed.

Warfarin would be the most appropriate anticoagulation option for this patient. Warfarin is avoided during pregnancy because it crosses the placenta, causes fetal anticoagulation throughout the pregnancy, and is a teratogen. Because heparins do not cross the placenta and do not cause fetal anticoagulation, patients receiving chronic warfarin therapy are typically transitioned to either unfractionated or low-molecular-weight heparin (LMWH) during pregnancy. However, warfarin is not present in breast milk in any substantial amount and does not induce an anticoagulant effect in the breastfed infant. It is, therefore, a good option for anticoagulation in this patient. Similarly, heparins are minimally excreted in breast milk, and any drug ingested by an infant is unlikely to have any clinically relevant effect because of the very low bioavailability of oral heparins. Thus, LMWH and warfarin are both appropriate anticoagulant options for women who want to breastfeed.

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It is unknown whether apixaban, dabigatran, or rivaroxaban are excreted in human milk. Therefore, known safe alternatives to these new oral anticoagulants should be used in women intending to breastfeed.

Fondaparinux has been demonstrated to be excreted in the milk of lactating rats. It is unknown whether it is excreted in human milk. Therefore, an alternative anticoagulant rather than fondaparinux is recommended for women who breastfeed.

KEY POINT

- Warfarin and low-molecular-weight heparin are considered safe for use by women requiring anticoagulant therapy who wish to breastfeed.

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Item 56 Answer: C

Educational Objective: Treat multiple myeloma–related bone disease.

In addition to chemotherapy, this patient should be treated with a bisphosphonate such as zoledronic acid. She has multiple myeloma requiring therapy with anemia and myeloma-related bone disease manifested by osteopenia with a T12 compression fracture. Studies have shown that bisphosphonates inhibit osteoclast-mediated osteolysis, reduce the risk of skeletal-related events (pathologic fracture, need for radiation therapy or surgery to bone, spinal cord compression), decrease bone-related pain, and improve median overall survival. The risk of skeletal-related events was reduced in patients with or without evidence of lytic bone disease on plain radiographs. Bisphosphonates therefore represent a critical aspect of care for patients with myeloma requiring therapy, and guidelines call for the use of zoledronic acid or pamidronate in all patients with newly diagnosed multiple myeloma.

Although vertebroplasty has not been shown to be beneficial in the management of osteoporotic vertebral body compression fractures, a small randomized study comparing balloon kyphoplasty with nonsurgical management of painful vertebral body compression fractures in patients with multiple myeloma and solid tumors demonstrated improved short-term physical functioning, pain control, and quality of life for those undergoing kyphoplasty. However, data on long-term outcomes with kyphoplasty are lacking in patients with cancer, and no role has been established for the procedure in the absence of pain.

Radiation therapy is typically reserved for pain related to lytic bone disease, particularly in patients with increasingly chemotherapy-resistant disease, and would not be appropriate in this patient.

Because of the documented efficacy of bisphosphonate therapy in patients with multiple myeloma requiring therapy, it would be inappropriate not to provide further treatment for this patient.

KEY POINT

- The bisphosphonates pamidronate and zoledronic acid should be used for all patients with newly diagnosed multiple myeloma requiring therapy.

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Item 57 Answer: B

Educational Objective: Diagnose exercise-induced hemolysis.

This patient likely has exercise-induced hemolysis, also known as march hemoglobinuria or runner's hemolysis. This is caused by erythrocyte damage through repetitive mechanical trauma such as running or marching, resulting in intravascular hemolysis. Hemolysis leads to increased levels of free hemoglobin in the plasma, which is filtered by the kidneys, resulting in hemoglobinuria. Urinalysis findings show evidence of blood in the urine by dipstick but no erythrocytes, as seen in this patient. With prolonged intravascular hemolysis, patients may become secondarily iron deficient through iron loss in the urine. Patients with this entity may show iron deficiency anemia with evidence of urine iron loss, indicated by the presence of hemosiderin in sloughed tubular cells by Prussian blue staining. Exercise-induced hemolysis is considered a benign condition and is treated by removal or reduction of the traumatic cause of erythrocyte injury.

Strenuous exercise is a well-described cause of either gross or microscopic hematuria. Although the mechanism for hematuria associated with exercise has not been fully elucidated, it is considered a benign condition and should resolve with termination of exercise. This patient has evidence of myoglobinuria but not of hematuria given the lack of erythrocytes in her urine, making this a less likely diagnosis.

An inflammatory myopathy, such as polymyositis, may cause muscle damage and the finding of positive blood on the urine dipstick without significant hematuria. However, inflammatory myopathies are usually associated with muscle weakness and tenderness and an elevated creatine kinase level, which are absent in this patient.

Rhabdomyolysis is caused by injury and necrosis of muscle with release of intracellular muscle contents into the circulation; myoglobin may be detected in the urine as hemoglobin in the absence of erythrocytes. However, rhabdomyolysis is usually associated with muscle pain and significant elevations in circulating muscle enzyme levels, including creatine kinase. This patient has no muscle

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tenderness and her creatine kinase level is normal, making this diagnosis unlikely.

KEY POINT

- Exercise-induced hemolysis (march hemoglobinuria or runner's hemolysis) is caused by erythrocyte damage through repetitive mechanical trauma such as running or marching, resulting in intravascular hemolysis with loss of iron in the urine

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Item 58 Answer: B

Educational Objective: Diagnose essential thrombocythemia.

Mutational analysis for *JAK2 V617F* should be conducted. The patient presented with iron deficiency anemia and thrombocytosis. Thrombocytosis is often associated with iron deficiency anemia, particularly if bleeding is the cause of the anemia. However, when the patient's anemia was corrected with oral iron and oral contraceptive pills for better regulation of menstruation, thrombocytosis persisted, suggesting a disorder in platelet regulation. Iron deficiency is the most common cause of reactive thrombocytosis, which corrects within weeks of correcting the iron deficiency. Infection, inflammation, and malignancy are other causes. With iron deficiency ruled out as a cause and no other causes clinically apparent, essential thrombocythemia (ET) becomes more probable. Her lack of splenomegaly is fairly typical. The *JAK2* activating mutation is present in 50% of patients with ET, so a negative result would not exclude the diagnosis, but a positive result supports the diagnosis of a myeloproliferative neoplasm (polycythemia vera, ET, or primary myelofibrosis).

BCR-ABL testing, then bone marrow aspiration and biopsy, would be performed if the platelet count remained persistently elevated after correction of serum iron levels with a negative *JAK2* mutation status, because myeloproliferative neoplasms other than ET can less commonly elevate the platelet count. In ET, general hypercellularity and megakaryocyte hyperplasia would be seen on the bone marrow examination.

Testing the prothrombin and activated partial thromboplastin times would not be the most appropriate choice, because it focuses the diagnosis on a bleeding diathesis rather than thrombocytosis. Similarly, von Willebrand factor antigen testing does not address the patient's persistently elevated platelet count.

KEY POINT

- A patient with iron deficiency and isolated thrombocytosis that persists after correction of iron deficiency should undergo *JAK2 V617F* mutational analysis as part of the evaluation for essential thrombocythemia.

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Item 59 Answer: B

Educational Objective: Manage refractory iron deficiency.

The most appropriate management is to perform a stool antigen assay for *Helicobacter pylori* infection. This patient has iron deficiency anemia. Iron deficiency is a common problem because of the precarious balance between iron intake and use. Women of reproductive age may lose enough iron through normal menstrual blood loss to become iron deficient in the absence of uterine or gastrointestinal disease. Iron malabsorption is a relatively uncommon cause of iron deficiency but should be considered when no other cause of iron deficiency is apparent and particularly when the deficiency is refractory to adequate iron replacement therapy. It is usually caused by generalized malabsorption conditions such as celiac disease, achlorhydria secondary to atrophic gastritis or proton pump inhibitor therapy, or, occasionally, *H. pylori* infection. This patient's history of chronic dyspepsia and refractoriness to oral iron therapy suggest the possibility of *H. pylori* infection. *H. pylori* infection is endemic in many developing countries. Patients treated for underlying *H. pylori* infection may have improved iron absorption, making oral iron replacement an effective treatment.

Although ascorbic acid can facilitate iron absorption, no convincing data suggest the addition of this agent is worth the increase in cost or gastrointestinal toxicity.

Celiac disease is an immunologic response to dietary gliadins in patients genetically at risk as deemed by the presence of *HLA-DQ2* or *HLA-DQ8*. The typical features of celiac disease are diarrhea, bloating, and weight loss; it is diagnosed mainly in whites of northern European ancestry and would be an unusual cause of refractory iron deficiency anemia in a woman of African descent with dyspepsia. Antigliadin assays have poor sensitivity and specificity and a high false-positive rate, so they are not recommended for diagnosing celiac disease.

Iron deficiency is most easily treated with oral iron salts. Oral ferrous sulfate is the least expensive preparation. Each 325-mg tablet of ferrous sulfate contains 66 mg of iron, 1% to 2% of which is absorbed. Although other oral iron salts such as ferrous gluconate or ferrous fumarate are available, none of these have proved superior to ferrous sulfate in tolerability or efficacy.

KEY POINT

- Iron malabsorption is usually caused by generalized malabsorption conditions such as celiac disease, achlorhydria, or *Helicobacter pylori* infection.

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Item 60 Answer: B

Educational Objective: Manage a patient undergoing colonoscopy and taking a new oral anticoagulant.

The patient should stop rivaroxaban, a new oral anticoagulant (NOAC), the day before his scheduled colonoscopy. Because polypectomy or biopsy of lesions may become necessary during this patient's colonoscopy, interruption of anticoagulation is suggested in patients who are not at high risk for thromboembolic events, which includes this patient, because his thrombotic event occurred more than 3 months ago. Compared with warfarin, it is not yet known at what residual drug level procedures and surgeries can be safely performed without undue bleeding risk in patients taking an NOAC. In the absence of clinical data about when to stop these drugs before surgery, the half-life of the anticoagulant is the most frequently used parameter to decide when to stop the drug. Reported half-lives are 14 to 17 hours for dabigatran, 7 to 11 hours for rivaroxaban, 8 to 14 hours for apixaban, and 5 to 11 hours for edoxaban. For surgical procedures with standard risk for bleeding, the NOAC should be discontinued 2 to 3 half-lives beforehand, and in procedures with high bleeding risk, 4 to 5 half-lives beforehand. Close attention to kidney function is needed, because kidney impairment leads to prolonged half-lives of the NOACs. In this patient with normal kidney function, stopping rivaroxaban 24 to 36 hours before the procedure would be appropriate.

Bridging with low-molecular-weight heparin (LMWH) is not indicated, because LMWHs have half-lives of 4 to 7 hours, not much shorter than the NOACs. Additionally, this patient is not at high risk for thromboembolism and would not need preprocedural bridging even if he were taking warfarin.

KEY POINT

- The new oral anticoagulants should be stopped 24 to 36 hours before surgeries with standard risk for bleeding and 2 to 4 days before surgeries with a high risk for bleeding in patients with normal kidney function.

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Item 61 Answer: A

Educational Objective: Manage α-thalassemia.

This patient should discontinue her oral iron supplementation, because she does not have iron deficiency. She likely has α-thalassemia trait presenting with a mild microcytic anemia. Microcytic hypochromic erythrocytes and target forms may be seen on the peripheral blood smear in α- and β-thalassemia, which can only be differentiated by hemoglobin electrophoresis, in which α-thalassemia shows a normal pattern and β-thalassemia typically has a slightly increased hemoglobin A_2 band. α-Thalassemia trait (or α-thalassemia minor, double gene deletion -α/-α or --/αα) is associated with mild anemia, microcytosis, hypochromia, target cells on the peripheral blood smear, and, in adults, normal hemoglobin electrophoresis results. The (-α/-α) variant is often mistaken for iron deficiency. Microcytic anemia associated with a normal or slightly increased erythrocyte count is characteristic of thalassemia but not of iron deficiency. The red cell distribution width (RDW) is also useful in distinguishing between thalassemia and iron deficiency, because the RDW is often elevated in iron deficiency but normal in thalassemia. No treatment or monitoring is necessary for α-thalassemia trait.

The mild anemia of α-thalassemia is often confused with iron deficiency anemia, especially in a patient who could have a plausible cause for iron deficiency from menstrual blood loss. However, this patient's iron values are not consistent with iron deficiency, and the normal RDW argues against iron deficiency and the need for iron replacement therapy. This also rules out the need for evaluation for gastrointestinal blood loss with fecal occult blood testing.

Starting an oral contraceptive pill could potentially lessen the patient's menstrual bleeding, but because she is not iron deficient, oral contraceptives would not correct her mild anemia.

KEY POINT

- α-Thalassemia trait (or α-thalassemia minor), which is associated with mild anemia, microcytosis, hypochromia, target cells on the peripheral blood smear, and, in adults, normal hemoglobin electrophoresis results, requires no treatment.

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Item 62 Answer: C

Educational Objective: Determine the appropriate contraceptive choice for a woman at increased risk for venous thromboembolism.

A progestin-releasing intrauterine device (IUD) would be most appropriate for this patient. Other choices include the progestin-only pill, depot injection, or implanted rod. She is at increased risk for venous thromboembolism (VTE) because of her family history of VTE in two first-degree relatives and her obesity. Progestin-releasing IUDs do not appear to increase VTE risk, so they are a good contraceptive choice for women who are at increased risk for VTE. It is uncertain if oral progestin-only contraceptives (min-ipill) lead to an increased risk of VTE; however, the risk appears to be more clearly increased

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if additional VTE risk factors are present (obesity, immobility, surgery). Injectable progestins do appear to increase the risk of VTE.

Oral contraceptive pills (OCPs) include combination estrogen-progestin products and progestin-only pills. Combinations with lower estrogen doses are as effective with fewer side effects. Combined products are also available as a patch and a vaginal ring. Contraindications to combination products include history or increased risk of thrombosis, liver disease, breast cancer, migraine with aura, and uncontrolled hypertension. Women older than 35 years who smoke more than 15 cigarettes per day should not be prescribed estrogen-containing preparations because of an increased risk of stroke. Because this patient is at increased risk for thrombosis, she should not use any method of contraception containing estrogen.

KEY POINT

- Progestin-releasing intrauterine devices are the most appropriate contraceptive option for women at increased risk for venous thromboembolism (VTE) because they are not associated with increasing the VTE risk further, whereas progestin-only pills, implants, and injections may slightly increase the risk for thrombosis.

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Item 63 Answer: C

Educational Objective: Manage pulmonary embolism with outpatient anticoagulation.

This patient can receive anticoagulant therapy in the outpatient setting. When treating acute pulmonary embolism (PE), it is essential to initiate anticoagulation immediately and achieve therapeutic levels of anticoagulation within 24 hours; failure to do so correlates with an increased risk of clinical progression and recurrence. Anticoagulation can be achieved with unfractionated heparin (either intravenous or subcutaneous), subcutaneous low-molecular-weight heparin (LMWH), or the pentasaccharide fondaparinux. Outpatient management is safe for up to 50% of patients with PE, including some with mild right heart strain on cardiac echocardiography. However, hospital admission is appropriate for patients who are too ill to be managed at home (those needing supplemental oxygen or requiring intravenous pain medications) and those with comorbid conditions that may contribute to rapid clinical deterioration (for example, high bleeding risk).

A 2012 guideline from the American College of Chest Physicians (ACCP) recommends thrombolytic therapy for patients with PE and a systolic blood pressure less than 90 mm Hg and without contraindications (for example, high bleeding risk). Thrombolytic therapy does not appear to have therapeutic benefit in unselected patients with acute PE and is associated with an increased risk for major hemorrhage. No clear evidence indicates thrombolytic therapy should be used in patients with evidence of pulmonary hypertension or right ventricular dysfunction detected by echocardiography, positive cardiac enzymes, or both. This patient has no indications for thrombolytic therapy. If thrombolytic therapy were appropriate, the ACCP's guidelines recommend systemic administration rather than catheter-directed thrombolysis.

KEY POINT

- Outpatient anticoagulation management is possible for patients with pulmonary embolism, unless they require supplemental oxygen, intravenous pain medications, or management of comorbid conditions that may contribute to rapid clinical deterioration or if home circumstances make outpatient therapy unfeasible.

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Item 64 Answer: A

Educational Objective: Diagnose amyloidosis.

This patient should undergo amyloid typing to classify his amyloidosis (for example, immunoglobulin light chain [AL], hereditary, or secondary [AA] amyloidosis). Amyloid typing can be accomplished by protein sequencing of the amyloid material from an involved biopsy specimen or by immunofluorescence or immunohistochemistry. He has an IgG κ monoclonal gammopathy, evidence of cardiac infiltration shown by diffuse myocardial thickening, and amyloid deposition seen on a fat pad aspirate; these findings suggest amyloid cardiomyopathy. The presence of an IgG κ monoclonal gammopathy suggests the possibility of AL amyloidosis. However, hereditary amyloidosis with incidental monoclonal gammopathy of undetermined significance (MGUS) must also be considered. The most common variant of hereditary cardiac amyloidosis is characterized by a Val-122Ile mutation in transthyretin. It is present in 3.5% of black persons and is associated with late-onset cardiac involvement, typically after the age of 50 years, without evidence of other end-organ damage related to amyloidosis. Mass spectroscopy, which has 98% sensitivity and specificity, can be used to sequence and identify the composition of the amyloid deposits. Amyloid typing to establish the correct type of amyloidosis syndrome is absolutely critical, particularly in light of the high prevalence of MGUS, to avoid exposing a patient to inappropriate and potentially difficult therapy.

Chemotherapy and autologous hematopoietic stem cell transplantation (HSCT) are appropriate therapies for a patient

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with an established diagnosis of AL amyloidosis but not hereditary amyloidosis. A diagnosis of AL amyloidosis requires initiation of chemotherapy or pursuit of autologous HSCT, whereas a diagnosis of Val122Ile transthyretin-mutated amyloidosis is treated supportively. Patients with earlier onset hereditary amyloidosis characterized by more extensive or severe organ involvement would be considered for liver transplantation.

Although a transmyocardial biopsy would show evidence of amyloid deposition in the heart, this invasive procedure is unnecessary in patients with a typical clinical presentation, consistent noninvasive cardiac imaging findings, and documented amyloid deposition on biopsy from a noncardiac site, as seen in this patient.

KEY POINT

- Patients with amyloidosis should undergo amyloid typing of amyloid deposits to further classify the type of amyloidosis present.

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Item 65 Answer: D

Educational Objective: Treat vaso-occlusive pain in a pregnant patient with sickle cell disease.

This patient should receive intravenous fluids and narcotic analgesics. She is experiencing a vaso-occlusive pain episode that does not differ greatly from those she typically experiences. Because no reliable physical findings or laboratory markers can objectively establish the vaso-occlusion, the diagnosis of vaso-occlusive pain is based on subjective reports by the patient. She has no signs of acute chest syndrome (ACS) (no fever or hypoxia [oxygen saturation >90% breathing room air]) or other end-organ damage (her creatinine and aminotransferase levels are normal). No randomized studies have been conducted on the effectiveness or harms of standard therapy for vaso-occlusive crisis during pregnancy. Expert opinion recommends this patient should receive the same treatment as nonpregnant patients with sickle cell disease, which includes rest, relaxation, warmth, NSAIDs (which are considered safe before 30 weeks' gestation), oral and intravenous hydration, and narcotic analgesia. Narcotics are safe to use during pregnancy, and she will benefit from hydration, which will theoretically correct any dehydration contributing to the vaso-occlusive episode.

Because neither the patient nor the fetus is displaying symptoms of anemia (significant shortness of breath, dizziness, and chest pain in the mother or fetal distress), transfusion is not indicated. The patient's hemoglobin level is slightly lower now than her prepregnancy baseline; however, neither transfusion nor exchange transfusion is indicated in asymptomatic patients without signs of end-organ damage. Neither has been shown to decrease maternal morbidity or mortality during pregnancy, but both would predispose the patient to iron overload and erythrocyte antibody production. Transfusion would be appropriate to treat symptomatic anemia or signs of end-organ involvement (stroke symptoms, kidney failure, ACS, hepatic involvement).

Hydroxyurea therapy results in decreased mortality in hemoglobin SS sickle cell anemia and is indicated in patients with recurrent painful episodes, ACS, and symptomatic anemia. However, because of its potential teratogenicity, hydroxyurea should not be administered during pregnancy. Proper contraception before hydroxyurea initiation should be discussed with the nonpregnant patient.

KEY POINT

- Expert opinion recommends that pregnant patients should receive the same treatment for acute vaso-occlusive crisis as nonpregnant patients with sickle cell disease.

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Item 66 Answer: D

Educational Objective: Diagnose polycythemia vera as a cause of Budd-Chiari syndrome.

The appropriate next step would be to test for the *JAK2 V617F* mutation. This patient likely has polycythemia vera (PV), a myeloproliferative neoplasm (MPN). Symptoms include generalized pruritus that often worsens after bathing, erythromelalgia (a burning sensation in the palms and soles), and hypermetabolic symptoms such as fever, weight loss, and sweating. On physical examination, patients may have plethora and hepatosplenomegaly. Twenty percent of patients experience arterial or venous thrombosis as their initial symptom. PV and the other MPNs predispose to the development of the Budd-Chiari syndrome (BCS), which is characterized by hepatic venous outflow tract obstruction (including the suprahepatic inferior vena cava) and other intra-abdominal thromboses, such as thrombosis of the portal, superior mesenteric, or splenic vein. Abdominal pain, ascites, liver and spleen enlargement, and portal hypertension occur with symptomatic BCS. Ninety-five percent of patients with PV have the *JAK2* mutation, so it is an appropriate confirmatory test for suspected PV. Anticoagulant therapy is recommended for all patients with BCS regardless of whether an underlying prothrombotic disorder is discovered. Phlebotomy to normalize the hematocrit (goal <45% in men, <42% in women) is indicated, and adding the myelosuppressive agent hydroxyurea to phlebotomy decreases thrombotic events in patients with PV.

Bone marrow aspirate and biopsy findings are nonspecific in PV; they may show an increased number of megakaryocytes in a moderately to markedly hypercellular marrow and an increase in reticulin. Because they are not diagnostic and the procedure is invasive, bone marrow

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biopsy is typically unnecessary and is not an appropriate early diagnostic test.

Although factor V Leiden is a risk factor for venous thromboembolism, it would not explain the patient's erythrocytosis, leukocytosis, or thrombocytosis. Therefore, it is not a helpful test to perform in this patient.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder that should be considered in patients with hemolytic anemia, pancytopenia, or unprovoked atypical thrombosis. Thrombotic complications of PNH may occur in atypical locations, such as the hepatic veins (BCS) or mesenteric or cerebral circulation, and develop more frequently in patients with large PNH clones. PNH is diagnosed by flow cytometry, which can detect CD55 and CD59 deficiency on the surface of peripheral erythrocytes or leukocytes. Erythrocytosis, leukocytosis, thrombocythemia, and generalized pruritus are not typical for PNH.

KEY POINT

- Arterial or venous thrombosis is the initial symptom in 20% of patients with polycythemia vera (PV) and should prompt testing for the *JAK2 V617F* mutation, which is found in nearly 100% of patients with PV.

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Item 67 Answer: D

Educational Objective: Treat a patient with venous thromboembolism with an initial combination of a parenteral anticoagulant and warfarin.

Heparin should be given for no less than 5 days and only discontinued at that time if the INR is therapeutic for 24 hours. Warfarin may be initiated on the first or second day of heparin therapy. Because factor II and X levels require at least 5 days to decline sufficiently, parenteral anticoagulation should overlap with warfarin for at least 5 days and until an INR of 2 or more is achieved.

The initial warfarin dose may be based on a patient's predicted maintenance dose using available calculators, and a patient's nutritional status, comorbid diseases, and age must be considered. Excessively high initial doses should be avoided because they can lead to supratherapeutic INR values and premature discontinuation of parenteral therapy. Patients should be followed closely with frequent INR studies at the initiation of therapy to achieve values consistently within the desired range. After patients achieve consistently stable INR levels with an established dose, INR monitoring may eventually be extended to every 12 weeks for the duration of treatment, but testing frequency should be determined individually. The duration of warfarin therapy is determined by the type of thrombotic event and the presence or absence of situational triggers (provoked versus unprovoked), thrombophilic states, active cancer, and a history of thrombotic events.

KEY POINT

- Parenteral anticoagulant administration must overlap with warfarin for at least 5 days and until the INR is greater than 2 for 24 hours.

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Item 68 Answer: D

Educational Objective: Diagnose cobalamin (vitamin B_{12}) deficiency.

The most appropriate diagnostic test is to measure the methylmalonic acid level. This patient likely has cobalamin (vitamin B_{12}) deficiency, which she is at risk for based on following a vegan diet for several years. Compared with folate deficiency, which develops within weeks, cobalamin deficiency develops over months to years. She also has neurologic findings typical of and concerning for cobalamin deficiency. If left untreated, neurologic function could continue to decrease. A macrocytic anemia is characteristic of cobalamin deficiency, and the peripheral blood smear shows a typical hypersegmented neutrophil, a result of ineffective myelopoiesis. In many patients with suspected cobalamin deficiency, vitamin B_{12} levels will be in the normal range, and further testing is indicated to obtain better sensitivity. Methylmalonic acid is elevated in 98% of people with cobalamin deficiency; therefore, this would be a sensitive and specific test to determine deficiency.

Cobalamin deficiency can occasionally present with pancytopenia, which could prompt a bone marrow examination; however, a bone marrow biopsy is not needed to diagnose suspected cobalamin deficiency. The patient's neutropenia will likely resolve as the cobalamin deficiency is corrected.

This patient is unlikely to have isolated folate deficiency considering her neurologic symptoms, which are commonly seen with cobalamin, but not folate, deficiency. Testing the methylmalonic acid level concomitantly rules out folate deficiency and diagnoses cobalamin deficiency, because methylmalonic acid levels will be normal in cases of folate deficiency.

Homocysteine levels are elevated in cobalamin deficiency, but they can also be elevated in folate deficiency, so checking the homocysteine level is not the best test to perform. Evaluating the methylmalonic acid level will more accurately provide a diagnosis.

KEY POINT

- The methylmalonic acid level is elevated in 98% of patients with cobalamin deficiency, making it a sensitive and specific laboratory test to use in determining deficiency.

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Item 69 Answer: C

Educational Objective: Manage Waldenström macroglobulinemia.

This patient should begin combination rituximab plus chemotherapy. He has symptomatic Waldenström macroglobulinemia, demonstrated by a neoplastic infiltrate consisting of clonal lymphocytes, plasmacytoid lymphocytes, plasma cells, and immunoblasts comprising 10% or more of the bone marrow cellularity with disease-related manifestations, including night sweats, weight loss, anemia, lymphadenopathy, and splenomegaly. Management of this low-grade, mature B-cell, non-Hodgkin lymphoma consists of the anti-CD20 monoclonal antibody, rituximab, as single agent therapy or combined with chemotherapy. Considering this patient's degree of symptoms and tumor burden, along with his otherwise good health, combined rituximab and chemotherapy would be highly appropriate. The chemotherapy regimen may consist of an alkylating agent base (such as cyclophosphamide) or purine analog base (such as fludarabine).

Management of anemia should be directed at treating the underlying cause, in this case the Waldenström macroglobulinemia. Plasma exchange is essential for patients presenting with symptomatic hyperviscosity and is occasionally used as adjunctive therapy for cold agglutinin disease, an autoimmune hemolytic anemia that can be associated with Waldenström macroglobulinemia. However, it would not be appropriate in this patient, who does not have symptoms of hyperviscosity. Although the patient is anemic and has an elevated lactate dehydrogenase level, the reticulocyte count is low considering the degree of anemia, no erythrocyte clumps appear on the peripheral blood smear, and the direct antiglobulin (Coombs) test is negative, making a diagnosis of cold agglutinin disease highly unlikely. Furthermore, the patient does not have any clinical manifestations of this disorder (such as acrocyanosis), so a cold agglutinin titer would not be appropriate.

The patient has no symptoms of hyperviscosity (blurry vision, headache, hearing loss, tinnitus, vertigo, dizziness, altered mental status) or findings on physical examination to suggest hyperviscosity (dilated, tortuous retinal veins on funduscopic examination). In the absence of signs and symptoms of hyperviscosity and an M protein of less than 4 g/dL, serum viscosity testing is of no significant value.

KEY POINT

- Initial therapy for Waldenström macroglobulinemia may consist of rituximab as monotherapy or combined with chemotherapy, which may include an alkylating agent or a purine analog.

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Item 70 Answer: C

Educational Objective: Diagnose glucose-6-phosphate dehydrogenase deficiency.

This patient's glucose-6-phosphate dehydrogenase (G6PD) activity should be measured in 2 months. G6PD deficiency is an X-linked disease and occurs more commonly in men, often in blacks. This variant typically leads to episodic hemolysis in response to oxidant stressors (for example, infections or drugs such as dapsone, trimethoprim-sulfamethoxazole, and nitrofurantoin). Elevated levels of G6PD are found in normal young reticulocytes, and levels may appear falsely normal during an acute hemolytic episode, causing a missed diagnosis. Consequently, G6PD levels should be checked a few months after the occurrence of an acute event. During an acute hemolytic episode, bite cells may be seen on the peripheral blood smear, as are apparent in this patient's peripheral blood smear.

Thrombotic thrombocytopenic purpura (TTP) should be suspected in patients who have anemia, schistocytes on the peripheral blood smear, increased serum lactate dehydrogenase level, and thrombocytopenia. TTP can be triggered by drugs, especially quinine, ticlopidine, mitomycin C, cyclosporine, or gemcitabine. The mechanism of disease is thought to be antibodies directed against the protease ADAMTS-13 that is responsible for cleaving the high-molecular-weight multimers of von Willebrand factor. Assays for ADAMTS-13 activity are available but are not needed for a TTP diagnosis and are not indicated in patients who lack the essential diagnostic criteria for TTP.

Hereditary spherocytosis should be suspected in patients with a personal or family history of anemia, jaundice, splenomegaly, or gallstones. Spherocytes are present on the peripheral blood smear, and the direct antiglobulin (Coombs) test is negative. The osmotic fragility test with 24-hour incubation is a key diagnostic step, demonstrating increased erythrocyte fragility in hypotonic saline compared with control erythrocytes. This patient's ethnic background, absence of splenomegaly, and presence of bite cells on the peripheral blood smear do not support a diagnosis of hereditary spherocytosis.

KEY POINT

- Glucose-6-phosphate dehydrogenase deficiency typically leads to episodic hemolysis in response to oxidant stressors (infections or drugs such as dapsone, trimethoprim-sulfamethoxazole, and nitrofurantoin).

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Item 71 Answer: B

Educational Objective: Treat a patient with warm autoimmune hemolytic anemia.

The patient should be given prednisone. She has warm autoimmune hemolytic anemia (WAIHA), indicated by the high reticulocyte count, elevated bilirubin and lactate dehydrogenase (LDH) levels, the positive direct antiglobulin (Coombs) test, and spherocytes seen on peripheral blood smear. In WAIHA, IgG antibodies are directed against erythrocyte surface membrane molecules, which leads to phagocytosis by macrophages that cause erythrocytes to become progressively more spherocytic. These abnormal erythrocytes are then destroyed in the spleen. WAIHA can manifest as a primary disorder or as a complication of another disorder, including autoimmune conditions (systemic lupus erythematosus) or lymphoproliferative disorders (chronic lymphocytic leukemia). Treatment is immunosuppression to halt the immune-mediated erythrocyte destruction and allow the patient's own bone marrow to regenerate the erythrocytes, if possible. The best initial treatment for this condition is a glucocorticoid such as prednisone.

Transfusion in patients with WAIHA is a topic of debate. Although this patient has severe anemia, she has no organ dysfunction, is not hypoxic, and has no signs or symptoms of heart failure or angina. Additionally, her bone marrow is able to respond to her hemolysis, and her hemoglobin level would be expected to recover with treatment of her hemolytic condition. Additionally, erythrocyte transfusions are complicated in patients with WAIHA, because the antibodies causing hemolysis may crossreact with transfused erythrocytes, making crossmatch-compatible blood difficult to find. Therefore, transfusion in patients with WAIHA should be approached carefully, and if necessary, should be performed with type-specific, crossmatch-incompatible blood. Consultation with a hematologist and transfusion medicine specialist is recommended.

Rituximab and splenectomy are typically reserved to treat patients in whom first-line therapy for WAIHA has failed; they are not used in the acute setting. An inadequate response to glucocorticoids may indicate the need for splenectomy or alternative immunosuppression.

Although the mean corpuscular volume is elevated, this patient's clinical picture is inconsistent with vitamin B_{12} deficiency, which typically includes a low reticulocyte count (although the LDH and total bilirubin levels can be quite elevated because of intramedullary hemolysis). Additionally, no hypersegmented neutrophils are seen, and she has no abnormal neurologic findings.

KEY POINT

- Treatment of warm autoimmune hemolytic anemia is based on initial immunosuppression with glucocorticoids to halt immune-mediated erythrocyte destruction and allow bone marrow to regenerate the erythrocytes.

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Item 72 Answer: D

Educational Objective: Manage low-risk myelodysplastic syndrome with observation.

Observation is appropriate for this patient with low-risk myelodysplastic syndrome (MDS), incidentally discovered by a complete blood count showing asymptomatic pancytopenia. The mild macrocytosis is typical. The bone marrow biopsy is appropriate to confirm a suspected diagnosis of myelodysplasia in the setting of the normal vitamin B_{12} and folate levels and to provide important prognostic information. This patient has low-risk disease by the revised International Prognostic Scoring System criteria despite two involved cell lines. The low-risk cytogenetics and low marrow blasts (<2%) indicate very low-risk MDS. Median survival is 8.8 years in a generally older adult population and the median time to 25% acute myeloid leukemia (AML) progression is more than 14 years. No therapy will improve prognosis in this situation.

5-Azacytidine is appropriate therapy for higher risk MDS for the purpose of improving blood counts, delaying AML progression, and extending survival. It would be indicated to lessen transfusion dependence or to improve prognosis for high-risk disease, but is inappropriate in this patient, whose disease is low risk.

Allogeneic hematopoietic stem cell transplantation is not justified, because this patient's disease is very low risk. In contrast, a patient with very high-risk disease has an expected median survival of less than 1 year, justifying the treatment-related morbidity associated with transplantation.

Erythropoietin is inappropriate because this patient is asymptomatic. Recombinant erythropoietin can be effective in approximately 25% of patients with MDS. However, the goal hemoglobin level is 10 g/dL (100 g/L), and targets to higher values have been associated with arterial and venous thrombosis.

KEY POINT

- Myelodysplastic syndrome should be managed based on risk stratification, with patients with low-risk disease requiring no treatment.

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Item 73 Answer: B

Educational Objective: Diagnose transfusion-associated circulatory overload.

The most likely diagnosis is transfusion-associated circulatory overload (TACO). TACO is an underdiagnosed condition that

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occurs in 0.3% to 8% of patients undergoing transfusion in the hospital and is associated with increased inpatient mortality and a longer length of hospital stay. TACO is defined as the new onset or exacerbation of at least three of the following findings within 6 hours of completing a transfusion: acute respiratory distress, elevated B-type natriuretic peptide (BNP) level, elevated central venous pressure (CVP), evidence of left heart failure, evidence of positive fluid balance, and radiographic evidence of pulmonary edema. Risk factors include age older than 60 years, chronic kidney disease, chronic heart failure, number of blood products transfused, and the volume transfused per hour. Preventive measures include a slower rate of infusion for those at risk (1 mL/kg/hour) and diuretic therapy to maintain euvolemia.

An acute hemolytic transfusion reaction (AHTR) is unlikely. The patient's hemoglobin level increased appropriately after the transfusion (1 g/dL/U [10 g/L/U]), and the lactate dehydrogenase and total bilirubin levels are not elevated. No protein was seen on urinalysis, kidney function is unchanged, and the patient is not hypotensive. Additionally, pulmonary opacities as seen on the radiograph would not be expected with AHTR.

Distinguishing TACO from transfusion-related acute lung injury (TRALI) can be challenging. Fever and hypotension occur in only one third of patients with TRALI. However, TRALI is not associated with signs of volume overload (increased jugular venous pressure, lower extremity edema, elevated CVP). BNP and N-terminal proBNP levels have not been studied in TRALI but are elevated with TACO.

Transfusion-associated sepsis is highly unlikely in the absence of fever and hypotension.

KEY POINT

- Patients experiencing acute respiratory distress, elevated B-type natriuretic peptide level, elevated central venous pressure, evidence of left heart failure, evidence of positive fluid balance, or radiographic evidence of pulmonary edema within 6 hours of transfusion should be diagnosed with transfusion-associated circulatory overload.

Bibliography

Murphy EL, Kwaan N, Looney MR, et al; TRALI Study Group. Risk factors and outcomes in transfusion-associated circulatory overload. Am J Med. 2013 Apr;126(4):357.e29-38. [PMID: 23357450]

Item 74 Answer: B

Educational Objective: Treat high-risk myelodysplastic syndrome with hematopoietic stem cell transplantation.

This patient should undergo allogeneic hematopoietic stem cell transplantation (HSCT). She has myelodysplastic syndrome (MDS), diagnosed by complete blood count results from an investigation of symptomatic pancytopenia. The monocytosis and mild macrocytosis are typical. Bone marrow examination is required to confirm the diagnosis and to provide prognostic information that can inform therapeutic recommendations. The International Prognostic Scoring System – Revised criteria weigh cytogenetics most heavily when determining risk. A complex karyotype places this patient in a high-risk group. Involvement of three cell lines and more than 5% marrow blasts specifies the highest risk group. In very high-risk disease, median survival is expected to be less than 1 year. Such a prognosis in a younger patient justifies the recommendation for allogeneic HSCT at diagnosis. Although transplantation is associated with significant risks, it is also the only curative therapy for MDS.

5-Azacytidine is appropriate for higher risk MDS but does not have curative potential. In a younger, fit patient, HSCT is a better choice. For older patients (generally older than 60 years) or those with significant comorbidities, 5-azacytidine would be an appropriate option.

Erythropoietic agents, such as epoetin and darbepoetin alfa, may improve hemoglobin levels in patients with symptomatic anemia and lower risk MDS but are not appropriate as single therapy for high-risk disease. This patient is at high risk of transforming from MDS to acute myeloid leukemia (AML); HSCT will mitigate that risk, but treatment with erythropoietin will not.

Because of this patient's high-risk MDS, observation would be inappropriate. The natural history of high-risk MDS is progression to AML. Because secondary AML is much harder to cure, primary therapy before transformation improves prognosis.

KEY POINT

- Younger, fit patients with high-risk myelodysplastic syndrome should receive allogeneic hematopoietic stem cell transplantation, which is the only curative therapy option.

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Item 75 Answer: B

Educational Objective: Treat anemia of chronic kidney disease.

This patient should receive erythropoiesis-stimulating agent (ESA) therapy. He has anemia of chronic kidney disease (CKD), which affects 90% of patients with a glomerular filtration rate less than 25 to 30 mL/min/1.73 m². Erythropoietin is made by interstitial peritubular fibroblasts of the kidney, so patients with reduced kidney function may have low erythropoietin levels; however, erythropoietin resistance also occurs. When patients with reduced kidney function develop anemia, evaluation for other causes is appropriate; in particular, relative iron deficiency is common. If iron stores are adequate and other causes have also been eliminated (such as cobalamin and folate deficiency, gastrointestinal bleeding), the anemia can be attributed to CKD. The routine measurement of erythropoietin levels plays no role in CKD, because this expensive

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test does not aid in the diagnosis or guide treatment decisions. ESAs should be considered for patients with symptomatic anemia attributable to erythropoietin deficiency when the hemoglobin level is less than 10 g/dL (100 g/L). Patients with CKD must be carefully counseled about the risks of ESAs, which include increased risk of thrombotic and cardiovascular events as well as increased blood pressure. Additionally, clinicians should explain that target hemoglobin values are lower than those used in the past, and that patients must be monitored regularly to titrate the dose to a target hemoglobin level of 10 to 11 g/dL (100-110 g/L).

Transfusions are avoided in patients with CKD unless a compelling reason exists, such as tissue ischemia. Transfusions sensitize patients to HLAs, which complicate kidney transplantation options.

Even though many patients benefit from iron replacement, this man has adequate iron stores, so replacement therapy is not indicated.

KEY POINT

- Erythropoiesis-stimulating agents should be considered for patients with chronic kidney disease and symptomatic anemia attributable to erythropoietin deficiency when the hemoglobin level is less than 10 g/dL (100 g/L).

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Item 76 Answer: B

Educational Objective: Diagnose delayed hyperhemolytic transfusion reaction.

This patient has delayed hyperhemolytic transfusion reaction (DHTR). Chronic transfusion in patients with sickle cell disease (SCD) can lead to iron overload, alloimmunization, and an increased risk for DHTR. DHTR is caused by an amnestic response of a preformed erythrocyte alloantibody after re-exposure to an erythrocyte antigen outside the ABO system. Additionally, an autoimmune component could be worsening the hemolysis. Following transfusion, a 1% to 1.6% chance exists of developing these antibodies. DHTR may then occur after re-exposure with subsequent transfusion. Clinical findings, which typically develop approximately 2 to 19 days after erythrocyte transfusion, include anemia, reticulocytosis, jaundice, a significant decrease in hemoglobin level, and increases in hemolytic markers such as lactate dehydrogenase and bilirubin levels, although many patients will be asymptomatic. Patients with SCD may present with a worsening pain crisis. Hemolysis is typically extravascular, and life-threatening complications are rare. Treatment is supportive. Subsequent transfusions should be minimized but not withheld when indicated, such as in situations of severely symptomatic anemia and multiorgan failure.

Transient aplastic crisis can occur when patients with chronic hemolytic anemia and shortened erythrocyte survival are infected with parvovirus B19, which leads to suppression of erythrocyte production identified by anemia and lack of reticulocytosis. Parvovirus B19 infection is a viral syndrome characterized by malaise, fever, and arthralgia; 25% of patients are asymptomatic.

A rare complication of SCD is hepatic sequestration crisis, characterized by large numbers of erythrocytes becoming trapped in the liver. Patients may develop acute anemia, reticulocytosis, hypovolemia, and distributive shock. Prominent symptoms include right upper quadrant pain, hepatomegaly, and anemia. The patient has none of these manifestations.

Splenic sequestration crisis occurs when splenic pooling of erythrocytes causes an acute anemia with reticulocytosis and a rapidly enlarging spleen. Patients may develop hypotension and shock. This condition is found primarily in children who have functional spleens that have not been subjected to multiple infarctions and subsequent development of fibrotic atrophy. This adult patient does not have splenomegaly. Splenic sequestration crisis is not the most likely diagnosis for anemia following a transfusion.

KEY POINT

- Delayed hyperhemolytic transfusion reaction can occur several days after transfusion and is diagnosed by a significant decrease in the hemoglobin level with reticulocytosis and concomitant increases in the bilirubin and lactate dehydrogenase levels.

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Item 77 Answer: C

Educational Objective: Diagnose Felty syndrome.

This patient has Felty syndrome, which is the clinical triad of rheumatoid arthritis (RA), splenomegaly, and neutropenia. Splenomegaly and lymphadenopathy may occur secondary to connective tissue disorders such as RA. The unusual cell seen on the peripheral blood smear is a large granular lymphocyte (LGL). LGLs may be seen in up to 40% of patients with Felty syndrome; they may also be associated with other collagen vascular diseases and autoimmune neutropenia. LGL leukemia may also occur in patients with rheumatoid arthritis. Because patients with Felty syndrome and LGL leukemia tend to share HLA-DR4 positivity, they are thought to be part of the same disease spectrum in which immune system dysfunction leads to expansion of this type of cell. The mechanism of neutropenia in Felty syndrome is considered partially autoimmune (likely related to the process leading to development of LGLs) and partially owing to sequestration associated with splenomegaly. Felty syndrome is the most appropriate diagnosis for this patient because the clinical triad is present. This is a

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useful syndrome to recognize clinically, because it may lead to an RA diagnosis when articular involvement is less prominent.

Aplastic anemia refers to conditions in which the bone marrow fails to produce blood cells, resulting in a hypocellular bone marrow and pancytopenia. It can be acquired or congenital and may be classified as moderate, severe, or very severe. This patient only has leukopenia, which is not consistent with aplastic anemia.

Autoimmune neutropenia is an acquired abnormality that may be associated with underlying disorders of immune regulation such as systemic lupus erythematosus or may exist in a more isolated form. The degree of neutropenia is generally not severe enough to be linked with frequent infections, and spontaneous remission may occur in patients with the primary form. Antineutrophil antibodies may be detected, although tests for them, which differ from the antineutrophil cytoplasmic antibody tests used to evaluate vasculitis, may not be widely available and have variable sensitivity and specificity. In patients in whom antineutrophil antibodies are not detected, the diagnosis is established by excluding other causes.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal progenitor cell disorder that should be considered in patients presenting with hemolytic anemia, pancytopenia, or unprovoked atypical thrombosis. PNH does not present with isolated leukopenia.

KEY POINT

- Felty syndrome is characterized by rheumatoid arthritis, splenomegaly, and neutropenia.

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Oncology Answers

Item 78 Answer: B

Educational Objective: Manage a patient with suspected central nervous system lymphoma.

In this patient who most likely has a primary central nervous system (CNS) lymphoma with evidence of mass effect, high-dose glucocorticoids should be administered immediately. Because the brain is enclosed in a fixed space, mass effect within the brain causes progressively increased intracranial pressure (ICP) that, if untreated, can lead to diffuse brain injury, permanent disability, and death. Headache is typically the first presenting symptom and is followed by nausea and vomiting; as ICP increases, more advanced findings include altered mental status, focal neurologic deficits (such as papilledema), and loss of consciousness. Because progression can be rapid, emergent CT or MRI imaging of the brain followed by immediate treatment are essential to avoid the late adverse consequences of increased ICP that lead to permanent neurologic dysfunction and death. Glucocorticoids remain the initial therapy of choice because of their rapid anti-inflammatory effect that decreases the edema associated with malignant mass lesions. Intravenous administration of dexamethasone is standard for later stages of increased ICP (impaired mentation, uncontrolled seizures) with a recommended dose of 8 to 10 mg every 6 hours. Higher-dose dexamethasone (100 mg/d) does not improve the response rate and is associated with more adverse effects.

Metastatic tumors originating from lung cancer and cutaneous melanoma are the most common malignancy-related causes of increased ICP. These tumors, particularly melanoma, are also associated with intracerebral hemorrhage. Other less common causes of increased ICP related to malignancy include lymphoma, primary brain tumors, and germ cell tumors. Because treatment of ICP varies markedly depending on the cause, a tissue diagnosis of the mass lesion is important in guiding subsequent therapy. A primary CNS lymphoma is the most likely diagnosis in this young patient with a brain mass and HIV infection that is not optimally treated. Because lymphomas are extremely glucocorticoid sensitive, early administration may make obtaining a tissue sample difficult by distorting histologic findings; it is therefore preferable to obtain a biopsy in a stable patient with possible or likely CNS lymphoma prior to glucocorticoid therapy if there are minimal sequelae of increased ICP. However, in all patients with more advanced complications of increased ICP such as this patient, immediate glucocorticoid treatment is indicated.

Combination chemotherapy is appropriate only after initial steps are taken to lower the ICP and a tissue diagnosis is established, which has not yet been done in this patient.

Intracranial pressure monitoring is used to follow the effectiveness of therapies intended to decrease pressure in the cranial space and is most often used in association with severe traumatic brain injury. Although the benefit of pressure monitoring needs to be evaluated in an individual patient, it would not be appropriate to delay administration of glucocorticoids while assessing this patient for monitoring.

Either whole brain or stereotactic radiation therapy may be appropriate for some tumors causing increased ICP, but this therapy would be indicated only after the patient receives acute treatment and a tissue diagnosis is established.

KEY POINT

- Patients who have increased intracranial pressure associated with suspected central nervous system lymphoma require immediate high-dose glucocorticoids to treat the mass effect and a brain biopsy to establish the tissue diagnosis.

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Item 79 Answer: C

Educational Objective: Treat a patient with malignancy-associated hypercalcemia.

The most appropriate next step in treatment for this patient with malignancy-associated hypercalcemia is an intravenous

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bisphosphonate. Initial therapy for hypercalcemia is high-volume normal saline hydration, and in those with kidney failure, forced diuresis with a loop diuretic such as furosemide. This helps restore intravascular volume and decreases serum calcium levels acutely. For tumors that are glucocorticoid-sensitive, such as multiple myeloma and some types of lymphoma, glucocorticoids are indicated to decrease tumor-associated osteoclast activation. Bisphosphonates are powerful inhibitors of osteoclast-mediated bone resorption with an onset of effect occurring several days after administration and a duration of up to several weeks depending on the specific agent used, which allows longer-term control of calcium levels. Hypercalcemia is usually a manifestation of advanced disease, is associated with poor prognosis, and occurs in up to 10% of patients with cancer. Hypercalcemia is most common among patients with multiple myeloma and breast, renal, and lung cancer. Patients initially present with nausea, vomiting, constipation, and polyuria. Polydipsia, diffuse muscle weakness, and confusion follow.

Cinacalcet is a calcimimetic agent that is used to lower the calcium level in patients with primary and tertiary hyperparathyroidism associated with chronic kidney disease. It is not effective or approved for use in malignancy-associated hypercalcemia.

Dialysis is an effective method for lowering serum calcium levels, although it is generally reserved for patients with severe, symptomatic hypercalcemia who have not responded to acute treatment with hydration and other measures or patients in whom aggressive hydration is contraindicated. Dialysis would not be appropriate in this patient whose response to hydration and other initial therapies has not been assessed.

Treatment with chemotherapy or disease-specific targeted agents would be appropriate for long-term control of hypercalcemia but would not be effective for short-term therapy of hypercalcemia.

KEY POINT

- Immediate hydration with large-volume normal saline infusion, forced diuresis with furosemide, glucocorticoid therapy for glucocorticoid-responsive malignancies such as multiple myeloma, and a bisphosphonate is appropriate treatment of malignancy-related hypercalcemia.

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Item 80 Answer: A

Educational Objective: Treat stage III colon cancer with adjuvant chemotherapy.

Chemotherapy with leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) is most appropriate for this patient with stage III colon cancer. Stage III colon cancer is potentially curable, and the likelihood of cure is modestly but statistically significantly increased by the use of adjuvant chemotherapy. Administration of leucovorin plus 5-fluorouracil (5-FU) was established as an appropriate standard adjuvant treatment for stage III colon cancer in the 1990s. However, in 2004, a large randomized trial comparing adjuvant leucovorin and 5-FU with FOLFOX adjuvant chemotherapy showed that the FOLFOX regimen led to improved disease-free and overall survival. Capecitabine is an oral prodrug that is converted to 5-FU in the body. The combination of capecitabine plus intravenous oxaliplatin (CAPOX) is also an acceptable regimen for adjuvant treatment of patients with stage III colon cancer.

Because local recurrence of colon cancer rarely develops and because it can be difficult to isolate the small bowel from the radiation field, radiation therapy, either alone or in combination with chemotherapy, does not have a role in the routine management of patients with stage III colon cancer. In addition, radiation to the small bowel may cause substantial toxicity. However, because local recurrence is a greater problem in patients with rectal cancer and because it is far easier to isolate the small bowel from the radiation field when treating rectal cancer, the combination of radiation therapy and chemotherapy, preferably preoperatively, is routinely used for treating patients with stage II and III rectal cancer.

Stage III colon cancer is potentially curable with surgery and adjuvant chemotherapy. For patients with good performance status, adjuvant chemotherapy with its associated survival advantage is preferred to observation alone.

KEY POINT

- Chemotherapy with capecitabine and oxaliplatin (CAPOX) or leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) is appropriate adjuvant therapy for patients with stage III colon cancer.

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Item 81 Answer: D

Educational Objective: Manage a patient with metastatic cancer and poor performance status.

Supportive, comfort-oriented care is most appropriate for this patient who has advanced metastatic adenocarcinoma in the setting of multiple severe chronic comorbidities and a debilitated medical condition resulting in a poor performance status. A key aspect of managing patients with cancer is an assessment of their performance status, defined as the specific level of well-being and ability to perform daily activities. Several formal measures of performance status are available, such as the Karnofsky score and the Zubrod score (also called the Eastern Cooperative Oncology Group/World Health Organization system). Scores on these measures correlate with the ability of an individual patient to tolerate potential therapeutic

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interventions. In patients with very low performance measure scores, a less aggressive and more supportive treatment approach is usually warranted based on likely outcomes of therapy. Virtually all oncology clinical trials showing efficacy of chemotherapy exclude patients with poor performance status because toxicity and harm occur more frequently and clinical benefit occurs less frequently in these patients. In addition, this patient has elevated serum bilirubin and creatinine levels. Because liver and kidney function affect metabolism of many oncology drugs, treatment of patients with chronic liver or kidney disease is challenging and is associated with a higher risk of complications. In some cases, poor performance has developed based on tumor-related symptoms and might be expected to improve with treatment of the cancer. However, this patient's poor performance status appears to be due to his chronic illnesses and is not likely to improve significantly following treatment of his cancer.

Combination chemotherapy is contraindicated in a debilitated patient and would likely cause severe and even life-threatening toxicity.

Single-agent, low-dose chemotherapy is highly unlikely to provide any benefit and is still associated with the risk of toxicity.

The patient is a poor candidate for surgery, has no evidence of colonic obstruction, and would likely have considerable postoperative and healing complications with little, if any, chance of benefit.

KEY POINT

- Supportive, comfort-oriented care is appropriate for a frail patient with metastatic cancer, significant medical comorbidities, and a poor performance status.

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Item 82 Answer: A

Educational Objective: Determine need for molecular testing in a patient with adenocarcinoma of the lung.

This patient with stage IV adenocarcinoma of the lung (based on the presence of a likely right adrenal metastasis) should undergo tumor testing for the presence of an epidermal growth factor receptor (EGFR) mutation. Because studies have documented improved survival in patients with EGFR mutations who are treated with an EGFR tyrosine kinase inhibitor (such as erlotinib, gefitinib, or afatinib), testing to identify this mutation is a key component of the initial evaluation of all patients diagnosed with metastatic nonsquamous non-small cell lung cancer (NSCLC). In patients with likely metastatic disease who might be candidates for therapy, ensuring that an adequate tissue sample is obtained (core needle biopsy at a minimum) is essential to allow for needed molecular testing.

Although K-*ras* testing can help determine the prognosis in patients with NSCLC, it is not currently considered a routine component of evaluation because existing renin-angiotensin system inhibitors used to treat patients with this mutation have not proven to be effective.

PET scanning has a role in evaluating patients who are believed to have potentially resectable disease. However, obtaining a PET scan in a patient who clearly has metastatic disease based on CT imaging is unnecessary.

Because this patient has both a pleural effusion and a likely adrenal metastasis that would classify his disease as stage IV, he is not considered a surgical candidate.

KEY POINT

- Testing to identify an epidermal growth factor receptor (EGFR) mutation is a key component in the initial evaluation of metastatic nonsquamous non-small cell lung cancer due to improved survival in patients with EGFR mutations who are treated with EGFR tyrosine kinase inhibitors.

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Item 83 Answer: C

Educational Objective: Manage posttreatment surveillance following therapy for head and neck cancer.

Periodic oral examinations and direct laryngoscopy are indicated for this patient. Following successful treatment of localized squamous cell carcinoma of the head and neck, patients remain at risk for developing both local cancer recurrence and second primary cancers, especially cancers due to tobacco and alcohol use. Tobacco and alcohol act as chemical carcinogens and induce genetic changes in the squamous mucosa of the head and neck that are not limited to the site involved with the cancer. These genetic changes expose patients to ongoing risk for development of second primary cancers. Therefore, surveillance must be directed at identifying both locally recurrent cancer and second primary cancers elsewhere in the head and neck. This is accomplished by assessment of the primary site (for example, in this patient by direct oral examination) and periodic assessment of the remaining squamous mucosa of the head and neck via direct laryngoscopy. In addition, this patient population is at high risk for non-small cell lung cancer, which represents the most commonly diagnosed second cancer in patients with head and neck cancer. This patient also meets the general criteria for lung cancer screening with low-dose CT as she is between the ages of 55 to 74 years with a smoking history of at least 30 pack-years within 15 years of quitting. Inclusion of low-dose CT surveillance for lung cancer should therefore be discussed with any patient being treated for tobacco-related head and neck cancer.

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Within the first 6 months following treatment, imaging of the primary tumor site and neck is performed to establish a baseline for future reference. Imaging techniques, including CT, MRI, PET, and ultrasonography, have been used in posttreatment surveillance for locoregional recurrence. Subsequent imaging is generally based on the presence of signs or symptoms. Biannual CT scans are not indicated, and the additional radiation poses an unnecessary danger to the patient.

Providing no posttreatment surveillance is not recommended, as this patient should be evaluated periodically for development of both locally recurrent cancer and a second primary cancer.

KEY POINT

- Posttreatment surveillance of patients with head and neck cancer should be directed toward identifying development of both locally recurrent cancer and a second primary cancer at a more distant site.

Bibliography

Chuang SC, Scelo G, Tonita JM, et al. Risk of second primary cancer among patients with head and neck cancers: A pooled analysis of 13 cancer registries. Int J Cancer. 2008 Nov 15;123(10):2390-6. [PMID: 18729183]

Item 84 Answer: C

Educational Objective: Manage ipilimumab-induced toxicity.

Initiation of high-dose intravenous glucocorticoids and aggressive supportive care in addition to discontinuing the offending medication is the most appropriate treatment for this patient with ipilimumab toxicity with severe diarrhea and evidence of autoimmune hepatitis. Ipilimumab is a new class of antineoplastic therapy that inhibits the function of T-cell checkpoint receptors (ipilimumab or PD-1 and PD-L1 inhibitors), thereby enhancing the function of the immune system and inducing remissions in patients with various solid tumors, particularly metastatic melanoma. However, T-cell checkpoint inhibitors also can cause many potentially permanent and life-threatening organ toxicities that are autoimmune-mediated based on their enhancement of immune function. These include dermatologic (rash, mucositis), gastrointestinal (diarrhea, colitis), liver (autoimmune hepatitis), and endocrine (hypothalamic/pituitary, thyroid, and adrenal insufficiency). Other organ involvement (eye, kidney, hematologic, pulmonary, and neurologic) has also been reported. Because the toxicity results from triggering an exaggerated immune response, treatment of these toxicities involves removing the causative agent and providing immunosuppression, preferably with high-dose glucocorticoids due to their nonspecific immune-suppressing effects and rapid onset of action. Recognition of the autoimmune effect of the treatment is critical since the autoimmune-triggered toxicity from this class of medications can be fatal if immunosuppressive therapy is delayed.

Because the mechanism of toxicity is not directly related to leukopenia and this patient has a normal leukocyte count with no objective evidence of infection, broad-spectrum antibiotics are not indicated, and delayed recognition of the drug-related syndrome from treatment of possible bacterial infection could be detrimental.

Similarly, because the toxicity of T-cell checkpoint inhibitors is not due to leukopenia, treatment with growth factors, such as granulocyte-macrophage colony-stimulating factor, does not have a role in either the prevention or treatment of complications associated with this class of drugs.

Because rapid immunosuppression may reverse the severe autoimmune reactions triggered by ipilimumab, discontinuation of the medication and supportive care alone is inadequate therapy for this patient.

KEY POINT

- Patients with acute ipilimumab toxicity should receive fluid replacement and immediate glucocorticoid therapy to reverse the damage this agent can cause; delay in treatment can be fatal.

Bibliography

Weber JS, O'Day S, Urba W, et al. Phase I/II study of ipilimumab for patients with metastatic melanoma. J Clin Oncol. 2008 Dec 20;26(36):5950-6. [PMID: 19018089]

Item 85 Answer: B

Educational Objective: Determine appropriate timing of prophylactic bilateral salpingo-oophorectomies for a *BRCA1* carrier.

Prophylactic bilateral salpingo-oophorectomies (BSO) by the age of 35 years is recommended for this patient. Patients with *BRCA1/2* mutations are at increased risk for ovarian cancer. The lifetime risk is 35% to 46% in *BRCA1* mutation carriers and 13% to 23% in *BRCA2* carriers. National guidelines recommend risk-reducing BSO in women who carry deleterious *BRCA1/2* mutations between ages 35 and 40 years, once childbearing is complete. A recent registry data analysis of almost 6000 women with *BRCA1* or *BRCA2* mutations proposed that risk-reducing BSO be done by age 35 years in women with *BRCA1* mutations due to a 4% risk of ovarian cancer between ages 35 and 40 years. Women with *BRCA2* mutations in this registry data did not develop ovarian cancers until after age 40 years and had an ovarian cancer risk under 1% if BSO was deferred to age 50 years.

Also shown was an 80% reduction in the risk of ovarian, tubal, or peritoneal cancer after prophylactic BSO and a 77% reduction in all-cause mortality. Previous studies have demonstrated a 48% reduction in breast cancer in *BRCA1/2* carriers who underwent prophylactic oophorectomy while premenopausal.

Hormone replacement can safely be given to healthy *BRCA1/2* carriers after BSO for relief of menopausal symptoms

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and preservation of bone health if nonhormonal options are not effective. Limited studies have not demonstrated an increased risk of breast cancer with hormone replacement therapy when stopped prior to the normal age of menopause.

At age 33 years, this patient will have two years to pursue further childbearing and still be able to have BSO by age 35 years. It is not necessary to recommend immediate BSO. In the study mentioned above, there was a 0.5% risk of ovarian cancer between the ages of 30 and 34 years and only one occult ovarian cancer found at prophylactic BSO during these ages.

Semi-annual transvaginal ultrasound and serum CA-125 monitoring is recommended for *BRCA1/2* mutation carriers starting at age 30 years, but the evidence shows very limited effectiveness of such screening. Prophylactic BSO is the only method that has been shown to decrease ovarian cancer mortality in women at high risk for ovarian cancer.

KEY POINT

- Risk-reducing bilateral salpingo-oophorectomies are recommended in women who carry deleterious *BRCA1* or *BRCA2* mutations between ages 35 and 40 years, once childbearing is complete.

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Finch AP, Lubinski J, Møller P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014 May 20:32(15):1547-53. [PMID: 24567435]

Item 86 Answer: A

Educational Objective: Determine the prognosis of a patient with newly diagnosed lymphoma.

Although all of the options listed above affect the prognosis of this patient with an aggressive B-cell lymphoma, the revised International Prognostic Index score (r-IPI) correlates most strongly with his chance of overall survival after standard therapy.

Non-Hodgkin lymphoma (NHL) consists of over 20 subtypes defined by cell surface antigen expression and other morphologic features, including unique molecular profiles. The first major distinction divides NHL into three categories based on immunophenotyping to a B-cell, T-cell, or natural killer (NK) cell lineage. B-cell lymphomas account for 85% of all cases of NHL, T-cell lymphomas for 13%, and NK-cell lymphomas for 2%. A history of farming is not uncommon among newly diagnosed patients with B-cell lymphomas because components in some fertilizers are thought to be causative. Staging of lymphoma consists of structural disease assessment using physical examination findings, CT imaging, biopsy findings of potential disease sites, and disease activity assessment using PET scanning to quantify the standard uptake value. Age, concomitant infection or immunodeficiency, and expression of driver gene mutations can all influence prognoses. The Ann Arbor Staging System criteria can be used for most forms of lymphoma, however, the r-IPI score is most predictive of outcomes in patients with diffuse large B-cell lymphoma. The r-IPI incorporates multiple clinical factors, including the patient's age, performance status, disease stage, degree of extranodal involvement, and serum lactate dehydrogenase level to generate a score that correlates with progression-free and overall survival after standard therapy. This patient has a high r-IPI score due to stage IV disease (bone marrow involvement), a high serum lactate dehydrogenase level, and poor performance status.

The presence of anemia and B symptoms might be indicative of aggressive disease, but are not incorporated into the r-IPI score, which is the best predictor of clinical outcome.

The presence of diabetes appears to have a minimal effect on the outcome of lymphoma and is therefore not an independent predictive factor.

KEY POINT

- The revised International Prognostic Index (r-IPI) score has the greatest influence on the prognosis in patients with diffuse large B-cell lymphoma.

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Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2007 Mar 1:109(5):1857-61. [PMID: 17105812]

Item 87 Answer: B

Educational Objective: Treat advanced cervical cancer with chemoradiation therapy.

Radiation therapy and concurrent cisplatin-based chemotherapy is the most appropriate treatment for this patient who has bulky stage III cervical cancer (extending to the pelvic wall and/or involving the lower third of the vagina). Cervical cancer remains the second most common cancer in women worldwide. Early-stage cervical cancer without spread to the pelvic wall or to the lower third of the vagina can be treated successfully with surgery alone, but more locally advanced cancer requires radiation therapy instead of surgery. In 1999, based on five published randomized clinical trials, the National Cancer Institute issued a clinical alert recommending chemoradiation therapy for locally advanced cervical cancer. These initial studies used cisplatin-based chemotherapy during radiation; results showed a decrease in local and distant recurrence compared with radiation therapy alone.

Chemoradiation has since become the standard of care, and weekly cisplatin administration during radiation is the most frequently used regimen, although non-platinum-based chemotherapy regimens also have been shown to be effective. Radiation therapy alone can be used for patients with stage I (confined to the cervix) or nonbulky stage II cervical cancer (invading beyond the uterus but not to the pelvic wall or lower third of the vagina) as an alternative to hysterectomy but should be combined with chemotherapy for patients with bulky stage II, stage III, and

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stage IVA cervical cancers (spread to adjacent organs but no distant metastases).

Radical hysterectomy is appropriate for patients with stage I or nonbulky stage IIA cervical cancer, which includes invasion beyond the uterus but not extending to the pelvic wall or to the lower third of the vagina. However, radical hysterectomy is not an option for this patient who has bulky disease extending to the pelvic wall (stage III).

There is no benefit to using adjuvant chemotherapy after hysterectomy or to administering chemotherapy prior to surgery. The survival benefit of chemotherapy is proven only when given with concomitant radiation therapy for patients with intermediate- and high-risk cervical cancer.

Patients with stage I cervical cancer may have ovarian preservation if maintaining fertility is desired. For microscopic disease confined to the cervix (stage IA), simple hysterectomy, cone biopsy, or removal of the cervix alone are options, all of which include ovarian preservation.

KEY POINT

- Patients with locally advanced cervical cancer should be treated with radiation therapy and concomitant chemotherapy, as use of chemoradiation is associated with a decrease in local and distant cancer recurrence compared with radiation therapy alone.

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Item 88 Answer: A

Educational Objective: Diagnose immunosuppression-induced non-Hodgkin lymphoma.

This patient, who presents with fixed, palpable lymphadenopathy in multiple sites and systemic B symptoms (night sweats, fever, and weight loss), most likely has non-Hodgkin lymphoma (NHL) associated with immunosuppression due to the long-term administration of infliximab. Viral infections including Epstein-Barr virus, HIV, human T-cell lymphotrophic virus type-1, and hepatitis B and C viruses are all capable of directly driving transformation of lymphoid tissue to lymphoma or contributing indirectly by causing immunodeficiency, a risk factor for lymphoma development. Specific examples include the development of posttransplant lymphoproliferative disorders presenting as high-grade B-cell NHL caused by ongoing immunosuppression with agents such as cyclosporine or tacrolimus to prevent rejection in solid organ transplantation or graft-versus-host disease in allogeneic hematopoietic stem cell transplantation. Excisional biopsy of an adequate tissue sample that preserves the architecture of the lymph node is required for the diagnosis of lymphoma.

Sarcoidosis can present with or without symptoms that include fatigue, weight loss, joint pain, cough, and shortness of breath. Sarcoidosis is believed to be a consequence of an immune reaction to an unknown antigen, and not immunosuppression.

Testicular cancer can occur late in life but usually does not present with fever and night sweats and would not likely be associated with axillary and cervical lymphadenopathy without mediastinal lymphadenopathy.

Tuberculosis occurs more commonly in patients treated with infliximab. A nonreactive tuberculin skin test cannot be used to exclude tuberculosis because of this patient's immunosuppressed state. However, his extensive extra-abdominal lymphadenopathy without mediastinal lymphadenopathy makes tuberculosis unlikely.

KEY POINT

- Patients receiving long-term immunosuppressive therapy are at greater risk for developing non-Hodgkin lymphoma.

Bibliography

Lenz G, Staudt LM. Aggressive lymphomas. N Engl J Med. 2010 Apr 15;362(15):1417-29. [PMID: 20393178]

Item 89 Answer: C

Educational Objective: Treat a patient with spinal cord compression caused by multiple myeloma.

This patient with spinal cord compression should receive immediate administration of intravenous high-dose glucocorticoids to prevent permanent neurologic deficits. This patient has MRI-confirmed spinal cord compression characterized by mid back pain and physical findings of lower extremity hyperreflexia and weakness. His known multiple myeloma with corresponding anemia and hypercalcemia suggest progression of his disease with a plasma cell tumor as the cause of his spinal cord compression. Glucocorticoid therapy is the initial treatment in most cases of malignant spinal cord compression as they decrease inflammation and reduce the mass effect due to edema associated with many tumors. In this case, glucocorticoid therapy has the added benefit of directly treating the hypercalcemia and plasma cell myeloma. Glucocorticoid treatment is then followed with more definitive therapy, often radiation and possible neurosurgical intervention in some cases.

Biopsy of the epidural mass is not necessary because of the patient's known likely causative disease and could delay initiation of glucocorticoids and radiation therapy and increase the risk of permanent nerve damage.

Although neurosurgical intervention consisting of decompressive surgery might be necessary in some patients with spinal cord compression, it would not be appropriate before administration of immediate glucocorticoids.

Definitive treatment with chemotherapy or an immunomodulator may be appropriate but would not have the required immediate effect of glucocorticoids in preventing progressive neurologic damage.

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CONT.

Radiation therapy alone would not address the swelling associated with spinal cord compression nor the hypercalcemia or underlying systemic plasma cell myeloma. However, radiation therapy is often a useful therapy for treating bulky disease.

KEY POINT

- Patients with cancer who develop symptoms of possible spinal cord compression require immediate administration of intravenous high-dose glucocorticoids to prevent permanent neurologic deficits.

Bibliography

Taylor JW, Schiff D. Metastatic epidural spinal cord compression. Semin Neurol. 2010 Jul;30(3):245-53. [PMID: 20577931]

Item 90 Answer: C

Educational Objective: Treat breast cancer with neoadjuvant chemotherapy in a patient who desires breast-conserving surgery.

This patient should receive neoadjuvant trastuzumab-based chemotherapy. Disease-free survival and overall survival are equivalent in patients treated with neoadjuvant and adjuvant chemotherapy. However, neoadjuvant chemotherapy may allow performance of more breast-conserving procedures by decreasing the size of the tumor. In addition, the response to neoadjuvant chemotherapy is predictive of long-term disease-free and overall survival. Cancers with the highest response rate to neoadjuvant chemotherapy are those that are either *HER2* positive or triple-negative tumors (tumors that are negative for estrogen receptor, progesterone receptor, and *HER2* amplification). Patients with these types of cancer can be offered neoadjuvant chemotherapy even if decreasing the tumor size in order to perform breast-conserving surgery is not needed. After neoadjuvant chemotherapy, pathologic complete response, defined as the absence of any residual invasive cancer in the breast or lymph nodes, occurs in up to 60% of patients with *HER2*-positive cancers and up to 40% of those with triple-negative cancers and correlates with an excellent long-term disease-free survival.

The regimens used for neoadjuvant chemotherapy are generally the same as those used for postoperative adjuvant chemotherapy. Patients are closely monitored with breast exams during neoadjuvant chemotherapy to make sure they are responding. Unless a patient has tumor progression or is on a clinical trial assessing the response of a new regimen, all of the chemotherapy is usually completed before surgery. A patient with a *HER2*-positive cancer would receive trastuzumab during the nonanthracycline part of adjuvant chemotherapy, receiving 1 year of trastuzumab in total. Trastuzumab-containing regimens without anthracyclines are an option, particularly for women with a higher risk of cardiomyopathy because of older age or pre-existing hypertension. Pertuzumab is a newly approved anti-*HER2* monoclonal antibody that may be used with trastuzumab and chemotherapy for neoadjuvant treatment of *HER2*-amplified breast cancers that measure 2 cm or more and/or are sentinel lymph node positive. The NeoSphere study demonstrated improved pathologic complete response rates (46% vs 29%) when pertuzumab was added to trastuzumab and docetaxel for *HER2*-amplified breast cancers with these higher risk features.

Immediate mastectomy is not required for this patient, who desires breast conservation and is likely to achieve this goal with neoadjuvant chemotherapy.

Neoadjuvant antiestrogen therapy (for example, with anastrozole) is an option for postmenopausal women with large or locally advanced breast cancers that are hormone receptor positive, particularly patients who are not good candidates for adjuvant chemotherapy because of advanced age or medical comorbidities. However, this therapy is not effective in patients with estrogen receptor-negative cancers.

As this patient does not have any worrisome symptoms or signs suggestive of systemic metastases, she does not need CT or bone scans for staging. Current American Society of Clinical Oncology (ASCO) guidelines recommend against performing PET, CT, or radionuclide bone scans in patients with stages 0 to II breast cancer in the absence of findings that would suggest metastatic disease.

KEY POINT

- Neoadjuvant chemotherapy may be indicated for patients with *HER2*-amplified or triple-negative breast cancers and for patients with larger cancers who desire breast-conserving surgery.

Bibliography

Kaufmann M, Hortobagyi GN, Goldhirsch A, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol. 2006 Apr 20;24(12):1940-9. Erratum in: J Clin Oncol. 2006 Jul 1;24(19):3221. [PMID: 16622270]

Item 91 Answer: A

Educational Objective: Treat metastatic estrogen receptor-positive breast cancer that involves only bone.

Because this patient's metastases involve only bone, her cancer is estrogen receptor positive, and she has had a long disease-free interval, she has a high likelihood of responding to primary antiestrogen therapy with anastrozole. Other aromatase inhibitors such as letrozole or exemestane would be equally effective. Aromatase inhibitors are superior to tamoxifen for first-line treatment of metastatic breast cancer because of improved response rates and disease-free survival. If she becomes resistant to aromatase inhibitor therapy, everolimus is a mammalian target of rapamycin (mTOR) inhibitor that is approved for treatment of metastatic breast cancer in combination with exemestane. If she responds to anastrozole and subsequently develops progressive disease, other antiestrogen agents, including tamoxifen and fulvestrant, could be used sequentially.

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Chemotherapy with agents such as paclitaxel is used instead of antiestrogen therapy for treatment of metastatic breast cancer in patients with hormone receptor–negative disease, those with an impending visceral crisis due to extensive metastases, or those who do not respond to antiestrogen therapy.

Radiation to symptomatic areas of bone metastases is an important palliative treatment. However, patients with asymptomatic or minimally symptomatic bone lesions are not treated with radiation therapy unless bone stability is a concern.

Radium-223 is an alpha particle–emitting isotope that targets bone metastases. It is only used in bone metastases due to castrate-resistant prostate cancer.

KEY POINT

- Patients with estrogen receptor–positive breast cancer who develop metastases limited to bone after a long disease-free interval should be treated initially with an aromatase inhibitor.

Bibliography

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Item 92 Answer: A

Educational Objective: Prevent breast cancer in a patient with atypical ductal hyperplasia.

This patient with atypical ductal hyperplasia (ADH) should be offered breast cancer chemoprophylaxis, with exemestane being the most effective agent for postmenopausal women. ADH is a breast lesion associated with an increased risk of development of breast cancer. Studies have shown a three- to fivefold increased risk of breast cancer after a diagnosis of ADH, with a cumulative incidence at 30 years of 35%. Patients with ADH are candidates for breast cancer chemoprophylaxis. Among the available chemoprophylactic agents, exemestane is associated with the greatest reduction in breast cancer risk. Exemestane is an aromatase inhibitor that prevents conversion of androgens to estrogens and profoundly suppresses estrogen levels in postmenopausal women. The National Cancer Institute of Canada's Exemestane Prophylaxis Study compared administration of exemestane for 5 years with administration of placebo for the same period in patients with a 5-year risk of breast cancer of at least 1.67%. Patients with ADH were included in this study. At a median follow-up of 3 years, there was a 65% relative reduction in the annual incidence of invasive breast cancer in patients taking exemestane. Toxicities included a low incidence of grade 3 arthralgia and hot flushes. There was no difference in the incidence of skeletal fractures or development of osteoporosis, cardiovascular events, or other cancers in patients taking either exemestane or placebo.

Alternate chemoprophylaxis options include tamoxifen and raloxifene. Tamoxifen decreases the risk of breast cancer by 49% though it has a 0.1% risk per year of endometrial cancer and a 1% risk of vascular events including venous thrombosis and strokes. Raloxifene does not increase the risk of endometrial cancer and has a 25% lower risk of vascular events. It is less effective than tamoxifen, retaining 76% of the benefit of tamoxifen, but is an option in patients who want to decrease toxicities. All three chemoprophylaxis agents (tamoxifen, raloxifene, and exemestane) can be used in postmenopausal women but only tamoxifen is an option in premenopausal or perimenopausal women.

Vitamin D supplementation is being studied for breast cancer prevention, but any benefits are currently unclear. Some studies have shown a mild decrease in breast cancer risk in persons with normal serum vitamin D levels compared with those having low levels, whereas other studies have found no benefit.

Bilateral prophylactic mastectomy is an option for women with a high risk of breast cancer due to inherited syndromes, such as women with *BRCA1/2* mutations, but is not appropriate for women with atypical lesions such as atypical hyperplasia or lobular neoplasia.

Continuing hormone replacement therapy will increase the risk of breast cancer and prevent chemoprophylactic medications such as tamoxifen, raloxifene, and exemestane from decreasing this risk.

KEY POINT

- Patients with newly diagnosed atypical ductal hyperplasia should be offered breast cancer chemoprophylaxis; exemestane is associated with the greatest reduction in breast cancer risk.

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Goss PE, Ingle JN, Alés-Martinez JE, et al; NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011 Jun 23;364(25):2381-91. Erratum in: N Engl J Med. 2011 Oct 6;365(14):1361. [PMID: 21639806]

Item 93 Answer: A

Educational Objective: Manage postoperative surveillance for a patient with stage III colon cancer.

This patient has completed therapy for high-risk stage III colon cancer, and postoperative surveillance should include physical examination and serum carcinoembryonic antigen measurement every 3 to 6 months, as well as CT scans of the chest and abdomen (and pelvis for patients with rectal cancer) annually for 3 to 5 years. Colonoscopy, if done preoperatively, should be performed 1 year after resection and then repeated at 3- to 5-year intervals. Because this patient was unable to undergo colonoscopy preoperatively, this procedure should be performed initially 6 months after surgery. Postoperative surveillance is done to identify patients with relapse of colorectal cancer that is potentially curable by surgery. The risks of radiation exposure and false-positive findings leading to additional tests and possibly invasive procedures must be balanced against the benefits of surveillance studies.

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Routine CT scans annually for 10 years is not indicated because most colorectal cancers recur within the first 3 years after surgery, and scanning beyond 3 to 5 years is therefore not warranted.

PET scans may be useful adjuncts to evaluate equivocal abnormalities seen on CT scans; however, they are not recommended for routine surveillance following resection of colorectal cancer and should not be used for this purpose.

A 2007 Cochrane review of follow-up strategies for patients treated for nonmetastatic colorectal cancer concluded that there is an overall survival benefit by intensifying the follow-up of patients after curative surgery, but because of the wide variations in follow-up programs included in the analysis, no conclusion could be drawn about the best combination and frequency of procedures and tests to maximize benefits and minimize harms. However, the results of this review imply that some intensity of surveillance is more beneficial than observation alone.

KEY POINT

- Postoperative surveillance for patients with colorectal cancer includes physical examination and serum carcinoembryonic antigen measurement every 3 to 6 months, and CT scans of the chest and abdomen (and pelvis for patients with rectal cancer) annually for 3 to 5 years; colonoscopy, if done preoperatively, should be performed 1 year after resection and then repeated at 3- to 5-year intervals.

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Meyerhardt JA, Mangu PB, Flynn PJ, et al; American Society of Clinical Oncology. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol. 2013 Dec 10;31(35):4465-70. [PMID: 24220554]

Item 94 Answer: B

Educational Objective: Recognize the risk of treatment-related complications following therapy for testicular cancer.

This patient is most likely to develop metabolic syndrome. Following treatment of testicular germ cell tumors, men remain at risk for both recurrent cancer and many other long-term medical complications. Although some complications occur during or soon after treatment, others develop years after initial therapy, particularly as many patients are relatively young at the time of diagnosis. The risks for an individual patient are associated with the type of treatment given. Both radiation therapy and chemotherapy are associated with specific risks. Among these is an increased risk for development of metabolic syndrome (insulin resistance, hypertension, dyslipidemia, abdominal obesity). The risk is particularly increased in men treated with combination chemotherapy. Data indicate that the risk for cardiovascular diseases (such as ischemic coronary disease, heart failure, peripheral vascular disease) is also increased in this patient population. Additional risks associated with treatment of testicular cancer that would be relevant to this specific patient include kidney disease, peripheral neuropathy, chronic pulmonary toxicity, secondary malignancy, and sexual dysfunction. Most of these would be evident either during or soon after completion of treatment. Secondary malignancy typically develops years following treatment.

The risk of gastric and duodenal ulcer disease is increased slightly in men treated with radiation therapy, which this patient did not have.

Obstructive uropathy is only rarely associated with treatment of testicular cancer, and that association occurs only in men treated with radiation therapy.

The risk of secondary solid tumors is increased in patients treated for testicular cancer, with the most common sites of involvement being the lung, colon, bladder, pancreas, and stomach. Soft tissue sarcomas are not commonly reported in these patients in the absence of radiotherapy, which is known to increase the risk of soft tissue sarcoma, typically diagnosed many years after treatment. As the patient in this case was not treated with radiation, he would not be expected to have an increased risk of soft tissue sarcoma.

KEY POINT

- Treatment-related complications in men who had therapy for testicular cancer include cardiovascular disease (specifically metabolic syndrome), kidney disease, peripheral neuropathy, chronic pulmonary toxicity, secondary malignancy, and sexual dysfunction.

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Item 95 Answer: D

Educational Objective: Treat diffuse large B-cell lymphoma with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

Standard therapy for all patients with diffuse large B-cell lymphoma (DLBCL), regardless of disease stage or prognosis, includes rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Acceptable management includes chemotherapy alone or a shorter course of chemotherapy with involved-field radiation in early stage disease. The lymphomas are of B-cell or T-cell phenotype. DLBCL is the most common form of lymphoma and, together with the less common T-cell phenotype, represents 30% of all lymphomas. Most patients with DLBCL present with advanced (stage III and IV) disease and have symptoms including fever, night sweats, and weight loss ("B" symptoms). Disease progression is rapid without therapy. The revised International Prognostic Index (r-IPI) score was developed to assist in determining prognosis before therapy. The r-IPI score is based on the patient's age, serum lactate dehydrogenase level, number of extranodal sites, disease stage, and performance status.

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Because this patient has limited disease and a low r-IPI score, standard R-CHOP chemotherapy should result in a durable complete remission. Expected cure rates range from less than 20% for patients with advanced disease and a high r-IPI score to greater than 80% for those with localized disease and a low r-IPI score. Studies are ongoing regarding the effectiveness of more aggressive initial therapy for patients with advanced disease associated with high r-IPI scores, such as using rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyper-CVAD) and adding novel agents, including immunomodulators such as lenalidomide. However, standard R-CHOP chemotherapy is appropriate for this patient at this time.

Allogeneic hematopoietic stem cell transplantation (HSCT) remains investigational as salvage therapy for patients with DLBCL due to the high risk of morbidity.

Autologous HSCT is reserved as salvage therapy for patients who have chemotherapy-sensitive relapsed disease associated with a greater than 1-year disease-free interval from the start of initial therapy. Early relapse patients have poor outcomes after autologous HSPCT and should be considered for clinical trials.

Involved-field radiation therapy is indicated for patients with bulky disease. This patient has no evidence of bulky disease at this time.

KEY POINT

- Standard therapy for all patients with diffuse large B-cell lymphoma, regardless of disease stage or prognosis, is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

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Item 96 Answer: A

Educational Objective: Manage metastatic melanoma with *BRAF* V600 mutation analysis.

The most appropriate next step in management is *BRAF* V600 mutation analysis. Approximately 50% to 70% of cutaneous melanomas carry mutations in *BRAF*, a gene coding for a protein that leads to tumor activation though the mitogen-activated protein kinase (MAPK) pathway; 80% to 90% of these are the V600E mutation, with the remainder being other mutations at the V600 position. Inhibitors of *BRAF* are associated with response rates of over 50% and improved overall and progression-free survival in metastatic melanoma with a V600 mutation. Therefore, all patients with metastatic melanoma should have their tumor tested for the presence of driver V600 *BRAF* mutation to determine whether treatment with a *BRAF* inhibitor is a therapeutic option. Vemurafenib and dabrafenib are the available *BRAF* inhibitors. These agents have a rapid onset of action and are preferred over immunotherapy for initial treatment in patients with poor risk characteristics, including visceral metastases to sites other than the lung, an elevated serum lactate dehydrogenase, or a poor performance status. If a V600 mutation is present in this patient with liver metastases and an elevated serum lactate dehydrogenase, treatment with a *BRAF* inhibitor should be offered as a treatment option.

Chemotherapy with dacarbazine, the only chemotherapeutic agent approved for treatment of metastatic melanoma, has a response rate of only 7% to 12% and has not been shown to improve overall survival. It is usually reserved for patients who are not candidates for high-dose interleukin-2 (IL-2), ipilimumab, or *BRAF* inhibitor therapy.

High-dose interferon alfa is used as adjuvant therapy for patients with nonmetastatic melanoma who are at high risk for recurrence but is inferior to other immunotherapy options, including ipilimumab and high-dose IL-2, for patients with metastatic melanoma.

Ipilimumab is a monoclonal antibody that targets cytotoxic T-lymphocyte antigen-4 (CTLA-4), which is a normal immune checkpoint molecule that down-regulates pathways of T-cell activation. CTLA-4 inhibition unleashes an immune response against the tumor. In patients with metastatic melanoma, treatment with ipilimumab improves overall survival. However, the response to ipilimumab can be delayed and there can be transient worsening of disease initially. In patients with poor prognostic features and a *BRAF* V600 mutation, the more rapid response of a *BRAF* inhibitor is preferred. If this patient's melanoma does not have a driver *BRAF* mutation, then treatment with ipilimumab would be offered.

KEY POINT

- All patients with metastatic melanoma should have their tumor tested for the presence of a driver V600 *BRAF* mutation. If this mutation is present in patients with poor prognostic features, treatment with a *BRAF* inhibitor is recommended as initial therapy.

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Item 97 Answer: E

Educational Objective: Treat oligometastatic colorectal cancer by surgical resection.

Right hepatectomy is most appropriate for this patient who underwent primary resection for stage II colon cancer 3 years ago and now has three new liver lesions in a surgically resectable pattern. The role of monitoring patients after initial resection is to detect recurrent, surgically curable tumors, such as oligometastatic liver or lung metastases, and monitor for the development of new primary cancer. Monitoring typically includes a physical examination and measurement of serum carcinoembryonic antigen levels every 3 to 6 months for the first 3 years and every 6 months

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during years 4 and 5. Surveillance CT scans of the chest and abdomen are recommended annually for at least the first 3 years postoperatively. This patient has oligometastatic disease that is potentially curable by surgical resection and should undergo right hepatectomy.

A needle biopsy is not indicated. The clinical presentation is so strongly indicative of metastatic colorectal cancer that a negative needle biopsy would not exclude the diagnosis of cancer and would therefore not alter management. Surgical resection would be warranted regardless of the biopsy results.

Hepatic artery embolization is a palliative technique used to treat patients with more vascular tumors, such as hepatocellular carcinoma and neuroendocrine tumors. It is not routinely used for treatment of metastatic colorectal cancer and would not be an appropriate consideration when a potentially curative alternative such as surgery is available.

Given that this patient's liver metastases are potentially curable, palliative chemotherapy is not indicated.

Radiation therapy is not routinely used to treat liver metastases and would also not be an appropriate consideration for a patient who is a candidate for potentially curative surgery.

KEY POINT

- The development of oligometastatic disease (usually to the liver or lung) in a patient who previously was treated for colorectal cancer is potentially curable by surgical resection.

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Item 98 Answer: C

Educational Objective: Determine preoperative staging for a patient with newly diagnosed colorectal cancer.

Contrast-enhanced CT scanning of the chest, abdomen, and pelvis is the preferred study for preoperative staging of patients with newly diagnosed colorectal cancer. This provides the most reliable means of detecting the presence of metastatic disease to the lungs, liver, intra-abdominal lymph nodes, and peritoneum, which are the most common sites of metastatic spread, and is useful in planning appropriate therapy.

A bone scan is not indicated at this time. Although bone metastases may be present in patients with several other types of cancer at presentation, this finding is extremely rare in patients with newly diagnosed colorectal cancer. Up to 10% of patients with colorectal cancer may develop bone metastases as a late complication of advanced metastatic disease, but evaluation at the time of diagnosis in the absence of specific and compelling symptoms is not warranted.

CT colonography appears to be an acceptable alternative to colonoscopy for screening of otherwise low-risk healthy individuals; however, this study is not part of the staging work-up for a patient with a known cancer diagnosis.

PET/CT scans have not been shown to improve the accuracy of preoperative staging for patients with colorectal cancer and are not recommended for either preoperative staging or postoperative surveillance.

KEY POINT

- Contrast-enhanced CT scanning of the chest, abdomen, and pelvis is the preferred study for preoperative staging of patients with newly diagnosed colorectal cancer.

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Item 99 Answer: B

Educational Objective: Treat acute tumor lysis syndrome with high-volume normal saline hydration and rasburicase.

This patient requires treatment with high-volume normal saline and rasburicase because he has spontaneous tumor lysis syndrome triggered by rapid cell turnover from his acute myelogenous leukemia. Malignancies associated with rapid cell turnover can release large quantities of electrolytes and procoagulants into the circulation, causing the potentially life-threatening complication of tumor lysis syndrome. Tumor lysis syndrome may occur spontaneously with some cancers, but most often occurs after the initiation of cytotoxic therapy for tumors with a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic agents. Therefore, treatment aimed at preventing tumor lysis syndrome should be considered prior to starting chemotherapy in patients at high risk. In tumor lysis syndrome, rapid cell breakdown results in hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and disseminated intravascular coagulation (DIC). Hyperuricemia can lead to urate nephropathy and acute kidney injury. Prevention or treatment involves aggressive hydration with normal saline to maintain renal perfusion and minimize uric acid or calcium phosphate deposition in the renal tubules. Because this patient already has evidence of kidney failure, hydration must be undertaken carefully to prevent significant volume overload. Hypouricemic agents are also indicated. Allopurinol is a competitive inhibitor of xanthine oxidase, which decreases the formation of new uric acid. Rasburicase is a urate oxidase (uricase) that catalyzes the breakdown of existing uric acid. Allopurinol is typically used in patients for prophylaxis for tumor lysis syndrome and in those without existing significant (>8 mg/dL [0.47 mmol/L]) elevations of serum urate. The more expensive rasburicase is usually used in patients with significantly elevated serum urate levels or in those with baseline kidney failure or in those with

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evidence of kidney injury related to tumor lysis, in order to rapidly decrease the serum urate level.

Fresh frozen plasma may be indicated if the patient develops DIC after initiating chemotherapy with resultant depletion of procoagulant. However, fresh frozen plasma would not treat tumor lysis syndrome and is only indicated when DIC is present. Based on this patient's normal serum fibrinogen level, this patient does not have DIC.

The initiation of multiagent chemotherapy prior to aggressive hydration and treatment with rasburicase is contraindicated in this patient who has acute kidney failure, likely due to tumor lysis syndrome, to prevent life threatening electrolyte abnormalities (such as hyperkalemia) associated with chemotherapy.

Platelet transfusions are indicated only for patients whose platelet count is less than 10,000/μL (10×10^9/L) or who develop spontaneous bleeding.

KEY POINT

- Patients with spontaneous tumor lysis syndrome in the setting of newly diagnosed leukemia or lymphoma should be emergently treated with high-volume normal saline prior to initiation of chemotherapy; rasburicase should also be administered in the case of kidney failure.

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Item 100 Answer: C

Educational Objective: Manage preservation of fertility in a patient about to start chemotherapy for stage II breast cancer.

Embryo cryopreservation or other fertility preservation methods before chemotherapy should be recommended to this patient who wishes to have additional children. She has stage II breast cancer that is hormone receptor positive and *HER2* positive. Adjuvant chemotherapy with trastuzumab should be started within 4 to 6 weeks of surgery. Although infertility effects of chemotherapy are age-, dose-, and drug-dependent, with younger women being affected less often than older women, patients of any age can become infertile, particularly after taking cyclophosphamide. Starting adjuvant chemotherapy and trastuzumab now will result in infertility in a significant percentage of women and is not the best option for this patient who desires continued fertility.

Fertility preservation is almost always done with the assistance of a fertility specialist with expertise in fertility preservation procedures and can usually be completed within a few weeks. An established fertility preservation option for a woman with a partner is in vitro fertilization with embryo freezing. Newer options, often done as part of clinical trials, include freezing of unfertilized eggs and ovarian cryopreservation with future reimplantation.

Trastuzumab does not cause infertility. It is the chemotherapy itself that can result in premature menopause and infertility. Adding trastuzumab to chemotherapy as adjuvant treatment for *HER2*-positive breast cancer decreases the risk of recurrence by 50% and should be included in this patient's adjuvant regimen.

Delaying chemotherapy until after the patient completes further childbearing will result in a higher risk of distant recurrence and is not a safe option. Studies evaluating the ideal sequence of adjuvant chemotherapy and primary breast radiation showed that giving chemotherapy after radiation was associated with a higher risk of systemic recurrence. Based on these studies, a delay of more than 12 weeks in starting adjuvant chemotherapy may be detrimental and should be avoided.

There is no reason to recommend against future pregnancies in this patient. Several large retrospective studies have shown that breast cancer recurrence is not increased and survival is not decreased in breast cancer survivors who become pregnant, including patients with hormone receptor-positive cancers.

KEY POINT

- Women being treated for breast cancer who wish to preserve fertility should be referred to a fertility specialist to discuss embryo cryopreservation or other fertility preservation methods before adjuvant chemotherapy is initiated.

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Item 101 Answer: A

Educational Objective: Treat adenocarcinoma of unknown primary site predominantly below the diaphragm in the same manner as a gastrointestinal malignancy.

This patient should be treated for a gastrointestinal malignancy. He has a moderately differentiated adenocarcinoma of unknown primary site, with most of the disease occurring below the diaphragm. When adenocarcinoma of unknown primary site presents in a pattern predominantly below the diaphragm, even when upper endoscopy and colonoscopy findings are normal, empiric treatment for a gastrointestinal malignancy is appropriate.

Platinum-based chemotherapy regimens such as carboplatin plus paclitaxel or cisplatin plus etoposide would be reasonable for treating patients with a poorly differentiated cancer of unknown primary site (CUP), such as a germ cell (testicular) tumor. This patient's biopsy findings, which show adenocarcinoma with moderately differentiated histology, do not support empiric treatment for germ cell cancer.

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Empiric lung cancer regimens may be used to treat patients with CUP occurring above the diaphragm. Because this patient has no evidence of involvement of the lungs, treatment using a lung cancer paradigm is not indicated.

Platinum-based chemotherapy regimens such as carboplatin plus paclitaxel or cisplatin plus etoposide would be reasonable for treating patients with a poorly differentiated neuroendocrine CUP. However, this patient's biopsy findings do not support a diagnosis of neuroendocrine cancer.

Antiandrogen therapy, which may have potential activity against prostate cancer, may be considered in male patients with extensive bone metastases, but that is not the case in this patient.

KEY POINT

- When adenocarcinoma of unknown primary site presents in a pattern predominantly below the diaphragm, even when upper endoscopy and colonoscopy findings are normal, empiric treatment for a gastrointestinal malignancy is appropriate.

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Item 102 Answer: E

Educational Objective: Treat a patient with asymptomatic, nonbulky follicular lymphoma.

Observation is most appropriate for this 60-year-old asymptomatic patient with follicular lymphoma who has nonbulky disease, no vital organ involvement or impingement, and a normal complete blood count. Follicular lymphoma accounts for 20% of all cases of non-Hodgkin lymphoma (NHL) in the United States and Europe and 70% of all indolent NHL, ranking second in incidence to diffuse large-cell lymphoma (30%). It is characterized by surface B-cell markers (CD10, 19, 20, and 22) and small cells on morphologic analysis. The incidence increases with age, and the median age at presentation is 60 years. There is no sex predilection. Diagnosis is confirmed by biopsy of palpable lymph nodes and cytogenetic studies showing a translocation [t(11:18)] that causes overexpression of the *BCL2* oncogene. Therapy is not curative, and early initiation of treatment does not improve survival in patients with grade 1 and 2 follicular lymphoma. Treatment is therefore withheld until patients become symptomatic. Some patients do not require therapy for several decades after the initial diagnosis.

Lenalidomide, used in combination with rituximab, is a new therapy that may be effective for patients with advanced symptomatic disease, which this patient does not have.

Systemic disease–causing symptoms require multiagent therapy that traditionally includes one of three combinations: (1) rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); (2) rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP); or (3) rituximab plus bendamustine. Radioimmunoconjugates (tositumomab and ibritumomab) have been used effectively to induce long-term remissions. Any of these approaches are suitable for patients requiring treatment.

Lymphoma causing localized symptoms can be treated effectively with involved-field radiation therapy in combination with rituximab, but such treatment is not yet needed for this patient.

KEY POINT

- Early treatment does not improve survival in patients with grade 1 and 2 follicular lymphoma.

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Item 103 Answer: B

Educational Objective: Diagnose human papillomavirus infection in a patient with head and neck cancer.

The most appropriate study to perform next in this patient is p16 immunohistochemistry testing. Although most squamous cell carcinomas of the head and neck were previously thought to be related primarily to tobacco and alcohol exposure, very recently, the important causative role played by human papillomavirus (HPV) has been widely recognized. HPV infection has definitively been associated with squamous cell carcinoma of the cervix for some time, and currently, it is estimated that most oropharyngeal cancers in North America and Europe are also linked to this infection. Evidence of underlying HPV infection is identified by testing for p16, which is a viral protein found in cancers that arise as a result of HPV infection. Although identifying evidence of HPV infection does not yet influence treatment decision-making, it does provide very important information regarding prognosis. The cure rate for locally advanced cancers that are linked with HPV is markedly higher than for those not linked with this virus. Because of this difference, testing for HPV is now a widely accepted intervention for any patient diagnosed with squamous cell carcinoma of the head and neck, particularly for patients with an oropharyngeal primary tumor.

A bone scan has no role in the management of this patient, as PET/CT scans have already been done. In addition, she has no indications for underlying bone metastasis based on her history.

MRI of the brain is not indicated because occult central nervous system metastases are very rare in patients with head and neck cancer, and this patient has no clinical indication of underlying brain metastasis.

Biopsy of the enlarged right cervical lymph node would provide no additional information, as the diagnosis has already been established based on biopsy of the lesion at the base of the tongue. Furthermore, because the cervical lymph node is so markedly enlarged, biopsy is not needed to establish involvement.

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KEY POINT

- p16 immunohistochemistry testing to detect human papillomavirus is now a widely accepted standard-of-care intervention to help determine prognosis in patients with squamous cell carcinoma of the head and neck, particularly those with oropharyngeal primary tumors.

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Item 104 Answer: A

Educational Objective: Manage a patient with lung cancer and superior vena cava syndrome.

Biopsy of the lung mass to obtain a histologic diagnosis is indicated. This patient has superior vena cava (SVC) syndrome, which is caused by inhibition of blood flow through the SVC or one of its major tributaries. The syndrome may occur in patients with both malignant and nonmalignant conditions. Cancers more commonly associated with SVC syndrome include lung cancer (both small cell and non-small cell lung cancer accounting for 65% of cases), aggressive lymphoma, thymoma, and primary mediastinal germ cell tumors. Nonmalignant causes include thrombosis and fibrosing mediastinitis. Presenting symptoms typically develop over weeks and include dyspnea, facial swelling, headache, and in more severe cases, stridor or mental status changes. The most common radiographic findings include mediastinal widening and pleural effusion; however, 16% of patients have a normal chest radiograph. Although in the past emphasis was placed on immediate treatment, current management emphasizes the importance of obtaining a histologic diagnosis, whenever possible, in patients with apparent malignant SVC syndrome. This allows for accurate decision-making regarding treatment of the underlying malignancy. Mediastinoscopy is routinely used to obtain tissue biopsy samples for histologic diagnosis. The complication rate from this procedure is only 5% in patients with SVC syndrome. Percutaneous transthoracic CT-guided needle biopsy appears to be a safe alternative to mediastinoscopy and has a sensitivity of 75%.

Although the patient clearly has SVC syndrome, he does not have stridor, laryngeal edema, or mental status decline. Immediate radiation therapy or stent placement is therefore not indicated.

Venography to identify a possible thrombosis is not indicated because the SVC syndrome in this patient is caused by external compression from a mediastinal mass and lymphadenopathy rather than by a thrombotic disorder.

KEY POINT

- In patients with apparent malignant superior vena cava syndrome, a histologic diagnosis should be established, whenever possible, before treatment is begun.

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Item 105 Answer: D

Educational Objective: Manage aromatase inhibitor arthralgia in a patient with aggressive breast cancer who requires antiestrogen therapy.

This patient should be started on tamoxifen. She has aggressive stage IIIA breast cancer with four positive axillary lymph nodes. With adjuvant chemotherapy alone, she remains at high risk for recurrence and should receive at least 5 years of antiestrogen therapy, ideally with at least 2 years of an aromatase inhibitor, if tolerated. As aromatase inhibitors may be associated with debilitating musculoskeletal symptoms, such as arthralgia in this patient, these agents should be discontinued if patients cannot tolerate them and tamoxifen should be started as an alternative antiestrogen therapy.

Approximately one third of patients taking aromatase inhibitors develop intolerable adverse effects that lead to discontinuation of these agents. In one study, 22% of all patients stopped taking these drugs following development of the aromatase inhibitor–induced arthralgia syndrome (AIIAS). Predictors of AIIAS include younger age, prior taxane chemotherapy, and a history of pre-existing joint pain. The cause of the musculoskeletal symptoms, which can occur in the upper or lower extremities, is unknown. This patient's symptoms of joint pain that are symmetric, bilateral, and worse when lying down or sitting are very typical of AIIAS.

Her symptoms are not concerning for metastases, especially because the arthralgia resolved when aromatase inhibitors were discontinued. Therefore, a PET scan is not indicated at this time.

For patients whose aromatase inhibitor–induced arthralgia does not respond to NSAIDs, treatment with duloxetine has been of benefit in clinical trials and is under further study. There is no known benefit to using prednisone for AIIAS. The Hormones and Physical Exercise (HOPE) trial showed that a regular exercise program can ameliorate arthralgia caused by aromatase inhibitors.

Restarting anastrozole will almost certainly cause the same intolerable arthralgia and is therefore not indicated. In one prospective trial of patients with AIIAS, stopping the initial aromatase inhibitor for 2 to 8 weeks and then switching to an alternate aromatase inhibitor resulted in 40% of patients being able to continue with the alternate agent. No studies to date support recommending a third attempt at use of aromatase inhibitor therapy.

KEY POINT

- In patients with aggressive breast cancer who develop severe arthralgia while on antiestrogen therapy due to an aromatase inhibitor, a second aromatase inhibitor should be tried; if the arthralgia fails to resolve, tamoxifen should be started.

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Item 106 Answer: A

Educational Objective: Manage metastatic colorectal cancer with K-*ras* and N-*ras* genotyping of the tumor.

This patient has metastatic colorectal cancer, and K-*ras* and N-*ras* genotyping of the tumor biopsy sample is necessary for treatment planning. The presence of multiple lung and liver metastases is not amenable to surgical resection and, as such, is incurable. In these cases, the goal of treatment is to extend survival and palliate symptoms. The increased number of chemotherapy options that are effective against metastatic colorectal cancer has prolonged median survival for patients with incurable disease from a median survival of 6 months without chemotherapy, to 12 months with 5-fluorouracil alone, to approximately 2 years with multiagent chemotherapy. This patient will likely benefit from systemic chemotherapy; the use of multiple chemotherapy agents can be anticipated, and all agents with demonstrated activity in colorectal cancer need to be considered. One consideration in planning treatment is determining whether the epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab can be included in the treatment plan. Approximately 50% of colorectal cancers have a mutation in the K-*ras* or N-*ras* genes. Tumors that carry these mutations will not respond to anti-EGFR agents, and patients with these tumors are therefore not candidates for treatment with these drugs.

Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme in the catabolism of 5-fluorouracil. Although assays are commercially available to measure DPD levels, these assays do not inform management and have no role in the routine treatment of patients with colorectal cancer at this time.

Patients with specific *UGT1A1* polymorphisms are more prone to irinotecan toxicity. Although commercial assays are also available to detect this polymorphism, they also do not inform management and are not indicated when treating patients with colorectal cancer at this time.

Multigene array prognostic assays are commercially available but also do not guide clinical decision making and therefore are not currently part of the routine management of patients with colorectal cancer.

KEY POINT

- Mutations in the K-*ras* or N-*ras* genes, present in approximately 50% of colorectal cancers, are associated with resistance to epidermal growth factor receptor–targeted agents (cetuximab, panitumumab).

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Item 107 Answer: E

Educational Objective: Determine need for diagnostic imaging studies in a patient with low-risk prostate cancer.

No imaging studies are indicated at this time. The United States Preventive Services Task Force has concluded that the harms of screening for prostate cancer outweigh the benefits in men of any age regardless of risk factors. In contrast, the American Cancer Society and American Urological Association recommend offering both serum prostate-specific antigen (PSA) measurement and digital rectal examination to men annually beginning at the age of 50 years. The American College of Physicians and American Academy of Family Physicians both recommend that clinicians have individualized discussions with their patients regarding obtaining PSA measurements and support measuring PSA levels after such discussions in patients 50 years and older who have life expectancies of at least 10 years. This patient has low-risk prostate cancer based on the presence of a TNM stage T1c tumor (identified after an elevated screening serum PSA level is found in the absence of symptoms), a serum PSA level less than 10 ng/mL (10 µg/L), and a Gleason score less than 8. Imaging studies are currently not recommended for men with low-risk disease, as there is no evidence that such studies reliably alter management decisions.

Prostate cancer is among the most commonly diagnosed cancers in men in the United States. Most men are diagnosed with clinically occult cancer, which is identified on the basis of an abnormal serum PSA value. Most often, there are no symptoms or indicative physical findings as in the patient described here. Once the diagnosis of prostate cancer is made, the focus moves to assessment and treatment decision making. The role of imaging studies in men diagnosed with prostate cancer is to assess disease status, particularly the presence of metastatic disease. Imaging studies are indicated to evaluate symptoms suggestive of metastatic disease and also to evaluate patients at high risk for occult metastatic disease. Currently accepted parameters for imaging studies include a serum PSA level of 20 ng/mL (20 µg/L) or higher, a PSA level of 10 ng/mL (10 µg/L) or higher associated with a T2 tumor, a Gleason score of 8 or higher, or a T3 or T4 tumor.

KEY POINT

- Imaging studies are not indicated for men with newly diagnosed early-stage prostate cancer in the absence of symptoms or other high-risk features.

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Item 108 Answer: C

Educational Objective: Treat a patient with a newly diagnosed intermediate-thickness melanoma.

Sentinel lymph node biopsy is recommended for patients with melanomas of 1- to 4-mm thickness to provide

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accurate staging. It is also recommended for lesions less than 1 mm with certain high-risk features, such as ulceration, more than 1 mitosis/mm^2, or lymphovascular invasion. A 2-cm excision margin is appropriate for melanomas that are 1 mm thick or deeper. Metastasis to regional lymph nodes is the most important prognostic factor in early-stage melanoma and is found in 20% of patients with intermediate-thickness melanomas. Patients with intermediate-thickness melanomas have an average 5-year survival of 70% if lymph nodes are negative but only 45% if positive lymph nodes are present. If a positive sentinel lymph node is found, complete lymphadenectomy is recommended, which improves regional disease control. However, it is not known whether this procedure improves overall survival.

Adjuvant chemotherapy is not of benefit in treating melanomas. Palliative chemotherapy can be used for metastatic melanomas, although immunotherapy or targeted treatments offer improved efficacy and are usually recommended instead for advanced disease.

Whether to recommend adjuvant interferon alfa is guided by lymph node status. Adjuvant interferon alfa is an option for patients with positive lymph nodes and/or melanomas that are 4 mm or more thick. In these high-risk patients who have a 25% to 75% risk of dying of metastatic melanoma, adjuvant interferon alfa improves relapse-free survival, with less clear benefit for overall survival. Adjuvant interferon alfa would only be recommended for this patient if lymph node involvement is present.

A meta-analysis showed an improvement in disease-free and overall survival with adjuvant interferon alfa. However, in one of the largest trials, the improvement in overall survival was lost with more prolonged follow-up. Given the toxicities of interferon alfa, including fatigue, myalgia, fever, depression, and autoimmune disease, participation in clinical trials of newer agents is encouraged as an alternative option. Observation alone is also reasonable.

Because of important staging and prognostic information, as well as guidance for potential additional treatment options obtained from a sentinel lymph node biopsy in patients with intermediate-thickness melanoma, performing no further testing would be inappropriate.

KEY POINT

- Sentinel lymph node biopsy is recommended for patients with melanomas of 1- to 4-mm thickness to provide accurate staging, as metastasis to regional lymph nodes is the most important prognostic factor in patients with early-stage melanoma.

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Item 109 Answer: B

Educational Objective: Understand chemotherapy terminology.

This patient should receive conversion chemotherapy for his currently unresectable tumor. Conversion chemotherapy is given for the purpose of shrinking a tumor that is unresectable usually due to its location, often because of proximity to significant vascular structures as in this patient. Through shrinkage of the tumor with conversion chemotherapy, an adequate plane of resection between the tumor and the middle hepatic vein may become available, allowing complete removal of the tumor. This is particularly important in this patient with localized metastatic colon cancer. Although metastatic colorectal cancer is generally considered treatable but not curable, some patients with metastatic disease confined to a single organ (usually the liver or lung) may be amenable to surgical resection, and complete removal of all gross disease may be curative. Patients with a limited number of liver-only lesions, such as this patient, have been reported to have long-term disease-free survival rates of 25% to 50%.

Adjuvant chemotherapy is the term used for treatment given *after* resection of a tumor is performed with curative intent. The purpose of adjuvant chemotherapy is to eradicate any residual microscopic metastatic disease that might still be present outside of the surgical field. Adjuvant chemotherapy would not be possible in this patient with currently unresectable disease.

Neoadjuvant chemotherapy is similar to adjuvant chemotherapy in that it is given in the setting of curative-intent surgery; however, neoadjuvant therapy is given *before* surgery in an attempt to eradicate any unseen micrometastases that might be present outside of the surgical field. Although neoadjuvant chemotherapy may have the effect of tumor shrinkage, it differs from conversion chemotherapy in that it is given in patients who have resectable disease preoperatively.

Palliative chemotherapy is given to a patient with incurable, unresectable cancer and is given without realistic curative intent. Palliative chemotherapy may be administered for the purposes of possibly prolonging survival and/or controlling tumor-related symptoms.

Because chemotherapy may increase the opportunity for cure in this clinical setting, it would be inappropriate to not offer this treatment option.

KEY POINT

- Conversion chemotherapy is given to patients with unresectable tumors in an attempt to shrink the tumor to a resectable size. Neoadjuvant and adjuvant chemotherapies are given before or after curative-intent surgery, respectively, for tumors that are resectable at presentation.

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Item 110 Answer: A

Educational Objective: Treat women with abdominal carcinomatosis of unknown primary site in the same manner as ovarian cancer.

Cytoreductive surgery followed by systemic chemotherapy is most appropriate in this patient with abdominal carcinomatosis due to cancer of unknown primary site (CUP). When evaluating a patient with CUP, it is important to identify whether the CUP is of a favorable or unfavorable prognostic subgroup to help guide management. Women with CUP presenting as abdominal carcinomatosis and ascites are classified as a favorable prognostic subgroup and should be assumed to have ovarian cancer until proved otherwise. Treatment is the same as for primary ovarian cancer and includes cytoreductive surgery (tumor debulking along with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, selective lymphadenectomy, and appendectomy, as well as administration of a platinum/taxane-containing chemotherapy regimen).

Ovarian cancer is unique in that its spread is mostly confined to the peritoneal cavity. The use of adjuvant intraperitoneal chemotherapy plus intravenous chemotherapy offers a survival advantage to intravenous chemotherapy alone. However, this survival advantage is associated with substantially increased toxicity. Combined intraperitoneal and intravenous chemotherapy without cytoreduction surgery is not adequate therapy for patients with CUP presenting as ovarian cancer–like disease.

Radiation therapy and concurrent chemotherapy are recommended for patients with stage IB through stage IV cervical cancer, as large randomized clinical trials have confirmed a survival advantage with this combined approach. This approach is not effective for patients with peritoneal carcinomatosis and ascites.

Systemic chemotherapy without cytoreductive surgery would be inadequate as the initial treatment of a patient with an ovarian cancer–like presentation.

Because this patient has a significant chance of meaningful benefit from treatment and has no comorbidities, providing only supportive care would be inappropriate.

KEY POINT

- Women with cancer of unknown primary site presenting as abdominal carcinomatosis and ascites are classified as a favorable prognostic subgroup and should be treated as if they have ovarian cancer.

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Item 111 Answer: B

Educational Objective: Treat recurrent superficial bladder cancer with cystectomy.

Cystectomy without prior chemotherapy is most appropriate for this patient who has superficial bladder cancer. Superficial bladder cancer is the most common form of bladder cancer and is characterized by cancer cells confined to the mucosa, with no evidence of invasion into the muscle layer of the bladder. It is best managed by transurethral resection of the bladder tumor (TURBT), followed in most patients by either bacillus Calmette-Guérin (BCG) or mitomycin infused directly into the bladder. Although this treatment is effective in eradicating superficial bladder cancer, recurrences are common. Careful observation with serial cystoscopy is therefore essential. Many patients with recurrent superficial bladder cancer can be managed with repeat TURBT and additional intravesical infusion. However, patients who develop recurrence within 6 to 12 months of initial TURBT, or after one to two courses of BCG infusion (such as the patient described here), should undergo cystectomy. Cystectomy in this setting is associated with improved disease-specific survival. This procedure is not indicated in the initial management of superficial bladder cancer unless patients have ongoing tumor-related symptoms that cannot be managed with TURBT alone or if they are subsequently found to have muscle-invasive disease.

Systemic chemotherapy, although used prior to cystectomy for patients with muscle-invasive disease, has no role in the treatment of patients with superficial bladder cancer who are to undergo cystectomy.

External-beam radiation therapy has no established role in the treatment of superficial bladder cancer.

Repeat TURBT and BCG infusion is not indicated because this treatment has already been ineffective on two occasions.

KEY POINT

- Cystectomy is indicated for patients who develop recurrence of superficial bladder cancer within 6 to12 months of undergoing initial transurethral resection of bladder tumor or after receiving one to two courses of intravesical bacillus Calmette-Guérin.

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Item 112 Answer: C

Educational Objective: Evaluate *HER2* expression status in a patient with metastatic gastric cancer.

HER2 expression status should be determined in this patient with metastatic gastric cancer. This patient continues to have adequate caloric intake and good performance status. As such, he is an appropriate candidate for systemic chemotherapy. Approximately 20% of gastric cancers and 30% of gastroesophageal junction tumors overexpress *HER2* growth factor receptor. The anti-*HER2* monoclonal antibody trastuzumab, when added to a systemic chemotherapy regimen, is beneficial in treating patients with these tumor types. For example, an early trial of patients with gastric and gastroesophageal junction adenocarcinomas expressing *HER2* found that the

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median survival was statistically significantly improved by adding trastuzumab to cisplatin plus 5-fluorouracil or capecitabine (13.5 months versus 11.1 months). Use of trastuzumab is limited to those patients whose tumors overexpress *HER2*.

BRAF mutations are present in 40% of melanomas, and patients with these tumors are treated with selective *BRAF* inhibitors. However, these agents are not part of gastric cancer therapy, and knowledge of the *BRAF* mutation status of a gastric tumor would not alter treatment.

Determining the estrogen and progesterone receptor status of a tumor is important when planning treatment of patients with breast cancer but is not relevant when selecting therapy for patients with gastric cancer.

K-*ras* genotyping is needed for all patients with newly diagnosed metastatic colorectal cancer, as K-*ras* mutations inhibit activity of the anti-epidermal growth factor receptor agents cetuximab and panitumumab that are used to treat many of these tumors. However, because these agents are not active in treating upper gastrointestinal malignancies, determining K-*ras* mutation status is not indicated for this patient.

KEY POINT

- Determination of *HER2* tumor status is indicated for patients with newly diagnosed metastatic gastric cancer, as the anti-*HER2* monoclonal antibody trastuzumab, when added to a systemic chemotherapy regimen, is beneficial in treating patients whose tumors overexpress *HER2*.

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Item 113 Answer: B

Educational Objective: Determine indications for *BRCA1/2* testing in a woman with newly diagnosed breast cancer.

This patient should be offered *BRCA1/2* testing before surgical treatment is recommended. Offering *BRCA1/2* testing prior to surgery is recommended for patients younger than 45 years with either newly diagnosed breast cancer or a family history of breast or ovarian cancer. *BRCA1/2* testing is also recommended for patients with breast cancer diagnosed at any age if one or more first-, second- or third-degree relatives have been diagnosed with ovarian cancer and is recommended for women with "triple negative breast cancer" (estrogen receptor–negative, progesterone receptor–negative, and negative for *HER2* amplification) diagnosed before age 60 years. Because this patient was diagnosed with breast cancer at age 34 years and has a family history of ovarian cancer in a paternal grandmother, she has an 18% risk of having a *BRCA1/2* mutation. Offering *BRCA1/2* testing prior to breast surgery is therefore recommended, particularly if the result will influence the patient's choice of surgery. If she tests positive for a *BRCA1* or *BRCA2* mutation, bilateral mastectomy should be considered because of the high risk for subsequent contralateral and ipsilateral breast cancers. The lifetime risk of contralateral breast cancer in women with breast cancer and a *BRCA1/2* mutation is 40% to 60%. The risk is highest in women younger than 40 years of age at diagnosis. In the United States, 50% to 70% of women with breast cancer who have a *BRCA1/2* mutation elect bilateral mastectomy, and studies suggest a survival benefit of prophylactic contralateral mastectomy in this situation.

If the patient were to test negative for a *BRCA1/2* mutation, bilateral mastectomy would not be recommended.

Left mastectomy is not usually required for a 2-cm breast cancer amenable to breast-conserving treatment, although it is an option if patients want to avoid radiation or have contraindications to radiation therapy. In addition, left mastectomy would not decrease the high risk of contralateral breast cancer for patients with a *BRCA1/2* mutation.

Lumpectomy with sentinel lymph node biopsy, followed by breast radiation therapy, is a reasonable option in patients with tumors measuring less than 5 cm that can be resected with clear margins. Survival following breast conservation therapy is equal to mastectomy in patients without *BRCA1/2* mutations.

KEY POINT

- Offering *BRCA1/2* testing prior to surgery is recommended for patients diagnosed with breast cancer before age 45 years, patients with breast cancer at any age and a family history of breast and/or ovarian cancer, and patients with triple-negative breast cancers diagnosed before age 60 years.

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Item 114 Answer: D

Educational Objective: Determine need for screening a patient at average risk for ovarian cancer.

Ovarian cancer screening is not indicated for this patient. The lifetime risk of developing ovarian cancer is 1.4%, and this patient is of average risk. She does not have a family history suggestive of a hereditary ovarian cancer syndrome, such as family members with ovarian cancer; premenopausal breast cancer; bilateral breast cancer; the presence of both ovarian and breast cancer on the same side of the family; or the presence of Lynch syndrome cancers such as colon, endometrial, or gastric cancers. She is multiparous, has no symptoms suggestive of ovarian cancer, and has a normal pelvic examination. In addition, she used oral

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contraceptives for 15 years, which lowers the risk of ovarian cancer by 50%, with the protective effect lasting 30 years.

Neither serum CA-125 testing nor transvaginal ultrasound is indicated for asymptomatic women at average risk for ovarian cancer. Serum CA-125 levels are elevated in approximately 50% of women with early-stage ovarian cancer and in 80% of those with advanced ovarian cancer, but this finding is not very specific. Levels are also elevated in approximately 1% of healthy women and fluctuate during the menstrual cycle. Elevated serum CA-125 values also occur in several benign conditions, such as endometriosis, uterine fibroids, hepatitis, and peritonitis, as well as in endometrial, breast, lung, and pancreatic cancers.

The largest randomized controlled trial evaluating ovarian cancer screening in women at average risk was the Prostate, Lung, Colon, and Ovarian (PLCO) Cancer Screening Trial, in which 78,216 women were assigned to either usual care or annual serum CA-125 testing for 6 years plus annual transvaginal ultrasound for the first 4 years. After a median follow-up of 12 years, ovarian cancer was diagnosed in 5.7% of women in the screening group and 4.7% of women in the usual care group, but there was no difference between the two groups in the number of deaths due to ovarian cancer. In addition, 3285 women had false-positive results, 1080 of whom underwent surgery; 163 of the women who underwent surgery experienced at least one serious complication (15% of surgical procedures).

Patients who have a high risk of ovarian cancer, such as women with *BRCA1/2* mutations, are recommended to have semi-annual screening with pelvic examinations, serum CA-125 testing, and transvaginal ultrasound beginning at age 30 years. However, even in this high-risk group, there is no evidence that screening decreases ovarian cancer mortality. For these women, prophylactic bilateral salpingo-oophorectomy once childbearing is completed, ideally by age 35 to 40 years, is recommended.

KEY POINT

- Screening is not recommended for asymptomatic women at average risk of developing ovarian cancer.

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Item 115 Answer: D

Educational Objective: Treat a patient with localized renal cell carcinoma after surgical resection.

Close observation is the standard of care for patients following surgical resection for nonmetastatic renal cell carcinoma. The primary treatment of suspected renal cell carcinoma is surgery. Staging is predicated on tumor size as well as extension into the renal vein and into or through the Gerota fascia. Although this patient presented with symptoms suggesting an underlying process, more early-stage renal cell carcinomas are currently being identified incidentally because of the development and more frequent use of sensitive imaging techniques. Various treatment options are available for patients with advanced disease, including immunotherapy and many small-molecule tyrosine kinase inhibitors. However, at present, there is no evidence that any of these approaches is clearly associated with improved survival following resection of nonmetastatic disease, and they are therefore not used as adjuvant therapy.

The tyrosine inhibitors sunitinib and temsirolimus have shown significant activity against renal cell carcinoma and are used in patients with metastatic disease. However, they have no established role as adjuvant therapies following surgical resection. Although studies are ongoing, particularly trials of some of the tyrosine kinase inhibitors, the current standard of care following surgical resection is close observation.

Radiation therapy has no role in the management of patients following resection for localized renal cell carcinoma, even when surgical margins are positive.

KEY POINT

- Close observation is the standard of care for patients following surgical resection for nonmetastatic renal cell carcinoma, as no studies to date have identified an adjuvant therapy that improves survival in these patients.

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Item 116 Answer: D

Educational Objective: Diagnose mantle cell lymphoma.

The most likely diagnosis of this patient with diffuse lymphadenopathy, B symptoms, extranodal involvement, and cyclin D1 overexpression is mantle cell lymphoma. Overexpression of cyclin D1, a cell cycle gene regulator, is associated with a chromosomal translocation [t(11;14)] that is diagnostic of mantle cell lymphoma. Mantle cell lymphoma is a rare form of non-Hodgkin lymphoma that has a varied clinical course depending on the extent of disease at presentation. Patients usually have advanced disease at presentation, including lymphadenopathy, weight loss, and sometimes fever, and are found to have diffuse sites of involvement, including the gastrointestinal tract, bone marrow, and blood stream.

Diffuse large B-cell lymphoma can also involve multiple organs, including the bowel; however, the cells in diffuse large B-cell lymphoma are large and do not overexpress cyclin D1.

Similarly, follicular lymphoma does not usually involve the bowel and is not characterized by overexpression of cyclin D1.

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Common findings in patients with Hodgkin lymphoma include palpable lymphadenopathy or a mediastinal mass. Hodgkin lymphoma is not associated with cyclin D1 overexpression or bowel involvement and is associated with a much better prognosis than mantle cell lymphoma, regardless of stage.

KEY POINT

- Mantle cell lymphoma is a rare form of non-Hodgkin lymphoma characterized by extranodal involvement and overexpression of cyclin D1, and it is associated with a poor prognosis.

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Item 117 Answer: D

Educational Objective: Diagnose a hereditary ovarian cancer syndrome.

This patient should undergo testing for Lynch syndrome (also known as hereditary nonpolyposis colon cancer). Because she has a personal history of both ovarian and endometrial cancer, as well as a family history of colon and endometrial cancer, her ovarian cancer is likely related to inheriting one of the genetic mutations present in patients with Lynch syndrome. This is an autosomal dominant cancer susceptibility syndrome caused by a germline mutation in one of the DNA-mismatch repair genes (*MLH1*, *MSH2*, and *MSH6* being the most common). Patients have an increased risk for several types of cancer, usually with early onset. The most common are a 70% risk for colon cancer, 27% to 71% risk for endometrial cancer, and 3% to 14% risk for ovarian cancer. Less common cancers include tumors of the upper urinary tract, bladder, stomach, small bowel, gallbladder, pancreas, brain, and sebaceous glands. Endometrial or, less often, ovarian cancer, can be the sentinel cancer in a patient with Lynch syndrome. Although identification of a Lynch syndrome mutation will not change the management of this patient's ovarian cancer, it will change screening for other cancers, including the need for colonoscopy every 1 to 2 years, annual skin examinations, and consideration of screening upper endoscopy. In addition, if she has Lynch syndrome, genetic testing should be offered to her first-degree relatives, with testing offered in addition to more distant relatives if first-degree relatives are unavailable or unwilling to be tested.

Based on National Comprehensive Cancer Network guidelines, all patients with ovarian cancer are eligible for *BRCA1/2* testing. Patients with *BRCA1/2* mutations are at risk for other cancers, particularly breast cancer, and additional screening and prophylaxis options should be discussed. In addition, patients with *BRCA1* mutations are eligible for clinical trials of agents that are particularly effective in *BRCA1*-related recurrent ovarian cancers, such as PARP inhibitors. If this patient does not have a Lynch syndrome–related mutation, testing for a *BRCA1/2* mutation would be recommended. However, because of her family and personal history of colon and endometrial cancers, testing for Lynch syndrome mutations is recommended first.

Serial abdominal/pelvic CT scans are not recommended to monitor patients with ovarian cancer. CT scans should be reserved for patients with symptoms or with recurrence of cancer based on clinical examination or elevated serum CA-125 levels.

Guidelines differ as to whether to monitor serum CA-125 levels in patients after treatment for ovarian cancer, and this should be discussed with individual patients. In one trial, patients with ovarian cancer treated with first-line platinum-based chemotherapy were randomized to receiving early treatment for ovarian cancer recurrence based on an increasing serum CA-125 level alone versus delaying treatment until clinical symptoms developed. Although patients in the early treatment arm started chemotherapy an average of 4.8 months earlier, there was no difference in overall survival.

KEY POINT

- Women with a personal and family history of ovarian, endometrial, and colon cancer should undergo testing for genetic mutations caused by Lynch syndrome (also known as hereditary nonpolyposis colon cancer).

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Item 118 Answer: C

Educational Objective: Treat a patient with stage I mycosis fungoides.

Topical glucocorticoids are most appropriate for this patient with mycosis fungoides, which is one form of cutaneous T-cell non-Hodgkin lymphoma. Lymphomas expressing T-cell surface antigens (CD4) are among the more common forms of cutaneous T-cell lymphomas. These antigens infiltrate skin and initially cause rash (mycosis fungoides) and, occasionally, also circulate in the blood (Sézary syndrome). The CD4-expressing malignant T cells are large and have classic "cerebriform"-appearing nuclei and clonal T-cell receptor gene rearrangements. Patients usually present with dry, pruritic, erythematous skin patches; mycosis fungoides confined to the skin can mimic these benign dermatologic conditions, and be undiagnosed for many years. Patients with progressive disease develop raised plaques, diffuse skin erythema, and cutaneous ulcers. In the final stages of progression, organ infiltration and evolving immunodeficiency cause recurrent bacterial infections, sepsis, and death.

Therapy is guided by disease stage. Early-stage disease (stages I and II) is limited to the skin, and patients have a

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median survival of over 20 years. Patients with early-stage disease are treated effectively with topical glucocorticoids. If there is no response to glucocorticoids, adding retinoids (such as bexarotene) and psoralen plus ultraviolet light (PUVA) therapy, at times combined with interferon alfa, may be effective. Patients with advanced disease (stages III and IV) have extensive skin and organ involvement and a median survival of 4 years. These patients require more aggressive therapy, including electron-beam radiation therapy; photopheresis; systemic therapy, including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy; histone deacetylase inhibitors (such as romidepsin and vorinostat); and monoclonal antibodies (such as alemtuzumab). Allogeneic hematopoietic stem cell transplantation may be curative in young patients who have advanced disease and an appropriate donor.

CHOP chemotherapy is indicated for patients with advanced disease, which this patient does not have due to absence of lymphadenopathy or organ involvement.

PUVA therapy may be effective for patients with early-stage disease who do not respond to topical glucocorticoids.

Monoclonal antibody therapy may be used in advanced stage mycosis fungoides using agents such as alemtuzumab, which is directed toward T cell surface proteins. Rituximab is a monoclonal antibody directed toward surface proteins typically found on immune system B cells and is not used in treatment of mycosis fungoides.

KEY POINT

- Patients with early-stage mycosis fungoides are treated initially with topical glucocorticoids; if glucocorticoids are ineffective, adding retinoids and psoralen and ultraviolet light therapy, sometimes combined with interferon alfa, may be effective.

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Item 119 Answer: D

Educational Objective: Treat stage I rectal cancer with surgical resection.

Surgical resection is indicated as the initial treatment for this patient who has stage I rectal cancer, which is defined as a tumor that invades into, but not fully through, the rectal wall, with no evidence of lymph node metastases (T2N0M0, stage I). The procedure for a tumor of the mid rectum, such as that in this patient, is a low anterior resection using the technique of total mesorectal excision to accomplish an en-bloc removal of the rectum with a fully intact mesorectum. The mesorectum is the fatty sheath that surrounds the rectum and contains the locoregional lymph nodes. Careful pathologic examination of the primary tumor and lymph nodes is necessary to confirm the disease stage. If pathology findings indicate that the tumor is a higher T stage than expected (T3 or T4) or if any of the locoregional lymph nodes in the mesorectum are found to contain cancer (N1 or N2), postoperative chemoradiation and chemotherapy would be indicated. However, if the final pathology report confirms stage I rectal cancer, the probability of cure with surgery alone is high, and no additional treatment is indicated.

Neither chemotherapy, radiation therapy, nor combined chemotherapy plus radiation has been demonstrated to improve outcomes in patients with stage I rectal cancer, and all of them would expose these patients to unnecessary risk and toxicity.

KEY POINT

- Surgical resection is the initial treatment for patients with stage I rectal cancer (defined as a tumor that invades into, but not fully through, the rectal wall, with no evidence of lymph node metastases).

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Item 120 Answer: B

Educational Objective: Diagnose early-stage ovarian cancer through exploratory surgery.

This patient, who has early-stage ovarian cancer (clinical stage II, with spread beyond the ovaries but confined to the pelvis), should undergo exploratory surgery. The diagnosis of ovarian cancer is usually made by surgical exploration, as there is survival benefit following intact removal of an adnexal mass in patients with early-stage disease. Survival is also improved when surgery is performed by a specialized gynecologic oncologic surgeon. If ovarian cancer is confirmed at surgery, appropriate procedures include peritoneal washings for cytology, total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, full abdominal and pelvic exploration with biopsy of any masses suspicious for cancer, lymph node evaluation, and, for patients with advanced ovarian cancer, debulking of the tumor by removing as much of the cancer as possible. Optimal tumor debulking (leaving residual masses that are each less than 1 cm) improves survival.

CT-guided or ultrasound-guided biopsy of a suspected ovarian mass is contraindicated, as this may cause rupture and dissemination of cancer cells. Rupture of an ovarian mass increases the risk of peritoneal recurrence; when such rupture occurs during surgery, it is an indication for adjuvant chemotherapy, even in early stage disease.

MRI of the abdomen and pelvis is sometimes used in the preoperative staging of ovarian cancer as an alternative to CT but is unlikely to yield additional information after CT scans and ultrasound examinations are done.

Based on National Comprehensive Cancer Network guidelines, all women with ovarian cancer are eligible for *BRCA1/2* testing. Ten percent to 15% of ovarian cancers are hereditary, with *BRCA1/2* mutations being the most

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common. Although the initial surgical and standard adjuvant chemotherapy treatments for ovarian cancer are the same regardless of the presence of a hereditary mutation, patients with *BRCA1/2* mutations are at risk for other cancers, particularly breast cancer, and additional screening and prophylaxis options would be discussed once treatment for ovarian cancer is complete. In addition, patients with *BRCA1* mutations are eligible for clinical trials of agents that are particularly effective in *BRCA1*-related recurrent ovarian cancers, such as PARP inhibitors. However, it is not yet known whether this patient has ovarian cancer, and testing before this diagnosis is established is inappropriate.

KEY POINT

- The diagnosis of ovarian cancer is usually made by surgical exploration, as there is survival benefit following intact removal of an adnexal mass in patients with early-stage disease.

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Item 121 Answer: A

Educational Objective: Manage a patient with gastric mucosa-associated lymphoid tissue (MALT) lymphoma associated with *Helicobacter pylori* infection.

In this patient with a gastric mucosa-associated lymphoid tissue (MALT) lymphoma associated with *Helicobacter pylori* infection, ranitidine should be discontinued and omeprazole, metronidazole, and clarithromycin begun. MALT lines the entire gastrointestinal tract, providing immune surveillance and initiating immunologic responses to pathogens. Chronic antigen stimulation can lead to clonal expansion of MALT. Malignant transformation of MALT to lymphoma can occur, originating in the B cells of the marginal zone of MALT and expressing the CD20 surface antigen. Gastric MALT lymphoma associated with *H. pylori* infection usually presents as local disease in patients with gastric ulcers. A complete response is generally obtained following administration of combination antimicrobial therapy and a proton pump inhibitor (PPI) to treat the *H. pylori* infection. Usually, amoxicillin is combined with omeprazole and clarithromycin, but because of this patient's penicillin allergy, metronidazole is substituted for amoxicillin. A complete remission rate of nearly 80% can be expected after a full course of therapy. The duration of therapy lasts from 6 to 8 weeks to several months and is guided by treatment response as assessed by repeat upper endoscopy.

Rituximab has no role in the initial treatment of a patient with a gastric MALT lymphoma. This agent is indicated for disease that does not resolve after a complete course of combination antimicrobial therapy plus a PPI and may be combined with chemotherapy, radiation therapy, or surgery when additional treatment is required.

Bone marrow biopsy is not indicated because of the extremely low likelihood of bone marrow involvement in this setting.

A PET/CT scan is not needed because gastric MALT lymphoma usually presents as local disease, and this patient's abdominal CT scan revealed no lymphadenopathy.

KEY POINT

- The initial treatment of a patient with gastric mucosa-associated lymphoid tissue (MALT) lymphoma associated with *Helicobacter pylori* infection is antimicrobial therapy plus a proton pump inhibitor.

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Item 122 Answer: C

Educational Objective: Treat squamous cell carcinoma of the neck with chemoradiation therapy following surgical resection.

Adjuvant combined-modality treatment with chemotherapy and radiation is most appropriate for this patient with locally advanced squamous cell carcinoma. Most patients with resected squamous cell carcinoma of the head and neck will require some form of adjuvant therapy. Combined-modality chemotherapy and radiation has been shown to improve survival in patients with either positive surgical margins or lymph node metastases associated with extracapsular extension. Although several earlier studies showed a survival benefit when combined-modality therapy was used for patients with multiple positive lymph nodes without extracapsular extension, more recent studies have failed to confirm a survival benefit in that setting. Therefore, currently, either the presence of positive surgical margins at the primary resection site or of extracapsular lymph node extension is the only standard indication for combined-modality adjuvant therapy. The patient described here clearly meets these criteria.

Although cetuximab alone can be used for patients with advanced disease, it has not been associated with improved survival in the adjuvant setting.

Neither adjuvant chemotherapy alone nor adjuvant radiation therapy followed by chemotherapy has a role in the care of patients with resected squamous cell carcinoma of the head and neck.

Although not listed as an option, adjuvant radiation therapy alone is most often used for patients with earlier-stage disease and is associated with significantly decreased recurrence rates. However, it is not appropriate for patients with either positive resection margins or those with metastatic lymph nodes associated with extracapsular extension. In both of those circumstances, recurrence rates following treatment with radiation alone are clearly higher than those associated with combined chemotherapy and radiation treatment.

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KEY POINT

- Adjuvant combined-modality chemotherapy and radiation has been shown to improve survival in patients with resected squamous cell carcinoma of the head and neck associated with either positive surgical margins or lymph node metastases with extracapsular extension.

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Item 123 Answer: A

Educational Objective: Manage a patient following radical inguinal orchiectomy for early-stage seminoma.

Active surveillance is appropriate for this patient with stage I seminoma following resection. Testicular germ cell tumors are divided into pure seminomas and nonseminomatous germ cell tumors (NSGCT). Recommended post-surgical treatments vary based on histologic findings and tumor stage. In general, pure seminoma is associated with a better prognosis than NSGCT. For men with stage I seminoma (disease confined to the testis), radical inguinal orchiectomy is curative in at least 80% of patients. This high cure rate with initial surgical treatment coupled with the ability to treat recurrent disease with curative intent makes active surveillance the lowest-risk approach with an expected good outcome. Active surveillance refers to a regimen of regular assessment with serum tumor marker measurement, CT scans of the abdomen and pelvis, and chest radiographic imaging. As this requires close and regular monitoring, it requires a reliable and motivated patient to be successful.

Other management options after surgery include adjuvant therapy with either single-agent carboplatin or para-aortic lymph node irradiation, although neither approach has been shown to improve overall survival. In addition, neither of these alternatives appears superior to the other, but they might be reasonable to consider in patients who wish to decline active surveillance.

Hematopoietic stem cell transplantation is used for treatment of patients with recurrent or refractory disease, usually only after treatment with multiple chemotherapeutic agents, in selected patients following adjuvant chemotherapy.

Platinum-based chemotherapy (specifically the combination of bleomycin, etoposide, and cisplatin) is the standard regimen for patients with more advanced seminoma, as well as for those with NSGCT. This regimen is not recommended for patients with stage I seminoma because of their very good prognosis and the significant potential for side effects associated with these drugs.

Retroperitoneal lymph node dissection is often used in the treatment of NSGCT but has no role in the treatment of patients with stage I seminoma.

KEY POINT

- Active surveillance is the recommended management strategy for patients with stage I seminoma diagnosed after radical inguinal orchiectomy; other options are adjuvant single-agent carboplatin or para-aortic lymph node irradiation.

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Item 124 Answer: C

Educational Objective: Treat a patient who responds to treatment for small cell lung cancer with prophylactic cranial irradiation.

Prophylactic cranial irradiation (PCI) is indicated. Following evaluation for pneumonia, this patient was diagnosed with limited-stage small cell lung cancer (SCLC). The definition of limited-stage disease consists of disease limited to one hemithorax, with hilar and mediastinal lymphadenopathy that can be encompassed within one tolerable radiotherapy portal. Combined chemotherapy and radiation therapy induced a significant near-complete response in this patient. At initial diagnosis and following treatment, there was no evidence of cerebral metastatic disease. Despite these results, she remains at significant risk for recurrence of small cell lung cancer. In addition, approximately one third of patients without cerebral metastatic disease at initial diagnosis will have brain metastases at the time of disease recurrence. Randomized trials assessing the role of PCI in patients with primary treatment-responsive SCLC have identified both a reduced incidence of brain metastases and an improvement in overall survival after irradiation. PCI is currently considered standard management following response to primary treatment in these patients.

Although limited-stage SCLC tumors are one of the most chemosensitive types of tumors, there are recurrences in 90% to 95% of patients. To date, attempts to improve outcomes by providing maintenance chemotherapy, adding other agents to the standard chemotherapy regimen, or by using high-dose chemotherapy with stem cell support have been unsuccessful.

PET/CT is not a standard imaging modality to assess patients with primary treatment-responsive SCLC and would provide no new information for this patient, given her CT imaging findings.

SCLC is considered a systemic disease at diagnosis, even if a potentially resectable peripheral lesion is the only finding after diagnostic studies are completed. All patients with SCLC now receive systemic chemotherapy as the mainstay

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of treatment. Surgery has no role in the management of patients with SCLC.

KEY POINT

- Patients with small cell lung cancer who experience a complete or near-complete response following treatment with chemotherapy or combined chemotherapy and radiation therapy should be offered prophylactic cranial irradiation to reduce the incidence of brain metastases and improve overall survival.

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Socha J, Kepka L. Prophylactic cranial irradiation for small-cell lung cancer: how, when and for whom? Expert Rev Anticancer Ther. 2012 Apr;12(4): 505-17. [PMID: 22500687]

Item 125 Answer: B

Educational Objective: Treat a patient with recurrent Hodgkin lymphoma who responds to salvage chemotherapy.

Autologous hematopoietic stem cell transplantation (HSCT) is the most appropriate treatment option for patients with recurrent Hodgkin lymphoma, particularly those who achieve a complete response to salvage chemotherapy. Prospective trials have consistently demonstrated a survival advantage when patients with chemotherapy-sensitive disease are treated with autologous HSCT compared with patients treated with continued salvage chemotherapy. Because this patient has achieved a complete remission following two cycles of dexamethasone, ifosfamide, cisplatin, and etoposide (DICE) chemotherapy, the next step is to administer hematopoietic growth factors, with or without chemotherapy, to mobilize, collect, and store hematopoietic progenitor cells. Once a sufficient quantity of hematopoietic progenitor cells are collected (>3 million CD34+ cells/kg patient body weight), high-dose multiagent chemotherapy followed by reinfusion of the stored progenitor cells can be completed.

Allogeneic HSCT is not indicated for patients with chemotherapy-sensitive recurrent Hodgkin lymphoma because of the significant risk of morbidity and mortality associated with allogeneic transplantation. The risk for fungal and viral infections occurring 3 months or more after transplantation is significantly greater after allogeneic than autologous transplantation. Lymphocytes derived from the donor can mount an immune response to the recipient's organs, leading to graft-versus-host disease, which may affect the skin, gastrointestinal tract, liver, ocular adnexa, lungs, bone marrow, and soft tissues. However, in patients with chemotherapy-resistant recurrent Hodgkin lymphoma, including patients who develop a relapse after autologous HSCT, allogeneic HSCT may result in prolonged disease-free survival.

Continuation of DICE chemotherapy is not optimal treatment for this patient because, as noted, patients with chemotherapy-sensitive Hodgkin lymphoma who are treated with autologous HSCT have a survival advantage compared with patients treated with continued salvage chemotherapy.

Radiation therapy in the salvage setting can be effective for patients with limited disease and may be associated with long-term disease-free survival. However, radiation therapy is much less likely to result in long-term disease-free survival in patients with advanced recurrent disease. In addition, radiation therapy would adversely affect the hematopoietic stem cells in patients being considered for autologous HSCT.

KEY POINT

- Autologous hematopoietic stem cell transplantation is indicated for patients with recurrent Hodgkin lymphoma, particularly patients who achieve a complete response to salvage chemotherapy.

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Rancea M, Monsef I, von Tresckow B, Engert A, Skoetz N. High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. Cochrane Database Syst Rev. 2013 Jun 20;6:CD009411. [PMID: 23784872]

Item 126 Answer: D

Educational Objective: Manage concerns about disease recurrence in a breast cancer survivor.

Diagnostic testing is not indicated for this patient at this time. She had stage I breast cancer treated 3 years ago and has no worrisome symptoms and no abnormal findings on physical examination. In asymptomatic patients with a history of early breast cancer, routine imaging studies (excluding annual mammography) or blood tests, including tumor marker studies, are not beneficial. These tests have a 10% to 50% false-positive rate, leading to unnecessary studies and procedures. Two randomized trials showed no survival benefit from intensive screening with routine blood and imaging tests compared with clinical evaluation alone in asymptomatic patients. One of the trials showed a decreased quality of life in the group undergoing more intensive screening.

Patients with cancer in one breast are at higher risk for contralateral breast cancer (absolute risk 0.5% to 1.0% per year), although this risk is decreased by use of antiestrogen therapy. All women with a diagnosis of breast cancer should have annual mammograms. Breast MRI is only indicated for patients with *BRCA1/2* mutations or other familial breast cancer syndromes or those with a very strong family history of breast cancer. None of these high-risk situations is present in this patient.

Except for patients with familial cancer syndromes, breast cancer survivors have no increased risks for other cancers except those related to certain treatments. Patients receiving adjuvant chemotherapy with cyclophosphamide and anthracyclines have a 0.5% risk of developing myelodysplasia and acute leukemia. Tamoxifen is associated with a 1/1000 per year risk of endometrial cancer in women over 55 years of age and a smaller risk of uterine sarcoma in this age group. These risks are low, however, and routine screening blood tests and imaging studies are not recommended in asymptomatic patients.

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In addition to cancer surveillance, survivor issues that should be addressed at follow-up visits include menopausal symptoms (selective serotonin reuptake inhibitors that do not interfere with tamoxifen activation or gabapentin may be helpful), sexual dysfunction including dyspareunia due to vaginal dryness (lubricants and cautious use of very low-dose vaginal estrogen are options), arthralgia from anti-estrogen therapy, cognitive dysfunction, depression, fatigue, weight gain, decreased bone density, cardiovascular disease due to radiation or chemotherapy, and thrombosis in patients taking tamoxifen.

KEY POINT

- In asymptomatic patients with a history of early breast cancer, routine imaging studies (excluding annual mammography) or blood tests, including tumor marker studies, are not beneficial.

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Hayes DF. Clinical Practice. Follow-up of patients with early breast cancer. N Engl J Med. 2007 Jun 14;356(24):2505-13. [PMID: 17568031]

Item 127 Answer: D

Educational Objective: Treat prostate cancer metastatic to bone with radium-223.

This patient, who has recurrent prostate cancer metastatic to bone, should be treated with the radiopharmaceutical agent radium-223. Patients with metastatic prostate cancer who are found to have a biochemical recurrence (a rising serum prostate-specific antigen level and no evidence of local disease progression) will typically respond to androgen deprivation therapy. However, they will also eventually develop clinical metastatic disease. Once this occurs, optimal management depends on multiple factors, including the extent and sites of metastases and the symptoms associated with the disease. One important consideration in this setting is use of a bone-seeking radiopharmaceutical agent. These agents concentrate in bone, and recent data indicate radium-223 is associated with improvement in both symptoms and overall survival. Radium-223 is indicated specifically for patients with bone-limited or bone-predominant symptomatic metastatic disease, such as that present in this patient.

Bilateral orchiectomy, while a very effective form of antiandrogen therapy, would not be indicated in a patient who has already been demonstrated to be castrate resistant.

Estrogen therapy has uncertain benefit in the treatment of castrate-resistant prostate cancer, and would not be considered an appropriate treatment option for this patient, especially given that radium-223 has been associated with both improved survival and symptom burden.

External-beam radiation to metastatic sites can be considered for treatment of patients with spinal cord compression or for those with focal symptomatic bone metastases, neither of which this patient has.

KEY POINT

- The radiopharmaceutical agent radium-223 is associated with improvement in both symptoms and overall survival when used to treat patients with bone-limited or bone-predominant symptomatic metastatic prostate cancer.

Bibliography

Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013 Jul 18;369(3):213-23. [PMID: 23863050]

Item 128 Answer: B

Educational Objective: Treat early-stage triple-negative breast cancer with adjuvant chemotherapy.

Anthracycline-based chemotherapy is the most appropriate treatment. Although this patient has a stage I cancer (measuring 2 cm or less and lymph node negative), it is a high-grade, triple-negative tumor (negative for estrogen receptor, progesterone receptor, and *HER2* amplification), and she is at high risk for systemic recurrence. In patients with triple-negative cancers that are 0.6 cm or greater in size, adjuvant chemotherapy, typically anthracycline-based chemotherapy, is recommended if there are no medical contraindications. Chemotherapy is the mainstay of treatment for triple-negative breast cancers, both when used as adjuvant therapy and when used for more advanced cancers. Based on retrospective analysis, adding a taxane agent to adjuvant anthracycline-based chemotherapy is of greater benefit in patients with hormone receptor–negative cancers than in patients with hormone receptor–positive cancers.

Triple-negative cancers constitute about 15% of breast cancers and are usually of high grade. They occur more frequently in young black and Hispanic women than in other ethnic groups. Patients with triple-negative cancers have a higher risk of *BRCA1/2* mutations, and *BRCA1/2* genetic testing is recommended for women diagnosed with triple-negative breast cancers before age 60 years. Most breast cancers in women with *BRCA1* mutations are triple negative.

Antiestrogen therapies such as anastrozole are not effective in hormone receptor–negative cancers and would not be used in this patient's treatment regimen.

Autologous bone marrow transplantation is not used as adjuvant treatment for breast cancer. Clinical trials on its use in both the adjuvant setting and the metastatic setting showed no improvement in survival compared to treatment with standard therapy and its use in breast cancer has been discontinued.

Epidermal growth factor receptor–targeted therapy with bevacizumab has not been found to improve disease survival or overall survival when added to adjuvant chemotherapy for patients with triple-negative breast cancers.

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KEY POINT

- Adjuvant chemotherapy, typically anthracycline-based chemotherapy, is recommended for patients with triple-negative breast cancers who have no medical contraindications to this regimen.

Bibliography

Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med. 2010 Nov 11;363(20):1938-48. [PMID: 21067385]

Item 129 Answer: B

Educational Objective: Screen for breast cancer in a patient who has received chest radiation therapy.

This patient should now be screened with mammography and accompanying breast MRI on an annual basis. Women who received chest wall radiation (such as mantle radiation therapy for Hodgkin lymphoma) between the ages of 10 and 30 years are at high risk for developing breast cancer and, according to the American Cancer Society 2007 guidelines, should be screened with breast MRIs as well as annual mammograms. Such women have a 30% to 50% lifetime risk of developing breast cancer within the radiation field. A recent study from England and Wales reviewed the incidence of breast cancer in 5002 women treated with supradiaphragmatic radiation therapy for Hodgkin lymphoma before age 36 years. This study showed an increased breast cancer risk starting 10 years after radiation exposure and peaking 25 to 34 years after exposure. At the 40-year follow-up, the risk of breast cancer was 48% for patients who received 40 Gy or more of mantle radiation therapy at a young age. Breast MRI is more sensitive, although less specific, than mammography for the detection of invasive breast cancers and has been studied prospectively in women with a high risk of breast cancer. However, mammography may still detect cancers not seen on MRI; therefore, a dual imaging strategy is recommended. In one study, the combination of mammogram and breast MRI had a sensitivity of 0.94 for detecting invasive breast cancer compared with a sensitivity of 0.39 with mammogram alone.

For the reasons noted above, yearly mammograms alone are less effective than a screening program including breast MRI.

Some groups, including the American Cancer Society, recommend annual mammography starting at age 40 years for women with an average breast cancer risk, whereas the American College of Physicians and the United States Preventive Services Task Force suggest initiating discussion with patients between the ages of 40 to 49 years who are at average risk for breast cancer regarding the risks and benefits of screening to determine the appropriate screening approach. Additionally, none of these groups recommends the use of MRI in screening for breast cancer in average risk women. This woman's breast cancer risk is far above average, and delaying mammography would be an inadequate screening approach for her.

There is no evidence that breast self-examination (BSE) decreases breast mortality. Some expert groups raise concerns about increased harm with BSE, such as unnecessary distress and procedures for benign lumps. Most guidelines from expert groups recommend against BSE, with a few recommending "breast self-awareness" or education about the benefits and limitations of BSE. BSE alone as a screening strategy in this high-risk patient is inadequate.

KEY POINT

- Women who received chest wall radiation (such as mantle radiation therapy for Hodgkin lymphoma) between the ages of 10 and 30 years are at high risk for developing breast cancer and should be screened with annual mammograms and breast MRIs.

Bibliography

Swerdlow AJ, Cooke R, Bates A, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: A National Cohort Study. J Clin Oncol. 2012 Aug 1;30(22):2745-52. [PMID: 22734026]

Item 130 Answer: A

Educational Objective: Treat non-small cell lung cancer with chemotherapy.

Chemotherapy is most appropriate for this patient with stage II non-small cell lung cancer (NSCLC). Although several combination chemotherapeutic regimens have been studied, so far only a cisplatin-based regimen has been shown to be effective in selected patients with NSCLC. Currently available studies indicate that adjuvant cisplatin-based chemotherapy, given for a total of four cycles, improves survival in patients who have undergone successful resection of stage II or stage III NSCLC, regardless of histologic type.

Erlotinib is a tyrosine kinase inhibitor with activity against tumors expressing mutations in the epidermal growth factor receptor (EGFR). Although erlotinib is effective in the treatment of EGFR mutation-positive patients with metastatic NSCLC, its effectiveness in the adjuvant treatment setting has not been established.

Although radiation therapy may decrease locoregional recurrence, it has not been shown to improve survival in patients with stage II lung cancer with clear margins after resection and therefore is not given to such patients as adjuvant treatment.

Observation alone is inappropriate because of the survival advantage associated with adjuvant chemotherapy and because this patient has no apparent contraindications to administration of chemotherapy. Potential contraindications to chemotherapy include poor performance status following surgery and the presence of medical comorbidities that predict for an increase in toxicity associated with chemotherapy treatment.

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KEY POINT

- Cisplatin-based adjuvant chemotherapy improves survival for selected patients who have undergone successful resection of stage II or stage III non-small cell lung cancer, regardless of histologic type.

Bibliography

Pignon, JP, Tribodet H, Scagliotti GV, et al; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008 Jul 20;26(21):3552-9. [PMID: 18506026]

Item 131 Answer: B

Educational Objective: Evaluate a patient with possible lymphoma with an excisional lymph node biopsy.

This patient most likely has lymphoma, and excisional or core needle biopsy of an enlarged lymph node should be done next to establish a tissue diagnosis. Optimally, an excisional biopsy should be performed to preserve lymph node architecture which is important in differentiating reactive lymphadenopathy from lymphoma. Core needle biopsy is able to sample some structural aspects of the lymph node, and may be used for deep lymph nodes in place of excision. This patient's presentation of asymptomatic but progressive lymphadenopathy, splenomegaly, and lymphocytosis is highly suggestive of lymphoma. To determine the subtype of lymphoma and to guide therapy, the biopsy specimen is sampled for histopathologic, cytogenetic, and fluorescence in situ hybridization (FISH) analysis, as well as immunophenotype and gene expression profiling. Routine blood studies include a complete blood count with differential, erythrocyte sedimentation rate, and serum chemistry studies, including serum urate level. Serum lactate dehydrogenase, β_2-microglobulin, and immunoglobulin levels should also be determined. Screening for viral infections, including hepatitis B and C, HIV, human T-cell lymphotrophic virus type 1, human herpesvirus-8, and Epstein-Barr virus (and, when indicated, screening for bacterial infection due to *Helicobacter pylori*), needs to be performed because these infections can be causative drivers of lymphoma. As active infections may reduce lymphoma response rates and duration, it is essential to treat both the lymphoma and any underlying infections.

Although bone marrow biopsy, generally iliac crest bone marrow biopsy, is needed to complete the evaluation, excisional or core needle biopsy should be done first to establish a tissue diagnosis prior to staging.

Fine-needle lymph node biopsy should not be used because it will not preserve the architecture of the lymph node that is required for the diagnosis of lymphoma.

Patients with aggressive lymphoma presenting with involvement of the testes, sinuses, bone marrow, and ocular sites have an increased risk of central nervous system involvement and require lumbar puncture for cerebrospinal fluid examination. This procedure is only appropriate following the diagnosis and staging of non-Hodgkin lymphoma.

PET scanning is performed to complete staging but, again, should not be done until a tissue diagnosis is established. Early repeat PET scanning (after two to three cycles of chemotherapy) provides important prognostic information for patients with Hodgkin lymphoma but not for those with non-Hodgkin lymphoma.

KEY POINT

- Excisional biopsy of an adequate tissue sample that preserves the architecture of the lymph node is required for the diagnosis of lymphoma.

Bibliography

Amador-Ortiz C, Chen L, Hassan A, et al. Combined core needle biopsy and fine-needle aspiration with ancillary studies correlate highly with traditional techniques in the diagnosis of nodal-based lymphoma. Am J Clin Pathol. 2011 Apr;135(4):516-24. [PMID: 21411774]

Item 132 Answer: E

Educational Objective: Manage early-stage prostate cancer in an elderly man with medical comorbidities.

Observation, or watchful waiting, is most appropriate for this elderly man with newly diagnosed prostate cancer and medical comorbidities after the benefits and risks of this approach are discussed with the patient. Observation is based on an assessment that a patient would not benefit from definitive treatment of prostate cancer, either because of significant comorbidities or a shortened life expectancy, with the expectation that palliative treatment could be provided if the disease progresses. This patient's prostate-specific antigen (PSA) level, extent of disease based on biopsy findings, and Gleason score are all predictors of low-risk disease. Furthermore, he has a significant medical history, including worsening heart failure. Given that this patient has very low-risk prostate cancer and a life expectancy most likely less than 10 years, observation is the most appropriate management option for this patient.

Active surveillance, in contrast to observation, is the postponement of definitive therapy with the intent to pursue treatment of curative intent if there is evidence of disease progression. Active surveillance involves a program of regular assessment with physical examination, PSA testing, and prostate biopsy. It would not be appropriate for this patient, given his life expectancy related to significant medical comorbidities.

Cryotherapy is a technique that freezes prostatic cancer cells to treat localized prostate cancer. However, its role as a treatment option for localized prostate cancer has not been established at present.

Both external-beam radiation therapy and radical prostatectomy are reasonable alternatives for definitive treatment in patients considered appropriate candidates for therapy. However, the risks of either would likely outweigh the benefits of treatment in this patient with low-risk disease and significant medical comorbidities.

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KEY POINT

- Observation is the appropriate management for an elderly man with newly diagnosed, low-risk prostate cancer and medical comorbidities that significantly limit life expectancy.

Bibliography

Shappley WV 3rd, Kenfield SA, Kasperzyk JL, et al. Prospective study of determinants and outcomes of deferred treatment or watchful waiting among men with prostate cancer in a nationwide cohort. J Clin Oncol. 2009 Oct 20;27(30):4980-5. [PMID: 19720918]

Item 133 Answer: D

Educational Objective: Determine the prognosis in a patient with newly diagnosed colon cancer.

Tumor stage is usually the most important prognostic factor in determining a patient's outcome. Staging typically involves ordering appropriate tests to identify the local extent of the primary tumor and to determine whether the disease has spread beyond the site of origin. Although specific staging will vary according to the unique anatomic and biologic features of the primary site, there are many common steps to the staging process. Most solid tumors are staged according to the American Joint Commission on Cancer (AJCC) TNM classification. "T" indicates the extent of the tumor (size and/or depth of penetration), "N" represents the number of locoregional lymph nodes that contain cancer, and "M" indicates whether metastases are present or absent. TNM scores are then classified on a scale of stage I to IV, with stage I tumors having the best prognosis and stage IV having the worst.

Although poorly differentiated tumors generally have a worse prognosis than well-differentiated tumors, this is a modest prognostic factor compared with staging.

Performance status, which is a designation of the patient's overall medical "wellness" and ability to perform routine daily activities, may have important prognostic implications within a particular stage of disease but is far less significant prognostically than the stage itself.

Tumor size may be a component of the "T" stage, but by itself has only modest prognostic significance relative to overall stage. Generally, the degree of lymph node involvement has a greater negative impact on prognosis than does a higher T stage, and the presence of metastatic disease beyond lymph node involvement has the worst prognosis.

KEY POINT

- Tumor stage is usually the most important prognostic factor in determining outcome in a patient with newly diagnosed cancer.

Bibliography

Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

Item 134 Answer: B

Educational Objective: Treat locally advanced anal cancer with radiation and concurrent chemotherapy.

This patient, who has locally invasive squamous cell carcinoma of the anus, requires pelvic radiation therapy and concurrent systemic chemotherapy, a regimen that is appropriate for patients with stage I, II, and III anal cancer. Compared with rectal cancer, which is typically adenocarcinoma for which resection is the initial therapeutic step, anal cancers are usually of squamous cell origin, with chemoradiation the primary treatment modality owing to increased cure rates. Mitomycin plus 5-fluorouracil (5-FU) has been used to treat patients with anal cancer since the 1970s and remains the standard chemotherapy regimen. Randomized clinical trials have demonstrated that radiation therapy plus chemotherapy is superior to radiation therapy alone and that the combination of 5-FU plus mitomycin is superior to use of 5-FU alone.

Radiation therapy alone is inadequate for treatment of anal cancer.

If radiation therapy and chemotherapy fail to eradicate this patient's anal cancer, surgery can be performed as salvage treatment. However, the procedure required to excise an anal cancer also requires removal of the anal sphincter and placement of a permanent colostomy. Consequently, surgery as either initial treatment or as a planned procedure following initial radiation therapy and chemotherapy without documentation of continuing metastases would not be appropriate because of the unacceptable level of morbidity.

Anal cancer is a squamous cell carcinoma that arises in the squamous epithelium of the anus and is typically associated with human papillomavirus exposure. It is a distinct entity from rectal cancer, which arises in the columnar epithelium of the rectum, is an adenocarcinoma, and is typically treated with a combination of radiation therapy, chemotherapy, and definitive surgery.

KEY POINT

- The standard treatment regimen for patients with stage I, II, or III anal squamous cell carcinoma is radiation therapy with concurrent chemotherapy consisting of mitomycin plus 5-fluorouracil.

Bibliography

James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomized, phase 3, open-label, 2 × 2 factorial trial. Lancet Oncol. 2013 May;14(6):516-24. [PMID: 23578724]

Item 135 Answer: D

Educational Objective: Manage a patient with a low-grade metastatic carcinoid tumor.

Repeat abdominal imaging with a contrast-enhanced CT scan of the abdomen in 3 to 4 months is most appropriate. This patient has an incidental finding of a metastatic low-grade carcinoid tumor that is asymptomatic and hormonally

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nonfunctional. It is impossible to know how long the tumor has been present. However, given the benign presentation and near-normal liver function studies, the tumor has probably been present for many years. Because urgent intervention is unlikely to be needed, expectant observation and repeat imaging studies in 3 to 4 months will be useful in establishing disease progression. For many patients, little or no change is seen on serial scans, and these patients may be followed with serial imaging studies two to three times each year. If substantial tumor progression or tumor-related symptoms develop, intervention should be considered.

Hepatic artery embolization may be effective in decreasing tumor volume in the liver or decreasing hormone production in patients with neuroendocrine tumors. However, this is an invasive procedure that carries risks of morbidity and mortality and would not be appropriate for an asymptomatic patient with small-volume, hormonally nonfunctional disease.

This patient does have a positive radiolabeled octreotide scan, indicating that somatostatin receptors are present on the tumor (as they are in most neuroendocrine tumors). Therefore, treatment with octreotide, a somatostatin analogue, could be considered in the future if the disease progresses. Although actual tumor regression following octreotide administration is rare, octreotide has been demonstrated to stabilize and delay progression of carcinoid tumors and would be an appropriate consideration if progression of this patient's tumor is seen on serial imaging.

Radiofrequency ablation is another invasive procedure that can be used to treat patients with a small number of liver lesions. However, it has no role in the treatment of patients with numerous lesions, such as the patient described here.

Systemic chemotherapy would also not be indicated in a patient with an asymptomatic neuroendocrine tumor in the absence of disease progression or disease-related symptoms.

KEY POINT

- Appropriate management for a patient with an incidental finding of a metastatic low-grade carcinoid tumor that is asymptomatic and hormonally nonfunctional consists of expectant observation and repeat imaging studies several times each year to determine whether the disease is progressing.

Bibliography

Kulke MH, Siu LL, Tepper JE, et al. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. J Clin Oncol. 2011 Mar 1;29(7):934-43. [PMID: 21263089]

Item 136 Answer: D

Educational Objective: Diagnose and stage pancreatic adenocarcinoma.

The most appropriate management is surgical resection of the pancreatic mass. This patient likely has localized and potentially resectable pancreatic adenocarcinoma. Strong supportive data include clinical risk factors (age ≥50 years, cigarette smoking, new-onset diabetes mellitus), symptoms (weight loss, dyspepsia), and CT imaging findings (a discrete, solid, low-attenuating mass with dilation of the upstream pancreatic duct and common bile duct ["double-duct sign"]).

Percutaneous or endoscopic ultrasound-guided tissue sampling is generally not recommended in patients who are operative candidates with potentially resectable (localized) pancreatic cancer because negative results may simply represent sampling error and are insufficient to rule out the presence of cancer. Thus, they entail risk and do not affect management.

The tumor marker CA 19-9 has variable sensitivity and specificity for pancreatic cancer and is generally not recommended as a screening test; management will not be changed by the results of this test at this time, however, it can add prognostic value for patients diagnosed with metastatic pancreatic cancer.

KEY POINT

- In patients who have imaging that is characteristic of resectable pancreatic cancer, tissue sampling prior to potential curative resection is not appropriate, and definitive resection without prior tissue confirmation should be pursued.

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Item 137 Answer: B

Educational Objective: Diagnose metastatic breast cancer through biopsy of a suspicious lesion.

Patients with a history of early breast cancer who develop findings suspicious for metastatic breast cancer should first have a biopsy of one of the suspected metastatic sites to confirm the diagnosis and to assess hormone receptor and *HER2* status, as these may differ from the original cancer. A study of suspected metastatic lesions in 121 women with newly metastatic breast cancer showed discordance between the primary and the metastatic site in 16% of specimens for estrogen receptor, 40% for progesterone receptor, and 10% for *HER2*. Biopsy led to a change in management in 14% of patients. Since bone biopsy specimens cannot be assessed for *HER2* status unless there is a soft tissue component, biopsy of an area other than bone is preferred, if possible.

Beginning chemotherapy is inappropriate before the diagnosis of metastatic breast cancer and its hormone receptor and *HER2* status are confirmed by biopsy.

Beginning antiestrogen therapy (for example, exemestane combined with everolimus) is also inappropriate before biopsy confirmation of metastatic breast cancer.

Although a PET/CT scan may be useful for staging disease and following response to treatment in patients with metastatic breast cancer, it is important first to establish the diagnosis by biopsy. In this patient, the ultrasound and

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CT scans have already identified an accessible location for biopsy, and a PET scan is not needed before proceeding to biopsy of one of the liver lesions.

KEY POINT

- Patients with a history of early breast cancer who develop findings suspicious for metastatic breast cancer should undergo biopsy of one of the suspected metastatic sites to confirm the diagnosis and to assess hormone receptor and *HER2* status, as these may differ from the original cancer.

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Amir E, Miller N, Geddie W, et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol. 2012 Feb 20;30(6):587-92. [PMID: 22124102]

Item 138 Answer: A

Educational Objective: Manage a patient with metastatic lung cancer and poor performance status.

Recommending comprehensive palliative care assessment for possible hospice care is indicated. Stage IV (metastatic) non–small cell lung cancer (NSCLC) is incurable. Because metastatic NSCLC is a systemic process, systemic chemotherapy is typically used as the primary treatment modality. Chemotherapy for stage IV NSCLC has been shown to prolong survival and improve quality of life. However, patients with poor performance status and advanced disease have a limited prognosis (less than 4 months) despite therapy. Goals of therapy for these patients are symptom palliation and possible prolongation of survival. This patient has progressive metastatic lung cancer based on imaging studies that were obtained after she completed four cycles of chemotherapy. She also has a clear decline in functional status. Based on these findings, hospice care would be most appropriate.

The response rate to second-line chemotherapy is very low in patients with NSCLC. In addition, all available evidence indicates that patients with an Eastern Cooperative Oncology Group/World Health Organization performance status of 2 or worse do not derive benefit from chemotherapy.

Providing artificial nutrition for patients with advanced cancer has not been shown to improve outcomes and is not usually recommended.

The pleural effusion identified on the most recent imaging studies is small and is not causing respiratory compromise. Thoracostomy tube drainage is therefore not indicated.

Radiation therapy should be considered to relieve pain, particularly bony pain, visceral pain (when secondary to capsular distension), or pain due to nerve/nerve root compression. Although this patient has pain due to a metastatic lesion involving the L3 vertebral body, the pain is mild, managed with a NSAID, and there is no evidence of cord compression; consequently, radiation treatment is not needed for palliation.

KEY POINT

- Patients with lung cancer and poor performance status do not benefit from chemotherapy and should undergo a palliative care assessment.

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Item 139 Answer: B

Educational Objective: Diagnose renal cell carcinoma in a patient with erythrocytosis and a high serum erythropoietin level.

This patient requires CT of the abdomen and pelvis to detect possible renal cell carcinoma. The findings of a markedly elevated serum erythropoietin level due to secondary erythrocytosis plus vague midback pain and microscopic hematuria suggest the presence of an underlying renal cell carcinoma. Renal cell carcinoma is associated with secondary erythrocytosis in about 1% to 3% of patients. Polycythemia vera (PCV), a myeloproliferative neoplasm that results in excessive and unregulated erythrocyte production, is associated with very low serum erythropoietin levels. In contrast, an elevated serum erythropoietin level indicates the presence of secondary erythrocytosis. Although the most common causes of secondary erythrocytosis are chronic hypoxia and elevated carboxyhemoglobin concentrations due to tobacco use, an important cause is an erythropoietin-producing tumor. Other tumors commonly associated with secondary erythrocytosis include hepatocellular carcinoma and pheochromocytoma.

Bone marrow biopsy is not indicated because of this patient's markedly elevated serum erythropoietin level, which suggests external erythropoietin production and not a bone marrow disorder as a cause of this patient's polycythemia.

JAK2 mutation testing, which would be appropriate to rule out PCV in a patient with a very low serum erythropoietin level, is not indicated for this patient who has a markedly elevated level that is not compatible with a diagnosis of PCV.

Peripheral blood flow cytometry would not add useful information because this patient has isolated polycythemia and no evidence of abnormal lymphocytes. Flow cytometry is best used to help establish a diagnosis when evaluating for a malignancy that would reveal a monoclonal population of cells with a specific phenotype.

KEY POINT

- The finding of a markedly elevated serum erythropoietin level in a patient with vague midback pain and microscopic hematuria suggests the presence of an underlying renal cell carcinoma.

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Item 140 Answer: B

Educational Objective: Treat a localized gastrointestinal stromal tumor with imatinib after surgical resection.

Imatinib for 3 years is the most appropriate adjuvant treatment for this patient, who has a localized gastrointestinal stromal tumor (GIST) associated with a relatively higher risk for recurrence. GISTs, although rare, are the most common sarcoma of the gastrointestinal tract. The most common site is in the stomach, but GISTs can arise anywhere in the digestive tract. Location outside the stomach, larger size, and higher mitotic index constitute relative high-risk factors for recurrence after resection. Patients with small gastric GISTs with low mitotic indices may often be managed with surgery alone. Higher-risk tumors, such as in this patient, require further treatment. A 3-year course of the oral tyrosine kinase inhibitor imatinib has been shown to improve outcomes when used as adjuvant therapy after surgical resection of localized higher-risk GISTs. Imatinib has also been shown to be highly active in treating patients with metastatic GISTs, in whom lifelong therapy is recommended. Finally, randomized clinical trials have shown a superior outcome for those patients with localized higher-risk GISTs who receive imatinib for 3 years compared with those receiving 1 year of treatment.

The MAGIC trial demonstrated the superiority of preoperative and postoperative chemotherapy (epirubicin, cisplatin, and 5-fluorouracil) compared with surgery alone for treatment of gastric and esophageal/gastroesophageal junction adenocarcinomas. In patients who undergo surgery as initial therapy, postoperative 5-fluorouracil and leucovorin plus radiation therapy have been shown to confer a survival benefit compared with postoperative observation alone. These therapies are not effective treatments for GISTs.

GISTs are relatively resistant to radiation, and adjuvant radiation therapy is not routinely indicated.

Observation following surgical resection is appropriate only for patients with GISTs associated with favorable risk factors, whereas this patient has a higher-risk tumor.

KEY POINT

- Patients with a localized gastrointestinal stromal tumor with a relatively higher risk for recurrence should be treated with imatinib for 3 years following resection of the tumor.

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Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA. 2012 Mar 28;307(12):1265-72. [PMID: 22453568]

Item 141 Answer: C

Educational Objective: Manage neutropenia and fever in a patient with leukemia.

This patient requires immediate parenteral administration of a broad-spectrum antibiotic such as piperacillin-tazobactam while blood and urine cultures are pending. Neutropenia is defined as an absolute neutrophil count less than 1000/μL (1.0×10^9/L). Monotherapy with a β-lactam agent with broad coverage of gram-positive and gram-negative organisms with antipseudomonal activity has been shown to be effective in treating neutropenic fever and is the most commonly used approach. Although combination antibiotic therapy is often used (such as the addition of an aminoglycoside for additional antipseudomonal coverage), no specific regimen has been shown to be superior to broad-spectrum monotherapy. It is also reasonable to further broaden directed antimicrobial therapy if a specific source is suspected, such as adding gram-positive coverage (for example, vancomycin) if a central catheter infection is considered likely. Antifungal agents are usually considered only for patients with mucosal barrier inflammation and prolonged neutropenia (>1 week), and antiviral agents are used only in patients whose disease or therapy is associated with immunosuppression. Antimicrobial therapy should be narrowed if a specific organism or organisms are identified on culture.

Because of resistance, fluoroquinolones are not frequently used as initial monotherapy for patients with neutropenic fever. However, they may have a role in selected low-risk patients with stable vital signs and an unremarkable physical examination who might be eligible for outpatient oral therapy at experienced centers with close monitoring capability. They may also be used as add-on therapy for specific infections or for directed therapy based on culture results.

Hematopoietic growth factors, including granulocyte-macrophage colony-stimulating factors, are effective in preventing neutropenia and allowing for continued full-dose chemotherapy when appropriate. These agents also may reduce the duration of neutropenia and the length of hospitalization for patients admitted if fever develops in the setting of neutropenia. However, hematopoietic growth factors are not a replacement for immediate antimicrobial therapy in patients with fever and neutropenia and do not have a clear role in treatment.

Waiting for culture results before administering antimicrobial agents in patients with neutropenia and fever is never appropriate. If patients do not receive parenteral antimicrobials immediately after cultures are taken, their condition can rapidly deteriorate over 12 to 24 hours, and they can experience sepsis, shock, and death.

Although gram-positive organisms are the most commonly identified cause of neutropenic fever, initial monotherapy with vancomycin is not appropriate because of the potential virulence of gram-negative organisms. Vancomycin is usually not a routine component of empiric

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CONT. broad-spectrum antibiotic therapy for neutropenic fever without a specific indication.

KEY POINT

- Patients with a neutrophil count less than 500/μL (0.5×10^9/L) or at any level in the presence of fever or other signs of infection require rapid administration of broad-spectrum antibiotics.

Bibliography

Paul M, Yahav D, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2006 Feb;57(2):176-89. [PMID: 16344285]

Item 142 Answer: A

Educational Objective: Manage a patient with prostate cancer recurrence following radical prostatectomy.

Androgen deprivation therapy is indicated for this patient with possible metastatic prostate cancer. Following surgery for early-stage prostate cancer, the serum prostate-specific antigen (PSA) level should be undetectable. A postoperative serum PSA level of 0.2 ng/mL (0.2 μg/L) or greater is therefore diagnostic of residual or recurrent prostate cancer. Although this finding can represent either locally recurrent or distant metastatic disease, timing is an important discriminating factor in ascertaining the likelihood of local versus distant recurrence. Men who have a persistently elevated PSA level, particularly a rising level immediately following surgery (such as the patient described here), have a high likelihood of harboring distant metastatic disease. Androgen deprivation therapy is therefore indicated for this patient. Prostate cancer cells usually need testosterone to grow. Surgical or chemical castration is highly effective in reducing serum testosterone levels and suppressing prostate cancer cell growth.

Patients with metastatic prostate cancer are first treated with androgen deprivation therapy. Although prostate cancer initially is androgen dependent, over time, cancer cells become androgen independent. Chemotherapy has recently been shown to prolong life expectancy in many of these patients. Since this patient has not yet been treated with androgen deprivation therapy, chemotherapy is not indicated.

A rising PSA level indicates biochemical recurrence, and estimates of survival can be made from the time of completion of treatment to the rise in the PSA, the rate of that rise, and the initial Gleason score. Although recurrent disease after definitive therapy of early-stage prostate cancer is incurable, significant palliation can be achieved with hormone deprivation therapy and chemotherapy. Continuing to monitor the PSA level without initiating therapy is not recommended.

Identification of biochemical recurrence 2 or more years after surgery is more consistent with local recurrence. Studies have shown that salvage radiotherapy is beneficial for men diagnosed with a biochemical recurrence 2 or more years after surgery. In contrast, radiotherapy does not seem to benefit men in whom a PSA level remains detectable following surgery.

KEY POINT

- Men who have a persistently elevated serum prostate-specific antigen level immediately following surgery for prostate cancer have a high likelihood of harboring distant metastatic disease and should be started on androgen deprivation therapy.

Bibliography

Zaorsky NG, Raj GV, Trabulsi EJ, Lin J, Den RB. The dilemma of a rising prostate-specific antigen level after local therapy: what are our options? Semin Oncol. 2013 Jun;40(3):322-36. [PMID: 23806497]

Item 143 Answer: D

Educational Objective: Treat locally advanced squamous cell carcinoma of the neck with radiation therapy or surgery alone.

Either radiation therapy or surgical resection is the most appropriate treatment for this patient with early stage squamous cell carcinoma of the oropharynx. Because head and neck cancers tend to recur locally rather than spread systemically, radiation therapy and surgical resection are the primary treatment modalities for stage I and II disease (without lymph node involvement) of the oropharynx. These tumors are highly curable with either modality, with the specific treatment typically selected based on factors such as surgical accessibility of the tumor and the expected morbidity and functional outcomes anticipated with either approach. In patients treated with surgery as the initial approach, adjuvant radiation or combined chemotherapy and radiation may also be indicated for follow-up treatment based on findings at surgery such as close or positive surgical margins, the presence of lymphovascular or perineural invasion, or identification of more advanced (T3 or T4) disease. An important exception to this general treatment approach for early stage head and neck squamous cell malignancies is nasopharyngeal cancer, which is treated with radiation alone for stage I disease and combined chemotherapy and radiation for stage II and higher disease because of a higher risk of distant disease occurrence with these tumors.

Because of their higher rate of locoregional recurrence, more locally advanced tumors (lymph node involvement) are usually treated with surgery (for accessible oral cavity tumors) or combined modality therapy (for other oropharyngeal anatomic sites) that includes radiation along with concurrent chemotherapy with a radiation sensitizer; cisplatin is the most commonly used agent for this purpose. Multiple studies have found that use of combined modality therapy results in significantly improved patient outcomes. However, treatment for locally advanced disease with cisplatin chemotherapy and radiation in this patient with early stage cancer would not be indicated.

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Radiation therapy is considered definitive treatment for early stage head and neck cancer. Therefore, adjuvant chemotherapy following radiation therapy is not indicated and would not be an appropriate treatment in this patient.

Cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor, also has an established role in the treatment of locally advanced squamous cell carcinoma of the head and neck when given with radiation therapy. The addition of either cisplatin or cetuximab has been shown to improve survival when compared with radiation therapy alone in patients with locally advanced disease. However, this is not the standard of care treatment for patients with early stage disease who have a much better prognosis and who can be effectively treated with either primary radiation therapy or surgery alone.

KEY POINT

- Patients with early stage head and neck cancer should be treated with either surgery or primary radiotherapy; use of combined chemotherapy and radiation is not indicated.

Bibliography

Gunn GB, Frank SJ. Advances in radiation oncology for the management of oropharyngeal tumors. Otolaryngol Clin North Am. 2013 Aug;46(4):629-43. [PMID: 23910474]

Item 144 Answer: A

Educational Objective: Treat metastatic pancreatic cancer with multiagent systemic chemotherapy.

Multiagent systemic chemotherapy, with a preferred regimen of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), is most appropriate for this patient, who has a history of stage II pancreatic cancer and now has developed a metastatic recurrence. Patients with pancreatic cancer remain at substantial risk of developing a metastatic recurrence within the first 2 years after undergoing appropriate surgical resection (Whipple procedure). For such patients who are otherwise medically fit and have good performance status, FOLFIRINOX chemotherapy is associated with improved outcomes compared with single-agent chemotherapy. More recently, the combination of nab-paclitaxel and gemcitabine has been shown to be modestly superior to gemcitabine alone.

Gemcitabine as single-agent therapy would be suitable for a patient with metastatic pancreatic cancer who is more debilitated (poor performance status) than the patient described here.

Radiation therapy to the liver might be appropriate for treatment of locally symptomatic liver disease but would not be effective for management of metastatic pancreatic cancer in a patient who is otherwise a good candidate for systemic chemotherapy.

Transarterial chemoembolization is used for treatment of metastatic lesions to the liver associated with a number of different cancers. It is most effective in treating larger, symptomatic metastatic lesions, but does not address systemic disease and would not be expected to be as effective as multiagent systemic chemotherapy.

KEY POINT

- Multiagent systemic chemotherapy with 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) is appropriate treatment for metastatic recurrence of pancreatic cancer in patients with good performance status.

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Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011 May 12;364(19):1817-25. [PMID: 21561347]

Item 145 Answer: C

Educational Objective: Treat Burkitt lymphoma with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyper-CVAD).

Combination chemotherapy consisting of rituximab plus hyperfractionated (rapidly cycled) cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyper-CVAD) is most appropriate for this patient with CD20-positive Burkitt lymphoma. The most aggressive forms of large cell lymphoma include Burkitt lymphoma and lymphoblastic lymphoma. Onset of disease is acute, and patients usually present with life-threatening metabolic and structural abnormalities (this patient has early tumor lysis syndrome and impending airway obstruction). Treatment with R-hyper-CVAD, which is also used to treat acute lymphoblastic leukemia, is associated with high response rates (80%) and is curative in nearly 50% of patients with CD20-positive disease. The International Prognostic Index (IPI) score was developed to assist in determining prognosis before therapy. The IPI score is based on the patient's age, serum lactate dehydrogenase level, number of extranodal sites, disease stage, and performance status. Patients with Burkitt lymphoma have high IPI scores and always warrant aggressive and immediate therapy. Careful monitoring is required when treating patients with Burkitt lymphoma because rapid cell turnover and cell death are exacerbated by initiation of chemotherapy. Aggressive intravenous hydration, urine alkalinization, and administration of allopurinol or rasburicase are indicated in addition to chemotherapy.

Although Burkitt lymphoma can be localized in presentation, it is considered a generalized disease process and is treated with systemic agents. Therefore, neither surgery nor involved-field radiation therapy is indicated as primary treatment.

Because of their association with *Helicobacter pylori* infection, gastric mucosa-associated lymphoid tissue lymphomas can often be induced into complete and durable remission with the combination of antimicrobial agents and a proton pump inhibitor such as amoxicillin, clarithromycin, and omeprazole without the need for additional chemotherapy. This

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CONT. regimen is not effective for patients with aggressive large B-cell lymphoma, such as Burkitt lymphoma.

KEY POINT

- Patients with Burkitt lymphoma always warrant aggressive and immediate therapy with combination chemotherapy and aggressive intravenous hydration, urine alkalinization, and administration of allopurinol or rasburicase.

Bibliography

Molyneux EM, Rochford R, Griffin B, et al. Burkitt's lymphoma. Lancet. 2012 Mar 31;379(9822):1234-44. [PMID: 22333947]

Item 146 Answer: A

Educational Objective: Treat advanced chronic lymphocytic leukemia that is resistant to standard therapy.

Hematopoietic stem cell transplantation (HSCT) is most appropriate for this patient who has aggressive B-cell chronic lymphocytic leukemia (CLL) refractory to therapy. CLL is the most common form of adult leukemia, accounting for 10% of all hematologic malignancies. Patients with CLL are usually diagnosed at a median age of 70 years. Many of these patients are asymptomatic at the time of diagnosis and are identified after detecting lymphocytosis on a complete blood count obtained for other purposes. The disease course is often indolent with many patients not requiring treatment. For those who do, newer therapies have improved the median survival for patients with CLL nearly to that of age-matched healthy controls. Although younger patients develop CLL less often, they usually have more aggressive disease as in this patient who had systemic symptoms at presentation in addition to significant lymphadenopathy and splenomegaly. In addition, his disease resistance to standard rituximab and multiagent chemotherapy, the presence of immune thrombocytopenia, and a 17p deletion together confer a limited likelihood of survival (median survival less than 3 years). Because of this, HSCT is the only therapeutic option for this patient that is associated with the potential for cure, and he has siblings who might serve as possible HLA-matched donors.

Leukapheresis is the selective removal of leukocytes from the blood and is typically used in patients with acute leukemias, particularly acute myelogenous leukemia, in which myeloblast counts typically exceeding 100,000/μL (100×10^9/L) result in leukostasis with resulting respiratory failure and central nervous system symptoms. Leukapheresis rapidly lowers the leukocyte count, decreasing leukostasis. However, leukostasis is rarely associated with CLL, and even with very high leukocyte counts, leukapheresis is not indicated in this patient without an extreme elevation of his leukocyte count or evidence of hyperviscosity.

The lymphocytes associated with CLL are usually exquisitely radiosensitive, and radiation of bulky lymph nodes may be helpful in managing symptoms associated with lymphadenopathy. It is frequently used in conjunction with other more definitive treatments or palliatively. However, this patient does not have significant symptoms related to his lymphadenopathy, and radiation therapy would also not address the underlying hematologic malignancy in this patient.

Splenectomy has been shown to be beneficial in patients with CLL who have marked splenomegaly or profound cytopenias in which splenomegaly may be a contributing factor. However, it is usually reserved for patients whose disease does not respond to chemotherapy or other treatments. Although this patient has evidence of splenomegaly and a low platelet count, he has no evidence of organ impingement from his enlarged spleen or bleeding from his thrombocytopenia. Therefore, there is no current indication for splenectomy at this time.

KEY POINT

- Allogeneic hematopoietic stem cell transplantation, a potentially curative therapy option, should be considered for a young patient with advanced chronic lymphocytic leukemia associated with a high risk of disease progression.

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van Besien K, Keralavarma B, Devine S, Stock W. Allogeneic and autologous transplantation for chronic lymphocytic leukemia. Leukemia. 2001 Sep;15(9):1317-25. [PMID: 11516091]

Item 147 Answer: C

Educational Objective: Treat a high-grade neuroendocrine tumor of unknown primary site with platinum-based chemotherapy.

This patient has a high-grade poorly differentiated neuroendocrine tumor of unknown primary site; such tumors often respond rapidly to systemic platinum-based chemotherapy, such as the regimens used to treat small cell lung cancer. Although these regimens can have substantial side effects, the potential for clinical benefit, including improved symptom control and prolonged survival, is significant. Bone metastases are also likely to respond to this chemotherapy regimen.

Hepatic artery embolization is a locoregional therapy that is often used to treat patients with low-grade neuroendocrine tumors, but this technique is not effective for treating patients with high-grade neuroendocrine tumors and would not provide therapy for the bone metastases.

Octreotide is useful for treating patients with low-grade neuroendocrine tumors and for managing hormonal symptoms caused by hormonally functional tumors, but it is not effective for treating patients with high-grade neuroendocrine tumors.

Radiation therapy for bone metastases is inappropriate because it would delay chemotherapy for the visceral metastases, which are clinically more important. In addition, chemotherapy may also treat the bone metastases.

Radiofrequency ablation is useful for treating patients with a limited number of small metastases of low-grade neuroendocrine tumors but would not be appropriate for

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treating patients with high-grade neuroendocrine tumors or for managing patients with bulky liver metastases.

KEY POINT

- High-grade poorly differentiated neuroendocrine tumors of unknown primary site often respond rapidly to systemic platinum-based chemotherapy, such as the regimens used to treat small cell lung cancer.

Bibliography

Reidy DL, Tang LH, Saltz LB. Treatment of advanced disease in patients with well-differentiated neuroendocrine tumors. Nat Clin Pract Oncol. 2009 Mar;6(3):143-52. [PMID: 19190591]

Item 148 Answer: B

Educational Objective: Treat a premenopausal patient who has completed breast cancer therapy with antiestrogen therapy.

This patient, who has completed breast surgery, adjuvant chemotherapy, and primary breast radiation, should now be started on antiestrogen therapy. Tamoxifen has been the standard treatment in premenopausal women. As her breast cancer is estrogen receptor positive, adjuvant antiestrogen therapy will reduce her risk of distant recurrence by 40% to 50%. For premenopausal women with hormone receptor–positive early-stage breast cancer, tamoxifen should be used for at least 5 years–preferably 10 years based on the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) and Adjuvant Tamoxifen Treatment Offers More (aTTom) trials.

Exemestane is an aromatase inhibitor that blocks peripheral conversion of androgens to estrogens. Aromatase inhibitors are therefore used only in postmenopausal women in whom the primary source of estrogen is peripheral conversion of adrenal androgens; therapy with exemestane alone would therefore not be appropriate in the woman with residual ovarian function. However, exemestane has recently been compared with tamoxifen in conjunction with ovarian suppression in premenopausal women. The Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function Trial (SOFT) trials have shown improved disease-free survival at 5 years for exemestane with ovarian suppression compared to tamoxifen with ovarian suppression, and this is now an option that can be discussed with premenopausal patients, particularly those at high risk of recurrence. There is at present no difference in breast cancer mortality between these two treatments and the toxicity analysis of these treatments with ovarian suppression compared to tamoxifen alone has not yet been done.

There is no evidence that maintenance chemotherapy is effective in early stage breast cancer and it has not been used outside of a clinical trial.

Without antiestrogen adjuvant therapy, the patient's risk of distant recurrence will increase. As above, antiestrogen therapy reduces the risk of breast cancer distant recurrence by 40 to 50% and also decreases the risk of contralateral breast cancers by 50%. Its use should be recommended in this patient with hormone receptor–positive early-stage breast cancer.

KEY POINT

- The recommended adjuvant endocrine therapy following breast cancer treatment for a premenopausal patient is tamoxifen for at least 5–preferably 10–years.

Bibliography

Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol. 2014 Jul 20;32(21):2255-69. [PMID: 24868023]

Item 149 Answer: A

Educational Objective: Manage non–small cell lung cancer and poor performance status with palliative care.

The most appropriate management for this patient with metastatic non–small cell lung cancer (NSCLC) and a poor performance status is a comprehensive palliative care assessment. While systemic chemotherapy treatment with a platinum-based doublet regimen has been shown to improve both overall survival and quality of life, this has only been shown for patients with good performance status (Eastern Cooperative Oncology Group/World Health Organization performance status of 2 or better). Patients with a performance status of 2 can carry out all self-care activities and they are also active more than 50% of waking hours. This patient clearly does not meet that definition, as he is spending significant time in bed and requires help with self-care activities. For a patient such as this, chemotherapy treatment has no benefit and instead is associated with potential harm and significant negative impact on quality of life. In contrast, palliative care instituted early in the disease course for patients with metastatic NSCLC has shown to improve symptom control and improve survival.

Pleurodesis, or obliteration of the pleural space, may be helpful in managing recurrent malignant pleural effusion. However, this patient has undergone thoracentesis without evidence of recurrent effusion. Therefore, pleurodesis would not be indicated in this patient.

Radiation treatment to sites of osseous metastases is indicated only for symptom control or for stabilization of a suspected impending fracture. Neither of these is indicated to be an issue for this patient.

KEY POINT

- Early palliative care has shown to improve symptom control and survival in patients with non–small cell lung cancer and associated poor performance status.

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Welcome to the Infectious Disease Section of MKSAP 17!

In these pages, you will find updated information on skin and soft tissue infection, community-acquired pneumonia, tick-borne disease, urinary tract infections, *Mycobacterium tuberculosis* and nontuberculous mycobacterial infection, sexually transmitted infection, travel medicine, infectious gastrointestinal syndromes, health care–associated infection, and many other clinical challenges. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of infectious disease.

The publication of the 17th edition of Medical Knowledge Self-Assessment Program (MKSAP) represents nearly a half-century of serving as the gold-standard resource for internal medicine education. It also marks its evolution into an innovative learning system to better meet the changing educational needs and learning styles of all internists.

The core content of MKSAP has been developed as in previous editions—newly generated, essential information in 11 topic areas of internal medicine created by dozens of leading generalists and subspecialists and guided by certification and recertification requirements, emerging knowledge in the field, and user feedback. MKSAP 17 also contains 1200 all-new, psychometrically validated, and peer-reviewed multiple-choice questions (MCQs) for self-assessment and study, including 108 in Infectious Disease. MKSAP 17 continues to include *High Value Care* (HVC) recommendations, based on the concept of balancing clinical benefit with costs and harms, with links to MCQs that illustrate these principles. In addition, HVC Key Points are highlighted in the text. Also highlighted, with blue text, are *Hospitalist*-focused content and MCQs that directly address the learning needs of internists who work in the hospital setting.

MKSAP 17 Digital provides access to additional tools allowing you to customize your learning experience, including regular text updates with practice-changing, new information and 200 new self-assessment questions; a board-style pretest to help direct your learning; and enhanced custom-quiz options. And, with MKSAP Complete, learners can access 1200 electronic flashcards for quick review of important concepts or review the updated and enhanced version of Virtual Dx, an image-based self-assessment tool.

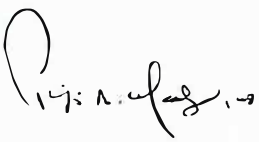
As before, MKSAP 17 is optimized for use on your mobile devices, with iOS- and Android-based apps allowing you to sync your work between your apps and online account and submit for CME credits and MOC points online.

Please visit us at the MKSAP Resource Site (mksap.acponline.org) to find out how we can help you study, earn CME credit and MOC points, and stay up to date.

Whether you prefer to use the traditional print version or take advantage of the features available through the digital version, we hope you enjoy MKSAP 17 and that it meets and exceeds your personal learning needs.

On behalf of the many internists who have offered their time and expertise to create the content for MKSAP 17 and the editorial staff who work to bring this material to you in the best possible way, we are honored that you have chosen to use MKSAP 17 and appreciate any feedback about the program you may have. Please feel free to send us any comments to mksap_editors@acponline.org.

Sincerely,



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The learning objectives of MKSAP 17 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence

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- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internists and primary care physicians
- Subspecialists who need to remain up-to-date in internal medicine and in areas outside of their own subspecialty area
- Residents preparing for the certification examination in internal medicine
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Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon (**HVC**).

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Errata for MKSAP 17 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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Infectious Disease High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 17 in several important ways. MKSAP 17 now includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Infectious Disease section of MKSAP 17.

- Viral meningitis is managed supportively, with empiric antimicrobials given only until cerebrospinal fluid cultures exclude bacterial meningitis.
- Skin infection is usually diagnosed clinically; radiography should be reserved for when the diagnosis is uncertain, necrotizing fasciitis is suspected, or when an associated abscess or foreign body is a concern.
- In community-associated methicillin-resistant *Staphylococcus aureus* infections, the primary treatment of a cutaneous abscess is incision and drainage.
- No antibiotic treatment is needed after incision and drainage of a simple furuncle, except in patients who are immunosuppressed, who do not respond adequately to incision and drainage or antibiotics without MRSA activity, or who have systemic signs of infection (see Item 103).
- Amoxicillin-clavulanate prophylaxis is recommended only for patients with animal bites who are immunosuppressed; have moderate-to-severe wounds, particularly on the face or hand; have wounds near a joint or bone; or have wounds associated with significant crush injury or edema.
- One of several decision support tools (Pneumonia Severity Index, CURB-65/CRB-65, Infectious Diseases Society of America/American Thoracic Society criteria for severe pneumonia) should be used to assess the need for outpatient versus hospitalized patients care of community-acquired pneumonia.
- Patients treated with intravenous antibiotics for community-acquired pneumonia with an appropriate clinical response can be switched to an oral agent, generally of the same antimicrobial class and with similar spectrum of activity, when clinical stability has been attained (see Item 51).
- Continued in-hospital monitoring of stable patients following the transition from parenteral to oral therapy has not been shown to improve outcomes.
- In patients taking intravenous antimicrobial therapy, a switch to oral therapy should be considered in all patients with an intact and functioning gastrointestinal tract and whose clinical status is improving (see Item 42).
- Empiric antimicrobial therapy should be modified or de-escalated as soon as culture results become available to provide the narrowest-spectrum agent available (see Item 53).
- Treatment courses for community-acquired pneumonia longer than 5 days have not shown clinical benefit and should be avoided to minimize unnecessary antimicrobial use and avoid extra expense of care.
- The routine use of follow-up chest radiography after successful treatment of community-acquired pneumonia is not recommended because findings may linger despite clinical improvement and symptom resolution.
- Antibodies may not be present early in Lyme disease infection; documentation of erythema migrans with a compatible epidemiologic history is sufficient for diagnosis, and serologic testing is not indicated and may be falsely negative in localized disease.
- Lyme arthritis is excluded if symptoms have been present for longer than 1 month and Western blot IgG result is negative; there is no need for further evaluation or treatment for Lyme disease in these patients (see Item 82).
- Post–Lyme disease syndrome or "chronic Lyme disease" occurs in some patients despite appropriate antibiotic therapy and includes nonspecific but disabling symptoms; management focuses on amelioration of symptoms

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and prolonged administration of antibiotics is contraindicated.

- Avoid inappropriate antibiotic use wherever possible; antimicrobial resistance among urinary pathogens is increasing in frequency in the community and hospital settings because of antibiotic overuse, inappropriate treatment of asymptomatic bacteriuria, and local differences in antibiotic use.
- A culture of midstream, clean-void urine should be reserved for patients with suspected pyelonephritis, complicated urinary tract infection, recurrent urinary tract infection, or multiple antimicrobial allergies and in those in whom the presence of a resistant organism is suspected.
- Fosfomycin has lower efficacy and is more expensive than nitrofurantoin or trimethoprim-sulfamethoxazole in first-line antimicrobial therapy for women with acute uncomplicated cystitis.
- Acute uncomplicated pyelonephritis should be treated with fluoroquinolones for 5 to 7 days, complicated infections should be treated for 14 days, and hospitalized patients treated initially with parenteral antibiotics can be switched to oral agents after clinical improvement is noted and oral therapy can be tolerated.
- The interferon-γ release assay should be reserved for persons who have received bacillus Calmette-Guérin vaccine previously or are members of groups that are unlikely to return to have their tuberculin skin test interpreted.
- Routinely combining a tuberculin skin test with interferon-γ release assay to test for tuberculosis adds expense but no additional value and should be avoided.
- Nucleic acid amplification testing targeting *Mycobacterium tuberculosis* in sputum from patients with high clinical suspicion of having tuberculosis (AFB smear–positive sputum) can expedite initiation of treatment, although it is more expensive and does not provide drug susceptibility and genotyping information necessary to guide long term treatment.
- At least monthly clinical evaluations are recommended during tuberculosis treatment, and routine laboratory monitoring is recommended for patients with baseline abnormalities or increased risk for adverse effects; otherwise, laboratory studies are reserved for those who develop potential drug-associated toxicities.
- Treatment of asymptomatic candiduria is indicated only in neutropenic patients and those undergoing urologic procedures; if an indwelling catheter is present, it should be removed if possible (see Item 73).
- Conventional plain radiography lacks sensitivity and specificity for diagnosing osteomyelitis and has a limited role.
- MRI is the best imaging technique for diagnosing osteomyelitis because of its high sensitivity for bone infection and superiority at delineating bone anatomy and providing excellent resolution of surrounding soft tissues; the role for follow-up MRI is limited to patients who do not clinically improve with therapy.
- Blood cultures should be obtained in all suspected cases of osteomyelitis because cultures are positive in more than 50% of cases and may avert more invasive testing.
- Culture samples obtained from superficial wounds or sinus tracts correlate poorly with deep cultures from bone and should not be obtained.
- Antimicrobial prophylaxis for traveler's diarrhea is effective, but it is generally not recommended because of the potential for adverse effects; prophylaxis should be considered in persons with coexisting inflammatory bowel disease, immunocompromised states (including advanced HIV), and comorbidities that would be adversely affected by significant dehydration.
- Fluid replacement with aggressive oral hydration is the mainstay of treatment for travelers' diarrhea (see Item 38); antimicrobials reduce the duration of diarrhea by 1 to 2 days but are recommended only in severe disease or immunosuppressed patients.
- Antibiotic treatment of otherwise healthy patients with mild diarrheal symptoms does not hasten recovery and may lead to prolonged asymptomatic shedding of *Salmonella* bacteria.
- In most cases of bacterial gastroenteritis, infection resolves spontaneously without therapy, and further evaluation or treatment is unnecessary (see Item 91).
- Therapy for mild nontyphoidal *Salmonella* gastroenteritis should be withheld in otherwise healthy patients because treatment may increase duration of bacterial shedding (see Item 58).
- Oral metronidazole and vancomycin are equally effective in treating mild-to-moderate *Clostridium difficile* infection, with the former preferred because of its lower cost; oral vancomycin is recommended for severe disease.
- Patients with hospital-acquired diarrhea who test negative for *Clostridium difficile* infection should be treated with antimotility agents to suppress symptoms and not undergo additional testing or treatment for *C. difficile* (see Item 7).
- Documenting clearance of *C. difficile* through testing serial stool samples after an initial positive test result has no role in management.
- Testing for parasites is not recommended for diarrhea lasting less than 7 days or for patients who develop diarrhea more than 3 days into a hospital stay because it is both expensive and unlikely to be helpful.
- Approximately 65% to 70% of catheter-associated bloodstream infections and urinary tract infections and 55% of ventilator-associated pneumonia cases and surgical site infections may be preventable.
- Preventing catheter-associated urinary tract infection relies on using urinary catheters only if they are essential to the patient's care and only for as short a period of time as possible (see Item 28).
- Routine urinalysis and culture should not be performed for patients with indwelling urinary catheters without symptoms or signs of urinary tract infection.

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- When culture data are available, therapy for catheter-associated urinary tract infections should be adjusted to the narrowest coverage spectrum possible.
- Continuing prophylactic antimicrobial agents postoperatively has not shown benefit in preventing surgical site infections.
- Hospitalized patients with central lines should be assessed daily to determine whether the line can be removed.
- No evidence indicates that hospital-acquired pneumonia or ventilator-associated pneumonia caused by *Pseudomonas* species requires combination therapy or that a synergistic combination improves outcomes.
- Avoiding intubation (if possible) and using noninvasive positive-pressure ventilation as an alternative (when feasible) can significantly decrease the risk for hospital-acquired pneumonia.
- Limiting transmission of antimicrobial-resistant organisms in health care settings is best accomplished by full compliance with hand hygiene protocols and contact precautions, cleaning and disinfecting the environment and patient care equipment before it is used for another patient, and judicious use of antimicrobial agents.
- Annual influenza vaccination is the most effective intervention for preventing influenza and is recommended for all persons 6 months of age or older.
- Tigecycline is a broad-spectrum antibiotic that should be used only when alternative treatments are not available, because it is expensive and should be reserved for treatment of resistant organisms.
- Suboptimal use of antimicrobial agents drives the emergence of antimicrobial resistance, leads to poor outcomes, and increases adverse events and costs.
- Outpatient parenteral antimicrobial therapy provides appropriately selected patients the ability to complete antimicrobial treatment in an outpatient setting.
- Patients with selective IgA deficiency require no specific therapy except for preventive measures against known potential complications and as-needed antibiotic therapy for those with recurrent sinopulmonary infections (see Item 84).
- Patients diagnosed with babesiosis who are asymptomatic should undergo a repeat polymerase chain reaction assay in 3 months to detect parasite clearance but do not need treatment (see Item 87).
- When a patient has been reasonably evaluated (laboratory studies, repeat blood cultures, imaging studies) for ongoing fever, a diagnosis of fever of unknown origin should be reached and the patient should be observed in case further interventions would be appropriate later (see Item 106).

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Central Nervous System Infections

Meningitis

Viral Meningitis

Causes

Viral meningitis is the most common cause of "aseptic" meningitis, in which cerebrospinal fluid (CSF) bacterial cultures are negative. Most patients have typical meningitis symptoms, such as fever, nuchal rigidity, headache, and photophobia.

A substantial proportion of viral meningitis is caused by enteroviruses, which commonly occur in the summer and fall in temperate climates when these organisms circulate in the environment. Enteroviral meningitis can also occur in winter and spring months; seasonal enteroviral infections are typically caused by coxsackievirus, echovirus, or other nonpolio enteroviruses.

Herpes simplex virus (HSV) can also cause meningitis. These meningitis syndromes can be related to primary infections, with central nervous system (CNS) involvement as a secondary consequence, or reactivation of latent infection presenting as aseptic meningitis. Most patients with HSV meningitis associated with primary infection will have genital lesions. HSV type 2 (HSV-2) is more commonly associated with meningitis, whereas HSV type 1 (HSV-1) is associated with encephalitis. An association exists between Mollaret meningitis, a benign recurring form of lymphocytic meningitis, and HSV-2; at least 84% of patients have evidence of HSV-2 in CSF.

Primary HIV infection can present with an aseptic meningitis syndrome, which may occur in isolation from the other symptoms. Meningitis due to acute HIV infection is typically self-limited and may be clinically indistinguishable from other viral meningitis syndromes.

Mumps virus can cause meningitis, with typical symptoms of fever, headache, and neck stiffness. Since the advent of universal childhood vaccination for measles, mumps, and rubella, the incidence of mumps-related meningitis has dramatically decreased. Meningitis from mumps virus can occur at any point during the course of clinical mumps infection. Parotitis or orchitis may be present.

Infections with arboviruses, such as West Nile virus or St. Louis encephalitis virus, can cause meningitis, although these infections more typically produce encephalitis. Cytomegalovirus, Epstein-Barr virus, adenovirus, and varicella virus infections can also cause meningitis.

Diagnosis

Symptoms of viral meningitis include fever, headache, neck stiffness, photophobia, and change in mental status and may be indistinguishable from symptoms of bacterial meningitis. Characteristics of the CSF profile are outlined in **Table 1**. Additional physical examination findings (rash and pharyngitis in acute HIV infection; parotitis or orchitis in mumps-related meningitis) can support the presumptive diagnosis. Polymerase chain reaction (PCR) and other molecular tests are available for diagnosis of numerous viral causes. CSF PCR studies may be used for diagnosing HSV and enterovirus meningitis; antibody detection in CSF is preferred for West Nile virus meningitis. Viral cultures of CSF are not clinically useful because of poor sensitivity and long turn-around times. Serologic testing may be an adjunctive diagnostic tool in meningitis caused by mumps.

TABLE 1. Typical CSF Findings in Patients with Viral and Bacterial Meningitis

CSF Parameter	Viral Meningitis[a]	Bacterial Meningitis
Opening pressure	≤250 mm H_2O	200-500[b] mm H_2O
Leukocyte count	50-1000/µL (50-1000 × 10^6/L)	1000-5000/µL (1000-5000 × 10^6/L)[c]
Leukocyte predominance	Lymphocytes[d]	Neutrophils
Glucose	>45 mg/dL (2.5 mmol/L)	<40 mg/dL (2.2 mmol/L)[e]
Protein	<200 mg/dL (2000 mg/L)	100-500 mg/dL (1000-5000 mg/L)
Gram stain	Negative	Positive in 60%-90%[f,g]
Culture	Negative	Positive in 70%-85%[g]

CSF = cerebrospinal fluid.

[a]Primarily nonpolio enteroviruses (echoviruses and coxsackieviruses).

[b]Values exceeding 600 mm H_2O suggest the presence of cerebral edema, intracranial suppurative foci, or communicating hydrocephalus.

[c]Range may be <100/µL (100 × 10^6/L) to >10,000/µL (10,000 × 10^6/L).

[d]May have neutrophil predominance early in infection, but lymphocyte predominance occurs after the first 6 to 48 hours.

[e]The CSF-to-plasma glucose ratio is ≤0.40 in most patients.

[f]The likelihood of a positive Gram stain correlates with number of bacteria in the CSF.

[g]The yield of positive results is significantly reduced by previous administration of antimicrobial therapy.

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Meningitis can also result from medications; autoimmune diseases; malignancy; and other nonviral infectious causes, including spirochetes, fungi, or mycobacteria. Serology may be helpful to diagnose aseptic meningitis caused by syphilis, *Borrelia burgdorferi* (Lyme disease), or certain fungal organisms.

Treatment

Anti-infective treatments are not available for viral meningitis with the exception of underlying herpes viruses. The primary focus of management in viral meningitis is to distinguish it from other causes of infectious meningitis, particularly bacterial meningitis. Symptomatic and supportive management for viral meningitis and rigorous evaluation to exclude bacterial meningitis are the cornerstones of management. Empiric antimicrobial agents may be initiated until full CSF profiles and cultures are finalized and bacterial meningitis can be excluded. Antibiotics can be started and continued as empiric treatment for 48 to 72 hours, after which most routine CSF cultures will show preliminary results. The increasing availability of enteroviral PCR testing can shorten the time required to exclude bacterial infection. Repeat lumbar puncture can be performed after the initial 2 to 3 days if lack of clinical response is a concern or if documenting the evolution of the CSF profile to that more characteristic of viral meningitis is desired.

KEY POINTS

- Viral meningitis is most commonly caused by enteroviruses, herpes simplex virus type 2, and arboviruses.
- Clinical signs and symptoms aiding in the diagnosis of viral meningitis include parotitis or orchitis with mumps virus, rash in enterovirus and HIV, pharyngitis with acute HIV, and genital lesions with herpes simplex virus.

HVC

- Viral meningitis is managed supportively, with empiric antimicrobials given only until cerebrospinal fluid cultures exclude bacterial meningitis.

Bacterial Meningitis

Causes

Bacterial meningitis usually results from bacteremic dissemination of meningeal pathogens that colonize the nasopharynx or from another distant focus of infection but may also occur from contiguous spread of infection to the CSF (sinusitis or otitis media), direct inoculation (traumatic injury or neurosurgical procedure), or prosthetic device infection (CSF shunts or drains, intracranial pressure monitors).

Individual host factors, such as colonization of the nasopharynx with potential meningeal pathogens, complement deficiency, anatomic or functional asplenia, glucocorticoid use, diabetes, hypogammaglobulinemia, and altered cell-mediated immunity, can also contribute to increased susceptibility to acute bacterial meningitis. Exposure to other persons with bacterial meningitis (for certain pathogens, such as *Neisseria meningitidis*) or travel to regions of the world where certain organisms are more prevalent and endemic (such as sub-Saharan Africa, where endemic meningococcal disease is present) will also increase the risk for bacterial meningitis.

The two most common organisms causing bacterial meningitis are *Streptococcus pneumoniae* and *N. meningitidis*, which together are responsible for more than 80% of infections (**Table 2**).

Diagnosis

Bacterial meningitis is classically described as producing fever, nuchal rigidity, and altered mental status. However, all three symptoms may not be present in many patients with confirmed disease. Other clinical manifestations that suggest bacterial meningitis include photophobia, headache (often a very severe headache distinctly different from what the patient may typically experience), and dermatologic manifestations (rash, petechiae, purpura) or neurologic abnormalities

TABLE 2. Causes of Bacterial Meningitis

Infecting Organism	Cases (%)	Comments
Streptococcus pneumoniae	>70	Many cases caused by serotypes not covered by pneumococcal vaccination; functionally and anatomically asplenic patients at greater risk
Neisseria meningitidis	12	Can be transmitted through droplet exposure; functionally and anatomically asplenic patients at greater risk
Group B streptococci	7	Persons with diabetes, alcoholism, malignancy, liver disease at risk
Staphylococcus aureus	<5	Primary infection is associated with neurosurgery or CNS prosthetic device; secondary infection arises from bacteremia
Haemophilus influenzae	6	Decreased prevalence in the pediatric age group since type B conjugate vaccine; functionally and anatomically asplenic patients at greater risk
Listeria monocytogenes	<5	Immunosuppressed and decreased cell-mediated immunity (because of medications or medical conditions) as well as age (very old and very young) are risk factors
Gram-negative bacteria	<5	Nosocomial settings; complication of neurosurgery

CNS = central nervous system.

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(focal neurologic or cranial nerve deficits, seizures). Physical examination maneuvers, such as testing for Brudzinski and Kernig signs, lack adequate sensitivity and specificity, although the presence of one or both of these findings is consistent with bacterial meningitis.

Before proceeding with lumbar puncture, it should be determined whether CT of the head should be performed. CT of the head before lumbar puncture is indicated if signs or symptoms of increased intracranial pressure or a CNS mass lesion, such as papilledema, focal neurologic deficits, or altered mental status, are present; it is also indicated in patients who are immunocompromised or have a history of CNS disease (mass lesion, stroke, focal infection). In the absence of these findings, lumbar puncture can be undertaken without CNS imaging. Elevated CSF opening pressure is common. Characteristic CSF profiles in bacterial meningitis are outlined in Table 1. CSF Gram stain and cultures, when obtained before antimicrobial therapy initiation, are usually diagnostic for the infecting organism. Rapid CSF tests, such as latex agglutination and molecular testing with PCR, can be supplemental diagnostic tools, although the diagnostic utility of latex agglutination testing is limited by a lack of specificity. Elevated CSF lactate levels suggest bacterial meningitis, but this is not a specific finding. Blood cultures, if obtained before antimicrobial therapy, are often positive and may be an adjunctive diagnostic tool in isolating the bacterial causative pathogen if CSF cannot be obtained before antibiotic administration.

Management

Suspected bacterial meningitis demands prompt therapy; because of the risk for substantial morbidity and mortality with delayed treatment, empiric therapy is often initiated before CSF results are available (**Figure 1**). When a presumptive diagnosis of bacterial meningitis has been made, empiric

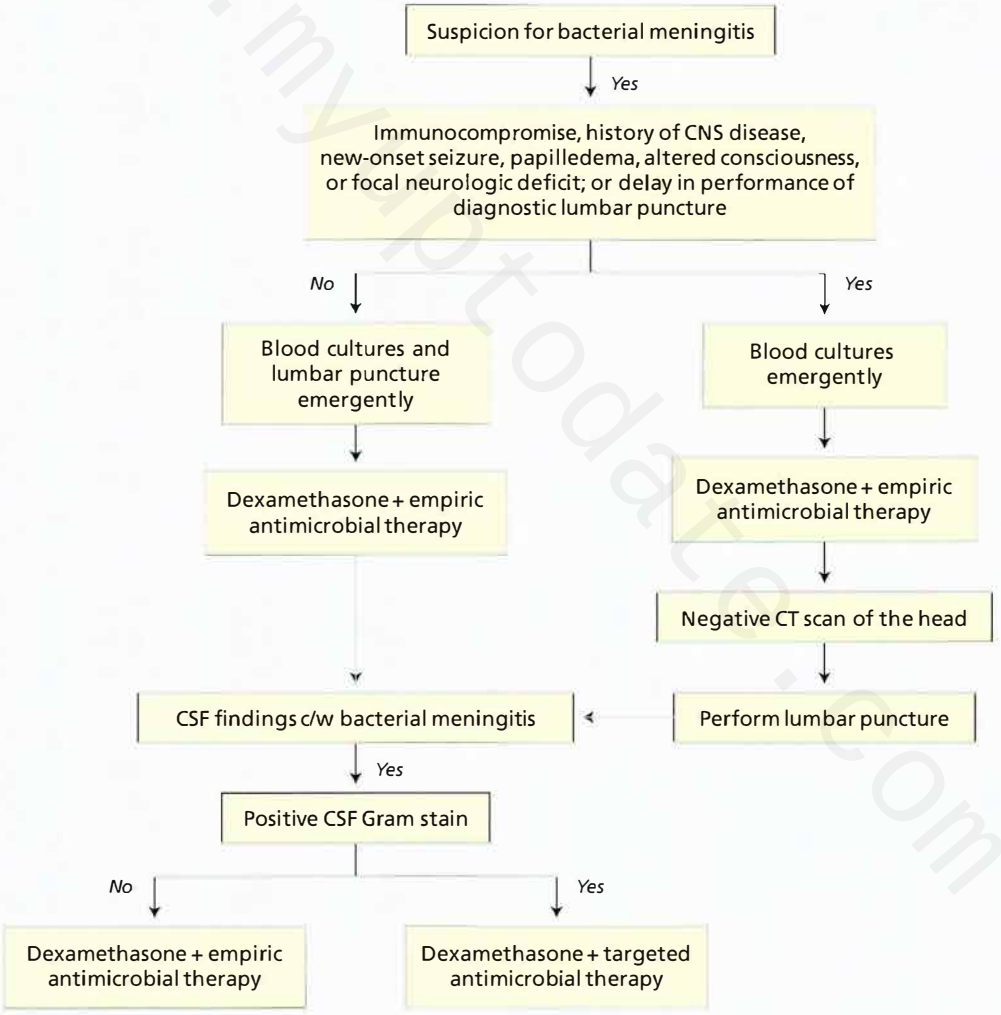

FIGURE 1. Management algorithm for adults suspected of having bacterial meningitis.

CNS = central nervous system; c/w = consistent with; CSF = cerebrospinal fluid.

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antimicrobials directed toward the most likely causes are initiated, as outlined in **Table 3**. Because of the potential neurologic complications of bacterial meningitis, particularly pneumococcal meningitis (seizures, hearing loss, cranial nerve deficits, paresis), adjunctive dexamethasone is recommended; it should be given approximately 15 minutes before administration of antimicrobial agents and should be continued for a full course (0.15 mg/kg every 6 hours for 4 days) in patients with suspected or confirmed pneumococcal meningitis. Although benefit has been shown with dexamethasone in developed countries, the drug has not been proven beneficial in resource-poor settings. When CSF cultures have been finalized, antimicrobial therapy can be altered on the basis of the specific cause and confirmed susceptibilities. Therapy duration varies depending on the causative agent and clinical response; duration may be 7 days (*N. meningitidis*, *Haemophilus influenzae*), 10 to 14 days (*S. pneumoniae*), or up to 21 days (staphylococcal, gram-negative, or *Listeria* meningitis).

KEY POINTS

- The most common organisms causing bacterial meningitis are *Streptococcus pneumoniae*, *Neisseria meningitidis*, group B streptococcus, *Haemophilus influenzae*, and *Listeria monocytogenes*.
- Empiric antimicrobial therapy should be initiated immediately in suspected bacterial meningitis, with more specific targeted therapy implemented after culture results are obtained.
- Dexamethasone is recommended as adjunctive therapy in all cases of bacterial meningitis in developed countries.

TABLE 3. Antibiotic Management of Bacterial Meningitis

Clinical Characteristics	Empiric Antibiotic Regimen
Immunocompetent host age <50 y with community-acquired bacterial meningitis	IV ceftriaxone *or* cefotaxime plus IV vancomycin
Patient age >50 y or those with altered cell-mediated immunity	IV ampicillin (*Listeria* coverage) plus IV ceftriaxone *or* cefotaxime plus IV vancomycin
Allergies to β-lactams	IV moxifloxacin instead of cephalosporin IV trimethoprim-sulfamethoxazole instead of ampicillin
Hospital-acquired bacterial meningitis	IV vancomycin plus either IV ceftazidime, cefepime, or meropenem
Neurosurgical procedures	IV vancomycin plus either IV ceftazidime, cefepime, or meropenem

IV = intravenous.

Focal Central Nervous System Infections

Brain Abscess

A brain abscess is a focal infection of the brain parenchyma that arises from hematogenous dissemination or, more commonly, direct spread of infection from contiguous anatomic structures. Multifocal brain abscesses more commonly arise from hematogenous routes of infection, whereas solitary brain abscesses most often result from extension of contiguous infections into the brain. Brain abscesses caused by contiguous infections may be a complication of otitis media, sinusitis, or odontogenic infections. Brain abscesses can also present as complications from foreign bodies that become lodged in the brain parenchyma or arise postoperatively from neurosurgical procedures. No source of infection is determined in approximately 20% to 40% of brain abscesses.

Many brain abscesses are polymicrobial, and a substantial proportion of cases involve anaerobic organisms. The microbiology and clinical characteristics of brain abscesses are outlined in **Table 4**.

Clinical presentation of brain abscess includes headache, which can be severe and unresponsive to analgesia; fever is not always present. Neck stiffness is typically present only with occipital lobe involvement. Mental status changes and vomiting indicate later-stage progression of the brain abscess and are poor prognostic signs. Physical examination may show focal neurologic signs and cranial nerve deficits. CNS imaging is the cornerstone of diagnosis; lumbar puncture is contraindicated because of the potential for increased intracranial pressure and risk for herniation. Although MRI is more sensitive than CT, contrast-enhanced CT can often be performed more rapidly. Stereotactic CT-guided aspiration can be performed to obtain microbiologic samples, but this invasive diagnostic method is often impractical before a clinical decision is made to treat a suspected brain abscess.

If brain abscess is suspected, empiric antimicrobial therapy should be started. Empiric regimens are based on predisposing conditions and suspected causative agents (see Table 4). Abscesses larger than 2.5 cm should be surgically excised or drained stereotactically. If abscesses are not drained, follow-up CNS imaging should occur within several days to assess for worsening cerebral edema. CNS imaging should be repeated urgently if any mental status or neurologic changes are noted.

Antimicrobial therapy duration is typically 4 to 8 weeks. Therapy duration should be guided by follow-up clinical evaluation and repeat neuroimaging, ideally by using the same modality as the original imaging study. Expert opinion recommends administration of glucocorticoids when substantial cerebral edema is present. A substantial portion of patients with brain abscess can have residual neurologic sequelae, particularly seizures.

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TABLE 4. Predisposing Conditions, Causative Agents, and Empiric Antimicrobial Therapy in Patients with Bacterial Brain Abscess

Predisposing Condition	Usual Causative Agents	Empiric Antimicrobial Therapy
Otitis media or mastoiditis	Streptococci (aerobic or anaerobic), *Bacteroides* species, *Prevotella* species, Enterobacteriaceae	Metronidazole plus a third-generation cephalosporin[a]
Sinusitis	Streptococci, *Bacteroides* species, Enterobacteriaceae, *Staphylococcus aureus*, *Haemophilus* species	Metronidazole plus a third-generation cephalosporin[a,b]
Dental sepsis	Mixed *Fusobacterium*, *Prevotella*, and *Bacteroides* species; streptococci	Penicillin plus metronidazole
Penetrating trauma or after neurosurgery	*S. aureus*, streptococci, Enterobacteriaceae, *Clostridium* species	Vancomycin plus a third-generation cephalosporin[a,c]
Lung abscess, empyema, bronchiectasis	*Fusobacterium*, *Actinomyces*, *Bacteroides*, and *Prevotella* species; streptococci; *Nocardia* species	Penicillin plus metronidazole plus a sulfonamide[d]
Endocarditis	*S. aureus*, streptococci	Vancomycin plus gentamicin
Hematogenous spread from pelvic, intra-abdominal, or gynecologic infections	Enteric gram-negative bacteria, anaerobic bacteria	Metronidazole plus a third-generation cephalosporin[a,b,c]
Immunocompromised patients HIV-infected patients	*Listeria* species, fungal organisms (*Cryptococcus neoformans*), or parasitic or protozoal organisms (*Toxoplasma gondii*); *Aspergillus*, *Coccidioides*, and *Nocardia* species	Metronidazole plus a third-generation cephalosporin[a,b,c,d,e]; antifungal or antiparasitic agent

[a]Cefotaxime or ceftriaxone; the fourth-generation cephalosporin cefepime may also be used.

[b]Add vancomycin if infection caused by methicillin-resistant *Staphylococcus aureus* is suspected. Vancomycin can then be transitioned to antistaphylococcal β-lactam (oxacillin-nafcillin)-penicillin if methicillin-sensitive *Staphylococcus aureus* is confirmed.

[c]Use ceftazidime or cefepime if infection caused by *Pseudomonas aeruginosa* is suspected. Meropenem can also be used for antipseudomonal coverage.

[d]Use trimethoprim-sulfamethoxazole if infection caused by *Nocardia* species is suspected.

[e]Use ampicillin if infection caused by *Listeria* species is suspected.

NOTE: If predisposing condition is unknown, empiric treatment should include vancomycin plus metronidazole and third-generation cephalosporin.

KEY POINT

- Empiric antimicrobial therapy should be initiated immediately if brain abscess is suspected, and successful treatment usually combines antimicrobial therapy with surgical drainage.

Spinal Epidural Abscess

Spinal epidural abscesses (SEAs) usually result from contiguous spread from infected vertebrae or intervertebral body disc spaces or hematogenous dissemination from a distant site. Risk factors include prolonged epidural catheter placement, paraspinal glucocorticoid or analgesic injections, diabetes mellitus, HIV infection, trauma, injection drug use, tattooing, alcoholism, and acupuncture. Most SEAs are caused by *Staphylococcus aureus*. Other, less frequent, causative organisms include gram-negative bacilli, *Streptococcus* species, anaerobic organisms, and, rarely, fungi or other unusual pathogens.

SEA can be challenging to diagnose because symptoms can be mild or nonspecific and fever may not always be present. A high index of suspicion, particularly in patients with atypical or persistent back pain, will facilitate more prompt diagnosis. Symptoms may progress from back pain to accompanying neurologic symptoms, such as bowel or bladder dysfunction, lower-extremity weakness, paresthesias, and, in the last stages, paralysis. MRI of the spine with contrast is the preferred imaging modality for diagnosis. If MRI cannot be done, CT of the spine with contrast may be an acceptable alternative. Microbiologic sampling with CT-guided needle aspiration can be attempted, and blood cultures should be obtained. At least two blood culture sets should be drawn in patients suspected of having SEA because the causative agent can be confirmed from these cultures more than 60% of the time. Empiric antibiotics can be started if the suspicion for SEA is high.

SEA is treated with a combination of antimicrobial therapy and surgical drainage. Medical therapy alone is often successful if no neurologic deficits are present at the time of diagnosis or if substantial complications from surgery are likely because of comorbid conditions. Serial clinical evaluations and follow-up MRI of the spine (at approximately 4-6 weeks into therapy or with any sign of clinical deterioration) are necessary adjuncts to management without surgery. Empiric parenteral antimicrobial therapy should include coverage for *S. aureus*, *Streptococcus* species, and gram-negative bacilli and may be narrowed on the basis of culture results, if available. Therapy typically lasts between 6 and 8 weeks (or until resolution of abscess on follow-up MRI) but may require

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modification depending on clinical and radiologic recovery. Antibiotic therapy is parenteral to ensure adequate penetration into the CNS.

KEY POINTS

- Spinal epidural abscesses often arise from infected vertebral discs or intervertebral body disc spaces; risk factors include prolonged epidural catheter placement, glucocorticoid or analgesic injections, diabetes mellitus, HIV infection, trauma, injection drug use, tattooing, alcoholism, and acupuncture.
- Microbiologic sampling with CT-guided needle aspiration of the spinal epidural abscess can be attempted, and two sets of blood cultures should be obtained.

Cranial Subdural Empyema

Subdural empyema is a focal infection or abscess that occurs between the dura mater and the arachnoid mater. This condition is a medical emergency warranting immediate neurosurgical intervention. Sinusitis, otitis media, or mastoiditis can be the inciting infection, with subdural empyema arising as a complication. Patients with subdural empyema initially have fevers and altered cognition, with deteriorating mental status as the infection progresses. Microbiologic testing of these infections reflects the source, with most subdural empyemas caused by *S. pneumoniae*, *H. influenzae*, aerobic and anaerobic *Streptococcus* species, *Staphylococcus* species (coagulase-positive and coagulase-negative), gram-negative bacilli, and anaerobic organisms (*Bacteroides* species). Diagnosis is based on clinical presentation, which often includes fever; headache; nausea and vomiting; mental status changes; and a history of preceding sinusitis, otitis, meningitis, mastoiditis, or recent neurosurgical procedures or sinus surgeries. The diagnosis is confirmed by MRI with gadolinium; CT with contrast is an alternative. Lumbar puncture is contraindicated when increased intracranial pressure is evident. Prompt and immediate neurosurgical intervention to drain the infected collection of purulent material is necessary. Empiric antimicrobial therapy consists of intravenous vancomycin, ceftriaxone (or another cephalosporin that penetrates the CSF well), and metronidazole. Therapy duration is guided by clinical and radiologic improvement. Surgical intervention directed toward the primary source of infection may be a necessary adjunct to successful treatment.

KEY POINT

- Cranial subdural empyema, usually arising as a complication of sinusitis, otitis media, or mastoiditis, is a medical emergency warranting immediate evaluation and neurosurgical intervention.

Encephalitis

Encephalitis is a life-threatening condition. Select viral pathogens causing encephalitis are shown in **Table 5**. Encephalitis often exists as an overlap syndrome with meningitis or inflammation of the spinal cord (encephalomyelitis). Clinically, encephalitis is defined as alteration in mental status lasting 24 hours or more that is associated with two or more of the following: fever, focal neurologic deficit, seizure, CSF pleocytosis, and abnormal findings on electroencephalography or

TABLE 5. Selected Viral Causes of Acute Encephalitis

Organism	Epidemiology and Transmission	Clinical Features	Laboratory Diagnosis	Treatment
Herpes simplex virus type 1	Reactivation of latent virus	Fever, altered mental status, temporal lobe seizures	Herpes simplex virus type 1 PCR on CSF[a]	Acyclovir (IV)
Varicella zoster virus	Can occur at time of acute infection or reactivation, increased risk in HIV	Cutaneous lesions variably present	Varicella zoster virus PCR on CSF, CSF antibodies (if vasculitis suspected)	Acyclovir (IV)
Enterovirus	Typically late summer-fall	Fever, altered mental status, variable rash or oral lesions	Enterovirus PCR on CSF	Supportive care
West Nile virus	Mosquito-borne (summer/fall)	Fevers, altered mentation with or without muscle weakness (including acute asymmetric flaccid paralysis); seizures rare	West Nile virus IgM antibody on CSF	Supportive care
Rabies virus	Bite from infected animal (most commonly bat)	Paresthesia at site of inoculation, hydrophobia, progressive obtundation	Nape of neck skin biopsy for immunohistochemistry Rabies PCR of saliva or CSF (testing coordinated with local health department)	Supportive care; prophylaxis of close contacts

CSF = cerebrospinal fluid; IV = intravenous; PCR = polymerase chain reaction.

[a]Herpes simplex virus PCR result can be negative at the time of initial presentation; must repeat test on a second CSF sample in 3-7 days if clinical suspicion remains high.

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neuroimaging. A specific cause is found in less than 50% of patients despite intensive investigation; even when a pathogen is identified, no antimicrobial therapy is available for many viral causes, and care is supportive. Nevertheless, an attempt to define the cause is indicated because establishing a diagnosis allows directed treatment, discontinuation of ineffective therapies, and determination of prognosis.

Initial management requires attention to potential comorbidities, particularly in patients with a decreased level of consciousness. All patients should undergo neuroimaging to exclude a mass lesion or cerebral edema as a contraindication to lumbar puncture. If the delay in obtaining CSF is significant (>30 minutes), empiric antimicrobial agents should be administered. Patients with evidence of cerebral edema are usually best managed in an intensive care setting with close neurologic monitoring and consideration of ventriculostomy for patients whose condition deteriorates with medical management. Electroencephalography should be considered in all patients with depressed consciousness, even without seizure activity, because nonconvulsive status epilepticus may be present in the absence of myoclonic movements.

Herpes Simplex Encephalitis

Infection with HSV-1 is the most common cause of endemic encephalitis in the United States. Most infections result from reactivation of latent virus. Herpes simplex encephalitis (HSE) is characterized by unilateral or bilateral localized infection of the temporal lobes, but the clinical presentation is nonspecific. Cerebrospinal fluid testing typically shows lymphocytic pleocytosis and, when necrosis is extensive, abundant erythrocytes. The presence of temporal lobe abnormalities on imaging is highly suggestive of HSE, with MRI (**Figure 2**) being more sensitive than CT. Periodic lateralizing epileptiform discharges on electroencephalography suggest HSE but may not be present.

Atypical presentations of HSE may occur, and laboratory testing for HSV-1 infection is recommended for all patients with encephalitis regardless of the presence of temporal lobe lesions. HSV PCR of the CSF allows rapid diagnosis of HSE, with sensitivity greater than 95% and specificity approaching 100%; however, very early in the course of infection, the result of this test may be negative. For cases with a high suspicion based on imaging consistent with HSE, testing should be performed on a subsequent CSF sample. PCR findings remain positive for up to 1 week following initiation of acyclovir treatment. The sensitivity of viral culture of CSF for HSV is less than 5%; as a result this test is discouraged. Serologic testing has limited utility because most adults have detectable HSV-1 antibody related to previous infection.

Delay in acyclovir therapy is a negative prognostic factor, and empiric therapy should be initiated for all patients suspected of having encephalitis. Acyclovir must be administered parenterally to achieve therapeutic levels in brain parenchyma. Empiric treatment can be discontinued when an alternative cause of encephalitis is discovered or, in patients with a relatively low suspicion of HSE, when the HSV PCR has negative results. When HSE is confirmed, high-dose intravenous acyclovir should be continued for 14 to 21 days.

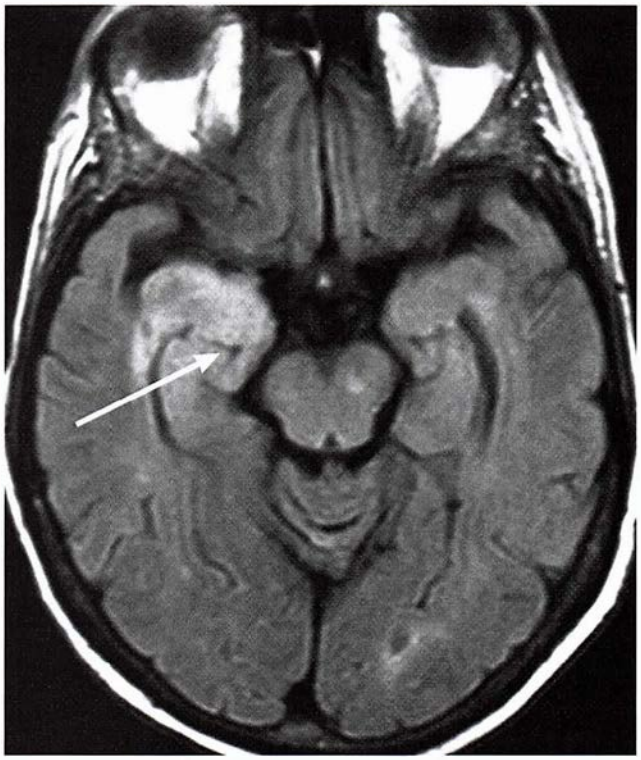

FIGURE 2. Brain MRI exhibiting right temporal lobe enhancement (*arrow*) in a patient with herpes simplex encephalitis.

KEY POINTS

- Herpes simplex encephalitis is characterized by unilateral or bilateral localized infection of the temporal lobes; cerebrospinal fluid testing typically shows lymphocytic pleocytosis and, when necrosis is extensive, abundant erythrocytes; and MRI may show temporal lobe abnormalities.
- Herpes simplex virus polymerase chain reaction testing on the cerebrospinal fluid is highly sensitive and specific for herpes simplex encephalitis.
- Empiric intravenous acyclovir therapy should be initiated for all patients suspected of having encephalitis.

Varicella-Zoster Virus Encephalitis

Varicella-zoster virus (VZV) encephalitis may occur at the time of acute varicella infection or with viral reactivation. VZV encephalitis is more common in patients with HIV/AIDS or defects in cellular immunity but also may occur in otherwise healthy persons.

Besides the characteristic skin findings, few specific features suggest VZV encephalitis. The time between the onset of zoster and the development of CNS symptoms may be prolonged, and in some cases encephalitis may predate onset of

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skin lesions. Even the presence of zoster in a patient with encephalitis is not sufficient proof of CNS infection because cutaneous reactivation may result from the physiologic stress of another infection. Most diagnostically challenging is the condition "herpes sine zoster," in which central nervous system infection occurs in the absence of skin lesions. VZV may also infect cerebral arteries, presenting as an ischemic stroke rather than encephalitis.

Confirmation of VZV encephalitis requires identification of viral infection of the CNS. Findings on VZV PCR of CSF are typically positive in cases of encephalitis associated with acute varicella or zoster. When vasculitis predominates, or when symptoms are more insidious, intrathecal VZV antibodies also should be measured because VZV PCR results can be negative in these cases. Although data on treatment are limited, parenteral acyclovir is recommended in cases of VZV encephalitis or vasculopathy.

KEY POINTS

- Varicella-zoster virus encephalitis is more common in patients with HIV/AIDS or defects in cellular immunity.
- Varicella-zoster virus polymerase chain reaction testing of cerebrospinal fluid should be performed to identify viral infection of the central nervous system.
- Parenteral acyclovir is recommended for varicella-zoster virus encephalitis or vasculopathy.

Neuroinvasive West Nile Virus

West Nile virus (WNV), first detected in the United States in 1999, has emerged as a national public health problem, with infections reported throughout the continental United States. Mosquitoes serve as the primary vector, and most human infections occur during the summer and early fall. Transmission through blood transfusion and organ transplantation has been reported but is much less frequent since the advent of universal screening of donor blood products. Most infected persons remain asymptomatic, with approximately 20% developing West Nile fever. The most severe clinical presentation, West Nile neuroinvasive disease (WNND), occurs in less than 1% of cases. These patients may present with meningitis, encephalitis, or myelitis, either singly or as overlap syndromes. WNND is significantly more common among adults age 50 years or older and in solid organ and bone marrow transplant recipients. HIV infection does not appear to be a significant risk factor for WNND.

Limb weakness, which may be symmetric or involve a single extremity, is a characteristic feature of WNND. Severe disease may manifest as acute asymmetric flaccid paralysis and may progress to cause respiratory failure, akin to that seen with poliomyelitis. Other clinical findings of WNND are rarely helpful in suggesting the diagnosis. Fever is almost universally present. A nonspecific viral exanthema may be found in less than 50% of patients. MRI may show focal lesions of the thalami, basal ganglia, and spinal cord in some patients.

CSF serology is the preferred test to confirm WNND. Most acutely infected patients have detectable IgM antibody to WNV in the first week of symptoms, although titers may remain detectable for more than 1 year. Detection of IgG antibody may confirm previous infection but is less sensitive for diagnosis of acute illness. Serologic cross-reactivity between WNV and other flaviviruses is significant, and caution should be used in interpreting a positive WNV IgG result in a patient with natural infection or vaccination against St. Louis encephalitis virus, Japanese encephalitis virus, yellow fever virus, or dengue virus. For these reasons, testing of CSF is preferred, and the presence of intrathecal WNV IgM antibody is considered diagnostic of acute infection. Results of WNV PCR of serum or CSF are infrequently positive except in immunocompromised patients, who may exhibit delayed viral clearance. Viral culture is insensitive and is not recommended.

No antiviral therapy is effective for WNV infection, and treatment is limited to supportive care. Patients with substantial muscle weakness should be monitored in an intensive care setting for impending respiratory failure.

KEY POINTS

- West Nile neuroinvasive disease occurs in less than 1% of infections with West Nile virus and presents with meningitis, encephalitis, or myelitis, either singly or as overlap syndromes.
- Cerebrospinal fluid serology is the preferred diagnostic test for West Nile neuroinvasive disease, with most patients having detectable IgM antibody to West Nile virus in the first week of symptoms.

Autoimmune Encephalitis

A newly described autoimmune condition termed anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) antibody encephalitis has emerged as an increasingly common cause of encephalitis. Anti-NMDAR encephalitis is associated with ovarian teratomas in greater than 50% of patients with the disease because of production of an antibody to a tumor protein that cross-reacts with neuronal tissue. In patients without evidence of teratoma, an inciting antigenic stimulus is rarely identified. The diagnosis is suggested by the presence of choreoathetosis, psychiatric symptoms, seizures, and autonomic instability and is confirmed by detection of anti-NMDAR antibody in serum. Treatment includes removal of the teratoma to eradicate the immune stimulus and immunosuppression with glucocorticoids or intravenous immune globulin.

KEY POINTS

- Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) antibody encephalitis presents with choreoathetosis, psychiatric symptoms, seizures, and autonomic instability; is associated with ovarian teratomas in greater than 50% of patients with the disease; and is confirmed by detection of anti-NMDAR antibody in serum.
- Treatment of anti-NMDAR encephalitis includes removal of the teratoma and immunosuppression with glucocorticoids or intravenous immune globulin.

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Prion Diseases of the Central Nervous System

Introduction

Prion diseases (also known as transmissible spongiform encephalopathies) are a group of rare, closely related, fatal, neurodegenerative conditions that occur in humans and other mammals. They are caused by an accumulation of aggregated forms of the prion protein in the central nervous system. Human prion diseases include sporadic, infectiously transmitted, and genetic disorders. Sporadic disease accounts for most cases. Known infectious acquisition is very rare in humans and accounts for less than 1% of cases in most populations.

The infectiously transmitted forms of prion disease are kuru, variant Creutzfeldt-Jakob disease (CJD), and iatrogenic CJD. Prion disease has been transmitted to humans through dietary practices and iatrogenic exposure. Kuru was the first prion disease recognized to be transmissible and was linked to cannibalism among tribes in New Guinea.

Creutzfeldt-Jakob Disease

CJD is the most common form of prion disease in humans, with most cases being sporadic. Iatrogenic transmission of CJD is possible and has resulted mainly from receipt of growth hormone prepared from cadaveric pituitaries and contaminated cadaveric dura mater allografts. Contaminated surgical instruments have also been documented to transmit CJD in rare instances. Sporadic CJD does not appear to be transmissible by blood. Although the age range of affected persons is wide, onset usually occurs in the seventh decade of life. The most prominent neurologic sign is disordered cognition. Typically, patients also have motor signs, such as ataxia or spasticity, vague sensory problems, or changes in visual perception. Myoclonus is common. Progressive neurologic decline resulting in death occurs rapidly, typically within 6 to 12 months.

Variant Creutzfeldt-Jakob Disease

Variant CJD is a novel infectious human prion disease caused by the bovine spongiform encephalopathy agent. Most infections have occurred after consumption of infected beef, although transmission by blood and blood products from donors with variant CJD has been reported. Compared with sporadic CJD, variant CJD has a younger age at onset, psychiatric and sensory signs earlier in the disease process, and development of dementia and motor signs more than 6 months after disease onset; however, it typically resembles sporadic CJD, with the most common neurologic sign being impaired cognition. Motor signs, such as ataxia, spasticity, and myoclonus, are prominent.

Prion disease should be considered in the differential diagnosis of any patient who presents with rapidly progressive dementia. Elevated cerebrospinal fluid levels of the 14-3-3 protein are relatively specific for CJD. Definitive diagnosis is made by brain biopsy. No effective treatment exists.

KEY POINTS

- Creutzfeldt-Jakob disease is the most common form of prion disease in humans, with most cases being sporadic.
- Iatrogenic transmission of Creutzfeldt-Jakob disease (CJD) has resulted mainly from receipt of growth hormone prepared from cadaveric pituitaries and contaminated cadaveric dura mater allografts, whereas variant CJD infection has occurred after consumption of infected beef as well as reports of transmission by blood and blood products from donors with variant CJD.

Skin and Soft Tissue Infections

Introduction

Skin and soft tissue infections (SSTIs) usually occur when skin microbes penetrate underlying layers of the epidermis. Predisposing conditions include skin trauma, onychomycosis, tinea pedis, vascular insufficiency, lymphatic compromise, obesity, diabetes mellitus, and immune suppression. The most common organisms causing SSTIs are β-hemolytic streptococci, particularly group A β-hemolytic streptococci (GABHS), and *Staphylococcus aureus*. See **Table 6** for cellulitis risk factors and the associated causative microorganisms.

Erysipelas is a superficial infection of the epidermis that usually involves the lower extremities or face. It is typically caused by GABHS. Involved skin is erythematous (with well-demarcated borders), glistening, indurated, painful, and warm. Fever and malaise are often present. Desquamation may develop, but necrosis of the skin does not.

Cellulitis is a diffuse, spreading skin infection that involves the dermis and subcutaneous tissues. Clinical features include warmth, redness, swelling, and tenderness in addition to fever and malaise; regional lymphadenopathy also may be present. Unlike erysipelas, cellulitis is characterized by poorly defined erythema. Cellulitis is categorized as purulent or nonpurulent. Cellulitis associated with purulent drainage or exudate is typically caused by methicillin-resistant *S. aureus* (MRSA). Nonpurulent cellulitis is usually caused by β-hemolytic streptococci.

Skin infection is usually diagnosed clinically. Radiography may be helpful when the diagnosis is uncertain, when necrotizing fasciitis is suspected, or when an associated abscess is a concern. A causative agent is established in few patients. Cultures obtained directly from a purulent skin lesion may be helpful. Blood cultures are positive in less than 5% of patients. It also is estimated that the clinical diagnosis of lower-extremity cellulitis is inaccurate in up to one third of patients. Mimics include stasis dermatitis, contact dermatitis,

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TABLE 6. Cellulitis Pathogens and Associated Risk Factors and Clinical Signs

Pathogen	Risk Factor	Comment
Aeromonas hydrophila	Contact with or participation in recreational sports in fresh water lakes, streams, or rivers (including brackish water) Contact with medicinal leeches	Cellulitis is nonspecific in clinical appearance; minor trauma to skin usually leads to inoculation of organism
Vibrio vulnificus, other *Vibrio* species	Contact with salt water or brackish water or contact with drippings from raw seafood	May cause cellulitis through direct inoculation into skin or may be ingested, leading to bacteremia with secondary skin infection Hallmark is hemorrhagic bullae in area of cellulitis
Erysipelothrix rhusiopathiae	Contact with saltwater marine life (also associated with freshwater fish); contact with infected animals such as swine and poultry	Cellulitis usually involves the hand or fingers in those handling fish, shellfish, or, occasionally, poultry or meat contaminated with bacterium Causes erysipeloid disease
Pasteurella multocida	Contact primarily with cats	Cellulitis occurs as a result of cat scratch or bite
Capnocytophaga canimorsus	Contact primarily with dogs	Cellulitis and sepsis particularly in patients with functional or anatomic asplenia
Bacillus anthracis	Contact with infected animals or animal products Target of bioterrorism	Edematous pruritic lesion with central eschar; spore-forming organism
Francisella tularensis	Contact with or bite from infected animal (particularly cats) or arthropod bites (particularly ticks)	Ulceroglandular syndrome characterized by ulcerative lesion with central eschar and localized tender lymphadenopathy; constitutional symptoms are often present
Mycobacterium marinum	Contact with fresh water or salt water, including fish tanks and swimming pools	Lesion often trauma-associated and often involving upper extremity; papular lesions become ulcerative at site of inoculation; ascending lymphatic spread can be seen ("sporotrichoid" appearance); systemic toxicity usually absent
Mycobacterium fortuitum	Exposure to freshwater footbaths/pedicures at nail salons; infection following augmentation mammoplasty and open heart surgery	Multiple boils; razor shaving strongly associated

H CONT. eczema, lymphedema, lipodermatosclerosis, erythromelalgia, deep venous thrombosis, erythema nodosum, hypersensitivity reaction, and thrombophlebitis. H

KEY POINTS

- Cellulitis associated with purulent drainage or exudate is typically caused by methicillin-resistant *Staphylococcus aureus*, whereas nonpurulent cellulitis is usually caused by β-hemolytic streptococci.
- HVC Skin infection is usually diagnosed clinically; radiography should be reserved for when the diagnosis is uncertain, necrotizing fasciitis is suspected, or when an associated abscess or foreign body is a concern.

Community-Associated Methicillin-Resistant *Staphylococcus aureus*

Community-associated MRSA (CA-MRSA) infections commonly present as a purulent SSTI such as a furuncle, which is infection of the hair follicle that extends into the dermis and subcutaneous tissues. Healthy young persons can become infected, especially in conditions of crowding, suboptimal hygiene (sharing of contaminated items, including razors and towels), and frequent antibiotic use. Outbreaks have been reported on athletic teams, in correctional facilities and day care centers, and among military recruits and men who have sex with men. MRSA is responsible for almost 60% of SSTIs in patients seen in the emergency department. The increased prevalence of CA-MRSA has affected the treatment of SSTIs, and the Infectious Diseases Society of America (IDSA) has published evidence-based clinical practice guidelines to inform when empiric treatment for CA-MRSA is appropriate.

The primary treatment of a cutaneous abscess is incision and drainage. Antibiotics generally are recommended only when the response to incision and drainage is inadequate; in extensive disease or rapid progression with associated cellulitis; in immunodeficiency and other comorbidities; for very young or very old patients; with clinical signs of systemic illness; when involved areas are challenging to drain, such as the genitalia, hands, or face; and in the presence of associated H

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septic phlebitis. Outpatients with purulent cellulitis can be treated empirically for CA-MRSA with a 5- to 10-day course of oral antibiotics, such as trimethoprim-sulfamethoxazole or doxycycline. Linezolid is another treatment option, although its expense and similar efficacy to other agents limit its use to very few clinical situations. Outpatient oral antibiotic therapy for nonpurulent cellulitis should include a β-lactam antibiotic, such as cephalexin or dicloxacillin, which is effective against β-hemolytic streptococci. When coverage of both CA-MRSA and β-hemolytic streptococci is desired, outpatient oral options include clindamycin alone or trimethoprim-sulfamethoxazole or doxycycline in combination with a β-lactam agent, such as amoxicillin; linezolid is also an option in specific patients. Patients who require hospitalization for complicated SSTIs (deep soft tissue infections and abscesses, cellulitis, necrotizing infection, trauma-associated wound infection, postsurgical wound infection, infected burn/ulcer) should receive surgical evaluation for debridement in addition to empiric broad-spectrum antibiotic coverage that includes MRSA agents, such as vancomycin, daptomycin, or, in specific patients, linezolid. Rifampin is not recommended for MRSA treatment, even in an adjunctive role. Ceftaroline is a fifth-generation cephalosporin approved for treatment of SSTIs, including those associated with MRSA. It is recommended as empiric antibiotic therapy for purulent skin infections in immunocompromised hosts or immunocompetent patients with signs of systemic infection. It costs considerably more than vancomycin but less than daptomycin, linezolid, or telavancin, all of which are recommended as empiric treatment for these patients.

KEY POINTS

HVC
- In community-associated methicillin-resistant *Staphylococcus aureus* infections, the primary treatment of a cutaneous abscess is incision and drainage.

HVC
- Antibiotic therapy generally is recommended for community-associated methicillin-resistant *Staphylococcus aureus* infections only if primary treatment is inadequate, if disease is extensive or marked by rapid progression and associated cellulitis, if immunodeficiency and other comorbidities are present, if the patient is very young or very old, if clinical signs of systemic illness are noted, if involved areas are challenging to drain, or if septic phlebitis is present.

Necrotizing Fasciitis

Necrotizing fasciitis (NF) is a potentially lethal necrotizing skin infection. Type I NF refers to a polymicrobial infection comprising aerobic and anaerobic gram-positive and gram-negative organisms. Type II NF is a monomicrobial infection typically caused by *Streptococcus pyogenes*, although *S. aureus*, *Vibrio vulnificus*, or *Streptococcus agalactiae* can be causative. Patients who are immunocompromised, particularly those with liver disease, are at increased risk for infection with *V. vulnificus* in the correct clinical setting (see Table 6). Type III NF (gas gangrene or clostridial myonecrosis) usually develops after surgery or other significant trauma and is primarily caused by *Clostridium perfringens*.

Necrotizing fasciitis usually arises from skin damage or trauma, although a portal of entry is not always apparent. It is more common in patients who have comorbidities, including diabetes mellitus, cancer, injection drug use, liver disease, and immunosuppression, but may occur in healthy young patients.

Cutaneous manifestations can initially resemble less complicated cellulitis. Clues to a potential underlying necrotizing process include systemic toxicity with fever, chills, altered mental status, and hypotension. The pain may be disproportionate to the physical examination findings, and loss of sensation may later result from cutaneous nerve destruction. Skin changes can evolve rapidly and become ecchymotic, vesiculobullous, and gangrenous in appearance. "Woody" induration and crepitus on palpation of the involved areas are characteristic.

Clinical suspicion is important and laboratory evaluation, although nonspecific, may be helpful. Six independent laboratory indicators that, when added together, are associated with an increased likelihood of necrotizing fasciitis are C-reactive protein (≥15.0 mg/dL [150 mg/L]), total leukocyte count (>15,000–25,000/μL [15–25 × 10^9/L]), hemoglobin (<11–13.5 g/dL [110–135 g/L]), sodium (<135 mEq/L [135 mmol/L]), creatinine (>1.6 mg/dL [141 μmol/L]), and glucose (>180 mg/dL [10 mmol/L]).

Plain radiographs of the affected area may demonstrate subcutaneous gas; MRI with contrast is quite sensitive and can help determine the extent of infection. Blood cultures may be useful in identifying the causative agent, but early surgical exploration is the gold standard for diagnosis and treatment. Cultures of intraoperative tissue specimens help direct antibiotic management; repeated surgeries are often necessary for source control.

Empiric broad-spectrum antibiotics are recommended for patients suspected of having NF. Initial coverage should target aerobic and anaerobic gram-positive and gram-negative bacteria, including MRSA. Appropriate regimens include an anti-MRSA agent, such as vancomycin or daptomycin, linezolid plus imipenem (or meropenem), or piperacillin-tazobactam. In type II NF secondary to GABHS and type III NF secondary to clostridial species, penicillin and clindamycin are recommended. Clindamycin is included because it inhibits toxin production and remains effective even in the presence of a high inoculum of bacteria. Discontinuation of antimicrobials is reasonable when surgical debridement is no longer required and the patient is clinically stable. No absolute recommendations exist for the use of adjunctive intravenous immune globulin (IVIG) in streptococcal necrotizing fasciitis, although some infectious disease experts recommend its use in patients with associated toxic shock syndrome (see following). Doxycycline plus ceftazidime is recommended for *Vibrio vulnificus*–associated NF, and doxycycline plus ciprofloxacin is recommended for *Aeromonas hydrophila*–associated NF.

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KEY POINTS

- Clues to a potential underlying necrotizing process include systemic toxicity with fever, chills, altered mental status, and hypotension; pain may be disproportionate to physical examination findings, and loss of sensation may occur because of cutaneous nerve destruction.
- Early surgical exploration is the gold standard for diagnosis and treatment of necrotizing fasciitis.

Toxic Shock Syndrome

S. aureus and *S. pyogenes* can produce toxins called super antigens that stimulate cytokine production, resulting in the systemic signs of toxic shock syndrome (TSS) (**Table 7**, **Table 8**). TSS secondary to *S. aureus* (including MRSA) may be associated with tampon use during menstruation, the presence of wounds, a history of injection drug use, burns, nasal packings, or catheters. Bacteremia is present in about 5% of cases. *S. pyogenes*–associated skin infections (particularly NF) can also produce a toxic shock–like syndrome. Bacteremia is present in about 60% of cases.

Early management consists of adequate resuscitation to maintain tissue perfusion, identification of the cause and focus of infection, and source control, which typically involves surgical debridement. Empiric antimicrobial agents are the same as those used in NF. When identified, pathogen-directed therapy for *S. pyogenes* consists of penicillin plus clindamycin. Methicillin-sensitive *S. aureus*–associated TSS therapy consists of nafcillin or oxacillin plus clindamycin; if TSS is associated with MRSA, vancomycin plus clindamycin or linezolid can be used. Some experts recommend the use of adjunctive IVIG for TSS, although data are limited. Neutralizing antibodies to streptococcal toxins in IVIG provide the rationale for its use.

Hyperbaric oxygen treatment has also been used adjunctively. Droplet precautions are recommended until effective antibiotic therapy has been administered for 24 hours to prevent transmission of group A streptococcal infection to others; contact precautions are also recommended if the wound is draining. Antibiotic prophylaxis against invasive group A streptococcal infections among household contacts of patients with streptococcal TSS-like syndrome may be considered in older adults or in patients with comorbidities, such as diabetes mellitus, HIV infection, cancer, varicella infection, heart disease, steroid use, and injection drug use. Benzathine penicillin G plus rifampin, clindamycin, or azithromycin is recommended.

TABLE 7. Diagnostic Criteria for Staphylococcal Toxic Shock Syndrome

Fever >38.9 °C (102.0 °F)
Systolic blood pressure <90 mm Hg
Diffuse macular rash with subsequent desquamation, especially on palms and soles
Involvement of three of the following organ systems:
Gastrointestinal (nausea, vomiting, diarrhea)
Muscular (severe myalgia or fivefold or greater increase in serum creatine kinase level)
Mucous membrane (hyperemia of the vagina, conjunctivae, or pharynx)
Kidney (blood urea nitrogen or serum creatinine level at least twice the upper limit of normal)
Liver (bilirubin, aspartate aminotransferase or alanine aminotransferase concentration twice the upper limit of normal)
Blood (platelet count <100,000/μL [100 × 10^9/L])
Central nervous system (disorientation without focal neurologic signs)
Negative results on serologic testing for Rocky Mountain spotted fever, leptospirosis, and measles; negative cerebrospinal fluid cultures for organisms other than *Staphylococcus aureus*

Adapted with permission from Moreillon P, Que YA, Glauser MP. *Staphylococcus aureus*. In: Mandell GL, Dolin R, Bennett JE, eds. Principles and Practice of Infectious Disease. 6th ed. Philadelphia, PA: Churchill Livingstone; 2005:2331. Copyright 2005, Elsevier.

TABLE 8. Diagnostic Criteria for Streptococcal Toxic Shock Syndrome

Definite case:
Isolation of GABHS from a sterile site
Probable case:
Isolation of GABHS from a nonsterile site
Hypotension:
The presence of two of the following findings:
Kidney (acute kidney injury or failure)
Liver (elevated aminotransferase concentrations)
Skin (erythematous macular rash, soft tissue necrosis)
Blood (coagulopathy, including thrombocytopenia and disseminated intravascular coagulation)
Pulmonary (acute respiratory distress syndrome)

GABHS = group A β-hemolytic streptococci.

KEY POINT

- Early management of toxic shock syndrome consists of adequate resuscitation to maintain tissue perfusion, identification of the cause and focus of infection, and source control, which typically involves surgical debridement.

Animal Bites

Animal bites, most of which are caused by cats and dogs, account for 1% of all visits to the emergency department; up

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to 20% become infected. Cat bites are more likely to become infected (approximately 40%) owing to deep puncture wounds caused by sharp narrow teeth; dog bites become infected in 5% to 15% of patients. The infections result from the host's skin flora and the animal's mouth flora. This flora is a mix of aerobic and anaerobic organisms, including staphylococci, streptococci, *Bacteroides* species, *Porphyromonas* species, *Fusobacterium* species, and *Pasteurella* species. *Capnocytophaga canimorsus* is a gram-negative bacillus that can cause overwhelming sepsis in patients with functional or anatomic asplenia who have experienced a dog bite or scratch.

The type of animal involved, circumstances under which the attack occurred, timing of the bite, location of the bite, type of injury incurred, and health status of the animal and patient are important. The extremities, particularly the hands, are more likely to become infected than other areas. Physical examination should include evaluation for purulence, necrosis, erythema, edema, and extent/depth of the wound as well as careful neurovascular assessment. Prompt wound irrigation with normal saline, removal of any foreign bodies, and debridement of necrotic tissue can decrease the risk for infection. Radiography is recommended if fracture or bone penetration is possible. Surgical consultation is recommended when the hand is involved. In general, primary wound closure is not performed, particularly if infection is suspected. The need for rabies and tetanus prophylaxis should be assessed in all cases of animal bites.

A 3- to 5-day course of prophylaxis with amoxicillin-clavulanate is recommended for patients who are immunosuppressed (including those with asplenia or who have significant liver disease); have moderate-to-severe wounds, particularly on the face or hand; have wounds near a joint or bone; or have wounds associated with significant crush injury or edema. Alternatively, doxycycline alone or a combination of a fluoroquinolone (ciprofloxacin or levofloxacin) or trimethoprim-sulfamethoxazole plus an anaerobic antibiotic (such as clindamycin or metronidazole) can be used in patients allergic to β-lactam antibiotics.

Infected wounds require antibiotics. Outpatient oral treatment consisting of the same agents used for prophylaxis can be given for 5 to 10 days. Patients with sepsis; infected hand bites; nerve, tendon, or crush injuries; or severe or deep infections should be hospitalized. Recommended intravenous antibiotic options include β-lactam/β-lactamase inhibitor combinations, such as ampicillin-sulbactam or piperacillin-tazobactam; carbapenems, such as imipenem, meropenem, or ertapenem; or cefoxitin. The combination of clindamycin or metronidazole and a fluoroquinolone, such as ciprofloxacin or levofloxacin, is an alternative for patients allergic to β-lactam antibiotics. The anticipated length of therapy is usually less than 14 days unless bone or joint involvement mandates longer courses.

KEY POINTS

- Prompt wound irrigation with normal saline, removal of any foreign bodies, and debridement of necrotic tissue can decrease the risk for infection of animal bites.
- The need for rabies and tetanus prophylaxis should be assessed in all patients with animal bites.
- Amoxicillin-clavulanate prophylaxis is recommended only for patients with animal bites who are immunosuppressed; have moderate-to-severe wounds, particularly on the face or hand; have wounds near a joint or bone; or have wounds associated with significant crush injury or edema. HVC

Human Bites

Human bite wounds usually result from occlusive injuries sustained after an intentional bite or from clenched fist injuries that develop after a punch to another's mouth. The microbiology of these wounds primarily reflects mouth flora, which is a mixture of aerobic streptococci (particularly viridans group streptococci); staphylococci; *Eikenella corrodens*; *Haemophilus* species; and β-lactamase–producing anaerobes, such as *Fusobacterium* species, peptostreptococci, *Porphyromonas* species, and *Prevotella* species.

The same general approach to management of animal bite–associated wounds is pursued. Additionally, evaluation for potential transmission of HIV, hepatitis B and C viruses, and other transmissible pathogens is recommended. Prophylactic antibiotics consisting of 3 to 5 days of amoxicillin-clavulanate should be given for all human bite wounds. Clenched-fist injuries require evaluation by a hand specialist and usually require hospitalization and intravenous ampicillin-sulbactam, a β-lactam/β-lactamase inhibitor, or a carbapenem, such as ertapenem. In patients allergic to β-lactam antibiotics, alternative regimens include fluoroquinolones, such as levofloxacin or ciprofloxacin plus metronidazole. While culture results are pending, an agent such as vancomycin can be considered in patients with risk factors for MRSA infection.

KEY POINT

- Prophylactic amoxicillin-clavulanate should be given for all human bite wounds.

Diabetic Foot Infections

Patients with diabetes mellitus often have associated immunodeficiency, neuropathy, and vasculopathy, which increase the risk for foot infection. Factors reported to be significantly associated with infection include persistent ulcer for more than 1 month, peripheral arterial disease in an involved limb, amputation involving a lower extremity, recurrent foot ulcers, posttraumatic foot wound, diagnosis of kidney insufficiency, walking barefoot, and the ability to palpate bone within the wound with a sterile metal probe.

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The Infectious Diseases Society of America has developed a validated system that classifies severity of foot infections as uninfected, mild, moderate, or severe. Uninfected wounds/ulcers demonstrate no clinical evidence of infection.

Mild infections are associated with at least two factors, including purulent discharge, warmth, pain/tenderness, swelling/induration, and erythema. The infection must not extend deeper than the skin and subcutaneous tissues, and any erythema must not expand more than 2 cm beyond the ulcer. The patient must not meet criteria for systemic inflammatory response syndrome (SIRS) (**Table 9**). The microbiology of these infections typically consists of aerobic streptococci and staphylococci. These patients can usually be treated with a short course of oral antibiotics directed against these organisms.

In moderate infections, the erythematous infection expands more than 2 cm around the ulcer or extends deeper than the skin and subcutaneous tissues as a deep tissue abscess, joint or muscle infection, fasciitis, or osteomyelitis. The patient must not meet SIRS criteria.

Infections are considered severe when SIRS criteria are met, other evidence of systemic infection is present (hypotension, confusion, vomiting, acidosis, severe hyperglycemia, acute kidney injury), or infection occurs in the presence of critical ischemia. The microbiology of severe infections is typically polymicrobial, consisting of staphylococci, streptococci, enteric gram-negative bacilli, *Pseudomonas aeruginosa*, and anaerobes. These limb-threatening infections require surgical evaluation and empiric broad-spectrum antibiotic coverage that includes MRSA. Antibiotics can be adjusted on the basis of culture results.

All patients with infection should be assessed for the possible presence of arterial insufficiency (using ankle-brachial index), sensory deficits, and biomechanical abnormalities. Wound care consisting of wound cleansing, debridement, and foot pressure off-loading is recommended. Cultures obtained should not be from superficial swab specimens but from deep tissue specimens. Foot imaging is recommended for all patients with new diabetic foot infections. A multidisciplinary team for diabetic foot infections is optimal.

TABLE 9. Definition of Systemic Inflammatory Response Syndrome

Presence of two or more of the following in the absence of other known causes:
Temperature >38.0 °C (100.4 °F) or <36.0 °C (96.8 °F)
Heart rate >90/min
Respiration rate >20/min or arterial Pco_2 <32 mm Hg (4.3 kPa)
Leukocyte count >12,000/μL (12×10^9/L) or <4,000/μL (4×10^9/L) or with 10% bands

KEY POINTS

- Wound care for diabetic foot infections consists of wound cleansing, debridement, and off-loading of foot pressure.
- Imaging of the foot is recommended for those with new diabetic foot infections.

Community-Acquired Pneumonia

Epidemiology

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality in adults, ranking as the seventh most frequent cause of mortality in the United States. Certain conditions, including COPD or emphysema, alcoholism, bronchiectasis, and smoking, increase the likelihood of developing CAP and also influence the causative organisms. Older adults are particularly affected by CAP, with some estimates of U.S. case surveillance data noting that more than 900,000 adults age 65 years or older will die of this infection annually. Rates of CAP increase with age, and prevalence appears higher among blacks than whites and among men than women.

KEY POINT

- Community-acquired pneumonia (CAP) is more prevalent among older adult patients, and certain conditions, including COPD, emphysema, alcoholism, bronchiectasis, and smoking, increase the likelihood of developing CAP.

Microbiology

When infection develops in the lower respiratory tract, the pulmonary and host defenses have been breached, leading to the entry of microorganisms present in the upper respiratory tract into the usually sterile lower respiratory airways. Because of this, the common microorganisms causing CAP represent the typical colonizers present in the upper respiratory tract. The most common organism causing CAP is *Streptococcus pneumoniae*; other important causes include *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Chlamydophila pneumoniae*, and respiratory viruses.

Respiratory viruses are an important contributor to CAP, particularly influenza A and B viruses. Other respiratory viral pathogens, including respiratory syncytial virus, parainfluenza virus, and adenoviruses, are a substantial source of morbidity from viral CAP. These viral infections can also lead to complications of postviral bacterial superinfection, most commonly with *S. pneumoniae*, *Staphylococcus aureus*, and *H. influenzae*. Postviral bacterial pneumonias typically occur approximately 1 to 2 weeks after viral infection symptoms start to resolve. Secondary bacterial pneumonias occurring after

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primary viral infection will manifest with fever, productive cough, shortness of breath, and pulmonary infiltrates. The index of suspicion for possible secondary bacterial pneumonia should be high in patients whose apparent recovery from a viral infection is complicated by clinical recrudescence.

Specific epidemiologic or geographic exposures may be associated with different and sometimes unusual pathogens causing CAP (**Table 10**).

The subcategory of "atypical" CAP pathogens refers to *M. pneumoniae*, *Legionella* species, *C. pneumoniae*, and *Chlamydophila psittaci*. Atypical CAP is often clinically indistinguishable from typical CAP syndromes. However, *M. pneumoniae* and *C. pneumoniae*, compared with many of the bacterial pathogens causing typical CAP, can be transmitted person to person. Legionellosis is particularly notable for outbreaks where the source of exposure is traced back to equipment or devices that aerosolize the organisms, such as air conditioning towers.

Gram-negative bacteria, including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* species, *Escherichia coli*, and *Enterobacter* species, are rarely implicated in CAP. Most patients with CAP caused by gram-negative bacteria have a predisposing risk factor (see Table 10), such as bronchiectasis, cystic fibrosis, or COPD, and develop severe pneumonia necessitating admission and care in the ICU.

TABLE 10. Possible Microbial Causes of Community-Acquired Pneumonia

Characteristics	Commonly Encountered Pathogens
Clinical Presentation	
Aspiration	Gram-negative enteric pathogens, oral anaerobes
Cough >2 weeks with whoop or posttussive vomiting	*Bordetella pertussis*
Lung cavity infiltrates	Community-associated methicillin-resistant *Staphylococcus aureus*, oral anaerobes, endemic fungal pathogens, *Mycobacterium tuberculosis*, atypical mycobacteria
Epidemiology or Risk Factor	
Alcoholism	*Streptococcus pneumoniae*, oral anaerobes, *Klebsiella pneumoniae*, *Acinetobacter* species, *M. tuberculosis*
COPD and/or smoking	*Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Legionella* species, *S. pneumoniae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydophila psittaci* (if poultry: avian influenza)
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals or parturient cats	*Coxiella burnetii*
Exposure to rodent excreta	Hantavirus
HIV infection (early)	*S. pneumoniae*, *H. influenzae*, *M. tuberculosis*
HIV infection (late)	*S. pneumoniae*, *H. influenzae*, *M. tuberculosis*, *Pneumocystis jirovecii*, *Cryptococcus* species, *Histoplasma* species, *Aspergillus* species, atypical mycobacteria (especially *Mycobacterium kansasii*), *P. aeruginosa*
Hotel or cruise ship stay in previous 2 weeks	*Legionella* species
Travel or residence in southwestern United States	*Coccidioides* species, hantavirus
Travel or residence in Southeast and East Asia	*Burkholderia pseudomallei*, avian influenza, severe acute respiratory syndrome-coronavirus (SARS-CoV)
Travel or residence in (or exposure to an ill traveler from) the Middle East	Middle East respiratory syndrome-coronavirus (MERS-CoV)
Influenza activity in community	Influenza, *S. pneumoniae*, *S. aureus*, *H. influenzae*
Injection drug use	*S. aureus*, anaerobes, *M. tuberculosis*, *S. pneumoniae*
Endobronchial obstruction	Anaerobes, *S. pneumoniae*, *H. influenzae*, *S. aureus*
Bronchiectasis or cystic fibrosis	*Burkholderia cepacia*, *P. aeruginosa*, *S. aureus*
Bioterrorism	*Bacillus anthracis*, *Yersinia pestis*, *Francisella tularensis*

Adapted with permission from Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44(suppl 2):S27-72. [PMID: 17278083] Copyright 2007, Oxford University Press.

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Group A streptococcus can lead to a rapidly progressive and complicated pulmonary infection, with subsequent empyema. CAP from group A streptococcus has a substantial mortality rate.

S. aureus CAP can occur in a heterogeneous group of settings. A postinfluenza bacterial pneumonia syndrome is typically attributed to *S. aureus*, although *S. pneumoniae* more commonly leads to this complication. Older adult patients are also susceptible to *S. aureus* CAP. *S. aureus* pneumonia is commonly seen among injection drug users. Methicillin-resistant *S. aureus* (MRSA) as a cause of CAP more commonly occurs with nosocomial exposures and in certain patient populations, such as those undergoing hemodialysis. Recent nursing home exposure and exposure to persons with skin and soft tissue infection are also risk factors for MRSA CAP. The morbidity from MRSA causing CAP is substantial because a significant proportion of patients present with necrotizing pneumonia, in which a portion of the involved lung tissue becomes devitalized. This complication leads to pulmonary airway hemorrhage, severe respiratory failure, and fulminant clinical deterioration.

KEY POINTS

- Community-acquired pneumonia is most commonly caused by *Streptococcus pneumoniae*.
- Influenza A and B are the most common respiratory viruses contributing to development of community-acquired pneumonia.
- Methicillin-resistant *Staphylococcus aureus* (MRSA) as a cause of community-acquired pneumonia more commonly occurs with nosocomial exposures and in certain patient populations, such as those undergoing hemodialysis; recent nursing home exposure or exposure to persons with skin and soft tissue infection are also risk factors for MRSA.

Diagnosis

Initial evaluation of the patient suspected of having CAP starts with a comprehensive history and physical examination. Suggestive clinical symptoms include fever, cough, sputum production, and dyspnea, although these are only at most 50% sensitive for a diagnosis of CAP. Pleuritic chest pain may be present. The absence of fever does not exclude CAP, particularly in older adults. Tachypnea is often present, and tachycardia can be seen. Pulmonary examination may be positive for adventitious sounds. However, no pathognomonic findings on physical examination can indicate CAP, so a combination of suggestive and supportive symptoms and examination findings are needed to make the diagnosis.

If clinical findings suggest a CAP diagnosis, chest radiography should be performed. Chest radiography must show an infiltrate for pneumonia to be diagnosed. Radiographic findings can be characterized as interstitial infiltrates, lobar consolidation, or cavitary lesions. When clinical symptoms and examination findings otherwise support the diagnosis of CAP, a false-negative chest radiograph is a possibility; volume depletion can cause an initial negative finding on chest radiograph that, upon rehydration and repeat imaging, may become positive.

Empiric antibiotic therapy for CAP is generally not recommended without evidence of positive findings on chest radiograph. However, empiric antimicrobial treatment may be instituted for hospitalized patients with a high clinical suspicion of CAP when the chest radiograph is negative, with repeat chest radiography in 1 to 2 days to confirm or exclude the diagnosis.

Although chest CT has higher sensitivity than chest radiography for diagnosing CAP and is particularly effective for detecting interstitial infiltrates, empyema, cavitary lung lesions, or hilar lymphadenopathy, no evidence indicates clinical outcomes are improved by using CT for diagnosing CAP. It is also substantially more expensive than plain chest radiography and involves more radiation exposure. Therefore, guidelines do not recommend its use in most patients with CAP, and it is reserved for specific clinical situations in which diagnostic uncertainty will affect management.

Although an infiltrate on chest radiograph is necessary to confirm the diagnosis of CAP, microbiologic confirmation is not typically an essential diagnostic criterion. The diagnostic yield of sputum cultures varies widely, and culture data for ambulatory patients with uncomplicated CAP do not positively influence outcomes relative to empiric antibiotic therapy. Therefore, sputum cultures are not recommended for these patients. Sputum cultures (with Gram stain to ensure the adequacy of the sample) are indicated for hospitalized patients with severe disease (ICU admission), complications (pleural effusions, cavitary lesions), underlying lung disease, active alcohol abuse, asplenia, liver disease, leukopenia, or unsuccessful outpatient antimicrobial therapy.

Blood cultures are positive in few CAP cases and are not recommended for ambulatory patients. However, they should be performed in patients with an indication for sputum culture. Blood cultures should be obtained before empiric antimicrobial therapy initiation for maximal diagnostic yield. Most positive blood cultures in hospitalized patients with CAP indicate *S. pneumoniae*.

Legionella and pneumococcal urinary antigen testing are also recommended when confirmation of a microbiologic diagnosis is indicated, when ICU admission is being considered, and when outpatient antimicrobial therapy fails. However, *Legionella* urinary antigen testing, although specific, detects only *Legionella pneumophila* type 1 and is, therefore, less sensitive. Molecular tests for *C. pneumoniae* and *M. pneumoniae* and numerous other respiratory viruses have recently become available. These tests are useful in confirming these pathogens because they are fast (test results within hours) and accurate (high sensitivity and specificity); however, they are not always routinely used in practice because of limitations in availability or cost. Particularly in instances of

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CAP caused by underlying viral infection, the availability of rapid polymerase chain reaction respiratory virus panel tests can lead to reduction of unnecessary antimicrobial therapy and additional diagnostic studies. The molecular tests for *C. pneumoniae* and *M. pneumoniae*, as well as respiratory viruses, should be considered when CAP outpatient therapy fails, when ICU admission is being considered, and when risk factors are present for more severe or complicated pneumonia (such as chronic lung disease, underlying liver disease, functional or anatomic asplenia, or alcoholism). For patients who present with CAP-associated pleural effusion, diagnostic thoracentesis is an additional indicated study.

An emerging area of interest in the evaluation of CAP is the use of biologic markers, such as C-reactive protein (CRP) and procalcitonin, to help differentiate between bacterial and nonbacterial pneumonia and help exclude a bacterial CAP diagnosis in outpatients. CRP is a marker of inflammation, and levels are increased in bacterial pneumonia. Procalcitonin is produced by cells as a response to bacterial toxins, which result in serum procalcitonin elevations in bacterial infections. In viral infections, procalcitonin levels are reduced. Procalcitonin and CRP can potentially be used to help reduce unnecessary antibiotic use because they can assist in the decision to stop empirically initiated antibiotics for presumed bacterial CAP. However, the use of procalcitonin and CRP in evaluating CAP should be one of several factors in determining bacterial vs viral cause and should be considered as adjunctive diagnostic tools that will support clinical, microbiologic, and radiologic data rather than take precedence over other information.

KEY POINTS

- Clinical symptoms of community-acquired pneumonia include fever, cough, sputum production, and dyspnea, with or without pleuritic chest pain.
- Pulmonary infiltrate on chest radiograph is required for a pneumonia diagnosis.
- Microbiologic testing and sputum and blood cultures are recommended in hospitalized patients with severe disease necessitating ICU admission, complications (pleural effusions, cavitary lesions), underlying lung disease, active alcohol abuse, asplenia, liver disease, leukopenia, or unsuccessful outpatient antimicrobial therapy.

Management

Site of Care

An initial step in managing CAP is to determine the appropriate site of care based on disease severity. Decision support tools have been formulated to help determine the site of care for CAP. The Pneumonia Severity Index (PSI) tabulates points based on sex; age; comorbid conditions; and physical examination, laboratory, and radiologic findings to determine a score predicting one of five classes of mortality risk. The higher the PSI, the greater the need is for hospital admission. Although effective, the PSI encompasses multiple data points and may be challenging to use, particularly in office-based settings.

The CURB-65 tool uses five categories to predict a patient's morbidity risk, assigning 1 point for each category that is positive: confusion, blood urea nitrogen >20 mg/dL (7.14 mmol/L), respiratory rate ≥30/min, blood pressure (systolic <90 mm Hg, diastolic ≤60 mm Hg), and age 65 years or older. Those patients with a CURB-65 score of 0 or 1 are considered safe to manage in the ambulatory setting. Those with a CURB-65 score of 2 should be admitted for management. CURB-65 scores of 3 or greater warrant consideration of patient admission to the ICU. The modified CRB-65, which omits the BUN component of the original tool, can be used in office-based settings to expedite determining the need for hospitalization. A CRB-65 score of anything other than 0 warrants hospital admission.

The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines use a combination of major and minor criteria to classify severe CAP. Patients who have one or more major criteria or at least three minor criteria for severe CAP warrant ICU admission. Major criteria include invasive mechanical ventilation and septic shock with need for vasopressors. Minor criteria are provided in **Table 11**. Recognizing severe CAP is essential to help prevent associated morbidity and mortality because those with severe disease may have a 30-day mortality rate as high as 40%. Prompt and appropriate placement of patients who warrant hospitalization

TABLE 11. IDSA/ATS Minor Criteria for Severe Community-Acquired Pneumonia

Clinical Criteria
Confusion (new-onset disorientation to person, place, or time)
Hypothermia (core temperature <36.0 °C [96.8 °F])
Respiration rate ≥30/min[a]
Hypotension necessitating aggressive fluid resuscitation
Multilobar pulmonary infiltrates
Laboratory Criteria
Arterial Po_2/FIo_2 ratio ≤250[a]
Leukopenia (<4000 cells/μL [4.0×10^9/L])[b]
Thrombocytopenia (<100,000 platelets/μL [10×10^9/L])
Blood urea nitrogen ≥20 mg/dL (7.1 mmol/L)

IDSA/ATS = Infectious Diseases Society of America/American Thoracic Society; Po_2/FIo_2 = partial pressure of oxygen/fraction of inspired oxygen.

[a]A patient who requires noninvasive positive-pressure ventilation should be considered to meet this criterion.

[b]As a result of infection alone.

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CONT. or ICU management can reduce poor outcomes; use of objective criteria in accurately triaging the appropriate management setting can help standardize care and minimize practice variation.

KEY POINT

HVC
- One of several decision support tools (Pneumonia Severity Index, CURB-65/CRB-65, Infectious Diseases Society of America/American Thoracic Society criteria for severe pneumonia) should be used to assess the need for outpatient versus hospitalized patients care of community-acquired pneumonia.

Antimicrobial Therapy

Empiric antimicrobial treatment for CAP is usually started before a pathogen is identified, so drug selection is based on the predicted or suspected causative organism, clinical history, radiologic findings, and epidemiologic clues. Concerns about emerging drug resistance with community-acquired *S. pneumoniae* and *S. aureus* as well as potential nosocomial resistance may influence empiric therapy. Risk factors for drug-resistant *S. pneumoniae* include age older than 65 years, recent (within the past 3-6 months) antimicrobial therapy (with a β-lactam, macrolide, or fluoroquinolone antibiotic), alcoholism, immunosuppression, and certain medical comorbidities (COPD, chronic liver or kidney disease, cancer, diabetes mellitus, functional or anatomic asplenia, chronic heart disease). Those who work or live in nursing homes and children and workers in day care centers can develop antibiotic-resistant pneumococcal infections. Guidance for empiric treatment in outpatients depends on underlying risk factors (**Table 12**).

TABLE 12. Antibiotic Therapy for Community-Acquired Pneumonia in Outpatients

Risk Factors	Treatment
Previously healthy and no risk factor(s) for drug-resistant *Streptococcus pneumoniae*	Macrolide (azithromycin, clarithromycin, or erythromycin) or doxycycline
Risk factor(s) for drug-resistant *S. pneumoniae* or underlying comorbidities[a]	Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) or β-lactam[b] plus a macrolide or doxycycline

[a]Comorbid conditions (chronic heart, lung, liver, or kidney disease; diabetes mellitus; alcoholism; malignancies; asplenia; and immunosuppressive conditions or use of immunosuppressive drugs), recent (within 3 months) antimicrobial use, or residence in regions with a high rate (>25%) of infection with high-level (minimum inhibitory concentration ≥16 μg/mL) macrolide-resistant *S. pneumoniae*.

[b]Amoxicillin, 1 g every 8 hours, or amoxicillin-clavulanate, 2 g every 12 hours (preferred), or cefpodoxime or cefuroxime, 500 mg twice daily (alternative).

For patients who require hospitalization for CAP from an emergency department setting, the first antimicrobial dose should be given in the emergency department. The time to first antimicrobial dose has been a focus of quality-of-care evaluations, with several retrospective studies of the Medicare population showing significantly reduced mortality among patients who received antimicrobial therapy within 4 to 8 hours of presentation to the emergency department. However, IDSA/ATS guidelines do not include specific timing for antibiotic administration and only support administering the first antimicrobial dose in the emergency department (**Table 13**).

Hospitalized patients initially treated with parenteral therapy can be switched to oral agents, generally of the same antimicrobial class and with similar spectrum of activity, when clinical stability has been attained. Clinically stable

TABLE 13. Empiric Antibiotic Therapy for Community-Acquired Pneumonia in Inpatients

Inpatient Setting	Treatment
Medical ward	β-lactam[a] plus a macrolide or doxycycline; *or* respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin)
ICU	β-lactam[b] plus either azithromycin or a fluoroquinolone[c]; if penicillin allergic, a respiratory fluoroquinolone[d] plus aztreonam[e]
If risk factor(s) for *Pseudomonas aeruginosa* or gram-negative rods on sputum Gram stain	Antipseudomonal β-lactam with pneumococcal coverage (cefepime, imipenem, meropenem, or piperacillin-tazobactam) plus ciprofloxacin or levofloxacin (750 mg); *or* antipseudomonal β-lactam with pneumococcal coverage plus an aminoglycoside plus azithromycin; *or* antipseudomonal[e] β-lactam with pneumococcal coverage plus an aminoglycoside plus a respiratory fluoroquinolone
If risk factor(s) for CA-MRSA, cavitary infiltrates, or compatible sputum Gram stain	Add vancomycin or linezolid to β-lactam[b] plus either azithromycin or a fluoroquinolone[c]

CA-MRSA = community-associated methicillin-resistant *Staphylococcus aureus*.

[a]Cefotaxime, ceftriaxone, or ampicillin; ertapenem is an alternative in patients with an increased risk for enteric gram-negative pathogens (not *P. aeruginosa*).

[b]Cefotaxime, ceftriaxone, or ampicillin-sulbactam.

[c]Moxifloxacin, gemifloxacin, ciprofloxacin, or levofloxacin.

[d]Moxifloxacin, gemifloxacin, or levofloxacin.

[e]Aztreonam can be used in a patient with a severe β-lactam allergy.

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CONT. patients are characterized as having (1) temperature of 37.8 °C (100.0 °F) or less, (2) heart rate of 100/min or less, (3) respiration rate of 24/min or less, (4) systolic blood pressure of 90 mm Hg or greater, (5) arterial oxygen saturation of 90% or more or partial pressure of oxygen of 60 mm Hg or greater breathing ambient air, (6) ability to maintain oral intake, and (7) normal mental status. Continued in-hospital monitoring of stable patients following the transition from parenteral to oral therapy has not been shown to improve outcomes.

If a specific pathogen is identified, the empiric antimicrobial regimen should be tailored to the isolated organism(s), with antimicrobial agent selection guided by in vitro susceptibility testing.

KEY POINTS

- Empiric therapy for community-acquired pneumonia should consist of a macrolide antibiotic or doxycycline in outpatients without comorbidities or recent antimicrobial use or a respiratory fluoroquinolone or β-lactam plus a macrolide (doxycycline as an alternative) in outpatients with comorbid conditions, recent antimicrobial use, or residence in an area where macrolide-resistant *Streptococcus pneumoniae* is prevalent.

HVC
- Hospitalized patients with community-acquired pneumonia who have received parenteral therapy can be switched to oral agents when clinical stability has been attained.

HVC
- Continued in-hospital monitoring of stable patients following the transition from parenteral to oral therapy has not been shown to improve outcomes.

Complications

Patients treated with the appropriate antimicrobial course will typically show improvement in clinical symptoms (fever, cough, dyspnea) within 2 to 3 days. Nonresponsive pneumonia is identified if patients do not show some clinical response within 72 hours of therapy initiation. Nonresponse to treatment can occur because of a pulmonary related complication, such as a complicated parapneumonic pleural effusion, empyema, lung abscess, or postobstructive or necrotizing pneumonia. Rarely, nonresponse may occur with extrapulmonary manifestations of the infectious process, such as meningitis or endovascular infection (endocarditis). In addition to nonresponse, CAP infection may progress or deteriorate. Progressive pneumonia can lead to the need for intubation and mechanical ventilation or, in fulminant cases, result in severe sepsis. Particularly in hospitalized patients, unrelated nosocomial infections (catheter-related infection, urinary tract infection, *Clostridium difficile* infection) can contribute to clinical deterioration or progressive disease. Unsuccessful treatment, because of inadequate coverage of the empiric regimen, host factors, or delayed response to appropriate therapy, is associated with risk factors such as multilobar pneumonia; infection with MRSA, *Legionella* species, or gram-negative bacilli; PSI of 90 or more; and initial treatment with an antimicrobial regimen to which the causative pathogen was not susceptible.

Clinical nonresponse may necessitate more detailed pulmonary imaging with chest CT to exclude the possibility of such complications. These infectious or anatomic complications merit directed targeted investigations and interventions to further define the extent of disease. Antimicrobial therapy may need to be modified to adequately treat extrapulmonary infections. More invasive management is often needed to address pulmonary complications, including thoracentesis for pleural effusions, video-assisted thoracoscopy for empyema, and bronchoscopy for postobstructive/necrotizing pneumonia or lung abscess. In severe enigmatic cases, thoracoscopic or open lung biopsy may be necessary. Multiorgan involvement may result from hematogenous spread or involvement of certain organisms (MRSA); in these subsets of CAP, the antimicrobial course and management will usually require longer therapy duration and further diagnostic studies.

KEY POINTS

- Patients with pneumonia treated with the appropriate antimicrobial course will typically show improvement in clinical symptoms within 2 to 3 days.
- Unsuccessful treatment, because of inadequate coverage of the empiric regimen, host factors, or delayed response to appropriate therapy, is associated with risk factors such as multilobar pneumonia; infection with methicillin-resistant *Staphylococcus aureus*, *Legionella* species, or gram-negative bacilli; Pneumonia Severity Index of 90 or more; and initial treatment with an antimicrobial regimen to which the causative pathogen was not susceptible.

Follow-up

Antimicrobial treatment duration for CAP is typically 5 days in outpatients. Longer treatment courses have not shown clinical benefit and should be avoided to minimize unnecessary antimicrobial use and avoid extra expense of care. Secondary symptoms of CAP, such as cough, fatigue, and other constitutional symptoms, may persist for several days after completion of antimicrobial treatment, but the ongoing presence of these symptoms, in the absence of continued fevers, does not mandate extending the course of therapy. For hospitalized patients, total course of antimicrobial therapy should continue until the patient has been afebrile at least 48 to 72 hours, does not require supplemental oxygen, and does not have more than one sign of clinical instability (defined as heart rate >100/min, respiration rate >24/min, and systolic blood pressure <90 mm Hg). Patients requiring hospitalization usually have intravenous therapy initiated, but they can be switched to oral therapy when they are hemodynamically stable, improving clinically, and able to take oral medications and their gastrointestinal tract function has normalized. Total duration of antimicrobial therapy in patients who respond clinically within

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the first 2 to 3 days of treatment is generally not longer than 7 days. Complications of CAP, such as lung abscess, empyema, necrotizing pneumonia, or extrapulmonary infections, will mandate longer courses of therapy. In these patients, management must be tailored to the particular circumstances and CAP complications. In the specific instance of MRSA CAP without metastatic infection, guidelines recommend between 7 and 21 days of treatment, depending on the severity and extent of infection and clinical response.

Findings on chest radiography can often linger despite clinical improvement and symptom resolution. As a result, the routine use of follow-up chest radiography after successful treatment is not generally recommended. Follow-up chest radiography may have the greatest utility in patients older than 50 years, particularly for men and smokers. In these subsets of patients, the posttreatment follow-up chest radiograph should be obtained 2 to 3 months after antimicrobial treatment.

An important aspect of treatment includes interventions to prevent future episodes of CAP. Administration of clinically indicated vaccinations, including pneumococcal and annual influenza vaccine (see MKSAP 17 General Internal Medicine), are important components of prevention of future CAP. Counseling to reduce or eliminate modifiable risk factors for CAP, such as smoking and heavy alcohol use, should be initiated. Stabilization of underlying chronic lung disease (COPD) may be an important adjunct to decreasing future CAP.

KEY POINTS

HVC
- Treatment courses for community-acquired pneumonia longer than 5 days have not shown clinical benefit and should be avoided to minimize unnecessary antimicrobial use and avoid extra expense of care.

HVC
- The routine use of follow-up chest radiography after successful treatment of community-acquired pneumonia is not recommended because findings may linger despite clinical improvement and symptom resolution.

Tick-Borne Diseases

Lyme Disease

Lyme disease, caused by infection with *Borrelia burgdorferi*, is the most common vector-borne infection in the United States. More than 30,000 new cases are reported each year, but the true incidence is likely several-fold higher. More than 95% of all cases occur in regions where the vector *Ixodes* tick is abundant (**Figure 3**). The *Ixodes* tick also serves as the vector for the pathogens causing anaplasmosis and babesiosis, and coinfections may occur. *Borrelia miyamotoi*, a newly described cause of fever and meningoencephalitis, is also transmitted by *Ixodes* ticks. See **Figure 4** for various tick life cycles.

Human infection occurs through inoculation of spirochetes in infected tick saliva and usually requires tick attachment for more than 36 hours. The clinical presentation and



FIGURE 3. Geographic distribution of cases of Lyme disease in the United States, 2013. One dot is placed randomly within county of residence for each confirmed case.

Reproduced from Centers for Disease Control and Prevention. Reported cases of Lyme disease - United States, 2013. www.cdc.gov/lyme/stats/maps/map2013.html. Updated March 4, 2015. Accessed June 30, 2015.

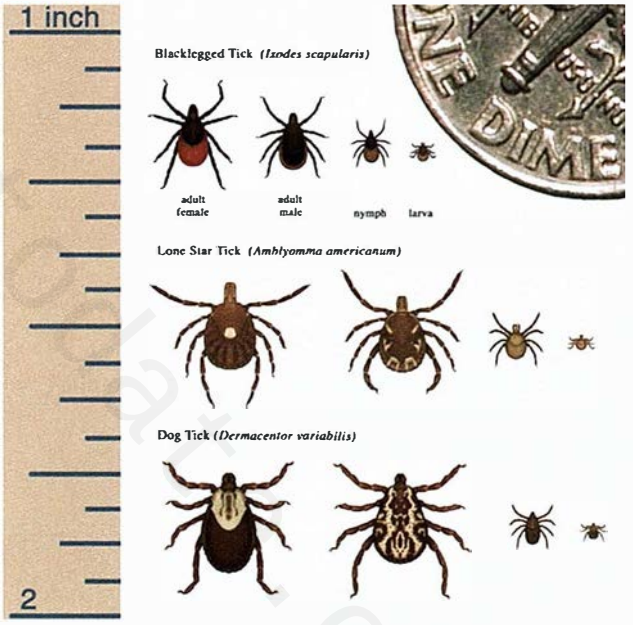

FIGURE 4. The life cycles of three hard tick species that spread disease.

Reproduced from Centers for Disease Control and Prevention. Life cycle of hard ticks that spread disease. www.cdc.gov/ticks/life_cycle_and_hosts.html. Updated February 3, 2014. Accessed June 30, 2015.

appropriate diagnostic strategy for Lyme disease vary according to the stage of infection (**Table 14**).

The first stage involves localized symptoms occurring 1 to 4 weeks after infection. This early stage is usually characterized by erythema migrans, a target lesion occurring at the site of tick attachment and present in 60% to 80% of localized infections (**Figure 5**). Fever and other systemic symptoms are rarely present. Results of serologic testing at this stage are frequently negative; therefore, documentation of erythema

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TABLE 14. Clinical Manifestations and Diagnostic Testing for Lyme Disease

Stage	Onset After Inoculation	Signs/Symptoms	Diagnosis	Treatment
Localized	1-4 weeks	Single erythema migrans at site of inoculation	Clinical	Oral doxycycline[a], amoxicillin, or cefuroxime axetil
Early disseminated	Weeks to months	Multiple erythema migrans, often with fever, headache, myalgias	Clinical (serologic testing can support diagnosis)	Same as for localized
		Heart block, myocarditis	Serologic testing	First-degree heart block: same as for localized
				Higher-grade heart block: ceftriaxone or intravenous penicillin G
		Cranial nerve palsies, meningitis	Serologic testing	Facial nerve palsy: doxycycline[a]
				Other neurologic manifestations: ceftriaxone or intravenous penicillin G
Late disseminated	Months to years	Oligoarticular arthritis	Serologic testing, PCR of synovium or synovial fluid	Doxycycline[a] or amoxicillin; intravenous ceftriaxone for recurrent symptoms
		Encephalopathy or encephalomyelitis	Serologic testing, intrathecal antibody, CSF PCR	Ceftriaxone or intravenous penicillin G

CSF = cerebrospinal fluid; PCR = polymerase chain reaction.

[a]Doxycycline should not be used in pregnancy; instead, a β-lactam antibiotic should be used.



FIGURE 5. An erythema migrans lesion characteristic of Lyme disease. These lesions are often found near the axilla, inguinal region, popliteal fossa, or at the belt line. Lesions typically expand over time and, when large enough, often demonstrate central clearing. Some will have more complex configurations, such as a target or bull's eye, as seen in this patient.

Figure courtesy of Karen Bloch, MD

migrans with a compatible epidemiologic history is sufficient for diagnosis, and laboratory confirmation is not indicated. Atypical skin lesions, including vesicles or erythematous patches without central clearing, are more diagnostically challenging. In these cases, testing acute and convalescent sera may allow retrospective diagnosis. Results of polymerase chain reaction (PCR) on a specimen from skin biopsy of erythema migrans are usually positive, but this invasive procedure is rarely necessary.

Treatment of early localized disease prevents progression of infection. Therapy is outlined in Table 14. Doxycycline offers the advantage of treating possible coinfection with *Anaplasma phagocytophilum*. Treatment of localized Lyme disease does not protect against subsequent infection.

Untreated patients may progress to early disseminated infection. This stage typically presents as a febrile illness associated with erythema migrans at multiple sites distant from the initial tick attachment. Constitutional symptoms are common and include fever, myalgia, arthralgia, and headache. Although antibodies to *B. burgdorferi* are typically present at this stage, the diagnosis of early disseminated disease is also clinical; treatment of uncomplicated disease is the same as for localized infection.

Focal cardiac or neurologic symptoms may also occur in early disseminated disease. Cardiac involvement ranges from asymptomatic PR interval prolongation to complete heart block. Progression to complete heart block may be rapid; therefore, symptomatic patients with dyspnea or presyncope, or any patient with second-degree or greater heart block, require hospitalization for cardiac monitoring. Oral antibiotics are effective for treatment of first-degree atrioventricular block, but parenteral therapy is necessary for higher degrees of atrioventricular block. Because Lyme-associated atrioventricular block is reversible with antibiotic treatment, implantation of a permanent cardiac pacemaker is not indicated. Less

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commonly, diffuse Lyme myocarditis may occur and may be fatal with minimal prodromal symptoms.

The most common neurologic manifestation of early disseminated Lyme disease is facial nerve palsy, which may be unilateral or bilateral. Oral antibiotics are typically curative, but resolution of neurologic deficits may take weeks or even months. Meningitis or other neurologic presentations require parenteral antibiotic therapy. In addition to positive results on serologic testing for *B. burgdorferi*, intrathecal measurement of antibody production or *B. burgdorferi* PCR on cerebrospinal fluid (CSF) may help confirm the diagnosis, although the significance of a positive CSF PCR result in the absence of positive serologic findings is uncertain.

Late manifestations of Lyme disease may occur months to years after infection. The most common clinical presentation is oligoarticular inflammatory arthritis involving large joints, such as the knee. The natural history is for arthritis to wax and wane, often resolving spontaneously only to recur in the same or a different joint. Results of serologic testing for *B. burgdorferi* are invariably positive at this stage and, in the absence of an alternative cause for arthritis, are diagnostic. PCR of synovial fluid or tissue may confirm the presence of infection, but the findings should be interpreted with caution if serologic results are negative. Treatment with prolonged oral antibiotics (1-2 months) is indicated; parenteral therapy may ultimately be required if the clinical response is incomplete.

Post-Lyme disease syndrome, sometimes erroneously termed "chronic Lyme disease," occurs in some patients despite appropriate antibiotic therapy. These patients experience nonspecific but disabling symptoms, such as fatigue, poor concentration, insomnia, diffuse pain, and malaise. No evidence of latent or persistent infection is found in these patients; symptoms may result from an exuberant host inflammatory response. Management focuses on amelioration of symptoms. Because of the absence of latent *B. burgdorferi* infection in these patients, prolonged administration of antibiotics is not beneficial and is contraindicated.

In patients requiring laboratory confirmation of Lyme disease, serologic testing is the primary means of diagnosis using a two-step serologic testing strategy (**Figure 6**). The initial test is an enzyme-linked immunosorbent assay (ELISA), which is extremely sensitive and is used as a screening test. Occasionally, an indirect immunofluorescence assay may be used. For positive or equivocal results, the more specific

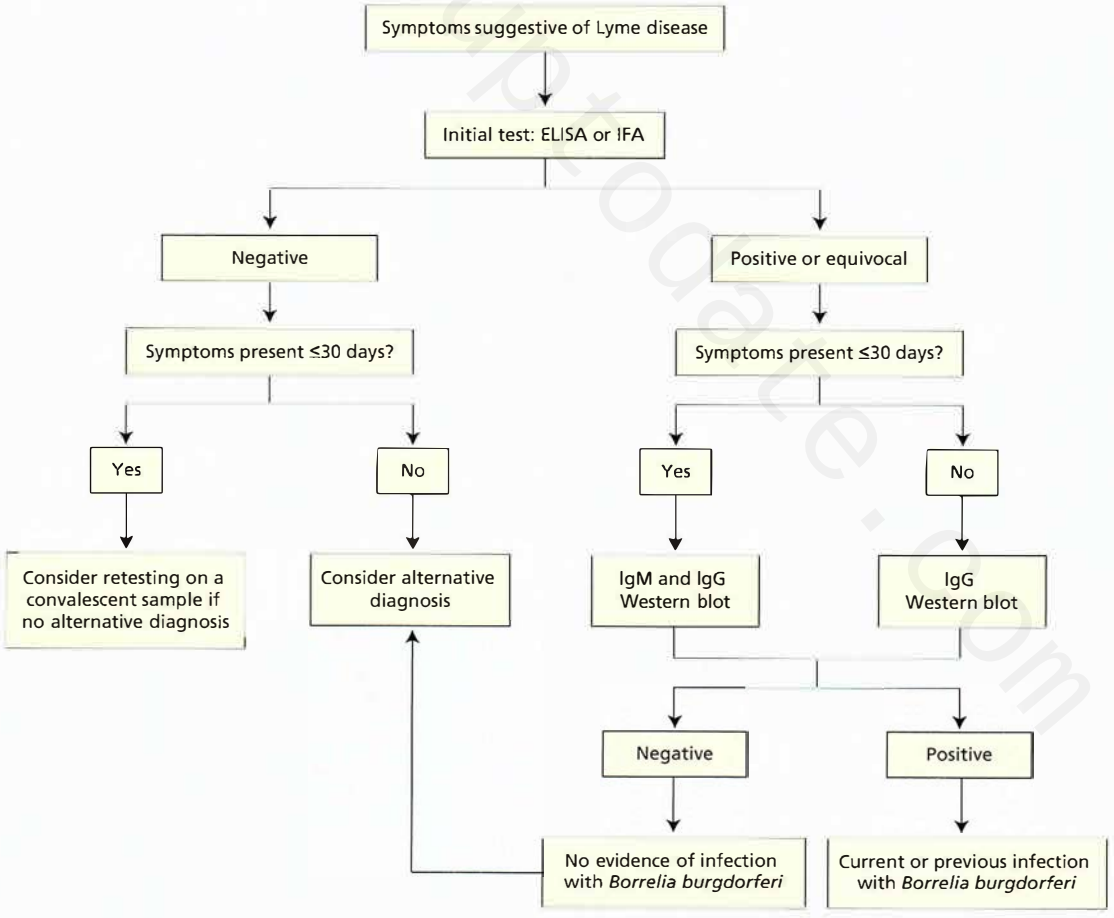

FIGURE 6. Two-tiered antibody testing for Lyme disease.

ELISA = enzyme-linked immunosorbent assay, IFA = immunofluorescence assay.

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Western blot test is required; a positive result on this second step confirms the presence of antibodies to *B. burgdorferi*.

Early in the course of infection, antibodies may not yet be detectable, and the development of an IgM antibody predates that of IgG. However, an isolated IgM Western blot in a patient with symptoms for more than 30 days suggests a false-positive result. Antibodies remain positive indefinitely, and repeat testing or re-treatment for persistently positive antibody is not indicated. Finally, patients who have acquired infection internationally may be infected with a *Borrelia* species that does not cross-react serologically with the *B. burgdorferi* assay. In these cases, an alternative ELISA that identifies antibodies to the highly conserved C6 *Borrelia* peptide is recommended for diagnosis.

KEY POINTS

- Lyme disease symptoms occur 1 to 4 weeks after infection and are characterized by erythema migrans, a single target lesion present in 60% to 80% of localized infections.

HVC
- Antibodies may not be present early in Lyme disease infection; documentation of erythema migrans with a compatible epidemiologic history is sufficient for diagnosis, and serologic testing is not indicated and may be falsely negative in localized disease.
- *Borrelia burgdorferi* antibodies will likely be present in later (disseminated) disease stages, and a two-step serologic testing strategy that uses an enzyme-linked immunosorbent assay as an initial screening test followed by a confirmatory Western blot is the best way to confirm the diagnosis of disseminated Lyme disease.

HVC
- Post–Lyme disease syndrome or "chronic Lyme disease" occurs in some patients despite appropriate antibiotic therapy and includes nonspecific but disabling symptoms; management focuses on amelioration of symptoms, and prolonged administration of antibiotics is not beneficial and is contraindicated.

Southern Tick-Associated Rash Illness

Southern tick–associated rash illness (STARI) was initially recognized in patients who presented with erythema migrans (see Figure 4) but had not traveled to an area endemic for Lyme disease. Results of laboratory testing for *B. burgdorferi* are invariably negative in patients with STARI, suggesting infection with an as-yet undiscovered tick-borne pathogen. STARI cases are most prevalent in the southeastern and southcentral parts of the United States, and disseminated infection has not been documented. However, because STARI is clinically indistinguishable from localized Lyme disease, treatment with an oral antibiotic active against localized Lyme disease is indicated (see Table 14).

KEY POINT

- Southern tick-associated rash illness is clinically indistinguishable from localized Lyme disease, so treatment with an oral antibiotic active against localized Lyme disease is indicated.

Babesiosis

Human babesiosis is caused by protozoal infection of erythrocytes. In the United States, babesiosis is primarily caused by *Babesia microti*, although other species are increasingly recognized. *B. microti* is transmitted by the same tick vector as Lyme disease and has similar geographic distribution (see Figure 3). Transmission through transfusion of infected blood products has been reported.

In most patients, infection is asymptomatic or causes a mild illness. The onset of symptoms is typically within the first month after infection. Mild infection presents with a febrile illness variably associated with myalgias, headache, and fatigue. In cases of transfusion-associated infection, the time from exposure to symptom onset may be as long as 6 months. Physical findings may include splenomegaly, hepatomegaly, and jaundice.

Patients with asplenia or those who are older or immunocompromised typically have higher parasitic burdens, leading to more severe disease. Patients with high-level parasitemia may present with acute respiratory failure, disseminated intravascular coagulation, or kidney injury. Splenic rupture can also occur.

Laboratory findings are related to hemolysis and include anemia, elevated reticulocyte count, increased lactate dehydrogenase, and decreased haptoglobin. Elevated liver enzyme levels and thrombocytopenia are also common. Organisms may be identified on blood smears by using Giemsa or Wright staining (**Figure 7**). Trophozoites appear as ring forms inside erythrocytes and may be confused with malaria unless a thorough travel history is obtained. Less commonly, protozoa may resemble a tetrad or Maltese cross formation. The sensitivity of microscopy depends on the level of parasitemia and the number of fields reviewed; however, if results are positive, this test is diagnostic for infection. For patients with mild disease and low parasitic burden, PCR is recommended as the initial test. The utility of serologic testing in the diagnosis of acute infection is limited. Among inhabitants of endemic areas, detection of antibody may indicate previous asymptomatic infection. A positive IgM antibody or seroconversion result denotes recent infection; however, the serologic response may be delayed and findings on antibody testing may be falsely negative early in the course of infection.

When *Babesia* infection is detected in an asymptomatic patient, monitoring for resolution of parasitemia is recommended. If organisms persist for more than 3 months, with or without symptoms, treatment is indicated. All patients with symptomatic babesiosis require therapy. Atovaquone

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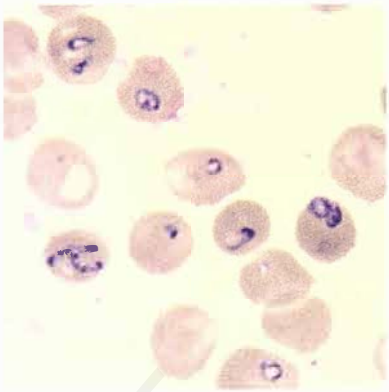

FIGURE 7. *Babesia* sp. trophozoites visualized as intraerythrocytic ring forms.

Reproduced from Centers for Disease Control and Prevention, DPDx. Babesiosis. www.cdc.gov/dpdx/babesiosis/gallery.html#thinblood. Updated November 29, 2013. Accessed June 30, 2015.

CONT. plus azithromycin is the treatment of choice for mild-to-moderate disease. This regimen is as effective as combination therapy with clindamycin and quinine but is associated with significantly fewer adverse effects. In severe disease, clindamycin plus quinine is preferable. Exchange transfusion should be considered in patients with 10% or greater parasitemia or multiorgan system failure. In immunocompromised patients or those with sustained parasitemia, antibiotics should be continued for at least 6 weeks. Relapse in immunosuppressed patients is common, and a repeat course of treatment is often necessary.

KEY POINTS

- Babesiosis is typically asymptomatic or causes a mild febrile illness variably associated with myalgias, headache, and fatigue, whereas more severe disease presents with acute respiratory failure, disseminated intravascular coagulation, kidney injury, and possibly splenic rupture.
- Polymerase chain reaction is a more sensitive test for diagnosing patients with mild babesiosis and low parasitic burdens; the sensitivity of microscopy of Giemsa- or Wright-stained blood smears depends on the level of parasitemia.
- When treatment for babesiosis is indicated, atovaquone plus azithromycin or clindamycin plus quinine are the therapies of choice, depending on disease severity.

Ehrlichiosis and Anaplasmosis

The clinical presentations of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) are similar despite transmission by different ticks. The vector for HME is the Lone Star tick, endemic to the southcentral and southeastern parts of the United States. HGA is transmitted by the same vector as are Lyme disease and babesiosis (Figure 3).

The spectrum of clinical disease with HME and HGA ranges from a nonspecific febrile condition to a fulminate illness, with a mortality rate of 1% to 3%. Fever is present in more than 90% of patients, followed in frequency by headache, myalgia, arthralgia, and meningismus. Rash is rare. Life-threatening complications may include acute kidney injury, meningoencephalitis, and acute respiratory distress syndrome.

Laboratory abnormalities raise suspicion for these diagnoses. Both conditions are associated with leukopenia and thrombocytopenia. Aminotransferases are frequently elevated, with bilirubin and alkaline phosphatase usually unaffected. Patients undergoing lumbar puncture may have lymphocytic pleocytosis.

Morulae, basophilic inclusion bodies composed of clusters of bacteria, may be found in leukocyte cytoplasm (**Figure 8**). Morulae are identified in monocytes in fewer than 30% of patients with HME but are seen in neutrophils in more than 50% of patients with HGA; considering the low sensitivity, other diagnostic tests are recommended when microscopic findings are negative. Antibodies are often absent at presentation; however, the sensitivity of serologic testing on a convalescent specimen is greater than 90%, allowing retrospective diagnosis. Whole-blood PCR is the most sensitive test for diagnosis of acute infection, particularly when performed before initiation of antibiotics.

Doxycycline is effective therapy for both infections. Therapy should be given empirically when a diagnosis of HME or HGA is considered because delay in therapy has been associated with adverse outcomes. Given their limitations, a negative result on serologic testing or microscopy should not affect the decision to start or continue doxycycline. A negative PCR result, particularly if obtained before initiation of doxycycline, would suggest an alternative diagnosis. Treatment options for patients allergic to or intolerant of doxycycline are limited, and desensitization may be required.

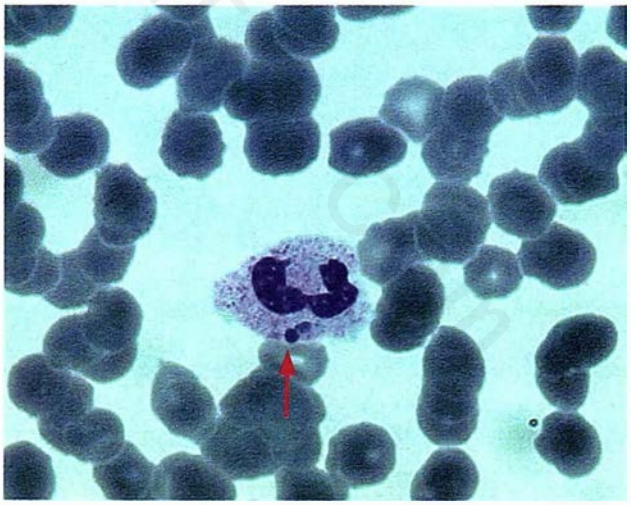

FIGURE 8. Morulae (*arrow*), appearing as basophilic inclusion bodies in leukocytes of a patient with ehrlichiosis.

Figure courtesy of Charles Stratton, MD

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KEY POINTS

- Human monocytic ehrlichiosis and human granulocytic anaplasmosis are associated with a nonspecific febrile illness, frequently accompanied by headache, myalgia, arthralgia, and meningismus.
- Whole-blood polymerase chain reaction is extremely sensitive for diagnosing ehrlichiosis and anaplasmosis when performed before antibiotic initiation and allows rapid diagnosis at acute presentation.
- Doxycycline should be given empirically when ehrlichiosis or anaplasmosis is a diagnostic consideration because delay in therapy is associated with adverse outcomes.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) has been reported throughout the United States. Infections predominate in warmer months when ticks are active. The hallmark of RMSF is a petechial rash, seen in more than 85% of patients by the end of the first week of illness (**Figure 9**). Skin lesions may lag behind other symptoms; only 50% of patients have visible rash by the third day of illness. Therefore, the diagnosis should be considered in any patient presenting with a fever and possible tick exposure regardless of the presence of a rash. Skin lesions typically start at the distal extremities and progress centrally. The rash involves the palms and soles in more than 30% of patients but usually spares the face.

Thrombocytopenia and elevated aminotransferase levels are common. The leukocyte count in RMSF may be elevated, normal, or low. When lumbar puncture is performed, CSF demonstrates a lymphocyte-predominant pleocytosis.

Development of rickettsial antibodies takes several weeks; therefore, serologic testing is of limited utility during the acute illness. Testing paired acute and convalescent serum may demonstrate seroconversion or a fourfold rise in antibody titer, both of which are diagnostic of acute infection. Serologic cross-reactivity is common, and a positive test result may represent infection with another spotted fever group *Rickettsia* species. Immunohistochemistry or PCR of a skin biopsy specimen allows diagnosis at the time of acute infection.

Doxycycline is effective against all spotted fever group rickettsioses. Symptoms typically improve within 72 hours, and continued fevers or progressive constitutional symptoms after this time period strongly suggest an alternative diagnosis. Doxycycline is contraindicated in pregnancy; chloramphenicol is an alternative option.

KEY POINTS

- The diagnosis of Rocky Mountain spotted fever should be considered in any patient presenting with a fever and possible tick exposure regardless of the presence of a rash.
- Serologic testing is of limited utility during acute illness with Rocky Mountain spotted fever.
- Doxycycline is the therapy of choice for all spotted fever group rickettsioses; chloramphenicol is an alternative option in pregnancy.



FIGURE 9. Petechial skin eruption on the lower extremity of a patient with Rocky Mountain spotted fever.

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Urinary Tract Infections

Epidemiology and Microbiology

Urinary tract infection (UTI) is broadly defined as infection anywhere in the urinary tract, including the urethra, the bladder, the ureters, and the kidneys. UTI accounts for more than eight million office visits and one million emergency department visits and results in approximately 100,000 hospital admissions each year in the United States. UTIs are common among hospitalized patients, with the predominant risk factor being bladder catheterization. Other risk factors for UTIs include female sex; postmenopausal status; previous UTI; sexual activity; genital trauma or surgery; diabetes; condom, diaphragm, or spermicide use in women; vaginal infection; obesity; genital tract abnormalities or obstructions; and host susceptibility, including genetic factors and immunosuppression. Bacteria that cause UTI generally have special virulence factors that enable them to survive in the urinary tract. Most of the research in bacterial uropathogenesis has been done with *Escherichia coli*. Uropathogenic *E. coli* expresses such traits as fimbrial and nonfimbrial adhesins for attachment, flagellae for motility, enterobactin that inactivates host defenses, metal acquisition systems that enhance survival in urine, toxins, and fimbrial phase variation mechanisms that change antigens before the host can respond.

E. coli is the most common organism associated with asymptomatic bacteriuria, cystitis, pyelonephritis, and catheter-associated UTI. The urinary tract is the most common source of bacteremia caused by gram-negative organisms. Other common urinary pathogens include *Klebsiella* species, *Proteus* species, *Pseudomonas aeruginosa*, and *Staphylococcus saprophyticus*, the latter being a frequent cause of acute uncomplicated cystitis. Infections with non-*E. coli* organisms are more likely to occur in men, in patients with recurrent UTIs, in those with obstruction, or in the presence of a urinary catheter. Multiple urinary pathogens may be isolated when structural abnormalities of the urinary tract or calculi are present. *Candida* species cause UTI in patients with diabetes mellitus or indwelling urinary catheters; however, in most patients, candiduria represents colonization and does not require treatment.

Antimicrobial resistance among urinary pathogens is increasing in frequency in the community and hospital settings because of antibiotic overuse, inappropriate treatment of asymptomatic bacteriuria, and local differences in antibiotic use. The frequency of resistant organisms varies by patient population and geographic location. Risk factors for multidrug-resistant organisms are current or recent hospitalization, immunocompromise, presence of underlying structural abnormalities of the urinary tract, previous UTI, kidney transplantation, and recent antimicrobial therapy.

KEY POINTS

- Risk factors for urinary tract infection (UTI) with multidrug-resistant organisms are current or recent hospitalization, immunocompromise, presence of underlying structural abnormalities of the urinary tract, previous UTI, kidney transplantation, and recent antimicrobial therapy.
- Antimicrobial resistance among urinary pathogens is increasing in frequency in the community and hospital settings because of antibiotic overuse, inappropriate treatment of asymptomatic bacteriuria, and local differences in antibiotic use. HVC

Diagnosis

UTIs are classified as uncomplicated or complicated. Acute cystitis and pyelonephritis occurring in healthy, premenopausal, nonpregnant women with no history of urinary tract abnormalities are classified as uncomplicated. Complicated UTI is defined as infection occurring in a patient with comorbid conditions or anatomic abnormalities of the urinary tract that increase the risk for adverse outcomes, including poor response to therapy, a need for hospitalization, presence of resistant organisms, and morbidity. Common complicating factors are diabetes, pregnancy, male sex, advanced age, kidney transplantation, anatomic or functional abnormalities of the urinary tract, urinary catheterization or manipulation, recent antibiotic exposure, and recent hospitalization.

Urine dipsticks are used to assess for pyuria and bacteriuria by detecting leukocyte esterase and nitrites, respectively, which are markers of infection in the urine. They are easy to use and fairly reliable in confirming infection if results are positive and the patient has signs or symptoms consistent with UTI. Sensitivity of both tests together (with results of one or both being positive) is between 68% and 88%, depending on patient group. When both results of tests are positive, specificity and predictive value increase. Negative results for both tests, however, strongly predict the absence of UTI when the pretest probability is low. Reasons for a false-negative nitrite test result include inability of some organisms, such as *Enterococcus faecalis*, to convert nitrate to nitrite; low urinary excretion of nitrate; low urine pH; and insufficient bladder incubation time. On urine microscopy, the presence of at least 10 leukocytes/μL of unspun urine from a midstream, clean-catch specimen indicates significant pyuria; 5-10 leukocytes/hpf on a centrifuged specimen of urine is also significant. Pyuria is a nonspecific finding and may or may not indicate infection.

A urine culture is used to confirm the presence of bacteriuria and yield the causative organism for antimicrobial susceptibility testing. A urine culture should be obtained in patients with suspected pyelonephritis, complicated UTI, recurrent UTI, and multiple antimicrobial allergies and in

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CONT. those in whom the presence of a resistant organism is suspected. It is also recommended that urine cultures be obtained in pregnant women during the first trimester of pregnancy to screen for asymptomatic bacteriuria and for patients undergoing urologic procedures so that appropriate therapy can be instituted. Urine cultures are not indicated for the diagnosis of uncomplicated cystitis because patient history is reliable in establishing the diagnosis and treatment is completed before the availability of culture results. Because contamination of urine from bacteria that normally colonize the urethra and periurethral areas is frequent, quantitating bacteria in midstream, clean-void urine allows for differentiation of contamination and infection. Patients with infection usually have at least 105 colony-forming units (CFU)/mL on culture. In symptomatic patients with pyuria, a colony count between 102 and 105 CFU/mL may still indicate a UTI. Standard criteria are insensitive for cystitis because up to half of women with cystitis have colony counts of 102 to 104 CFU/mL. Reasons for this are unclear but may represent an earlier stage of infection or bladder washout during urination. Similarly, low colony counts may still indicate infection in patients receiving antimicrobial therapy, in men, and in those with organisms other than *E. coli* and *Proteus* species. Diagnosis is complicated in patients with indwelling catheters. Most patients with catheter-associated UTI have colony counts of 10^5 CFU/mL or greater. Symptoms may be nonspecific. Although pyuria is frequently found in asymptomatic patients who are catheterized, the absence of pyuria in a symptomatic patient should prompt consideration of an alternative diagnosis.

KEY POINT

HVC
- A culture of midstream, clean-void urine should be reserved for patients with suspected pyelonephritis, complicated urinary tract infection, recurrent urinary tract infection, or multiple antimicrobial allergies and in those in whom the presence of a resistant organism is suspected.

Management

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is defined by the presence of bacteria (two consecutive voided specimens with isolation of the same strain in counts $\geq 10^5$ CFU/mL in women, a single voided specimen with one bacterial species in counts $\geq 10^5$ CFU/mL in men, or a single catheterized specimen with isolation of one species in a count $\geq 10^2$ CFU/mL in women or men) in an uncontaminated urine specimen collected from a patient without signs or symptoms. It is important to recognize that screening for and possibly treating asymptomatic bacteriuria are supported by only two indications: pregnancy and medical clearance before an invasive urologic procedure. In actual practice, treatment decisions are usually based on a single voided specimen without a repeat culture. Urinalysis and urine culture are not indicated as part of routine health surveillance in asymptomatic patients and should not be performed.

Cystitis in Women

The most common symptoms of cystitis in premenopausal women are dysuria, frequency, urgency, and suprapubic discomfort. Postmenopausal women with cystitis may present with incontinence or gross hematuria. Fever is unusual. Progression to pyelonephritis is rare. Recommended first-line antimicrobial agents for acute uncomplicated cystitis in women include nitrofurantoin and trimethoprim-sulfamethoxazole; fosfomycin has lower efficacy and is more expensive than the first two options. Trimethoprim-sulfamethoxazole should not be used if it was taken in the preceding 3 months or if the prevalence of resistance is known to exceed 20%. Resistance rates for nitrofurantoin and fosfomycin are low. Short-course regimens (single dose to 5 days, depending on the agent used) are recommended. They are as effective in achieving cures as longer regimens and have fewer adverse effects. Fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin) and β-lactams are considered second-line therapy. Oral β-lactams are less effective than fluoroquinolones. Increasing resistance of urinary isolates of *E. coli* to fluoroquinolones has been reported. Strains that produce extended-spectrum β-lactamases have increased in frequency.

KEY POINTS

- Urinalysis and urine culture are not indicated as part of routine health surveillance in asymptomatic patients and should not be performed.
- Fosfomycin has lower efficacy and is more expensive than nitrofurantoin or trimethoprim-sulfamethoxazole in first-line antimicrobial therapy for women with acute uncomplicated cystitis. HVC

Acute Pyelonephritis

Clinical manifestations of acute pyelonephritis include fever, chills, back flank pain, nausea, and vomiting. Antecedent or concurrent symptoms of cystitis may or may not be present. Most episodes of acute uncomplicated pyelonephritis are treated in the ambulatory setting. This is appropriate for patients who are otherwise healthy and have mild to moderate uncomplicated illness, but close supervision is essential. Empiric therapy should be initiated after a urine culture is obtained. Fluoroquinolones (ciprofloxacin, levofloxacin, or ofloxacin) are recommended for outpatient empiric therapy. Indications for hospitalization include hemodynamic instability, inability to tolerate oral medications, host factors such as pregnancy or presence of kidney stones or other obstructions, presence of comorbidities, and an unstable social situation that may compromise adherence or follow-up. Inpatient antimicrobial regimens include intravenous fluoroquinolones, aminoglycosides with or without ampicillin.

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extended-spectrum cephalosporins or extended-spectrum penicillins with or without an aminoglycoside, and carbapenems. Ceftolozane-tazobactam was recently approved for treatment of complicated UTI caused by resistant organisms, including those producing extended-spectrum β-lactamases. Imaging with CT (preferred) or ultrasonography should be performed if symptoms and fever persist longer than 72 hours to rule out perinephric or intrarenal abscess. In patients who have symptoms suggesting a stone or obstruction, a urologic evaluation should be performed emergently.

The duration of therapy for acute uncomplicated pyelonephritis treated with fluoroquinolones is 5 to 7 days; complicated infections should be treated for 14 days. Hospitalized patients who are treated initially with parenteral antibiotics can be switched to oral agents after clinical improvement is noted and they are able to tolerate oral therapy. Oral therapy can be chosen on the basis of susceptibility results from urine culture; however, oral cephalosporins generally should be avoided. Trimethoprim-sulfamethoxazole or fluoroquinolones are preferred. Bacteremia is not uncommon in patients who require hospitalization for pyelonephritis; although these patients may take longer to reach clinical stability, more prolonged courses of parenteral antibiotics are not required.

KEY POINTS

HVC

- Acute uncomplicated pyelonephritis should be treated with fluoroquinolones for 5 to 7 days, complicated infections should be treated for 14 days, and hospitalized patients treated initially with parenteral antibiotics can be switched to oral agents after clinical improvement is noted and oral therapy can be tolerated.
- Trimethoprim-sulfamethoxazole or fluoroquinolones are preferred for oral therapy in acute pyelonephritis, and oral cephalosporins should generally be avoided.

Recurrent Urinary Tract Infections in Women

Recurrent UTI is defined as three episodes of UTI in the preceding 12 months or two episodes in the preceding 6 months. Recurrent UTI is common in women. A recurrent UTI may be a relapse or reinfection. Relapse is defined as an infection caused by the same strain (by repeat culture) as the initial UTI and occurs within 2 weeks of the completion of initial therapy. Reinfection is diagnosed if the UTI is caused by a different strain than that causing the initial infection or if a sterile urine culture was documented between the episodes. Most recurrences are reinfections. For relapsed UTI, therapy can be given with the same antibiotic for a longer period; 7 to 10 days is reasonable.

Prevention includes considering an alternate method of contraception in patients using condoms, diaphragms, and spermicides. Low-dose antimicrobial prophylaxis with a daily or every-other-day dose of nitrofurantoin or trimethoprim-sulfamethoxazole, usually taken at bedtime, is an effective method to prevent frequent UTIs but does not alter the long-term risk for recurrence after prophylaxis is discontinued. This strategy may aid women who desire a respite from recurrent UTI. Antimicrobial prophylaxis, consisting of a single dose of an agent (such as nitrofurantoin or trimethoprim-sulfamethoxazole), can be administered after sexual intercourse and reduces the rate of recurrent cystitis. This strategy is useful when recurrent UTI is clearly linked to sexual intercourse. An additional, nonpreventive strategy is for patients with previously diagnosed cystitis to self-diagnose and self-treat at the onset of symptoms. In postmenopausal women, two small studies have shown the use of topical vaginal estrogens reduces the number of UTIs compared with placebo. Some cranberry products decrease the frequency of recurrent UTIs by about one third but are less effective compared with low-dose antimicrobial prophylaxis.

A urologic evaluation is indicated if a structural or physiologic abnormality is suspected, if multiple relapses occur caused by the same strain, and when renal calculi as a nidus for infection are a concern.

KEY POINTS

- Continuous antimicrobial prophylaxis with a daily bedtime dose of nitrofurantoin or trimethoprim-sulfamethoxazole reduces recurrences of cystitis, but adverse effects are common.
- Antimicrobial prophylaxis, consisting of a single dose of an agent (such as nitrofurantoin or trimethoprim-sulfamethoxazole), can be administered after sexual intercourse and reduces the rate of recurrent cystitis when it has been linked to sexual activity.

Acute Bacterial Prostatitis

Acute bacterial prostatitis is a common and important infection. Patient groups at high risk include those with diabetes, immunosuppression, and cirrhosis. Risk factors include unprotected sexual intercourse, the presence of indwelling urinary catheters, urinary tract manipulation, urinary stasis (obstruction), and benign prostatic hyperplasia. Most cases result from ascending urethral infection and intraprostatic reflux, although bacterial cystitis, epididymo-orchitis, and seeding during a transrectal prostate biopsy can also lead to acute bacterial prostatitis. Rarely, prostatitis can develop from spread from the rectum by the lymphatic system or hematogenously during bacterial sepsis. Common symptoms include fever, chills, malaise, nausea and vomiting, dysuria, urgency, frequency, and pain in the lower abdomen, perineum, and rectum. Patients may be quite ill. On rectal examination, the prostate is very tender and tense. Excessive palpation of the prostate should be avoided due to lack of diagnostic or therapeutic benefit and because bacteremia may result. The causative organisms are the same as those that cause most UTIs, including *E. coli* and

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other gram-negative organisms and *Enterococcus* species. *Neisseria gonorrhoeae* may cause acute prostatitis in sexually active men. The diagnosis is established in most cases by a urine Gram stain and culture. Blood cultures should be obtained in patients who require hospitalization and in outpatients who have systemic symptoms. The therapy of choice for uncomplicated cases in patients with low risk for a sexually transmitted infection is an oral fluoroquinolone (levofloxacin or ciprofloxacin) for 4 to 6 weeks; trimethoprim-sulfamethoxazole is an alternative. Follow-up evaluation with repeat culture is necessary to ensure response to treatment.

Complications include development of prostatic abscess, infarction, chronic bacterial prostatitis, and granulomatous prostatitis. Imaging studies are not necessary unless a prostatic abscess is suspected. Chronic prostatitis is discussed in MKSAP 17 General Internal Medicine.

KEY POINT

- The therapy of choice for uncomplicated acute prostatitis is an oral fluoroquinolone (levofloxacin or ciprofloxacin) for 4 to 6 weeks, with repeat culture needed to ensure response to treatment.

Mycobacterium tuberculosis Infection

Epidemiology

One third of the world (approximately 2 billion people) is infected with *Mycobacterium tuberculosis*. In 2012, almost 9 million people worldwide developed active tuberculosis, and 1.3 million people died as a result of tuberculosis. The greatest number of new cases reported was in Asia (60% of all new cases worldwide), but the largest tuberculosis case rate was reported in sub-Saharan Africa. More than one third of persons with HIV worldwide are also infected with tuberculosis, a concern because active disease is 25 times more likely in this population than in those without HIV. More than 1 million new HIV-associated tuberculosis cases were reported in 2012, and 20% of HIV-associated deaths occur because of tuberculosis.

In 2013, the total number of tuberculosis cases in the United States was 9582, the lowest since reporting began in 1953. The incidence rate of infection in foreign-born persons is 13 times higher than that of persons born in the United States. The percentage of cases in foreign-born persons was 65% of all cases in the United States and has continued to increase since 1993, when the percentage was 29%. Eighty percent of all cases of tuberculosis in foreign-born persons living in the United States occurred in those of Hispanic and Asian descent.

Ninety-five cases of primary multidrug-resistant (MDR) tuberculosis were reported in the United States in 2013, and 89.5% of these infections occurred in foreign-born persons. Extensively drug-resistant (XDR) tuberculosis remains rare in the United States.

KEY POINTS

- The percentage of tuberculosis cases in foreign-born persons was 65% of all cases in the United States in 2013; this rate has continued to increase since 1993, when the percentage was 29%.
- More than one third of persons with HIV worldwide are infected with tuberculosis, which is 25 times more likely in this population than in those without HIV; 20% of HIV-associated deaths occur because of tuberculosis.

Pathophysiology

Actively infected patients transmit tuberculous mycobacteria by aerosolized droplets. Even patients whose sputum specimens are negative on an acid-fast bacilli (AFB) smear but positive on AFB culture can infect others. Approximately 90% of patients who become infected after inhaling viable mycobacteria remain asymptomatic with latent infection. The risk for active tuberculosis after initial infection is approximately 5% within the first 24 months and then approximately 5% for the remainder of the person's lifetime. Active disease that occurs early after infection is known as primary progressive tuberculosis. Reactivation tuberculosis, which represents at least two thirds of all recognized cases, refers to active disease that develops remotely after infection. Patients who are most likely to develop active disease are those with impaired host defenses from immunocompromising conditions, such as HIV infection; malignancy; diabetes mellitus; chronic kidney disease; injection drug use; tobacco smoking; and malnutrition; or those receiving such medications as cytotoxic chemotherapy, glucocorticoids, and tumor necrosis factor α inhibitors.

KEY POINT

- Patients most likely to develop active tuberculosis are those with impaired host defenses from immunocompromising conditions, such as HIV infection, malignancy, diabetes mellitus, chronic kidney disease, injection drug use, tobacco smoking, and malnutrition or from medications.

Clinical Manifestations

Latent infection with tuberculosis is asymptomatic. In patients with active disease, pulmonary tuberculosis accounts for 70% of cases. Patients typically present with an indolent syndrome characterized by fever, chronic cough, purulent or blood-streaked sputum, chest pain, malaise, weight loss, night sweats, anorexia, and fatigue. Physical examination

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findings of pulmonary crackles, rhonchi, or evidence of pleural effusion are nonspecific, resulting in a delay of diagnosis. This is particularly true in patients with HIV and low CD4 cell counts (<200/μL), who can present with subtle and atypical features. *M. tuberculosis* can also disseminate through the lymphatic system and blood stream, resulting in miliary tuberculosis, which can present fulminantly with sepsis and acute lung injury. Extrapulmonary tuberculosis, more commonly seen in immunocompromised patients, can involve any organ, including the pleura, lymph nodes, central nervous system, skeletal system, pericardium, larynx, peritoneum, and genitourinary system.

KEY POINT

- Pulmonary tuberculosis, which accounts for 70% of active disease, is characterized by fever, chronic cough, purulent or blood-streaked sputum, chest pain, malaise, weight loss, night sweats, anorexia, and fatigue.

Diagnostic Testing

Diagnostic testing is used to detect latent tuberculosis infection (LTBI) or confirm tuberculosis infection in those with clinical findings suggesting active disease. The tuberculin skin test (TST) and interferon γ release assay (IGRA) are the initial diagnostic studies used to evaluate for tuberculosis infection. However, neither test can distinguish between latent and active tuberculosis, nor should they be administered to persons who are at low risk for infection with *M. tuberculosis* (targeted testing is reserved for those at high risk). The exception includes persons who will be at increased future risk, such as those beginning employment in a hospital setting.

LTBI is diagnosed when an asymptomatic patient has a positive TST or IGRA result without clinical evidence of active tuberculosis infection by history, physical examination, or chest imaging. In patients suspected of having active disease, additional microbiologic testing, including AFB staining and culture and nucleic acid-based testing, is indicated to confirm the diagnosis.

KEY POINT

- Latent tuberculosis infection is diagnosed when an asymptomatic patient has a positive tuberculin skin test or interferon-γ release assay result without clinical evidence of active tuberculosis infection.

Tuberculin Skin Test

The Mantoux TST requires intradermal injection of 5 tuberculin units into the volar aspect of the forearm. Forty-eight to 72 hours later, the transverse width of induration (not erythema) is measured in millimeters, serving as a marker of a delayed hypersensitivity cell-mediated immunity response. Skin test reactivity develops 2 to 12 weeks after infection. The criteria for a positive reaction have been established by the Centers for Disease Control and Prevention (CDC) based on the patient's risks for tuberculosis (**Table 15**). An increase in induration of 10 mm or more within 2 years is also considered a positive TST reaction in persons without a history of reactive TST. False-negative TST results can occur in patients who are immunosuppressed, are very young or old, or have active overwhelming tuberculosis. Conversely, false-positive TST reactions can result from infection with nontuberculous mycobacteria or in patients who have received bacillus Calmette-Guérin (BCG) as a vaccine or chemotherapy. In adults who received BCG vaccine as a child, TST results should be interpreted in the same way as in those who have not received BCG. Patients with a remote history of tuberculosis infection who have an initially negative skin test result may receive a second "booster" TST up to 4 weeks later that causes a true-positive skin test result. This two-step testing is also administered as a baseline assessment for persons who will need to undergo serial testing in the future.

TABLE 15. Interpretation of Tuberculin Skin Test Results

Criteria for Tuberculin Positivity by Risk Group		
≥5 mm Induration	**≥10 mm Induration**	**≥15 mm Induration**
HIV-positive persons Recent contacts of persons with active TB Persons with fibrotic changes on chest radiograph consistent with old TB Patients with organ transplants and other immunosuppressive conditions (receiving the equivalent of ≥15 mg/d of prednisone for >4 weeks)	Recent (<5 years) arrivals from high-prevalence countries Injection drug users Residents or employees of high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with AIDS, homeless shelters Mycobacteriology laboratory personnel; persons with clinical conditions that put them at high risk for active disease; children aged <4 years or exposed to adults in high-risk categories	All others with no risk factors for TB

TB = tuberculosis infection.

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KEY POINT

- False-negative tuberculin skin test results can occur in patients who are immunosuppressed, are very young or old, or have active overwhelming tuberculosis, whereas false-positive reactions can result from infection with atypical mycobacteria or in patients who have received bacillus Calmette-Guérin as a vaccine or chemotherapy.

Interferon-γ Release Assays

IGRAs are in vitro blood tests that measure T-cell–mediated interferon-γ release in response to specific *M. tuberculosis* antigens. These assays are felt to be more specific (no *Mycobacterium bovis*–associated BCG strain antigens are included) than the TST while attaining similar sensitivity in diagnosing tuberculosis infection. Like the TST, IGRAs should not be used to assess persons who have low risk for tuberculosis infection or active disease unless they will be at increased future risk (such as employment in a health care setting). According to the CDC, an IGRA can be used instead of a TST in all cases in which TST is recommended. However, the IGRA is preferred for those who have received BCG previously or are members of groups that are unlikely to return to have their TST interpreted (homeless population or drug users). A TST is preferred for evaluation of children younger than 5 years.

Two IGRAs are commercially available that have been approved by the FDA. The QuantiFERON-TB Gold In-Tube test measures the interferon-γ concentration, with possible results listed as positive, negative, or indeterminate. The T-SPOT TB test measures the number of cells that secrete interferon-γ, with results listed as positive, negative, indeterminate, or borderline. When results are reported, both of these standard qualitative test interpretations and the quantitative assay measurements should be included so that the best-informed decision can be reached.

A TST or repeat IGRA can be considered when the result from the initial IGRA reflects an uncertain likelihood of tuberculosis infection, that is, a borderline or indeterminate result, and a reason for ongoing assessment persists. Routine use of both a TST and IGRA is not recommended. In certain circumstances, however, using both tests when the result of the initial test is negative might be helpful when the risk for infection or progression is increased or risk for poor outcome exists, such as in children younger than 5 years who have been exposed to a patient with active tuberculosis or in patients with HIV infection. Use of a second test for diagnosing infection when the result of the first test is negative can also be considered when the suspicion of tuberculosis is strong based on clinical presentation or radiographic imaging. Conversely, using both tests when the result of the initial test is positive might be helpful when additional evidence to enhance patient adherence with treatment is needed or to evaluate a suspected false-positive result in a person at low risk for infection and progression to active disease.

IGRAs have several advantages in addition to the need for only a single visit to perform the test. These include availability of test results within 1 day, the lack of a booster response with subsequent tests, and fewer false-positive results in patients infected with nontuberculous mycobacteria (including those vaccinated with BCG). Disadvantages of IGRA testing include increased expense compared with TST, need for specialized personnel and equipment, and the need to process blood samples within 8 to 30 hours.

KEY POINTS

- The interferon-γ release assay is preferred for persons who have received bacillus Calmette-Guérin vaccine previously or are members of groups that are unlikely to return to have their TST interpreted. **HVC**
- Routine use of both a tuberculin skin test and interferon-γ release assay is not recommended. **HVC**

Imaging

Lung imaging, although nonspecific, is recommended for all patients being evaluated for tuberculosis. Primary pulmonary tuberculosis may present with mid- to lower-zone unilateral infiltrates, hilar lymphadenopathy, and pleural effusions. Reactivation tuberculosis classically presents with fibrocavitary disease in the apical-posterior segments of the upper lobes or superior segments of the lower lobes (**Figure 10**). Chest radiographs may be normal, particularly in primary tuberculosis. CT is more sensitive for detecting abnormalities in the lung (particularly lymphadenopathy) or at other sites of involvement, although it is not typically used for initial screening for active disease. When pericardial disease is suspected, echocardiography can provide information about the amount of pericardial fluid present and any potential hemodynamic effects, including cardiac tamponade.

Culture and Additional Microbiologic Testing

Confirmatory diagnostic testing requires growth of *M. tuberculosis* from culture or detection by nucleic acid-based testing. Initial screening of sputum specimens with

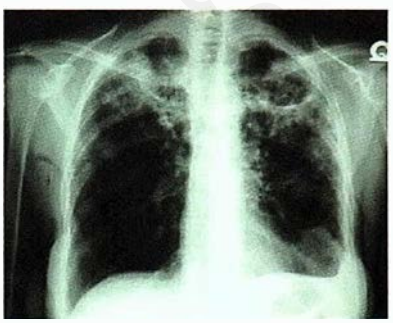

FIGURE 10. Chest radiograph demonstrating upper-lobe infiltrates and cavitation consistent with reactivation pulmonary tuberculosis.

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AFB staining is followed by culture in a liquid medium, which allows for faster growth and detection (approximately 2 weeks) than a solid medium (approximately 3-4 weeks). A positive AFB test result is helpful but not diagnostic because nontuberculous mycobacteria will stain similarly. Because culture recovery can be slow, faster molecular tests have been developed that can identify *M. tuberculosis* in culture media within 1 to 2 days, which speeds the diagnostic process significantly. Additionally, nucleic acid amplification testing (NAAT) is available that can target *M. tuberculosis* in sputum from patients suspected of having pulmonary tuberculosis and can expedite initiation of treatment, although this form of testing is expensive. The positive predictive value of a positive NAAT result in a patient with AFB smear–positive sputum is greater than 95%. In patients in whom tuberculosis is strongly suspected, the NAAT result is positive in approximately 65% of patients whose sputum is negative on AFB smear but eventually positive on culture. NAATs are not recommended for patients in whom the suspicion for tuberculosis is low. One FDA-approved NAAT that can detect *M. tuberculosis* infection and rifampin resistance (sensitivity of 95%; specificity of 99%) within 2 hours, the Xpert MTB/RIF test, has the potential to make a significant public health impact on the control of tuberculosis in endemic areas; however, its cost may be prohibitive. Because rifampin resistance often coexists with isoniazid resistance, this test can more rapidly identify MDR tuberculosis. Although results are available quickly with this NAAT, conventional mycobacterial cultures are still recommended for performance of drug susceptibility testing and genotyping.

Pleural tuberculosis may be difficult to diagnose from pleural fluid cultures, which typically are positive in less than half of infection cases. Pleural biopsies demonstrating caseating granulomatous inflammation may be needed to confirm the diagnosis. Adenosine deaminase levels in pleural fluid may also be helpful in the evaluation of suspected pleural tuberculosis, particularly in patients with a high clinical suspicion but negative results on culture and pleural biopsy. Tuberculous meningitis should be considered when the cerebrospinal fluid (CSF) profile demonstrates a lymphocytic pleocytosis with elevated protein and decreased glucose levels. Serial CSF sampling is recommended to increase the yield of AFB smears and cultures in the diagnosis of CSF tuberculosis. NAAT of the CSF is highly specific, but a negative test result does not rule out the diagnosis (sensitivity of approximately 50%). Pericardial fluid usually reveals an elevated protein level and leukocyte count that is lymphocytic predominant in tuberculosis pericarditis. AFB smears and cultures are recommended but often are not positive (approximately 50% of the time). Adenosine deaminase levels in pericardial fluid may be helpful, particularly in endemic areas. If findings on pericardial fluid analysis are negative, a pericardial biopsy may be considered for pathologic and microbiologic evaluation.

KEY POINT

- Nucleic acid amplification testing targeting *Mycobacterium tuberculosis* in sputum from patients with high clinical suspicion of having tuberculosis (AFB smear–positive sputum) can expedite initiation of treatment, although it is more expensive and does not provide drug susceptibility and genotyping information necessary to guide long term treatment.

HVC

Treatment

If active tuberculosis is excluded in a patient with positive results on TST or IGRA, treatment for LTBI is indicated. Several treatment options exist, and the regimen chosen should be based on comorbidities, knowledge of the drug-susceptibility data from the source patient, and possible drug interactions (**Table 16**). If isoniazid is chosen, the addition of pyridoxine is recommended for patients with diabetes, uremia, alcoholism, HIV infection, malnutrition, seizure disorder, and pregnancy because of an increased risk **for** isoniazid-associated peripheral neuropathy.

The 12-week regimen of once-weekly isoniazid and rifapentine must be administered as directly observed therapy (that is, a health care worker directly observes the ingestion of a medication) and can be used instead of 9 months of isoniazid alone for healthy adult patients, including those with HIV coinfection who are not taking antiretroviral agents. It is not recommended for patients suspected of having rifampin- or isoniazid-resistant tuberculosis strains or patients who are pregnant or plan to become pregnant while taking these agents. Four months of rifampin is acceptable for patients in whom infection with isoniazid-resistant tuberculosis is suspected or who cannot take isoniazid. A 9-month regimen of isoniazid is usually recommended for patients with HIV receiving antiretroviral medications. In pregnant patients, isoniazid is recommended for treatment of LTBI if the patient has been recently exposed to a person with known tuberculosis or if she has HIV. If not, many experts would recommend that treatment of LTBI be deferred until after delivery. Isoniazid treatment is not a contraindication for breastfeeding.

Treatment of active tuberculosis usually consists of multiple drugs for 6 to 9 months administered in two phases: initial and continuation (**Table 17**). The core first-line antituberculous agents include isoniazid, rifampin, pyrazinamide, and ethambutol (**Table 18**). These agents are administered for 8 weeks as part of the initiation phase, and then isoniazid and rifampin are continued for 4 or 7 months as part of the continuation phase. The longer course is recommended in patients who have cavitary pulmonary disease at diagnosis and positive sputum cultures after completing initial therapy, patients who did not receive pyrazinamide as part of the initial therapy, and patients who are receiving once-weekly rifapentine and

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TABLE 16. Treatment Regimens for Latent Tuberculosis Infection

Drugs	Duration	Dose[a]	Frequency	Total Doses
Isoniazid	9 months	5 mg/kg Maximum dose: 300 mg	Daily	270
		15 mg/kg Maximum dose: 900 mg	Twice weekly[b]	76
	6 months	5 mg/kg Maximum dose: 300 mg	Daily	180
		15 mg/kg Maximum dose: 900 mg	Twice weekly[b]	52
Isoniazid and rifapentine	3 months	Isoniazid[c,d]: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum Rifapentine[c,d]: 10.0–14.0 kg: 300 mg 14.1–25.0 kg: 450 mg 25.1–32.0 kg: 600 mg 32.1–49.9 kg: 750 mg ≥50.0 kg: 900 mg maximum	Once weekly[b]	12
Rifampin	4 months	10 mg/kg Maximum dose: 600 mg	Daily	120

[a]Doses listed are for adults.

[b]Intermittent regimens must be provided by directly observed therapy in which a health care worker observes the ingestion of medication.

[c]Isoniazid is formulated in 100-mg and 300-mg tablets. Rifapentine is formulated in 150-mg tablets in blister packs that should be kept sealed until use.

[d]For isoniazid and rifapentine, doses listed are for anyone older than 12 years.

Adapted from Centers for Disease Control and Prevention. Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. Treatment of Latent TB Infection. Table 2. Choosing the Most Effective LTBI Treatment Regimen. www.cdc.gov/tb/publications/ltbi/treatment.htm#2. Accessed June 30, 2015.

TABLE 17. Tuberculosis Treatment Regimens

Treatment Phase	Preferred Regimen	Alternative Regimens
Initial	Daily INH, RIF, PZA, and EMB[a] for 56 doses (8 weeks)	Daily INH, RIF, PZA, and EMB[a] for 14 doses (2 weeks), then twice weekly for 12 doses (6 weeks)
		Thrice-weekly INH, RIF, PZA, and EMB[a] for 24 doses (8 weeks)
Continuation	Daily INH and RIF for 126 doses (18 weeks) *or* Twice-weekly INH and RIF for 36 doses (18 weeks)	Twice-weekly INH and RIF for 36 doses (18 weeks) Thrice-weekly INH and RIF for 54 doses (18 weeks)

EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin.

[a]EMB can be discontinued if drug susceptibility studies demonstrate susceptibility to first-line drugs.

NOTE: A continuation phase of once-weekly INH/rifapentine can be used for patients who are HIV negative who do not have cavitary lesions on the chest film and who have negative acid-fast bacilli smears at the completion of the initial phase of treatment.

Source: Tuberculosis. Treatment for TB Disease. Table 1. Basic TB Disease Treatment Regimens. www.cdc.gov/tb/topic/treatment/tbdisease.htm. Accessed August 27, 2014.

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isoniazid whose sputum cultures remain positive after the initial 2-month phase.

Completion of treatment is dictated by how many doses are taken over a specified duration. When treatment interruptions of 2 weeks or more occur during the initial 2-month phase, the treatment regimen should be restarted from the beginning. In general, treatment recommendations are the same for patients with HIV with tuberculosis, with careful consideration given to the potential for drug interactions in patients receiving antiretroviral therapy.

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TABLE 18. Antituberculous Drugs

Agent	Adverse Effects	Notes
First-Line Medications		
Isoniazid	Rash; liver enzyme elevation; hepatitis; peripheral neuropathy; lupus-like syndrome	Hepatitis risk increases with age and alcohol consumption. Pyridoxine may prevent peripheral neuropathy. Adjust for kidney injury.
Pyrazinamide	Hepatitis; rash; GI upset; hyperuricemia	May make glucose control more difficult in patients with diabetes. Adjust for kidney injury.
Rifampin	Hepatitis; rash; GI upset	Contraindicated or should be used with caution when administered with protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Do not administer to patients also taking saquinavir/ritonavir. Colors body fluids orange.
Rifabutin	Rash; hepatitis; thrombocytopenia; severe arthralgia; uveitis; leukopenia	Dose adjustment required if taken with protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Monitor for decreased antiretroviral activity and for rifabutin toxicity.
Rifapentine	Similar to rifampin	Contraindicated in patients who are HIV positive (unacceptable rate of failure/relapse).
Ethambutol	Optic neuritis; rash	Baseline and periodic tests of visual acuity and color vision. Patients are advised to call immediately if visual acuity or color vision changes. Adjust for kidney injury.
Second-Line Medications[a]		
Streptomycin	Auditory, vestibular, and kidney toxicity	Avoid or reduce dose in adults age >59 years. Monitor hearing and kidney function test results. Adjust for kidney injury.
Cycloserine	Psychosis; convulsions; depression; headaches; rash; drug interactions	Pyridoxine may decrease CNS adverse effects. Measure drug serum levels.
Capreomycin	Kidney, vestibular, and auditory toxicity	Monitor hearing and kidney function test results. Adjust for kidney injury.
Ethionamide	GI upset; hepatotoxicity; hypersensitivity	May cause hypothyroidism.
Kanamycin and amikacin	Auditory, vestibular, and kidney toxicity	Not approved by the FDA for TB treatment. Monitor vestibular, hearing, and kidney function.
Levofloxacin, moxifloxacin	GI upset; dizziness; hypersensitivity; drug interactions	Not approved by the FDA for TB treatment. Should not be used in children.
Para-aminosalicylic acid	GI upset; hypersensitivity; hepatotoxicity	May cause hypothyroidism, especially if used with ethionamide. Measure liver enzymes.
Bedaquiline	Nausea, joint pain, headache, elevated aminotransferases, hemoptysis, prolonged QT interval	FDA-approved oral agent for MDR pulmonary TB treatment indicated for combination therapy when other alternatives are not available. Novel mechanism of action inhibits mycobacterial adenosine triphosphate synthase. Should be given as directly observed therapy.

CNS = central nervous system; GI = gastrointestinal; MDR = multidrug resistant; TB = tuberculosis.

[a]Use these drugs in consultation with a clinician experienced in the management of drug-resistant TB.

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Similar to pulmonary tuberculosis, extrapulmonary tuberculosis is usually treated with a 6-month treatment course. However, a 9- to 12-month regimen is recommended for tuberculous meningitis. Adjunctive glucocorticoids are also recommended for patients with tuberculosis-associated meningitis and pericarditis.

Drug susceptibility testing should be performed on the initial isolate in all patients. Patient education about the adverse effects associated with antituberculous therapy is important. Before therapy begins, serum creatinine level, liver function tests, a complete blood count, and hepatitis B and C serologic testing (for patients at risk for these diseases) should be obtained. If pyrazinamide or ethambutol is to be used, uric acid levels or visual acuity and color vision testing are recommended, respectively. At least monthly clinical evaluations are recommended during treatment (see Table 18). Routine laboratory monitoring is recommended for patients with baseline abnormalities or increased risk for adverse effects; otherwise, laboratory studies are reserved for those who develop potential drug-associated toxicities.

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KEY POINTS

- Several treatment options exist for latent tuberculosis infection, including a 12-week regimen of once-weekly isoniazid and rifapentine, which can be used instead of 9 months of isoniazid alone for healthy adult patients.
- The core, first-line, antituberculous agents for active tuberculosis include isoniazid, rifampin, pyrazinamide, and ethambutol, which are administered for an 8-week initiation phase followed by 4 to 7 months of continuation-phase therapy with rifampin and isoniazid.

HVC

- At least monthly clinical evaluations are recommended during tuberculosis treatment, and routine laboratory monitoring is recommended for patients with baseline abnormalities or increased risk for adverse effects; otherwise, laboratory studies are reserved for those who develop potential drug-associated toxicities.

Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis

Resistance can develop because of suboptimal treatment regimens, medication nonadherence, drug malabsorption, or drug interactions resulting in subtherapeutic drug levels. By definition, MDR tuberculosis strains are resistant to at least rifampin and isoniazid. Extensively drug-resistant tuberculosis strains are resistant to rifampin and isoniazid, any fluoroquinolone, and at least one injectable second-line drug (kanamycin, amikacin, or capreomycin). Multiple drugs, including second-line agents (five or six agents usually), and extended courses (at least 18–24 months) are required to treat these resistant strains of tuberculosis and should be guided by expert consultation. Recently, bedaquiline, the first antituberculous drug with a novel mechanism of action approved by the FDA since 1971, became available for treatment of MDR tuberculosis. To ensure optimal outcomes, it is essential to give as directly observed therapy.

Prevention

In health care settings in which tuberculosis is encountered, effective infection control to prevent transmission includes quick identification of infected patients, initiation of airborne isolation (including use of negative-pressure rooms) and prompt treatment of suspected and proven cases. The CDC has established three criteria that must be met to establish a patient as no longer infectious: adequate treatment for tuberculosis for greater than 2 weeks; improvement of symptoms; and three consecutive negative sputum smears (collected at 8- to 24-hour intervals, including one early-morning collection).

Although not routinely administered in the United States, *Mycobacterium bovis*–associated BCG vaccine is used in countries in which tuberculosis is endemic to prevent disseminated disease and meningitis in children. It has not been shown to prevent primary infection or reactivation of pulmonary tuberculosis. In nonendemic countries, such as the United States, BCG vaccination can be considered for children who have a negative TST result and are consistently exposed to adults who have untreated tuberculosis or tuberculosis caused by MDR strains. Vaccination of TST-negative adult health care workers who will be traveling to areas with a high prevalence of MDR tuberculosis can also be considered. BCG is a live attenuated vaccine, so it is contraindicated in patients who are pregnant or immunosuppressed.

KEY POINT

- In countries where tuberculosis is endemic, *Mycobacterium bovis*–associated bacillus Calmette-Guérin vaccine is used to prevent disseminated disease and meningitis in children.

Nontuberculous Mycobacterial Infections

Nontuberculous mycobacteria (NTM) are ubiquitous environmental acid-fast bacilli belonging to species other than *Mycobacterium leprae* or *Mycobacterium tuberculosis* complex. These opportunistic organisms most frequently cause infection in the lungs, lymph nodes, skin or soft tissue, and blood stream (disseminated disease) (**Table 19**). NTM are classified into general groups based on colony-associated morphologic features, pigmentation, and growth rate; rapidly growing mycobacteria (RGM) are a form of NTM that are unique because of their rapid growth rate in culture and different antibiotic susceptibilities relative to more slowly growing species.

Although infection may occur in normal hosts, the risk for disseminated disease is increased with immunologic abnormalities, including low CD4 lymphocyte counts and abnormalities in the interleukin-12, interferon-γ, and signal transducer and activator of transcription 1 (STAT1) pathways. Lung disease is associated with underlying structural abnormalities, such as COPD and bronchiectasis.

Isolation of NTM from clinical specimens may result from colonization, environmental contamination, or active infection. When NTM are isolated from a sterile site, pathogenic infection is more likely. With documented infection, identification to the species level is recommended. Specific DNA probes exist to rapidly identify *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii*, and high-performance liquid chromatography can be used to identify other mycobacterial species. Identification of RGM may require additional testing, including biochemical studies, ribosomal DNA sequencing, antimicrobial susceptibility testing, and

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TABLE 19. Clinical Syndromes Caused by Selected Nontuberculous Mycobacteria

NTM Species	Disseminated	Lymphadenitis	Lung	Skin and Soft Tissue
M. abscessus	X		X	X
M. avium complex	X	X	X	X
M. chelonae	X			X
M. fortuitum	X			X
M. genavense	X			
M. haemophilum	X	X		X
M. kansasii	X		X	
M. malmoense		X	X	
M. marinum				X
M. mucogenicum	X			
M. scrofulaceum		X		
M. simiae	X	X		
M. ulcerans				X
M. xenopi	X		X	

NTM = nontuberculous mycobacteria. Genus for all organisms is *Mycobacterium*.

CONT.

polymerase chain reaction restriction fragment-length polymorphism analysis.

Guidelines for diagnosing infection and initiating treatment based on clinical, microbiologic, and radiographic criteria have been developed by the American Thoracic Society and Infectious Diseases Society of America (**Table 20**). Isolation of persons with NTM infections is not required.

KEY POINT

- With documented mycobacterial infection, species-level identification is recommended; specific DNA probes exist to rapidly identify *Mycobacterium avium* complex and *Mycobacterium kansasii*, and high-performance liquid chromatography can be used to identify other mycobacterial species.

TABLE 20. Diagnostic Criteria for Nontuberculous Mycobacterial Lung Disease

Criteria	Findings
Clinical and imaging criteria	Evidence of pulmonary symptoms and abnormal findings on chest imaging studies (nodular or cavitary lung lesions on radiographs or high-resolution CT scans), with exclusion of other possible causes
Laboratory (microbiologic) criteria	Positive isolation of NTM from at least two separate sputum samples *or*
	Positive isolation of NTM from at least one bronchoalveolar lavage sample *or*
	Histopathologic demonstration of AFB and/or granulomatous disease with a positive culture for NTM from lung tissue specimen; or histopathologic demonstration of AFB and/or granulomatous disease on lung tissue specimen with a positive culture for NTM from one or more sputum samples or bronchoalveolar lavage sample
Other considerations	The isolation of an unusual NTM species or of an NTM species that is usually a contaminant should prompt consultation with an infectious diseases or pulmonary specialist
	The suspicion of NTM lung disease that does not fulfill the above diagnostic criteria should prompt follow-up until a definitive diagnosis is made or excluded
	Whether to treat pulmonary infections due to NTM should be based on the potential benefits and risks for individual patients

AFB = acid-fast bacilli; NTM = nontuberculous mycobacteria.

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Mycobacterium avium Complex Infection

Pulmonary disease is the most common manifestation of NTM infection, and MAC is the most common causative species. Pulmonary disease, a classic presentation of MAC infection, is seen in middle-aged to older adult male smokers with underlying lung disease who clinically and radiographically resemble patients with tuberculosis. Nonsmoking postmenopausal women with pectus excavatum, mitral valve prolapse, scoliosis, and joint abnormalities are another characteristic group. A chronic cough and purulent sputum production without constitutional symptoms are often noted. Radiographs reveal nodular bronchiectatic disease.

MAC is responsible for most cases of NTM lymphadenitis. Disseminated MAC infection develops in patients with HIV who have CD4 counts less than 50/μL and are not receiving MAC prophylaxis. The clinical presentation often consists of fever, night sweats, weight loss, and gastrointestinal symptoms.

Clarithromycin susceptibility testing is routinely recommended for all MAC isolates. Treatment of MAC infection usually consists of clarithromycin or azithromycin with ethambutol and either rifampin or rifabutin.

KEY POINTS

- Pulmonary disease is the most common manifestation of nontuberculous mycobacterial infection, and *Mycobacterium avium* complex (MAC) is the most common causative species.
- Disseminated MAC infection develops in patients with HIV who have CD4 counts less than 50/μL and are not receiving MAC prophylaxis.

Mycobacterium kansasii

M. kansasii most commonly causes a lung infection that mimics tuberculosis, with cough, fever, weight loss, and cavitary lung disease. Risk factors for infection include COPD, cancer, HIV, alcohol abuse, and drug-associated immunosuppression. Treatment of *M. kansasii* pulmonary disease consists of isoniazid, rifampin, and ethambutol.

KEY POINT

- *Mycobacterium kansasii* most commonly causes a lung infection that mimics tuberculosis, with cough, fever, weight loss, and cavitary lung disease.

Rapidly Growing Mycobacteria

Mycobacterium abscessus is the most common RGM-associated cause of pulmonary infection, even in patients without underlying lung disease. *M. abscessus* and *Mycobacterium fortuitum* have been associated with lymphadenitis. Disseminated *M. abscessus*, *M. fortuitum*, and *Mycobacterium chelonae* infections are seen in immunosuppressed patients and appear to be increasing in incidence as a cause of localized skin and soft tissue infections, usually after trauma, surgery (often associated with implanted prosthetic material), catheter insertion, or cosmetic procedures (including pedicures, tattooing, and body piercing). Contaminated, nonsterile water is the source of these infections.

RGM are usually not susceptible to antituberculous agents. Susceptibility testing of amikacin, doxycycline, fluoroquinolones, sulfonamides, cefoxitin, clarithromycin, linezolid, imipenem (*M. fortuitum* only), and tobramycin (*M. chelonae* only) is routinely recommended for RGM. At least two to three drugs are recommended for a prolonged course depending on the type of infection, the NTM species, and the antimicrobial susceptibility profile. Consultation with infectious diseases or pulmonary experts is recommended.

KEY POINT

- Disseminated *Mycobacterium abscessus*, *Mycobacterium fortuitum*, and *Mycobacterium chelonae* infections are seen in immunosuppressed patients and appear to be increasing in incidence as a cause of localized skin and soft tissue infections, usually after trauma, surgery (often associated with implanted prosthetic material), catheter insertion, or cosmetic procedures (including pedicures, tattooing, and body piercing).

Fungal Infections

Systemic Candidiasis

Systemic or invasive candidiasis includes candidemia, focal organ involvement, and disseminated candidiasis, with candidemia being the most common. Candidemia occurs most frequently in the presence of an intravascular catheter and may lead to focal organ involvement or disseminated infection as a consequence of hematogenous spread. Risk factors for candidemia and other forms of systemic candidiasis include neutropenia, malignancies, organ transplantation, broad-spectrum antimicrobial agents, immunosuppressive agents, chemotherapeutic agents, intravascular catheters, hemodialysis, parenteral nutrition, and major abdominal surgery.

Clinical Manifestations and Diagnosis

Clinical manifestations, signs, and symptoms in focal organ involvement may be specific to that organ. Focal infections include urinary tract infections (UTIs) (catheter-related or non-catheter-related), peritonitis, bone and joint infections, and central nervous system infections. Pneumonia occurs rarely and generally only in severely immunosuppressed patients. When *Candida* is isolated from the sputum, it usually reflects contamination from the oral mucosa. With disseminated disease, microabscesses have been described in all organs.

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Systemic candidiasis is usually diagnosed by a positive culture from blood or a normally sterile body site, although a negative culture does not exclude the diagnosis. In the case of organ involvement, tissue biopsy specimens should be obtained for culture and histopathology. In suspected disseminated disease, white exudates may be seen in the retina on ophthalmoscopic examination (**Figure 11**), and painless skin papules or pustules on an erythematous base may be present on the skin; a biopsy of a characteristic skin lesion can aid in rapid diagnosis. When *Candida* is isolated from the blood or a normally sterile body site, identification of species should be performed to guide appropriate antifungal therapy. Antifungal susceptibility testing is indicated against the triazoles and echinocandins for *Candida glabrata* isolates from blood and sterile sites and for other *Candida* species that have failed to respond to antifungal therapy.

KEY POINT

- Common focal infections in systemic candidiasis include urinary tract infections (catheter-related or non-catheter-related), peritonitis, bone and joint infections, and central nervous system infections.

Treatment

Systemic candidiasis has a high mortality, so therapy should be initiated promptly when it is suspected or diagnosed. An echinocandin (anidulafungin, caspofungin, or micafungin) is recommended as initial therapy for most patients with candidemia (**Table 21**) but not for those with meningitis, UTI, or endophthalmitis because of poor organ penetration. Step-down therapy from an echinocandin to an azole (fluconazole or voriconazole) is appropriate if the *Candida* isolate is known to be susceptible and the patient is clinically stable. In patients with *Candida glabrata* infection, susceptibility testing is necessary before switching to an azole. Fluconazole is recommended for *Candida parapsilosis* complex infection because *C. parapsilosis* may have reduced susceptibility to echinocandins. Treatment duration for uncomplicated candidemia is 14 days after clearance of the organism from the bloodstream and resolution of symptoms. Treatment duration for focal organ involvement is based on resolution of signs and symptoms of infection and usually extends for several weeks to months.

Removal of an intravascular catheter in addition to antifungal therapy has been associated with a shorter duration of infection and improved outcomes in nonneutropenic patients with candidemia. *C. parapsilosis* candidemia is almost always catheter related. The role of catheter removal is less clear in neutropenic patients because they may develop candidemia from translocation across the gastrointestinal tract mucosa. If candidemia persists for more than a few days in a neutropenic patient with an intravascular catheter, the catheter should be removed.

Candida can cause UTI by direct entry into the urinary tract or hematogenously. Most cases of *Candida* pyelonephritis occur hematogenously. It may be difficult to ascertain whether candiduria represents a contaminated specimen, colonization of the bladder or urinary catheter, or an actual infection of the bladder or kidney. Most patients with candiduria are asymptomatic and rarely develop candidemia. Treatment of asymptomatic candiduria is indicated only in neutropenic patients and those undergoing urologic procedures. The treatment of choice is oral fluconazole.

KEY POINTS

- Therapy with an echinocandin is indicated for most patients with candidemia; however, an echinocandin should not be used to treat those with meningitis or endophthalmitis because of poor organ penetration.
- Intravascular catheter removal, in addition to antifungal therapy, is indicated for nonneutropenic patients with candidemia.
- Treatment of asymptomatic candiduria is indicated only in neutropenic patients and those undergoing urologic procedures. **HVC**



FIGURE 11. Disseminated candidiasis to the retina. Candida endophthalmitis is characterized by focal, white, infiltrative, often mound-like lesions on the retina. Endophthalmitis is a bacterial or fungal infection within the eye not caused by viruses or parasites.

Aspergillosis and Aspergilloma

Aspergillus is a ubiquitous environmental mold, and *Aspergillus fumigatus* is the most common human pathogen. The main route of acquisition is inhalation of aerosolized spores, with the lung being the principal site of clinical infection, followed by the paranasal sinuses. *Aspergillus* pulmonary disease may manifest as colonization, allergic bronchopulmonary aspergillosis, aspergilloma (fungus ball), or invasive aspergillosis.

Allergic bronchopulmonary aspergillosis, a hypersensitivity reaction that occurs with colonization of the larger airways by *Aspergillus*, is typically seen in the setting of chronic asthma or cystic fibrosis. Cardinal features include asthma-like symptoms, fleeting pulmonary infiltrates on chest

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TABLE 21. Therapy for Common Systemic Fungal Infections

Infection	Therapy of Choice	Alternatives
Candidemia	Echinocandin[a]	Fluconazole, voriconazole, lipid formulation of amphotericin B
Invasive aspergillosis	Voriconazole	Lipid formulation of amphotericin B, echinocandins, posaconazole, itraconazole, isavuconazonium
Allergic bronchopulmonary aspergillosis	Itraconazole or voriconazole	
Aspergilloma (fungus ball)	Itraconazole, voriconazole, posaconazole	
Mucormycosis	Liposomal amphotericin B, high-dose amphotericin B deoxycholate	Posaconazole, isavuconazonium
Cryptococcal meningitis		
Patients with AIDS	Induction period: amphotericin B and flucytosine for 2 weeks Consolidation period: oral fluconazole for 8 weeks Maintenance period: oral fluconazole for ≥1 year	Induction period: amphotericin B and fluconazole, fluconazole and flucytosine, or fluconazole monotherapy
Transplant recipients	Induction period: lipid formulation of amphotericin B and flucytosine for 2 weeks Consolidation period: oral fluconazole for 8 weeks Maintenance period: oral fluconazole for 6 months to 1 year	Induction period: lipid formulation of amphotericin B or amphotericin B deoxycholate for 4-6 weeks
Patients without HIV/AIDS or transplantation	Induction period: amphotericin B and flucytosine for ≥4 weeks Consolidation period: oral fluconazole for 8 weeks Maintenance period: oral fluconazole for 6-12 months	Induction period: amphotericin B for ≥6 weeks
Nonmeningeal cryptococcosis	Fluconazole	Itraconazole, amphotericin B plus flucytosine
Blastomycosis		
Cutaneous/pulmonary/extrapulmonary	Lipid formulation of amphotericin B followed by itraconazole	Itraconazole, fluconazole
CNS	Lipid formulation of amphotericin B followed by fluconazole	Itraconazole, voriconazole
Histoplasmosis		
Mild to moderate acute pulmonary[b]	Itraconazole	
Moderately severe to severe pulmonary	Lipid formulation of amphotericin B followed by itraconazole	
Acute progressive disseminated	Lipid formulation of amphotericin B followed by itraconazole	Conventional amphotericin B
Coccidioidomycosis		
Pulmonary (patient at low risk)	No treatment indicated	
Primary pulmonary (patient at high risk)[c]	Itraconazole, fluconazole	
Severe coccidioidal pneumonia or disseminated disease	Conventional or lipid formulation of amphotericin B until improved, then itraconazole or fluconazole	
Coccidioidal meningitis	Fluconazole	Conventional or lipid formulation of amphotericin B plus intrathecal amphotericin B or itraconazole, or voriconazole
Cutaneous sporotrichosis	Itraconazole	

CNS = central nervous system.

[a]Anidulafungin, caspofungin, or micafungin; no preference among the three available agents.

[b]Not sufficiently ill to require hospitalization.

[c]Factors include HIV/AIDS, solid organ transplantation, high-dose glucocorticoids, anti-tumor necrosis factor therapy, lymphoma, chemotherapy, pregnancy, diabetes mellitus, and African or Philippine ancestry.

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imaging, peripheral eosinophilia, elevated serum IgE levels, serum *Aspergillus*-precipitating antibodies, and cutaneous reactivity to *Aspergillus* antigens. In addition to standard therapy (see Table 21), acute or recurrent exacerbations should include glucocorticoids to control acute inflammation and to limit lung damage.

Aspergilloma is generally a consequence of colonization of a preexisting pulmonary cavity or cyst or in areas of devitalized lung. Symptoms include cough, hemoptysis, dyspnea, weight loss, fever, fatigue, and chest pain. Radiographic images show a round mass within a pulmonary cavity or cyst. Sputum cultures are usually positive. Patients who are asymptomatic and have stable radiographs do not require therapy. Surgical resection is indicated for hemoptysis and is considered definitive therapy. Antifungal therapy (see Table 21) is indicated for those who are symptomatic but unable to undergo surgery; it can be administered perioperatively to reduce the risk for pleural aspergillosis.

Risk factors for invasive or disseminated aspergillosis include profound and prolonged neutropenia and immunosuppression often associated with organ transplantation. The disorder is also increasingly reported in patients who are critically ill and in intensive care units, especially with exposure to glucocorticoids.

Aspergillus invades pulmonary blood vessels and causes distal infarction of lung tissue. Patients present with fever, cough, chest pain, and hemoptysis; pulmonary infiltrates, nodules, or wedge-shaped densities resembling infarcts may be seen on chest radiographs. CT scans may show a target lesion with a necrotic center surrounded by ring of hemorrhage (halo sign) (**Figure 12**). Central nervous system (CNS) involvement may manifest as a brain abscess or infarction. Other sites of involvement include blood vessels in the heart, gastrointestinal tract, or skin.

Invasive aspergillosis can be difficult to diagnose with certainty. It is definitively established by tissue biopsy. Although *Aspergillus* can spread hematogenously, blood cultures are rarely positive. The galactomannan antigen immunoassay is increasingly used for diagnosis. Galactomannan is a polysaccharide contained in the cell wall of *Aspergillus*, and its presence in serum or other body fluids suggests invasive infection. The sensitivity of the assay can be impaired by antifungal prophylaxis or specific antifungal therapy. The β-D-glucan assay, although not specific for *Aspergillus* species, can also be used to detect early infection.

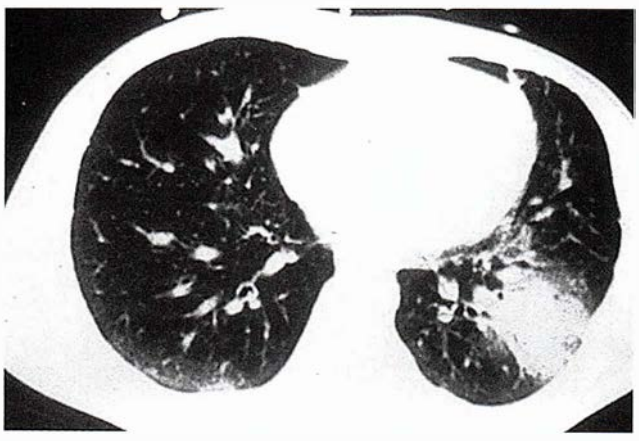

FIGURE 12. Aspergillosis. Chest CT scan demonstrates evidence of the halo sign, which is an area of low attenuation surrounding a nodule, reflecting hemorrhage into the tissues surrounding the fungus.

KEY POINTS

- *Aspergillus* pulmonary disease may manifest as colonization, allergic bronchopulmonary aspergillosis, aspergilloma (fungus ball), or invasive aspergillosis.
- Invasive aspergillosis is definitively diagnosed by tissue biopsy; the galactomannan antigen immunoassay is increasingly used for diagnosis.

Mucormycosis

Mucormycosis (formerly zygomycosis) is an increasingly common fungal infection that can present as acute and rapidly progressive with a high mortality rate. Various organisms are responsible for causing mucormycosis; *Rhizopus* and *Mucor* species are most common. Risk factors include immunocompromise from hematologic malignancies, organ transplantation, and cancer chemotherapy; patients with uncontrolled diabetes or ketoacidosis have a unique susceptibility. Patients treated with deferoxamine for iron-overload states also are at risk. Patients with severe burns or trauma can contract mucormycosis through contamination of wounds. Outbreaks have also been reported during natural disasters.

The most common presentation is rhinocerebral. This is a rapidly fatal infection that spreads from the sinuses retroorbitally to the CNS. Symptoms and signs include headache, epistaxis, and ocular findings, including proptosis, periorbital edema, and decreased vision. A pathognomonic finding on physical examination of the nose or palate is the presence of a black eschar. Other sites of involvement include the lungs, gastrointestinal tract, and skin. Pulmonary mucormycosis with thrombosis and infarction most frequently develops in patients with hematologic malignancies. Cutaneous involvement is rare, developing most often in burn or trauma patients or resulting from dissemination from another site. Isolated CNS mucormycosis may result from hematogenous spread or dissemination in injection drug users.

Mucormycosis is diagnosed by tissue biopsy and culture. Histologically, the organism appears as broad, irregular, and ribbon-like aseptate hyphae that have right-angle branching. Blood cultures are usually negative. A combined medical (see Table 21) and surgical approach is required for effective therapy.

KEY POINT

- The most common presentation of mucormycosis is a rapidly fatal rhinocerebral infection, with headache, epistaxis, and ocular findings (proptosis, periorbital edema, and decreased vision).

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Cryptococcosis

Two cryptococcal species exist, *Cryptococcus neoformans* and *C. gattii*, but *C. neoformans* is the predominant species causing human infection. In the United States, most infections with *C. gattii* occur in California. Cryptococcus is inhaled and causes an initial pulmonary infection. Healthy persons generally contain the initial infection owing to intact cell-mediated immunity; however, immunocompromised persons are at risk for dissemination. Pulmonary cryptococcosis found incidentally in an asymptomatic immunocompetent person may resolve without treatment; however, if the person becomes immunosuppressed, the organism can reactivate and disseminate. Therefore, treatment (typically fluconazole for 6-12 months) is given to patients with mild to moderately severe pulmonary cryptococcosis to prevent progressive or disseminated disease.

Risk factors for dissemination include AIDS, organ transplantation, glucocorticoid treatment, diabetes mellitus, liver dysfunction, and kidney injury. The CNS is the most common site of disseminated cryptococcosis, which manifests as a subacute or chronic meningoencephalitis. Common symptoms include headache, alternations in mental status, and fever. Visual abnormalities, including diplopia, decreased visual acuity, and extraocular nerve palsies, may also occur. Dissemination can occur to the skin (**Figure 13**), prostate, bone, eye, and urinary tract. When cryptococcosis is found outside of the CNS, a lumbar puncture should be done to determine whether CNS infection is present. Skin lesions (papules, nodules, ulcers, plaques, cellulitis) imply disseminated disease.

Cryptococcosis can initially be diagnosed by suggestive histopathology or by the detection of cryptococcal antigen in serum or cerebrospinal fluid (CSF). Diagnosis is confirmed by culture. The latex agglutination assay for cryptococcal antigen is highly sensitive and specific for the diagnosis of meningitis. The serum assay has been used successfully to screen febrile patients with AIDS who are at high risk, especially those with headache. However, the sensitivity of the serum assay is lower in patients without HIV infection; therefore, a negative test result in these persons cannot be used to exclude meningitis. In cryptococcal meningitis, lumbar puncture may show a high opening pressure, and the CSF typically shows a lymphocytic pleocytosis. Patients with AIDS often have normal or mildly abnormal CSF findings and may have minimal pleocytosis.



FIGURE 13. Cryptococcosis. Skin lesions, which are molluscum-like, are characteristic of disseminated cryptococcosis.

The treatment of cryptococcal meningitis differs in those with AIDS and those without AIDS (see Table 21). Maintenance therapy is indicated for patients with AIDS until they have responded to antiretroviral therapy (CD4 cell count ≥100/μL for ≥3 months) and have been receiving antifungal therapy for at least 1 year. Maintenance therapy is administered for 6 to 12 months in patients who are not infected with HIV. If a patient is receiving appropriate antifungal therapy and other measures to reduce elevated intracranial pressure have failed, management by frequent lumbar punctures and removal of CSF or placement of a ventriculoperitoneal shunt is required. Organ transplant recipients who must continue taking high-dose immunosuppressive therapy may require life-long antifungal therapy.

KEY POINTS

- The central nervous system is the most common site of disseminated cryptococcosis.
- The latex agglutination assay for cryptococcal antigen is highly sensitive and specific for the diagnosis of meningitis in symptomatic patients with AIDS.
- Maintenance therapy is indicated for patients with AIDS and cryptococcal meningitis until they have responded to antiretroviral therapy (CD4 cell count ≥100/μL for ≥3 months) and have been receiving antifungal therapy for at least 1 year.

Blastomycosis

Blastomyces dermatitidis is endemic to the Ohio and Mississippi river valleys, the Great Lakes, and the St. Lawrence River. Infection occurs by inhalation of spores and primarily involves the lungs. The second most frequent site of infection is the skin, followed by the bones, joints, and prostate. Most patients with acute pulmonary blastomycosis are asymptomatic. Those with acute pneumonia have nonspecific systemic symptoms, a nonproductive cough, and nonspecific pulmonary infiltrates on chest radiographs. Skin lesions are the most common manifestation of disseminated disease and may vary in appearance, including papules, nodules, verrucous lesions, or draining lesions. Presumptive diagnosis is based on finding characteristic yeast forms with broad-based buds on histopathologic samples. Definitive diagnosis is established by culture.

Acute pulmonary blastomycosis may be mild and self-limited in otherwise healthy persons and may not require therapy, although therapy may prevent extrapulmonary

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H CONT.

dissemination. All immunocompromised patients and patients with moderate to severe pneumonia or disseminated infection require therapy (see Table 21). All patients with disseminated blastomycosis should have a bone scan to detect occult osteoarticular involvement. Genitourinary infection may be asymptomatic or associated with symptoms of prostatism. A urine culture should be obtained to document involvement because the prostate may serve as a nidus for infection and lead to relapses. Current serologic assays serve no role. Extrapulmonary blastomycosis can occur in the absence of lung disease. H

KEY POINT

- Blastomycosis infection primarily involves the lungs, followed by skin; other sites of infection include bones, joints, and prostate.

H Histoplasmosis

Histoplasma capsulatum is the most common endemic mycosis in the United States and is found in the Ohio and Mississippi river valleys. Although infection usually is asymptomatic, acute and chronic pulmonary disease, granulomatous mediastinitis, fibrosing mediastinitis, broncholithiasis, pulmonary nodules (histoplasmomas), and acute and chronic disseminated disease may occur. Acute progressive disseminated histoplasmosis presents with nonspecific symptoms, including high fever and weight loss, hepatosplenomegaly, and pancytopenia. Small yeast forms within neutrophils may be seen on peripheral blood smear. The definitive diagnosis requires culture, which may take up to 6 weeks. Additional diagnostic modalities include histopathologic studies and antigen (primarily from the urine) determination. Because the sensitivity of these studies differs, depending on the extent of infection and the time following exposure, several different tests are usually required to confirm the diagnosis.

In most immunocompetent, symptomatic patients, pulmonary disease is mild and resolves without therapy. Therapy is indicated in those with moderately severe or severe infection, acute diffuse pulmonary infection, and chronic cavitary pulmonary disease (see Table 21). Therapy should also be considered for patients with mild infection who are immunocompromised or have had symptoms for 4 or more weeks. H

KEY POINT

- Although histoplasmosis infection is usually asymptomatic, acute and chronic pulmonary disease, granulomatous mediastinitis, fibrosing mediastinitis, broncholithiasis, pulmonary nodules (histoplasmomas), and acute and chronic disseminated disease may occur.

H Coccidioidomycosis

Coccidioides immitis and *Coccidioides posadasii* are endemic to desert areas of the southwestern United States, including Arizona, New Mexico, Texas, and the central valley of California, and to parts of Central and South America. Rates of infection in endemic areas are highest during dry months and increase when the soil is disturbed. Most infections are caused by inhalation of spores and are asymptomatic. Primary pulmonary infection most frequently presents as community-acquired pneumonia occurring 1 to 3 weeks after exposure. In endemic areas, up to one third of cases of community-acquired pneumonia are caused by *Coccidioides* species. Valley fever is a subacute infection with respiratory symptoms, fever, and erythema nodosum. Arthralgia of multiple joints, termed "desert rheumatism," is frequent. Risk factors for dissemination include immunosuppression, AIDS, or pregnancy. However, disseminated infection may occur in patients who have no underlying disease. The most common sites for disseminated infection include skin, bones (including vertebrae), joints, and the meninges.

Coccidioidomycosis is definitively diagnosed by isolation of the organism in culture. Serologic tests are useful for diagnosis and for monitoring the course of therapy, and they are the preferred method for diagnosing primary coccidioidal infections. Serologic studies are more helpful than cultures in diagnosing chronic coccidioidal meningitis because cultures of CSF are frequently negative. A negative serologic test result does not exclude infection; therefore, repeat tests are needed to improve sensitivity.

Treatment is indicated for patients with severe disease or those with an increased risk for disseminated infection (see Table 21). For those with meningitis, therapy should be lifelong because relapses are common after medication is discontinued. Azoles should be avoided in women during the first trimester of pregnancy because of their teratogenic potential. H

KEY POINTS

- Primary coccidioidomycosis infection most frequently presents as community-acquired pneumonia occurring 1 to 3 weeks after exposure.
- Serologic tests are useful for diagnosis and for monitoring the course of therapy and are the preferred method for diagnosing primary coccidioidal infections; however, repeat tests may be needed to improve sensitivity.

Sporotrichosis

Sporothrix schenckii is found in soil, moss, and other vegetation and occurs almost exclusively in persons who encounter the organism through an occupation or hobby, such as landscaping or gardening. Infection is almost always acquired through inoculation of the organism into the skin or subcutaneous tissue. A papule appears days to weeks later at the inoculation site and usually ulcerates. Similar lesions then occur along lymphatic channels proximal to the inoculation site. Risk factors for pulmonary and osteoarticular infection include diabetes mellitus, alcoholism, and COPD. Those with HIV infection are at risk for disseminated infection. The diagnosis is established by culture. Itraconazole is the therapy of choice for cutaneous and osteoarticular sporotrichosis.

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KEY POINT

- Itraconazole is the therapy of choice for cutaneous and osteoarticular sporotrichosis.

Exserohilum

Exserohilum rostratum is a mold that has rarely been described as a human pathogen. Since the fall of 2012, it has been the predominant pathogen in an outbreak of meningitis and other infections in patients who received epidural, paraspinal, or joint injections with contaminated lots of methylprednisolone acetate from a single compounding pharmacy. In addition to meningitis, epidural abscesses, arachnoiditis, and infection involving the sacroiliac and peripheral joints have occurred. Most patients infected with *Exserohilum rostratum* have been treated with voriconazole (with or without liposomal amphotericin B) for CNS and paraspinal infections and with voriconazole for bone and joint infections.

Sexually Transmitted Infections

Introduction

The Centers for Disease Control and Prevention (CDC) estimates that 20 million sexually transmitted infections (STIs) occur annually in the United States, accounting for an estimated $16 billion in health care expenditures. Half of these infections occur in persons aged 15 to 24 years. The appropriate evaluation and management of STIs affect the health of the patient and can help decrease the transmission of infections in the community.

Chlamydia trachomatis Infection

C. trachomatis is the most commonly reported STI in the United States. It may cause several clinical syndromes but also may be asymptomatic or subclinical and lead to potentially significant complications, including ectopic pregnancy, tubal infertility, and chronic pelvic pain syndromes. Because of this, screening is recommended for women at risk for infection. The U.S. Preventive Services Task Force (USPSTF) recommends at least annual screening for all sexually active women aged 24 years and younger; older women should be screened if they have risk factors, including a previous STI, new or multiple partners, inconsistent condom use, or a history of exchanging sex for money or drugs. The CDC recommends screening for all pregnant women. Routine screening is not recommended for most men, although heterosexual men can be screened if they report risk factors for STIs; men who have sex with men should be screened at least annually.

Nucleic acid amplification testing (NAAT) is the preferred diagnostic test for chlamydia. NAAT can be performed on first voided urine samples or urethral swabs from men and on vaginal or endocervical swabs from women. NAAT is not FDA approved for the detection of chlamydia from rectal swabs; however, some laboratories have met the Clinical Laboratory Improvement Amendments standards for NAAT on these samples, so physicians should confer with the director of the laboratory they use to understand what testing is available. Repeat testing to document cure of infection (at 3-4 weeks) is recommended only for pregnant women. Repeat testing is recommended for all patients 3 months after a diagnosis of *C. trachomatis* infection because of the high risk for reinfection. Sexual partners who had contact during the 60 days before the onset of a patient's symptoms or diagnosis should be referred for evaluation; if the last sexual contact occurred more than 60 days before diagnosis, the most recent sexual partner should be referred.

KEY POINTS

- The U.S. Preventive Services Task Force recommends at least annual screening for *Chlamydia trachomatis* in all sexually active women age 24 years and younger and in older women if they have risk factors; men who have sex with men should be screened at least annually.
- Nucleic acid amplification testing is the preferred diagnostic test for *Chlamydia trachomatis* infection and can be performed on first voided urine samples or urethral swabs from men and on vaginal or endocervical swabs from women.

Neisseria gonorrhoeae Infection

N. gonorrhoeae is the second most common bacterial STI in the United States, and infection rates are highest among young women aged 15 to 19 years. Many infected women are asymptomatic. The USPSTF recommends screening for gonorrhea in sexually active women with a history of infection, another STI, new or multiple partners, inconsistent condom use, or a history of exchanging sex for money or drugs. The USPSTF does not recommend screening of men; however, the CDC recommends annual screening for men who have sex with men.

In addition to causing cervicitis, pelvic inflammatory disease, urethritis, and epididymitis, *N. gonorrhoeae* can cause pharyngeal infection (usually asymptomatic) and anorectal infections. Disseminated gonococcal infection (DGI) may cause two syndromes: an arthritis-dermatitis syndrome (in which patients have the triad of migratory polyarthralgia, subsequent tenosynovitis, and, eventually, frank arthritis without purulent joint infection) or purulent arthritis alone without skin findings. The classic skin lesion of DGI is a vesiculopustular lesion on an erythematous base; however, petechial, macular, and papular lesions can also occur.

NAAT is the preferred diagnostic test for *N. gonorrhoeae* infections. NAAT can be performed on first voided urine or urethral swabs from men and on vaginal or endocervical swabs

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from women. NAAT is not FDA approved for pharyngeal or anorectal samples; however, some laboratories have established performance standards for testing of these specimens, and results can be used for clinical management. If available, a Gram stain of urethral discharge is highly sensitive and specific for the diagnosis of urethritis due to *N. gonorrhoeae* in men who are symptomatic; Gram stain of endocervical or vaginal specimens is inadequately sensitive to exclude infection. Blood and joint fluid cultures should be obtained if DGI is suspected but they may be negative; a presumptive diagnosis can be made by demonstrating the organism at a mucosal site (cervix/urethra, pharynx, or rectum) with NAAT or by culture.

A disadvantage of non–culture-based testing for *N. gonorrhoeae* is the lack of availability of antimicrobial susceptibility data. Because of increasing drug resistance among *N. gonorrhoeae*, culture is recommended, if possible, to provide antimicrobial susceptibility results to guide additional therapy for patients in whom treatment fails. Test of cure is not recommended; however, patients should be retested at 3 months because the risk for reinfection is high even when sexual partners have been referred for treatment. Sexual partners should be referred for evaluation as described for *C. trachomatis* infections. Patients should be advised to avoid sexual contact until therapy is completed and symptoms have resolved.

KEY POINTS

- The U.S. Preventive Services Task Force recommends screening for gonorrhea in sexually active women with a history of infection, another sexually transmitted infection, new or multiple partners, inconsistent condom use, or a history of exchanging sex for money or drugs.
- The U.S. Preventive Services Task Force does not recommend screening men for gonorrhea; however, the CDC recommends annual screening for men who have sex with men.
- Nucleic acid amplification testing is the preferred diagnostic test for *Neisseria gonorrhoeae* infection.

Specific Syndromes

Cervicitis

Women with cervicitis present with vaginal discharge and intermenstrual bleeding, especially after intercourse, although infections may be asymptomatic. In addition to *N. gonorrhoeae* and *C. trachomatis*, cervicitis can be caused by herpes simplex virus (HSV), particularly primary infection; *Mycoplasma genitalium* infection and bacterial vaginosis presenting as cervicitis have also been reported. Purulent or mucopurulent discharge can be visualized from the cervical os, and passage of a cotton-tipped swab through the os elicits bleeding owing to inflamed, friable mucosa. Gram staining in women is less useful in differentiating *N. gonorrhoeae* because other gram-negative flora may be present in the vagina. Cervicitis can also result from chemical irritation, for example from douching, so a careful history of any potential chemical exposures should be obtained.

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is an ascending infection of the genital tract that is polymicrobial. *C. trachomatis* and *N. gonorrhoeae* are implicated in approximately two thirds of cases. Because the sequelae of untreated infection of the upper genital tract are significant, a diagnostic strategy that maximizes the sensitivity of the diagnosis is recommended. Sexually active women with lower genital tract symptoms who have cervical motion tenderness, uterine tenderness, or adnexal tenderness should be evaluated and treated for PID. Clinical manifestations of PID may include right upper quadrant pain and tenderness due to perihepatitis (Fitz-Hugh-Curtis syndrome). Fever, mucopurulent cervical discharge, numerous leukocytes on microscopic examination of a wet mount of vaginal fluid, and elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate) increase the specificity of the diagnosis. NAAT for *C. trachomatis* and *N. gonorrhoeae* should be obtained, and women should be screened for other STIs, including HIV infection. Outpatient management is appropriate for most women with PID. Indications for hospitalization include inability to tolerate an oral regimen, severe signs of systemic toxicity, pregnancy, inability to exclude a surgical emergency (ectopic pregnancy, appendicitis), and suspected tubo-ovarian abscess. Women who do not respond to outpatient therapy within 72 hours should also be hospitalized. If the presence of *C. trachomatis* or *N. gonorrhoeae* is confirmed, repeat testing in 3 to 6 months is recommended because the incidence of reinfection is substantial. The risk for PID is increased in the first 3 weeks after intrauterine device insertion, but removal of the intrauterine device because of a PID diagnosis is not recommended as long as the patient responds to treatment. Sexual partners of women diagnosed with PID should be referred for evaluation.

Urethritis

Men with urethritis usually have symptoms of urethral discharge, dysuria, and pruritus, although infections can be asymptomatic. Causative agents of urethritis include *C. trachomatis*, *N. gonorrhoeae*, and *M. genitalium*. Nongonococcal urethritis can also be caused by HSV, *Trichomonas* species, and adenovirus. Purulent urethral discharge may be visualized at the urethral meatus or expressed by applying gentle pressure with the thumb on the ventral surface and the forefinger on the dorsum of the base of the penis and moving toward the meatus. A positive result on a leukocyte esterase test on a first voided urine sample or leukocytes (≥10/hpf) on microscopic examination of urine sediment supports the diagnosis.

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Epididymitis

In sexually active young men, epididymitis is usually caused by *C. trachomatis* or *N. gonorrhoeae;* men who have insertive anal intercourse can have infections due to enteric gram-negative organisms, such as *Escherichia coli*. In older men, epididymitis can occur as a complication of urinary tract infection, often in the presence of benign prostatic hyperplasia unrelated to STI (see MKSAP 17 General Internal Medicine). Patients typically have pain and swelling of the ipsilateral testis and the spermatic cord (epididymo-orchitis) on presentation. The differential diagnosis includes testicular torsion; abrupt onset of symptoms and the absence of signs of urethral inflammation should raise concern about the possibility of this diagnosis. A Gram stain of urethral discharge with leukocytes (>5/hpf) or positive leukocyte esterase result or a first voided urine sample with leukocytes (≥10/hpf) supports the diagnosis. Patients should have NAAT for *C. trachomatis* and *N. gonorrhoeae*, and the urine should be cultured. Men with epididymitis who are at risk for STIs should be screened for other STIs and encouraged to refer sexual partners for evaluation.

Anorectal Infections

Men and women who engage in receptive anal intercourse can develop proctitis because of sexually transmitted pathogens, including *N. gonorrhoeae*, *C. trachomatis*, syphilis, and HSV. Anorectal infection can also occur in women with cervicitis because of autoinoculation, which occurs when infected secretions from the vagina come in contact with the anal region. Persons with proctitis present with anal pain or pruritus, discharge (which may be bloody), constipation, and tenesmus.

KEY POINTS

- Nucleic acid amplification testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* should be obtained when pelvic inflammatory disease and epididymitis are diagnosed.
- Signs and symptoms of pelvic inflammatory disease include cervical motion, uterine, or adnexal tenderness; fever, mucopurulent cervical discharge, leukocytes on microscopic examination of a wet mount of vaginal fluid, and elevated inflammatory markers increase the specificity of the diagnosis.
- Men with epididymitis present with pain and swelling of the ipsilateral testis and the spermatic cord.

Treatment

Recommended treatment of cervicitis, urethritis, proctitis, and their associated complications is outlined in **Table 22**. The emergence of drug resistance among isolates of *N. gonorrhoeae* has had a major impact on the antimicrobial regimens recommended for the treatment of clinical syndromes caused by this pathogen. Fluoroquinolone-resistant strains have been reported throughout the United States, so fluoroquinolones are no longer recommended for the treatment of infections due to *N. gonorrhoeae*. Additionally, cephalosporin minimal inhibitory concentrations among *N. gonorrhoeae* isolates have increased in the past several years, and cephalosporin-resistant strains of *N. gonorrhoeae* have been reported. As a result, the recommended dose of ceftriaxone has been increased from 125 mg to 250 mg, and the use of cefixime, an oral third-generation cephalosporin, is recommended only if parenteral ceftriaxone is unavailable. If cefixime is used for treatment, a test of cure using NAAT should be performed 1 week after completion of therapy; however, if results on repeat testing are positive, a culture should be obtained so that antimicrobial susceptibility testing is available to guide further treatment.

Treatment of possible concomitant *C. trachomatis* infection in persons diagnosed with gonococcal infection is recommended, and the addition of azithromycin or doxycycline to treatment regimens for *N. gonorrhoeae* may increase the chances of eradication of this pathogen. Patients with cervicitis, urethritis, and proctitis can be treated empirically at the time of presentation or on the basis of diagnostic test results. Persons seen in emergency departments, urgent care centers, or any other setting where likelihood of follow-up is a concern should receive empiric therapy. Diagnostic testing for the presence of *C. trachomatis* and *N. gonorrhoeae* should be performed even if empiric therapy is given because these infections are reportable, and the results of diagnostic testing may be helpful if the patient returns with persistent symptoms. If a *Trichomonas* species is determined as the cause of urethritis, treatment with metronidazole (500 mg twice daily for 7 days) is recommended; HSV treatment is discussed later. Patients should be offered testing for other STIs, including HIV infection, and encouraged to refer their sexual partners for evaluation.

Patients treated for chlamydial, gonococcal, or trichomonal infection should be retested 3 months after treatment.

KEY POINTS

- Fluoroquinolones are no longer recommended for the treatment of gonorrhea, the recommended ceftriaxone dose has been increased to 250 mg, and oral cefixime is recommended only if parenteral ceftriaxone is not available.
- The addition of azithromycin or doxycycline to treatment regimens for *Neisseria gonorrhoeae* may increase the chances of eradication of this pathogen.

Genital Ulcers

Herpes Simplex Virus

HSV is the most common cause of genital ulcer disease in the United States. The epidemiology of primary genital HSV infections has shifted, and up to half are now caused by HSV-1 rather than HSV-2. However, HSV-1 is less able to

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TABLE 22. Treatment of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Infections and Their Complications

Clinical Syndrome	Preferred Regimen	Alternative Regimen
Cervicitis and urethritis (empiric therapy)	Ceftriaxone, 250 mg IM single dose, plus azithromycin, 1 g PO single dose (preferred), or doxycycline 100 mg PO twice daily for 7 days	Cefixime, 400 mg PO single dose, plus doxycycline,[a] 100 mg PO twice daily for 7 days
Chlamydia cervicitis, urethritis, or proctitis	Azithromycin, 1 g PO single dose, or doxycycline, 100 mg PO twice daily for 7 days	Erythromycin base, 500 mg PO four times daily, or erythromycin ethylsuccinate, 800 mg PO four times daily, or levofloxacin, 500 mg PO daily, or ofloxacin, 300 mg PO twice daily for 7 days
Gonococcal cervicitis, urethritis, or proctitis and pharyngeal infection[b]	Ceftriaxone, 250 mg IM single dose, plus azithromycin, 1 g PO single dose (preferred), or doxycycline, 100 mg PO twice daily for 7 days	Cefixime, 400 mg PO single dose, plus azithromycin, 1 g PO single dose (preferred), or doxycycline, 100 mg PO twice daily for 7 days Test of cure of *Neisseria gonorrhoeae* 1 week after treatment
Disseminated gonococcal infection[c]	Ceftriaxone, 1 g IM or IV every 24 h	Cefotaxime, 1 g IV every 8 h, or ceftizoxime, 1 g IV every 8 h
Pelvic inflammatory disease		
Parenteral therapy[d]	Cefotetan, 2 g every 12 h, or cefoxitin, 2 g every 6 h, plus doxycycline, 100 mg PO or IV every 12 h, or clindamycin, 900 mg every 8 h, plus gentamicin, 2 mg/kg loading dose followed by 1.5 mg/kg every 8 hours or a single daily dose of 3-5 mg/kg/d	Ampicillin-sulbactam, 3 g every 6 h, plus doxycycline, 100 mg PO or IV every 12 h
Oral/IM therapy	Ceftriaxone, 250 mg IM single dose, plus doxycycline, 100 mg PO twice daily for 14 days with or without metronidazole, 500 mg PO twice daily for 14 days, or cefoxitin, 2 g IM single dose, with probenecid, 1 g PO, plus doxycycline, 100 mg PO every 12 h for 14 days, with or without metronidazole, 500 mg PO twice daily for 14 days	
Epididymitis[e]	Ceftriaxone, 250 mg IM single dose, plus doxycycline, 100 mg PO twice daily for 10 days	

IM = intramuscularly; IV = intravenously; PO = orally.

[a]Doxycyline should be avoided/used with caution in pregnant patients. Cefixime should be used only if ceftriaxone is unavailable.

[b]Treatment for possible chlamydial infection is recommended for all patients diagnosed with gonorrhea.

[c]Parenteral therapy should be used until clinical improvement. Uncomplicated infections can then be treated with cefixime, 400 mg twice daily, to complete a total of 7 to 10 days of treatment. Septic arthritis should be treated for 7 days with parenteral therapy.

[d]Patients can be switched to oral therapy within 24 to 48 hours of clinical improvement using doxycycline, 100 mg PO twice daily, with or without metronidazole, 500 mg PO twice daily, to complete a total of 14 days of therapy

[e]The recommended regimen for acute epididymitis likely due to enteric gram-negative organisms is levofloxacin, 500 mg PO daily, or ofloxacin, 300 mg PO twice daily, for 10 days.

establish latency in the genital region, so most recurrent genital infections are due to HSV-2. Most patients with serologic evidence of HSV-2 infection have never had a recognized episode of genital ulcers. Patients with genital HSV infection initially have painful lesions that begin as vesicles and progress to ulcers on an erythematous base (**Figure 14**). In immunocompromised patients, HSV may appear as extensive, painful, shallow ulcers. Those with primary infection often have multiple genital lesions accompanied by regional lymphadenopathy and systemic symptoms, such as fever, myalgia, and malaise. Recurrent episodes are often heralded by prodromal symptoms, such as tingling, burning, pruritus, or pain, and are generally much less severe and without systemic symptoms.

The initial episode of HSV genital infection should be microbiologically confirmed. In primary infections, it is particularly important to distinguish between HSV-1 and HSV-2 because the former is much less likely to cause recurrent disease. Polymerase chain reaction testing of clinical specimens obtained from ulcers and mucocutaneous sites is



FIGURE 14. Penile lesions seen in herpes simplex virus type 2.

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the most sensitive diagnostic modality available. The use of type-specific serum antibody testing is not preferred for the diagnosis of symptomatic ulcer disease.

Antiviral therapy can reduce the severity and duration of symptoms of primary and secondary infections. Patients with frequent or severe recurrences should be offered long-term suppressive therapy. Because the frequency of recurrence decreases over time, the need for continued suppressive therapy should be reassessed periodically. Daily therapy with valacyclovir also decreases the risk for transmission to uninfected sexual partners. Treatment of HSV-associated genital ulcers is outlined in **Table 23**.

An important aspect of managing HSV-associated genital ulcer disease is counseling and education of the patient regarding the chronic nature of the infection and risks for transmission. Infected persons should understand the importance of informing sexual partners and should be counseled to abstain from sexual intercourse or oral-genital contact when prodromal symptoms or ulcers are present. It is also important that infected persons understand that asymptomatic viral shedding can occur and result in transmission of infection. Suppressive therapy does not eliminate the risk for transmission. Condoms, however, can reduce this risk. Men and women should be educated about the risk for neonatal HSV. Women should be encouraged to inform their obstetric providers and pediatricians of their history or the history of their male partner during pregnancy. Type-specific serologic antibody testing of an asymptomatic sexual partner can be useful in determining whether they are already infected and, therefore, not at risk for transmission.

TABLE 23. Treatment of Herpes Simplex Virus Genital Infections

Clinical Syndrome	Recommended Regimen[a]
Primary infection[b]	Acyclovir, 400 mg three times daily, *or* acyclovir, 200 mg five times daily, *or* famciclovir, 250 mg three times daily, *or* valacyclovir, 1 g twice daily; all regimens for 7-10 days
Recurrent infection	Acyclovir, 400 mg three times daily for 5 days, *or* acyclovir, 800 mg twice daily for 5 days, *or* acyclovir, 800 mg three times daily for 2 days, *or* famciclovir, 125 mg twice daily for 5 days, *or* famciclovir, 1 g twice daily for 1 day, *or* famciclovir, 500 mg once followed by 250 mg twice daily for 2 days, *or* valacyclovir, 500 mg twice daily for 3 days, *or* valacyclovir, 1 g once daily for 5 days
Suppressive therapy	Acyclovir, 400 mg twice daily, *or* famciclovir, 250 mg twice daily, *or* valacyclovir, 500 mg daily, *or* valacyclovir, 1 g daily[c]

[a]All regimens are given orally.

[b]Therapy can be extended if healing is incomplete after 10 days of treatment.

[c]The 500-mg dose of valacyclovir may be less effective than the 1-g dose in patients who have very frequent recurrences (≥10 episodes per year).

KEY POINTS

- Patients with genital herpes simplex virus infection present with painful lesions that begin as vesicles and progress to ulcers on an erythematous base; those with primary infection often have multiple genital lesions, regional lymphadenopathy, fever, myalgia, and malaise.
- Polymerase chain reaction is the most sensitive modality available for diagnosing herpes simplex virus.

Syphilis

The incidence of infection with *Treponema pallidum* reached historic low levels in the United States in 2000 and then began to rise. Outbreaks among men who have sex with men are well described; however, the incidence of infection among women also has risen, as has the incidence of congenital syphilis.

Primary syphilis presents as a painless ulcer (chancre) at the site of inoculation (**Figure 15**). Chancres begin as papular lesions, which then ulcerate; the ulcer has a firm, raised border and the ulcer bed is clean. Up to one quarter of patients have multiple lesions. Regional lymphadenopathy is common. Chancres heal in 3 to 6 weeks. Secondary syphilis is a systemic illness characterized by a generalized macular and papular rash that normally involves the trunk and extremities, including the palms and soles. Lesions can coalesce in intertriginous

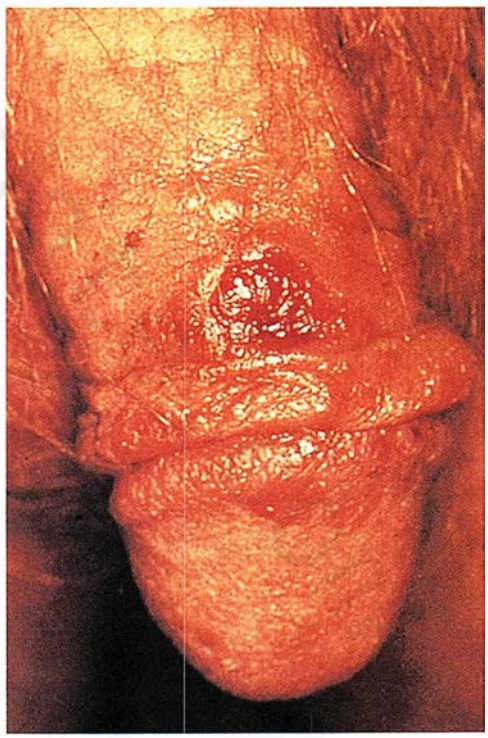

FIGURE 15. The primary ulcerative lesion (chancre) in patients with syphilis develops approximately 3 weeks after infection occurs, has a clean appearance with heaped-up borders, and is usually painless. It is often unrecognized. The primary chancre resolves spontaneously, and the infection progresses to a more advanced stage.

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areas to form plaques (condyloma lata), and superficial erosions may occur on mucosal surfaces (mucous patches). Fever, malaise, and generalized lymphadenopathy are common. Complications of tertiary syphilis (cardiovascular disease, gumma) are now rarely seen. Neurosyphilis can be asymptomatic or present as meningovascular, parenchymatous, or ocular disease.

Cerebrospinal fluid examination should be performed in patients with neurologic symptoms or signs and those who do not have an appropriate serologic response to treatment. Latent syphilis is the presence of serologic evidence of infection in the absence of clinical signs. Latent syphilis is divided into early-latent (infection ≤1 year in duration) or late-latent (infection >1 year) categories. In the absence of previous serologic results, asymptomatic patients with positive serologic findings are classified as having syphilis of unknown duration.

Primary syphilis can be diagnosed by dark field examination of scrapings from the ulcer base; however, this is not available in many clinical settings, so patients may need to be treated empirically. Serologic testing is the mainstay of syphilis diagnosis. Results of nonspecific tests (rapid plasma reagin [RPR] test, VDRL test) may be negative in primary infection but will be positive, generally at high titers, in secondary syphilis. Titers are lower in latent and tertiary infection. Positive findings on nonspecific tests should always be confirmed with a specific treponemal test (*T. pallidum* particle agglutination assay or fluorescent treponemal antibody absorption test) because biologic false-positive results can occur. Many commercial laboratories are now using a "reverse serology" testing algorithm that entails a specific treponemal test, most commonly an enzyme immunoassay (EIA), as the initial screening test followed by a nonspecific test (RPR or VDRL) for patients with a positive result on a specific test. These treponemal-specific assays allow automation of testing in the laboratory and increase the sensitivity of diagnosis because patients with longstanding untreated syphilis may have negative results on nonspecific tests. Although the specificity of the EIA is excellent, persons with a positive EIA and a negative VDRL or RPR finding should have a second specific treponemal test to confirm the positive result. Persons with a positive (confirmed) EIA and a negative RPR or VDRL result should be offered treatment for late latent syphilis if they have no history of treatment.

Penicillin remains the treatment of choice at all stages of syphilis, and treatment recommendations are outlined in **Table 24**. Patients with primary and secondary syphilis should have repeat serologic testing at 6 and 12 months with the same testing method used for initial diagnosis; a fourfold decrease in the RPR or VDRL titer is considered significant. Patients should be offered screening for HIV infection, and sexual partners should be referred for evaluation. Partners exposed within the preceding 90 days to persons diagnosed with primary, secondary, or early latent syphilis should receive treatment regardless of serologic results.

KEY POINTS

- Primary syphilis presents as a painless ulcer at the site of inoculation, with a firm, raised border and clean bed; secondary syphilis is characterized by a generalized macular and papular rash that normally involves the trunk and extremities, including the palms and soles; and tertiary syphilis includes symptoms of cardiovascular disease and gumma.
- Penicillin is the treatment of choice for all stages of syphilis.
- Sexual partners should be referred for evaluation, and those exposed within the preceding 90 days of diagnosis should receive treatment regardless of serologic results.

TABLE 24. Treatment of Syphilis

Stage	Recommended Regimen[a]	Alternative Regimen for Penicillin-Allergic Patients
Primary and secondary	Benzathine penicillin G, 2.4 million units IM single dose	Doxycycline, 100 mg PO twice daily, *or* tetracycline, 500 mg PO four times daily, for 14 days
Early latent	Benzathine penicillin G, 2.4 million units IM single dose	Doxycycline, 100 mg PO twice daily, *or* tetracycline, 500 mg PO four times daily, for 14 days
Late latent or syphilis of unknown duration	Benzathine penicillin G, 2.4 million units IM at 1-week intervals for 3 doses	Doxycycline, 100 mg PO twice daily, *or* tetracycline, 500 mg PO four times daily, for 28 days
Neurosyphilis	Aqueous crystalline penicillin G, 18-24 million units daily given as 3-4 million units IV every 4 h or by continuous infusion for 10-14 days, *or* procaine penicillin, 2.4 million units IM daily, plus probenecid, 500 mg PO four times daily, both for 10-14 days	Ceftriaxone, 2 g IM or IV daily for 10-14 days[b]

IM = intramuscularly; IV = intravenously; PO = orally.

[a]Penicillin is the only effective antimicrobial agent for treatment of syphilis at any stage in pregnancy; therefore, pregnant penicillin-allergic patients should be desensitized and treated with the appropriate penicillin regimen as outlined above.

[b]Limited data are available to support the use of this alternative regimen, and the possibility of cross-reaction in penicillin-allergic patients must be considered.

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Chancroid

Chancroid, caused by *Haemophilus ducreyi*, is a common cause of genital ulcer disease worldwide but is uncommon in the United States. On presentation, patients have a painful genital ulcer and tender inguinal lymphadenopathy, which often suppurates. Culture of the organism is difficult. The CDC recommends consideration of this diagnosis if all of the following criteria are met: (1) presence of one or more painful genital ulcers, (2) no evidence of syphilis by dark field examination and serologic testing, (3) negative test result for HSV from the ulcer, and (4) clinical presentation consistent with chancroid. Treatment is outlined in **Table 25**. Patients who do not respond should be referred to a physician with expertise in the management of genital ulcer disease.

KEY POINT

- Patients with chancroid present with a painful genital ulcer and tender inguinal lymphadenopathy, which often suppurates.

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is caused by three specific serovars of *C. trachomatis* (L1, L2, and L3). Infection presents with a genital papule or ulcer followed by tender unilateral inguinal lymphadenopathy. LGV is reported as a cause of proctocolitis, especially among men who have sex with men. Results of NAAT and most serologic tests will be positive for evidence of infection with *C. trachomatis* but cannot distinguish the LGV serovars, so the diagnosis must be made on clinical and epidemiologic grounds. Treatment is outlined in Table 25.

KEY POINT

- Lymphogranuloma venereum infection presents with a genital papule or ulcer followed by tender unilateral inguinal lymphadenopathy.

Genital Warts

Genital warts are most commonly caused by human papillomavirus (HPV) types 6 and 11. They are typically painless lesions, although they can present with pain or pruritus. The lesions are flesh colored and exophytic (**Figure 16**); pedunculated lesions often occur. Diagnosis is generally based on clinical appearance; biopsy is indicated if the diagnosis is uncertain or lesions progress or do not respond to therapy. Pigmented or ulcerated lesions should also be biopsied. Treatment is indicated for symptomatic lesions and can be offered to patients concerned about the cosmetic appearance of the warts, although up to 80% of patients will clear the infection spontaneously. Treatment does not prevent HPV transmission. Patient-applied and provider-administered treatments are available. Patient-applied agents include podofilox (podophyllotoxin), imiquimod, and sinecatechins. Provider-administered treatments include podophyllin resin, trichloroacetic acid, cryotherapy, and surgical removal. See MKSAP 17 General Internal Medicine for discussion of HPV vaccination. Only the quadrivalent vaccine (HPV4) protects against genital warts.

KEY POINTS

- Genital warts are typically painless, flesh-colored, and exophytic lesions.
- Treatment of genital warts does not prevent human papillomavirus transmission.

TABLE 25. Treatment of Chancroid and Lymphogranuloma Venereum

Clinical Entity	Recommended Regimen
Chancroid	Azithromycin, 1 g PO single dose, *or* ceftriaxone, 250 mg IM single dose, *or* ciprofloxacin, 500 mg PO twice daily for 3 days, *or* erythromycin base, 500 mg PO three times daily for 7 days
Lymphogranuloma venereum	Doxycycline,[a] 100 mg PO twice daily for 21 days (preferred), *or* erythromycin base, 500 mg PO four times daily for 21 days (alternative)

IM = intramuscularly; PO = orally.

[a]Doxycyline should be avoided/used with caution in pregnant patients.

Osteomyelitis

Pathophysiology and Classification

Osteomyelitis occurs by hematogenous spread, by direct introduction secondary to surgery or trauma, or contiguously from infected or colonized adjacent soft tissues. Osteomyelitis can be acute or chronic, depending on time of onset and histologic changes.

Hematogenous seeding of bone accounts for approximately 20% of adult cases, and the vertebral column is the most common location. Bloodborne pathogens are more likely

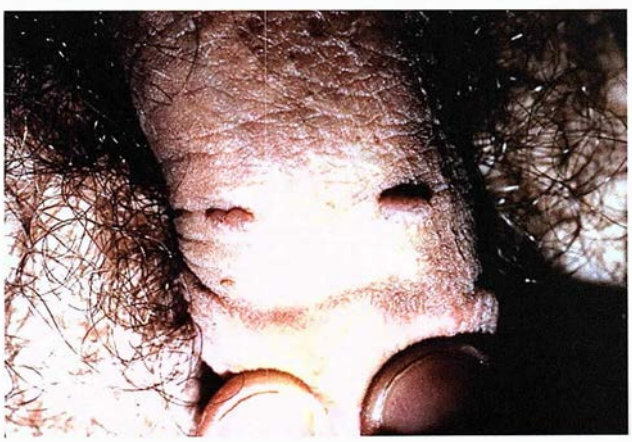

FIGURE 16. Genital warts due to human papillomavirus infection.

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to infect the sternoclavicular and sacroiliac bones, particularly in injection drug users. Frequent sources of hematogenous osteomyelitis are distant foci of infection (for example, skin and soft tissue, genitourinary, gastrointestinal), intravascular catheters, and infective endocarditis. Hematogenous osteomyelitis is typically monomicrobial, and *Staphylococcus aureus* is the most commonly isolated pathogen; however, aerobic, gram-negative bacilli cause disease in many patients. Certain patient-specific conditions are associated with less common bacterial organisms, including *Salmonella* osteomyelitis in persons with sickle cell disease and *Pseudomonas aeruginosa* bone infection in injection drug users.

Osteomyelitis associated with contiguous foci of infection, decubitus ulcers, and vascular insufficiency is often polymicrobial, although monomicrobial disease also occurs, with *S. aureus* as the most commonly involved organism. Osteomyelitis resulting from contaminated open or postsurgical closed traumatic fractures may involve soil organisms, skin flora, or hospital-acquired pathogens. The presence of a foreign body and diminished host defenses can predispose patients to infection from less pathogenic organisms.

KEY POINT

- *Staphylococcus aureus* is the most commonly isolated pathogen causing hematogenous osteomyelitis; however, aerobic, gram-negative bacilli such as *Salmonella* and *Pseudomonas aeruginosa* can cause disease in patients with sickle cell disease and in injection drug users, respectively.

Clinical Manifestations

In acute osteomyelitis, signs and symptoms typically present gradually. Often, patients report a dull pain that may intensify at the site of the infected bone, followed by local erythema, warmth, edema, and tenderness. Constitutional symptoms rarely occur. Although the clinical features of chronic osteomyelitis resemble those of acute disease, the presence of a draining sinus tract is pathognomonic of chronic infection in the bone.

KEY POINT

- The presence of a draining sinus tract is pathognomonic of chronic osteomyelitis infection in the bone.

Diagnosis

Bone biopsy is the definitive diagnostic study for osteomyelitis. However, other diagnostic studies are usually obtained for patients with suspected osteomyelitis before bone biopsy is pursued.

Imaging Studies

Conventional plain radiographs lack sensitivity and specificity when used for diagnosing osteomyelitis because bony abnormalities can take up to 2 weeks to be detectable.

Three-phase bone scanning, gallium scanning, and tagged leukocyte scanning are potentially useful nuclear imaging modalities, especially in the setting of acute disease. Three-phase bone scans involve injection of a radionuclide with imaging of the suspected infection site at three time points: immediately after injection, 15 minutes later, and 4 hours after injection. In patients with osteomyelitis, enhancement occurs in all three phases. Gallium-67 has an affinity for acute-phase reactants and will accumulate at sites of infection following injection. Tagged leukocyte scans use a radiotracer to label autologous leukocytes, which accumulate at sites of infection or inflammation after injection. The sensitivity of these nuclear scanning modalities is high (>90%) for osteomyelitis, but specificity is more variable because patients may have alternative causes of bone inflammation or turnover, such as degenerative joint disease, surgery, trauma, or cancer. The specificity of these tests is significantly heightened if plain radiographs fail to demonstrate evidence of another osseous process. A normal result on a radionuclide imaging test has excellent negative predictive value for ruling out bone infection.

MRI is the best imaging technique for diagnosing osteomyelitis. Because of its high sensitivity for bone infection, a negative scan can reliably exclude disease in the area imaged. Additionally, it is more effective than nuclear imaging in detecting osteomyelitis in certain anatomic locations, such as the feet and vertebrae. However, bone marrow edema changes seen on MRI may be from other causes (such as fracture, surgery, contusion, and Charcot arthropathy). Gadolinium contrast-enhanced MRI is helpful in identifying abscesses and sinus tracts. Because MRI changes persist for an extended duration following effective therapy, follow-up MRI may be misleading and result in additional unwarranted treatment; thus, it should be limited to verifying equivocal clinical improvement.

CT is useful for assessing bone anatomy and delineating adjacent soft tissue and is a reasonable alternative in situations when MRI is contraindicated. Ultrasonography has limited utility in the diagnosis of osteomyelitis. PET scans are currently considered investigational.

KEY POINTS

- Conventional plain radiography lacks sensitivity and specificity for diagnosing osteomyelitis. **HVC**
- MRI is the best imaging technique for diagnosing osteomyelitis because of its high sensitivity for bone infection and superiority at delineating bone anatomy and providing excellent resolution of surrounding soft tissues; the role for follow-up MRI is limited to patients who do not clinically improve with therapy. **HVC**

Laboratory Studies

Generally, inflammatory markers, erythrocyte sedimentation rate, and C-reactive protein are increased, but normal values do not exclude osteomyelitis. Blood cultures identify bacteremia in few cases (almost all are acute osteomyelitis), but when

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CONT. present, the organism isolated is likely the same as the bone pathogen. Accordingly, blood cultures should be obtained in all suspected cases of osteomyelitis because a positive culture may avert more invasive testing.

KEY POINT

HVC
- Blood cultures should be obtained in all suspected cases of osteomyelitis because a positive culture may avert more invasive testing.

Bone Biopsy

The demonstration of a microorganism(s) coupled with characteristic histologic features makes bone biopsy the gold standard for diagnosing osteomyelitis. Biopsies can be accomplished by open surgical procedure or percutaneously. It is best to obtain specimens before the initiation of empiric antimicrobial agents.

With the exception of *S. aureus*, microorganisms isolated from culture samples obtained from superficial wounds or sinus tracts correlate poorly with deep cultures from bone; therefore, this practice is of limited value.

KEY POINTS

- Bone biopsy is the gold standard for diagnosing osteomyelitis.

HVC
- Culture samples obtained from superficial wounds or sinus tracts correlate poorly with deep cultures from bone.

Treatment

Identification of the inciting pathogen, administration of adequate antimicrobials for a prolonged duration (usually 6 weeks), surgical debridement (if warranted), and removal of orthopedic prosthetic devices (if feasible) influence the success of osteomyelitis treatment. Parenteral antimicrobials are used to treat osteomyelitis, except in certain circumstances in which oral therapy may be appropriate, such as using oral fluoroquinolones for infections with certain gram-negative bacilli. Long-term suppressive oral antimicrobial treatment may be indicated in patients for whom cure is not possible. Negative pressure is an adjunctive therapy used to manage open wounds that applies subatmospheric pressure to the wound surface and may benefit select patients. Hyperbaric oxygen therapy has been advocated as an adjunctive therapy for refractory osteomyelitis. However, few randomized, controlled clinical trials support its use in this setting.

KEY POINTS

- Successful osteomyelitis treatment involves antimicrobial administration for a prolonged period, surgical debridement, and removal of orthopedic hardware.
- Parenteral antimicrobials are used to treat osteomyelitis except in certain circumstances; however, chronic osteomyelitis can be treated with oral agents alone.

Evaluation and Management of Diabetes Mellitus-Associated Osteomyelitis

Patients with diabetes mellitus are prone to frequent skin and soft tissue infections of the feet with subsequent ulcer formation, which, if left unrecognized, eventually result in contiguous osteomyelitis.

Patients with diabetes and complex foot infections often lack classic signs of infection, including fever. Characteristic findings that predict contiguous osteomyelitis are ulcers that have been present for 2 weeks or longer, ulcer size greater than 2 cm, grossly visible bone or the ability to probe to bone, and an erythrocyte sedimentation rate greater than 70 mm/h.

The same imaging and laboratory studies are used for patients with diabetes-associated osteomyelitis as in those without diabetes. However, these tests may not be necessary when bone is visualized or probable using a sterile instrument in the depth of a foot ulcer.

A combined medical and surgical approach incorporating meticulous attention to wound management, glycemic control, assessment of vascular supply, and adequate antimicrobial administration are imperative to maximize chances for a successful outcome. Curetted samples from the ulcer base following debridement, or preferably bone biopsy specimens obtained before antimicrobial initiation, provide the best method for identifying the likely pathogen(s). Early surgical intervention for debridement and drainage decreases the risk for subsequent amputations. If indicated, revascularization procedures improve the arterial blood supply, promoting healing and preventing further ischemic necrosis.

Broad-spectrum antimicrobial therapy is usually required considering the polymicrobial nature of diabetic foot infections. Parenteral administration is necessary in patients with severe infections or those suspected of having osteomyelitis. Oral agents with reliable bioavailability may be adequate in the setting of milder infections. Standard antimicrobial regimens use monotherapy or combinations of agents against staphylococci, streptococci, aerobic gram-negative bacilli, and anaerobes. Acceptable choices include advanced-generation cephalosporins (ceftriaxone and cefepime) and fluoroquinolones (ciprofloxacin or levofloxacin) combined with an agent with anaerobic activity, such as metronidazole or clindamycin. Similarly, β-lactam/β-lactamase inhibitor combinations or carbapenems would provide appropriate coverage. The increasing prevalence of methicillin-resistant *S. aureus* underscores the importance of making an accurate microbiologic diagnosis and may require the use of agents active against this pathogen (vancomycin, daptomycin, linezolid, and ceftaroline) until its presence is excluded. After culture and sensitivity information becomes available, modifications to narrow the initial empiric antimicrobial regimen should be undertaken, keeping in mind that not every isolate from these polymicrobial infections requires treatment. Generally, antimicrobials are continued until the wound adequately heals and

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the signs of infection have resolved (usually 2-4 weeks). In patients with osteomyelitis, 6 weeks of antimicrobial therapy after surgical debridement is the preferred treatment course, unless all infected bone and soft tissue has been removed, in which case antimicrobial agents can be stopped when the wound has adequately healed.

The use of vacuum-assisted wound closure is advantageous in achieving complete closure in diabetic foot ulcers. The benefit of hyperbaric oxygen therapy is less clear.

KEY POINTS

- Findings that predict contiguous osteomyelitis are ulcers that have been present for 2 weeks or longer, ulcer size greater than 2 cm, grossly visible bone or the ability to probe to bone, and an erythrocyte sedimentation rate greater than 70 mm/h.
- Debridement and culturing of samples before antimicrobial initiation are the best methods for identifying the offending pathogen(s).
- In patients with diabetes-associated osteomyelitis, 6 weeks of antimicrobial therapy after surgical debridement is the norm.

Evaluation and Management of Vertebral Osteomyelitis

The term *spondylodiskitis* refers to infection of the vertebrae and contiguous disk space. Most infections are hematogenous in origin. Less commonly, infection results from the direct introduction of bacteria or other microorganisms at the time of spinal surgery, is a rare complication from local injection or catheter placement, or is caused by contiguous spread from organs adjacent to the spine. The lumbar spine is involved most frequently, followed by the thoracic and cervical vertebrae. Most patients are men older than 50 years. *S. aureus* (including methicillin-resistant strains) is the pathogen most often isolated. Gram-negative bacilli, streptococci, *Candida* species, and unusual organisms (*Brucella* species) may be involved.

A diagnosis of vertebral osteomyelitis should be considered in patients reporting worsening back or neck pain without an alternative explanation. Local tenderness over the site of spinal infection is frequently detected. Radicular pain, motor weakness, and sensory changes may be present. If infection spreads posteriorly into the epidural space, more severe neurologic deficits may develop. Fever is present in approximately half of infected patients.

Blood cultures should be obtained before administration of empiric antimicrobials because cultures will be positive in more than 50% of patients and help guide appropriate therapy and limit unnecessary testing. Increased erythrocyte sedimentation rate (often >100 mm/h) and C-reactive protein level are noted in more than 80% of patients. Leukocyte counts are often normal, so they are less helpful.

Early in the course of disease, the utility of plain radiography is limited because of its lack of sensitivity. MRI is the most sensitive imaging modality to detect vertebral osteomyelitis, but results can be falsely positive in cases of uninfected fractures. With the exception of gallium scanning, other radionuclide scanning is less reliable in diagnosing vertebral osteomyelitis. When blood cultures are negative, CT-guided percutaneous needle aspiration biopsy and culture are required to confirm the microbiologic diagnosis. A second biopsy attempt is strongly recommended to help determine the microbial cause if the first sample is nondiagnostic.

Lengthy parenteral antimicrobial therapy is the mainstay of treatment. When no pathogen is successfully isolated, empiric antimicrobial therapy must include a reliable agent aimed at gram-positive cocci, such as vancomycin or daptomycin, together with a broad-spectrum antimicrobial against gram-negative bacilli, such as ceftriaxone, ceftazidime, cefepime, or a fluoroquinolone. Because anaerobic bacteria are uncommon pathogens in this setting (except when the pathogenesis is secondary to contiguous infection), the inclusion of empiric antimicrobial agents with specific anaerobic activity is not necessary.

Oral antimicrobial agents are generally used only to treat vertebral osteomyelitis in specific situations, such as when a fluoroquinolone-sensitive, gram-negative bacillus proves to be the infecting pathogen or, possibly, when long term-term chronic antimicrobial suppression is warranted, such as in patients with retained orthopedic prosthetic devices.

Antimicrobial therapy is given for 6 to 8 weeks, but longer treatment courses may be necessary in patients with extensive or advanced disease. Surgical intervention is indicated in few patients, except when required to stabilize the spine, drain an abscess, or pursue the diagnosis when empiric treatment is ineffective.

Follow-up MRIs should be performed in patients without expected improvement, when complications develop, or when inflammatory markers remain elevated without explanation.

KEY POINTS

- Worsening back or neck pain without an alternative explanation, local tenderness, radicular pain, motor weakness, sensory changes, or more severe neurologic deficits should prompt evaluation for vertebral osteomyelitis; fever is present in approximately half of infected patients.
- Blood cultures will be positive in more than 50% of patients and help guide therapy and limit unnecessary testing. HVC
- Antimicrobial therapy is generally given for 6 to 8 weeks.

Fever of Unknown Origin

Introduction

Fever is a common problem, although it is usually self-limited or the cause is promptly diagnosed. Fever of unknown origin (FUO) is a sustained, unexplained fever despite a comprehensive

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diagnostic evaluation. FUO can be classified into classic, nosocomial, neutropenic, and HIV-associated categories based on the clinical setting and the patient's underlying immune status (**Table 26**).

Causes

The spectrum of diseases causing classic FUO changed considerably in recent decades with improved diagnostic modalities for infections, malignancies, and connective tissue diseases. Better methods of diagnosing bacterial and viral infections have become available; with the development of serologic studies to detect connective tissue diseases and improved imaging techniques to detect malignancies, the proportion of patients with classic FUO that remains undiagnosed following evaluation has decreased from half to one third of all cases. The most recently available data show classic FUO is caused by infection (25%-50%; most commonly tuberculosis, abscesses, system fungal infections, infective endocarditis, cytomegalovirus infection), malignancy (20%-30%, leukemia, lymphoma, solid tumors, carcinomatosis), and connective tissue disease (15%-30%; systemic lupus erythematosus, temporal arteritis, Still disease, polyarteritis nodosa, rheumatoid arthritis). Miscellaneous causes include thromboembolic disorders, pancreatitis, medications, inflammatory bowel disease, and granulomatous hepatitis.

KEY POINT

- Fever of unknown origin is primarily caused by infections, malignancies, and connective tissue diseases.

Evaluation

The longer a fever persists without a diagnosis, the less likely it is to have an infectious origin. Most patients with undiagnosed FUO recover spontaneously. The diagnostic evaluation should be based on a detailed history and physical examination, with further evaluation based on the most likely cause in a given patient. Initial studies in most patients typically include a complete blood count with differential, complete metabolic profile with kidney and liver studies, at least three blood culture sets (preferably obtained over 24 hours) and cultures of other bodily fluids (such as urine or from other sources based on clinical suspicion), an erythrocyte sedimentation rate, tuberculosis testing (skin testing or interferon-γ release assay), and serology for HIV. It is reasonable to perform chest imaging (radiography or CT) and a CT of the abdomen as initial diagnostic imaging. CT of the chest showing patchy or nodular infiltration (especially if cavitary) in the lung apices suggests pulmonary tuberculosis, which can occur in those with normal chest radiographs; however, culture is the gold standard for diagnosis. Miliary tuberculosis has nonspecific symptoms, but anemia and pancytopenia are common. The diagnosis is most often established by culture and histopathology of tissue from enlarged lymph nodes, liver biopsy if aminotransferases and alkaline phosphatase are elevated, or bone marrow biopsy if pancytopenia is present. Mycobacterial blood cultures may also be positive. Blood cultures are the most important test for the diagnosis of infective endocarditis. Echocardiography should also be performed if endocarditis is suspected. In cases

TABLE 26. Categories and Common Causes of Fever of Unknown Origin

Category	Definition	Common Causes
Classic	Temperature >38.3 °C (100.9 °F) for at least 3 weeks with at least 1 week of in-hospital investigation[a] *or* Temperature >38.3 °C (100.9 °F) for at least 3 weeks that remains undiagnosed after 2 visits in the ambulatory setting[b] or 3 days in hospital	Infection (endocarditis, tuberculosis, abscesses, complicated urinary tract infection), neoplasm, connective tissue disease
Health care associated	Temperature >38.3 °C (100.9 °F) in patients hospitalized ≥72 hours but no fever or evidence of potential infection at the time of admission, and negative evaluation of at least 3 days	Drug fever, septic, thrombophlebitis, pulmonary embolism, sinusitis, postoperative complications (occult abscesses), *Clostridium difficile* enterocolitis, device- or procedure-related endocarditis
Neutropenic (immune deficient)	Temperature >38.3 °C (100.9 °F) and neutrophil count <500/μL for >3 days and negative evaluation after 48 hours	Occult bacterial and opportunistic fungal infections (aspergillosis, candidiasis), drug fever, pulmonary emboli, underlying malignancy; cause not documented in 40%-60% of cases
HIV associated	Temperature >38.3 °C (100.9 °F) for >3 weeks (outpatients) or >3 days (inpatients) in patients with confirmed HIV infection	Primary HIV infection, opportunistic infections (cytomegalovirus, cryptococcosis, typical and atypical mycobacteria, toxoplasmosis), lymphoma, IRIS

IRIS = immune reconstitution inflammatory syndrome.

[a]First definition of fever of unknown origin.

[b]The ambulatory setting is the preferred venue for evaluation and treatment.

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CONT. of culture-negative endocarditis, serologic tests for Q fever, psittacosis, and *Bartonella* species may yield a causative organism. Brain imaging and cultures and histopathology of biopsy specimens of lung, bone marrow, and liver may establish a diagnosis in HIV-associated FUO. Imaging and bacterial cultures are potentially useful in diagnosing hospital-acquired and neutropenic FUO.

KEY POINT

- The longer a fever persists without a diagnosis, the less likely it is to have an infectious origin.

Primary Immunodeficiencies

Introduction

Diseases of primary immunodeficiency are relatively uncommon, and many, including X-linked agammaglobulinemia and severe combined immunodeficiency, are initially diagnosed in infancy or early childhood. This discussion focuses on immunodeficiencies most likely to be encountered in adults. Immunodeficiencies are classified as B-cell antibody immunodeficiencies, T-cell or cellular immunodeficiencies, and immunodeficiencies associated with the phagocytic or complement system. Most primary immunodeficiencies manifest with infection at certain sites (sinopulmonary, gastrointestinal) and with recurrent infection. The most frequent B-cell immunodeficiencies are diagnosed in young adults.

Selective IgA Deficiency

IgA deficiency is one of the most common B-cell immunodeficiencies. Inheritance may be autosomal dominant or recessive; most cases are sporadic. Patients with selective IgA deficiency may be asymptomatic or present with recurrent sinopulmonary infections (otitis media, sinusitis, pneumonia) or gastrointestinal infections (giardiasis). Other common manifestations include inflammatory bowel disease; celiac disease; an increased frequency of autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, and chronic active hepatitis; and allergic disorders, including asthma, allergic rhinitis, and food allergies. Additionally, some patients may develop anti-IgA antibodies that may react with blood products containing IgA; anaphylactic transfusion reactions can occur. IgA deficiency is defined as a serum IgA level less than 7 mg/dL (0.07 g/L). A low level should be confirmed by repeat measurement. Levels of IgM and IgG are normal. IgA deficiency has no specific treatment; however, prophylactic antimicrobial agents may prevent recurrent sinus and pulmonary infections.

KEY POINT

- Patients with selective IgA deficiency may be asymptomatic; present with recurrent sinopulmonary infections, gastrointestinal infections, inflammatory bowel disease, or celiac disease; and have an increased frequency of autoimmune or allergic disorders.

Common Variable Immunodeficiency

Common variable immunodeficiency involves B- and T-cell abnormalities and results in clinically significant immune dysregulation. The primary manifestation is hypogammaglobulinemia, and adults present with recurrent respiratory infections. The gastrointestinal tract is frequently involved and causes malabsorption or chronic diarrhea. Infection with *Giardia*, *Campylobacter*, or *Yersinia* species may occur, as may opportunistic infections. Concurrent autoimmune disorders occur in up to 25% of patients and include endocrinopathies; chronic active hepatitis; and neurologic, hematologic, or rheumatologic disorders. Pernicious anemia is also a potential complication. The risk for malignancy is increased, including gastrointestinal cancers and non-Hodgkin lymphoma. Patients also have a poor or absent response to protein and polysaccharide vaccines. Serum immunoglobulin levels are usually low, circulating B cells may be normal or low, and T-cell function varies. The diagnosis is made by confirming low levels of total IgG and IgA or IgM, as well as by a poor antibody response to vaccines. Early diagnosis and treatment with intravenous immune globulin improve survival.

KEY POINTS

- Common variable immunodeficiency primarily manifests with hypogammaglobulinemia, and patients present with recurrent respiratory infections and gastrointestinal tract involvement with malabsorption or chronic diarrhea.
- Common variable immunodeficiency is diagnosed by confirming low levels of total IgG and IgA or IgM, as well as by a poor antibody response to vaccines.

Abnormalities in the Complement System

The complement system plays several important roles in host defense, including opsonization to improve phagocyte function, induction of the humoral immune response, clearance of immune complexes, and clearance of apoptotic cells. Complement deficiencies occur in approximately 5% of patients with primary immunodeficiency disorders. Complement deficiencies are classified as those affecting the early classic complement pathway, the alternative complement pathway, the mannose-binding proteins and proteases, and

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the late complement pathway (**Figure 17**). The most common of the early complement disorders is C2 deficiency; C6 deficiency is the most common of the late complement disorders. Patients lacking one of the early components usually present with a rheumatologic disorder, such as systemic lupus erythematosus, scleroderma, vasculitis, or dermatomyositis. Deficiencies of late complement components are sometimes associated with lupus-like illnesses or vasculitis. Those with late complement component deficiencies usually present with recurrent, invasive meningococcal or gonococcal infections. Patients with recurrent bloodstream infection with encapsulated bacteria or invasive meningococcal or gonococcal disease should be screened for complement deficiency by assaying for total hemolytic complement (CH_{50}) activity. If CH_{50} is normal, alternate pathway function should be assessed with an alternative complement pathway (AH_{50}) assay. If results of either assay are abnormal, specific component concentrations should be determined. Patients with late complement deficiency should be immunized with a quadrivalent conjugate meningococcal vaccine. Pneumococcal vaccination is also indicated for patients with complement deficiencies (in particular, C1, C2, C3, and C4 deficiencies) (see MKSAP 17 General Internal Medicine).

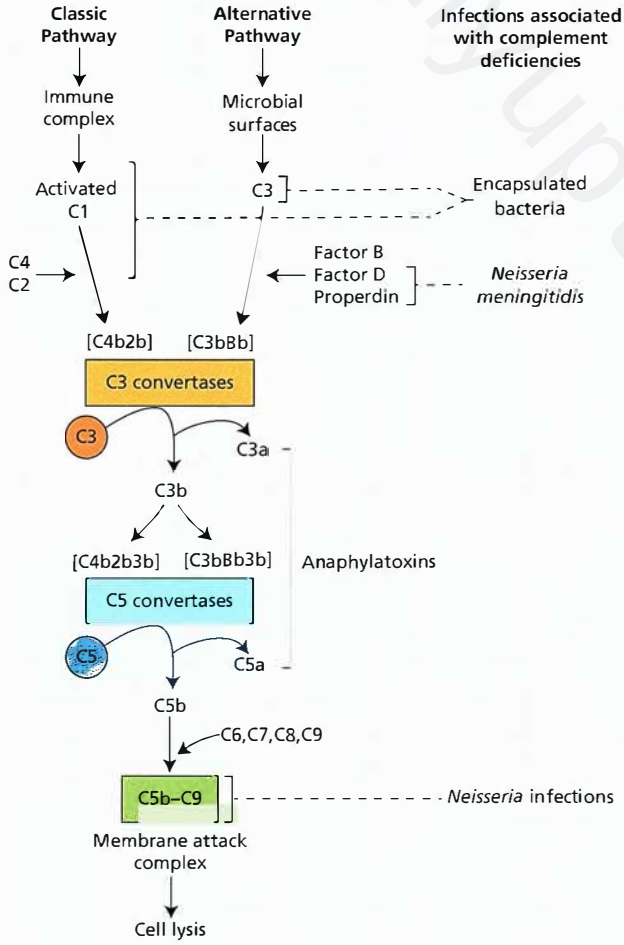

FIGURE 17. The complement reaction sequence and infections associated with deficiency states.

Redrawn with permission from Nairn R. Immunology. In: Brooks GF, Butel JS, Morse SA, eds. Jawetz, Melnick, and Adelberg's Medical Microbiology. 23rd ed. New York: Lange Medical Books/McGraw Hill; 2004.

KEY POINT

- Patients with recurrent bloodstream infection with encapsulated bacteria or invasive meningococcal or gonococcal disease should be screened for complement deficiency by assaying for total hemolytic complement (CH_{50}) activity.

Bioterrorism

Introduction

Bioterrorism is the intentional release of pathogens or toxins for the purpose of harming or killing civilians. Agents that could potentially be used in bioterrorist events have been prioritized into three groups (**Table 27**). Because they have the highest risk for use, group A agents are discussed here.

Epidemiologic characteristics that distinguish a bioterrorism attack from a naturally occurring infection include sudden onset; large number of cases; increased severity or uncommon clinical presentation; and unusual geographic, temporal, or demographic clustering of cases.

Anthrax

Anthrax is caused by *Bacillus anthracis*, a gram-positive, aerobic organism. It is ubiquitous in soil and causes human

TABLE 27. Potential Agents of Bioterrorism

Class A[a]	Class B[b]	Class C[c]
Anthrax	Q fever	Emerging infectious diseases
Botulism	Brucellosis	Nipah virus
Plague	Glanders	Hantavirus
Smallpox	Melioidosis	
Tularemia	Viral encephalitis	
Viral hemorrhagic fever	Typhus fever	
	Ricin toxin	
	Staphylococcal enterotoxin B	
	Psittacosis	
	Foodborne illness	
	Waterborne illness	

[a]Greatest potential, easy dissemination or person-to-person spread, high mortality, and profound public health implications.

[b]Less easily spread, fewer illnesses and deaths, fewer public health preparation measures.

[c]Future ability to engineer for mass dissemination and significant mortality.

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infection by spore exposure (**Figure 18A** and **18B**). Spores may be acquired by cutaneous contact, resulting in a distinctive black eschar (**Figure 18C**); ingestion; or inhalation (most likely to be used for bioterrorism). Spores are easily dispersed by aerosolization and can be sent by mail. Even a single case of inhalational anthrax should raise the suspicion of bioterrorism.

Patients with inhalational anthrax present with low-grade fever, malaise, myalgia, and headache accompanied by cough, dyspnea, and chest pain. Chest radiograph showing mediastinal widening (**Figure 18D**) from hemorrhagic lymphadenitis is characteristic. Diagnosis is confirmed by culture or polymerase chain reaction (PCR) of blood, tissues, or fluid samples. Initial treatment is outlined in **Table 28**. Ciprofloxacin, levofloxacin, moxifloxacin, or doxycycline should be provided as soon as possible following any actual or suspected case of anthrax that raises concern for a bioterrorism attack. Raxibacumab, a monoclonal antibody that neutralizes *B. anthracis* toxin, is approved for the treatment and prevention of inhalational anthrax. Uncomplicated cutaneous anthrax is defined as the absence of systemic symptoms and involvement of the head or neck in the absence of extensive swelling. A non-FDA-licensed, cell-free anthrax vaccine is available for postexposure immunization.

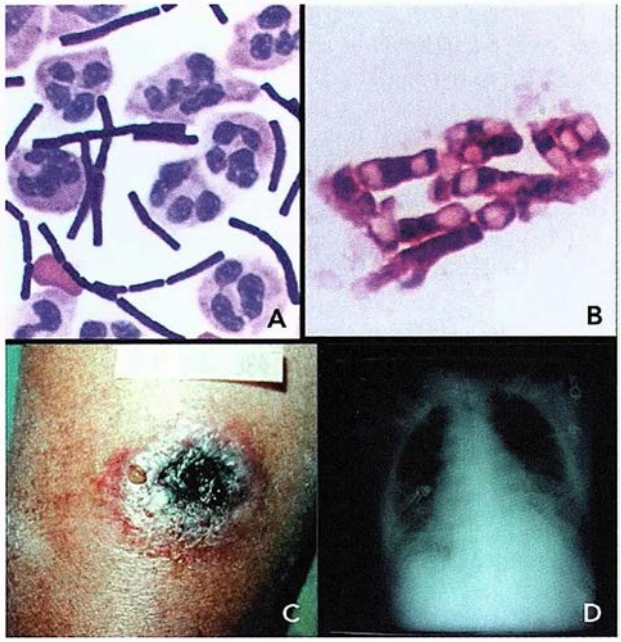

FIGURE 18. (*A*) "Box-car"-shaped, gram-positive *Bacillus anthracis* bacilli in the cerebrospinal fluid of the index case of inhalational anthrax resulting from bioterrorism in the United States. (*B*) Terminal and subterminal spores of *B. anthracis*. (*C*) Black eschar lesion of cutaneous anthrax. (*D*) Chest radiograph of a patient with anthrax showing a widened mediastinum due to hemorrhagic lymphadenopathy.

TABLE 28. Class A Bioterrorism Agents

Disease - Agent	Incubation Period	Clinical Features	Treatment	Prophylaxis
Anthrax - *Bacillus anthracis*	1-60 days	Inhalational: febrile respiratory distress Cutaneous: necrotic eschar Gastrointestinal: distention, peritonitis	Ciprofloxacin, levofloxacin, moxifloxacin, or doxycycline plus one or two additional agents[a] for 60 days	Ciprofloxacin, levofloxacin, moxifloxacin, or doxycycline
Smallpox virus - variola virus	7-17 days	Fever followed by pustular cutaneous rash	Supportive care	Vaccine if exposure occurred in the previous 7 days
Plague - *Yersinia pestis*	1-6 days	Fulminant pneumonia and sepsis	Streptomycin or gentamicin for 7 to 10 days Alternatives: doxycycline or levofloxacin if aminoglycosides contraindicated	Doxycycline or levofloxacin for 7 days
Botulism - *Clostridium botulinum*	2 hours to 8 days	Cranial nerve palsies and descending flaccid paralysis	Antitoxin and supportive care	Antibotulinum antitoxin (equine serum heptavalent botulism toxin)
Tularemia - *Francisella tularensis*	3-5 days	Fever, respiratory distress, and sepsis	Streptomycin or gentamicin (severe disease) for 7 to 14 days Doxycycline or ciprofloxacin (nonsevere disease) for 14 days	Doxycycline or ciprofloxacin
Viral hemorrhagic fevers - Ebola and Marburg viruses	Variable	Hemorrhage and multiorgan failure	Supportive care	None available

[a]Penicillin, ampicillin, imipenem, meropenem, clindamycin, linezolid, rifampin, vancomycin, or clarithromycin.

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KEY POINTS

- Even a single case of inhalational anthrax should raise the suspicion of deliberate bioterrorism-related spread.
- Patients with inhalational anthrax report symptoms consisting of low-grade fever, malaise, myalgia, and headache accompanied by cough, dyspnea, and chest pain.
- Postexposure prophylaxis with ciprofloxacin or doxycycline should be provided to appropriate persons as soon as possible following an actual or suspected case of anthrax that raises concern for a bioterrorism attack.

Smallpox (Variola)

Because smallpox was declared eradicated worldwide in 1979-1980, even a single case of suspected or proven disease justifies concern for bioterrorism. Infection is acquired by inhalation; deliberate aerosolization into a largely nonimmunized population could potentially result in a disastrous epidemic.

Patients with severe illness develop high fever, headache, vomiting, and backache. The rash first appears on the buccal and pharyngeal mucosa followed by cutaneous spread to the hands and face and then the arms, legs, and feet. The skin lesions evolve synchronously (same stage or maturation on any one area of the body) from macules to papules to vesicles to pustules and eventually become crusted (**Figure 19**). Patients remain contagious until all scabs and crusts are shed.

Treatment of smallpox is supportive. The nucleotide analogue cidofovir possesses good in vitro activity and may offer some therapeutic benefit. Postexposure vaccination with vaccinia, targeting close contacts of patients with smallpox who will be at greatest risk for contracting the disease ("ring vaccination"), offers some protection from the infection and is best if provided within 3 days after exposure.



FIGURE 19. Diffuse synchronous skin lesions of smallpox.

KEY POINTS

- Because smallpox was declared eradicated worldwide, even a single case of suspected or proven disease would justify concern for bioterrorism.
- Patients with smallpox develop high fever, headache, and vomiting accompanied by backache, with a rash first appearing on the buccal and pharyngeal mucosa followed by cutaneous spread to the hands and face and then the arms, legs, and feet, which evolve synchronously from macules to papules to vesicles to pustules and eventually become crusted.

Plague

Infection with *Yersinia pestis* most often occurs by the bite of an infected flea but may also arise from inhalation of an intentional bioterrorism-related aerosol release of pathogen. Pneumonic plague most often arises through hematogenous spread from a bubo (an infected, swollen lymph node) but may be primary from direct inhalation. Patients present with sudden high fever, pleuritic chest discomfort, a productive cough, and hemoptysis. The chest radiograph is nonspecific. Sputum Gram stain (and possibly blood smear) may identify gram-negative bacilli demonstrating the classic bipolar staining or "safety pin" shape.

Pneumonic plague is universally and rapidly fatal unless prompt treatment is provided (see Table 28). Asymptomatic persons known to have been exposed to aerosolized *Y. pestis* or those known to have had close contact with an infected patient should be given postexposure prophylaxis (see Table 28).

KEY POINT

- Pneumonic plague presents with sudden high fever, pleuritic chest discomfort, a productive cough, and hemoptysis.

Botulism

Clostridium botulinum produces botulinum toxin, the most lethal biologic substance known. Inhalational botulism through the deliberate release of botulinum toxin or toxin ingestion following deliberate contamination of food would be most likely in a bioterrorism attack. The toxin blocks acetylcholine-mediated neurotransmission. Patients present with symmetric, descending flaccid paralysis with prominent bulbar signs (the "4 Ds": diplopia, dysarthria, dysphonia, and dysphagia), absence of fever, and normal mental status. Paralysis may progress to involve the respiratory muscles, necessitating ventilator-assisted support.

Confirmation of disease depends on identifying botulinum toxin from samples of blood, stool, and gastric contents, as well as from suspected foods. Treatment includes supportive care and early administration of antitoxin; antitoxin will not reverse existing paralysis.

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KEY POINT

- Symptoms of botulism usually occur within 24 to 72 hours of toxin exposure and consist of a classic triad of symmetric, descending flaccid paralysis with prominent bulbar signs, absence of fever, and normal mental status.

Tularemia

Francisella tularensis is mainly a zoonotic disease; it is highly infectious and can cause significant illness through low inocula inhalation. Disease is heralded by the abrupt onset of fever, chills, myalgia, and anorexia.

Pneumonic tularemia is characterized by a nonproductive cough, dyspnea, and substernal or pleuritic chest pain. Severe respiratory failure may ensue. Chest radiographs reveal infiltrates, hilar lymphadenopathy, and pleural effusion.

Cultures of blood, sputum, pleural fluid, and tissue are frequently negative. PCR assays and direct fluorescent and immunohistochemical stains of clinical specimens assist in rapid diagnosis.

Treatment is outlined in Table 28. Mild or moderate infection can be treated with oral agents, which are also used for postexposure prophylaxis. Overall mortality is 1% with adequate treatment, but may be as high as 30% in untreated patients with pneumonic or typhoidal tularemia. H

KEY POINTS

- *Francisella tularensis* disease onset is heralded by abrupt occurrence of fever, chills, myalgia, and anorexia followed by respiratory symptoms.
- Polymerase chain reaction assays and direct fluorescent and immunohistochemical stains applied directly to various clinical specimens have proven successful in making a rapid tularemia diagnosis.

Viral Hemorrhagic Fever

Viral hemorrhagic fevers (VHFs) are caused by zoonotic RNA viruses (see Table 28). Characteristics such as high infectivity, virulence after low-dose exposure, capacity for causing significant morbidity and mortality, and limited prophylactic and therapeutic options render them likely candidates for use as biologic weapons.

Outside of a known epidemiologic exposure or travel to an endemic area, the occurrence or clinical suspicion of even one case of VHF should raise concern for bioterrorism, and simultaneous presentation of multiple patients should be expected.

A febrile prodrome, accompanied by myalgia and prostration occurs. Early signs of infection include conjunctival injection, petechial hemorrhages, easy bruising, flushing, and mild hypotension. As the disease advances, patients experience shock and generalized bleeding from the mucous membranes, skin, and gastrointestinal tract. Ultimately, multiorgan failure ensues.

Diagnostic confirmation requires RNA detection by reverse transcription PCR, the presence of viral protein antigens, development of IgM antibodies, or isolation of the virus. Treatment is primarily supportive. H

KEY POINT

- A high febrile prodrome universally occurs with viral hemorrhagic fever, accompanied by varying degrees of myalgia and prostration, with early signs of infection including conjunctival injection, petechial hemorrhages, easy bruising, flushing, and mild hypotension.

Travel Medicine

Introduction

The risk for specific travel-associated infections varies by destination; specialized travel clinics provide individualized advice tailored to itinerary and planned activities. Recommended immunizations for travel are listed in **Table 29**. Trip-specific

TABLE 29. Immunizations for Travel[a]

Recommended According to Destination, Itinerary, and Purpose of Travel
Hepatitis A[b]: 1 month before travel, booster at 6-12 months
Hepatitis B[b]: 0, 1 month, 6 months; accelerated schedule: 0, 1 week, 3 weeks, and 12 months (combination vaccine with hepatitis A available)
Typhoid[c]: Live-attenuated oral vaccine (Ty21a); 0, 2 days, 4 days, 6 days; capsular Vi polysaccharide intramuscular vaccine; 1 dose (preferred for immunocompromised persons)
Cholera: Killed, whole-cell-B subunit; 0, 1 week (not available in the United States)
Rabies: Inactivated; 0, 7 days, 21-28 days
Japanese encephalitis: Inactivated; 0, 28 days
Tick-borne encephalitis: Inactivated; 0, 1-3 months, 9-12 months (not available in the United States)
Required for Certain Destinations
Yellow fever: Live attenuated; 1 dose
Meningococcal: Quadrivalent conjugate (MenACWY), or polysaccharide (MPSV4); 1 dose; travel to Saudi Arabia during the Hajj

[a]All patients being evaluated for travel should receive or be up to date with all scheduled immunizations, including influenza, pneumococcal, tetanus-diphtheria-pertussis, polio, varicella, and zoster vaccines. See MKSAP 17 General Internal Medicine for routine immunization recommendations.

[b]If not received as part of routine scheduled immunizations. If the vaccine series was completed as part of scheduled immunization, repeat immunization is not required.

[c]Oral vaccine should not be administered within 24 hours of the antimalarial drug mefloquine because of the potential to decrease the vaccine's immunogenicity; patients must not take any antibiotic for at least 72 hours before receiving the vaccine.

Data from Centers for Disease Control and Prevention. CDC Health Information for International Travel 2014. New York: Oxford University Press; 2014. Available online at http://wwwnc.cdc.gov/travel/page/yellowbook-home-2014. Accessed December 2014.

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information is also available from the Centers for Disease Control and Prevention (CDC) Travel Health website (http://wwwnc.cdc.gov/travel/). A consultation should be scheduled at least 1 month before departure to assess the traveler's risk based on underlying medical conditions, travel destination, and planned activities and to provide appropriate immunizations.

The most significant and potentially severe travel-associated infections are listed in **Table 30**, with several key infections discussed in the following sections.

Malaria

The *Anopheles* mosquito transmits malaria. Transmission is minimized by limiting outdoor exposure between dusk and dawn, using bed nets and insect repellents containing 30% to 50% *N,N*-diethyl-3-methylbenzamide (DEET), and adhering to chemoprophylaxis. Despite these measures, malaria remains a common cause of febrile illness, particularly in travelers returning from sub-Saharan Africa and large parts of Asia.

The incubation period is 12 to 35 days. Patients commonly present with fever (characterized by paroxysms occurring in 48- or 72-hour cycles), headache, myalgia, nausea, vomiting, abdominal pain, and diarrhea. Severe disease most often results from *Plasmodium falciparum* infection. Hyperparasitemia (5%-10% parasitized erythrocytes) results in sequestration in small blood vessels, causing infarcts, capillary leakage, and organ dysfunction. Complications include alterations in mentation, seizures, hepatic failure, disseminated

TABLE 30. Travel-Associated Infections

Condition	Clinical Clues
Febrile illnesses	
Malaria	Paroxysmal fever, intraerythrocytic parasites, thrombocytopenia
Dengue fever	"Saddleback" (biphasic) fever pattern, frontal headache, lumbosacral pain, extensor surface petechiae
Typhoid fever	Prolonged fever, diarrhea or constipation, "rose spot" rash (faint salmon-colored macules on the abdomen and trunk)
Rickettsial infection	Tick or flea exposure, maculopapular or petechial rash, eschar, lymphadenopathy
Coxiella infection (Q fever)	Animal contact, atypical pneumonia, elevated aminotransferases
Yellow fever	Abrupt fever and headache, relative bradycardia, jaundice
Viral hepatitis	Fatigue and anorexia, low-grade fever, hepatomegaly, dark urine, clay-colored stools
Mononucleosis syndrome (cytomegalovirus and Epstein-Barr virus)	Sore throat, fever, lymphadenopathy, splenomegaly, atypical lymphocytes
Brucellosis	Zoonotic exposure, undulant fever, arthralgia, hepatosplenomegaly
Leptospirosis	Conjunctival suffusion (conjunctival erythema without inflammatory exudates), calf and lumbar spine muscle tenderness, aseptic meningitis, jaundice, kidney failure
Chikungunya fever	Fever, rash, and small joint polyarthritis
Histoplasmosis	Nonproductive cough, chest pain, fever
Legionellosis	Pneumonia, diarrhea, fever, elevated aminotransferases, hyponatremia
Novel coronaviruses (severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS-CoV])	Flu-like syndrome prodrome, diarrhea, dry cough with progressive dyspnea, lymphopenia, thrombocytopenia, elevated lactate dehydrogenase
Japanese encephalitis	High fever, altered consciousness, cranial nerve palsies
Hemorrhagic fever viruses (Ebola, Marburg, and Lassa)	Fever, malaise, myalgia, vomiting, diarrhea, coagulation disorders and bleeding
Rabies	Paresthesias or pain at wound site, fever, nausea and vomiting, hydrophobia, delirium, agitation
Travelers' diarrhea	
Bacterial agents: *Escherichia coli, Campylobacter* species, *Salmonella* species, *Vibrio* species, *Shigella* species	Abrupt onset, crampy diarrhea, blood in stools
Viral agents: rotavirus, norovirus	Closed setting (such as cruise ship or classroom) acquisition, vomiting, diarrhea, short duration
Protozoa: *Cryptosporidium* species, microsporidia, *Giardia* species, *Entamoeba histolytica,* and *Isospora* species	Gradual onset, progressive and prolonged diarrhea, foul-smelling and greasy stools, mucus or visible blood in stools

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CONT. intravascular coagulation, brisk intravascular hemolysis, metabolic acidosis, kidney insufficiency and hemoglobinuria, and hypoglycemia. Patients may develop anemia and splenomegaly and frequently have elevated aminotransferases and thrombocytopenia. Various *Plasmodium* species infections are summarized in **Table 31**.

Diagnosis relies primarily on identifying parasitized erythrocytes on a peripheral blood smear. Morphologic features determine the malarial species. Rapid diagnostic tests capable of detecting malaria antigens are available. Tests differ in their ability to detect *P. falciparum* or other *Plasmodium* species and provide only qualitative information. Polymerase chain reaction (PCR) and other molecular tests for malaria detection are increasingly available for clinical use.

Accurate identification of *P. falciparum* and *Plasmodium knowlesi* is critical because of the risk for severe and potentially lethal infection. *P. falciparum* should be suspected if the patient travelled to Africa; symptoms begin soon after return from an endemic area, and the peripheral blood smear shows a high level of parasitemia with typical morphologic features (thin, delicate rings on the inner surface of erythrocytes, banana-shaped gametocytes). *P. knowlesi* is a more recently recognized human pathogen; infection may be severe because of high levels of parasitemia. Examination of the peripheral blood smear reveals all stages of the parasite; the findings may be difficult to distinguish from those for *Plasmodium malariae*, a milder form of malaria. The epidemiologic history is helpful because *P. knowlesi* is not encountered in Africa.

Recommendations for chemoprophylaxis depend on the travel destination and are outlined in **Table 32**. Detailed information about malaria prophylaxis and treatment is provided in the CDC's Yellow Book (http://wwwnc.cdc.gov/travel/page/yellowbook-home).

KEY POINTS

- The most common symptoms of malaria are fever, headache, myalgia, nausea, vomiting, abdominal pain, and diarrhea. *(Continued)*

KEY POINTS *(continued)*

- *Plasmodium falciparum* malaria should be suspected if the patient travelled to Africa and the peripheral blood smear shows a high level of parasitemia with typical morphologic features.

Typhoid Fever

Typhoid fever is caused by *Salmonella enterica* serotype Typhi. Most cases occur from consuming water or food contaminated by human feces. Travelers to South and East Asia are at especially increased risk for infection. Nontyphoidal *Salmonella* infection is discussed elsewhere (see Infectious Gastrointestinal Syndromes).

The incubation period is 8 to 14 days. Patients present with gradual onset of fever, headache, arthralgia, pharyngitis, anorexia, and abdominal pain and tenderness. Diarrhea may occur early and resolve spontaneously but can become severe late in disease. However, numerous patients have constipation at diagnosis. Without treatment, temperature increases progressively and may remain elevated (up to 40 °C [104 °F]) daily for 4 to 8 weeks ("enteric fever"). Relative bradycardia and prostration may occur. In at least 20% of patients, discrete, pink, blanching lesions (rose spots) appear in crops on the chest and abdomen. Hepatosplenomegaly, leukopenia, anemia, thrombocytopenia, and liver chemistry abnormalities are common and pulmonary infiltrates may be present. Occasionally, secondary bacteremia leads to extraintestinal infection. Serious complications, including intestinal hemorrhage or perforation, may occur 2 to 3 weeks after infection develops. Invasion of the gallbladder by typhoid bacilli may result in a long-term carrier state. Patients with gallstones and chronic biliary disease are at greatest risk.

Diagnosis is made by isolating the organism from blood, stool, urine, or bone marrow. Serologic assays that detect specific *S. enterica* serotype Typhi antibodies have good sensitivity and specificity.

Preferred antibiotics include ceftriaxone, fluoroquinolones, and azithromycin; in consideration of increasing antibiotic resistance, in vitro susceptibility testing should always be

TABLE 31. Characteristics of *Plasmodium* Species

Characteristics	*P. vivax*	*P. ovale*	*P. malariae*	*P. falciparum*	*P. knowlesi*
Incubation period	10-30 days	10-20 days	15-35 days	8-25 days	Indeterminate
Geographic distribution	Tropical and temperate zones	West Africa and Southeast Asia	Tropical zones	Tropical and temperate zones	South and Southeast Asia
Parasitemia	Low	Low	Very low	High	Can be high
Risk for disease severity	Low risk	Low risk	Very low risk	High risk	High risk
Disease relapse risk	Yes	Yes	Yes	No	No
Chloroquine resistance	Yes	No	Rare	Yes	No

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TABLE 32. Antimalarial Chemoprophylaxis Regimens

Drug	Dose	Time of Prophylaxis Initiation (before Travel)	Time of Prophylaxis Discontinuation (after Returning)
For endemic areas with chloroquine-resistant *Plasmodium falciparum*			
Atovaquone/proguanil[a]	250 mg/100 mg once daily	1-2 days	7 days
Mefloquine	250 mg once weekly	≥2 weeks	4 weeks
Doxycycline[a]	100 mg once daily	1-2 days	4 weeks
For endemic areas with chloroquine-sensitive *P. falciparum*			
Chloroquine	500 mg once weekly	1-2 weeks	4 weeks
Hydroxychloroquine	400 mg once weekly	1-2 weeks	4 weeks
Atovaquone/proguanil	250/100 mg once daily	1-2 days	7 days
Mefloquine	250 mg once weekly	≥2 weeks	4 weeks
Doxycycline	100 mg once daily	1-2 days	4 weeks
Primaquine[b]	26.3 mg once daily	1-2 days	1 week
For endemic areas with *Plasmodium vivax*			
Primaquine[b]	52.6 mg once daily	1-2 days	7 days
Chloroquine	500 mg once weekly	1-2 days	4 weeks
Hydroxychloroquine	400 mg once weekly	1-2 weeks	4 weeks
Atovaquone/proguanil	250/100 mg once daily	1-2 days	7 days
Mefloquine	250 mg once weekly	≥2 weeks	4 weeks
Doxycycline	100 mg once daily	1-2 days	4 weeks
Prophylaxis for relapse due to *Plasmodium vivax* or *Plasmodium ovale*			
Primaquine[b]	52.6 mg once daily	As soon as possible	14 days

[a]Should not be used in pregnant women.

[b]Contraindicated in persons with severe forms of glucose-6-phosphate dehydrogenase deficiency or methemoglobin reductase deficiency; should not be administered to pregnant women.

NOTE: Chloroquine is safe during pregnancy; however, pregnant women are advised against entering malarial areas because they experience more severe disease that often leads to maternal and perinatal adverse outcomes. If travel is essential to areas where chloroquine-resistant malaria is present, mefloquine may be safely prescribed.

Recommendations from Centers for Disease Control and Prevention. CDC Health Information for International Travel 2016. http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria. Updated July 10, 2015. Accessed July 17, 2015.

CONT. performed. Glucocorticoids may be added to treat severe toxicity, which can manifest as shock or encephalopathy. Vaccination is outlined in Table 29. Vaccination provides protection to 55% to 75% of recipients.

KEY POINTS

- Typhoid fever has an incubation period of 8 to 14 days and presents with fever, headache, arthralgia, pharyngitis, anorexia, and abdominal pain and tenderness.
- Preferred antibiotics for typhoid fever include ceftriaxone, fluoroquinolones, and azithromycin.

Travelers' Diarrhea

Diarrhea secondary to infection is estimated to occur in 40% to 60% of travelers to developing areas of the world. It is defined as three or more unformed stools per day with at least one other clinical sign (fever, cramps, nausea, vomiting, or blood in the stools); most episodes develop within 2 weeks of travel. It is usually self-limited; however, life-threatening volume depletion or severe colitis with systemic manifestations can occur. A few travelers develop chronic diarrhea or a postinfective irritable bowel syndrome. *Escherichia coli* is the most common causative agent. Other pathogens are outlined in Table 30. Persons who take gastric acid–reducing medications or have abnormal gastrointestinal motility or altered anatomy are at increased risk.

Travelers should be advised to avoid consuming tap water (through drinks and ice made with it or brushing teeth with it), undercooked meats and poultry, unpasteurized dairy products, and fruits that are not peeled just before eating. Wine, beer, and carbonated drinks are considered safe. Water can be purified by boiling for 3 minutes or by adding 2 drops of sodium hypochlorite (bleach) or 5 drops of tincture of iodine per 1.89 L of water. Antimicrobial prophylaxis for traveler's diarrhea is effective, but it is generally not recommended

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because of the potential for adverse effects. Prophylaxis should be considered in persons with coexisting inflammatory bowel disease, immunocompromised states (including advanced HIV), and comorbidities that would be adversely affected by significant dehydration. Antimicrobial agents appropriate for prophylaxis are listed in **Table 33**. Bismuth subsalicylate can be used to prevent diarrhea, but the doses required are inconvenient and can lead to salicylate toxicity.

Fluid replacement is the mainstay of treatment in patients who develop travelers' diarrhea, and most cases will resolve within 3 to 5 days with this therapy alone. Antimicrobials reduce the duration of diarrhea by 1 to 2 days but are recommended only in severe disease, generally defined as more than four unformed stools daily, fever, or blood or pus in the stool. Treatment may also be considered in patients with milder disease if symptoms significantly disrupt a vacation or business trip. Appropriate antimicrobial agents for use in treating traveler's diarrhea are listed in Table 33. Prior to travel, travelers can be given a prescription for antibiotics that can be self-administered according to specific guidelines given to the patient if severe diarrhea develops. Self-treatment with a fluoroquinolone, azithromycin (preferred in South and Southeast Asia), or rifaximin is usually sufficient in most cases. Antimotility drugs, such as loperamide and diphenoxylate, should be given only in conjunction with antimicrobial therapy but should not be used in cases of dysentery or bloody diarrhea because of increased risk for colitis and colonic perforation.

TABLE 33. Oral Treatment and Prophylaxis of Travelers' Diarrhea

Agent	Regimen
Treatment	
Bismuth subsalicylate	1 oz every 30 min for 8 doses
Norfloxacin	400 mg twice daily for 3 days
Ciprofloxacin	500 mg twice daily for 3 days
Ofloxacin	200 mg twice daily for 3 days
Levofloxacin	500 mg once daily for 3 days
Azithromycin	1000 mg, single dose
Rifaximin	200 mg three times daily for 3 days
Prophylaxis	
Bismuth subsalicylate	Two tablets chewed 4 times daily
Norfloxacin	400 mg daily[a]
Ciprofloxacin	500 mg daily[a]
Rifaximin	200 mg once or twice daily[a]

[a]Chemoprophylaxis is recommended for no more than 2 to 3 weeks (the duration studied in trials and a period short enough to minimize the risk for antimicrobial-associated adverse effects).

Adapted with permission from Hill DR, Ericsson CD, Pearson RD, et al; Infectious Diseases Society of America. The practice of travel medicine: guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006 Dec 15;43(12):1499-539. [PMID: 17109284] Copyright 2006 Oxford University Press.

KEY POINTS

- Antimicrobial prophylaxis for traveler's diarrhea is effective, but it is generally not recommended because of the potential for adverse effects; prophylaxis should be considered in persons with coexisting inflammatory bowel disease, immunocompromised states (including advanced HIV), and comorbidities that would be adversely affected by significant dehydration. HVC
- Fluid replacement is the mainstay of treatment; antimicrobials reduce the duration of diarrhea by 1 to 2 days but are recommended only in severe disease. HVC

Dengue Fever

Dengue fever, transmitted by the *Aedes aegypti* mosquito (a daytime feeder that prefers urban environments) is the most prevalent arthropod-borne viral infection in the world. Endemic areas are Southeast Asia, the South Pacific, South and Central America, and the Caribbean.

The incubation period is 4 to 7 days. Patients may be asymptomatic or present with acute febrile illness associated with frontal headache, retro-orbital pain, myalgia, and arthralgia, with or without minor spontaneous bleeding (purpura, melena, conjunctival injection). Gastrointestinal or respiratory symptoms may predominate. Severe lumbosacral pain is characteristic ("breakbone fever"). As the fever abates, a macular or scarlatiniform rash, which spares the palms and soles and evolves into areas of petechiae on extensor surfaces, may develop. Fever resolves after 5 to 7 days; however, a small percentage of patients experience a second febrile period ("saddleback" pattern). A prolonged period of severe fatigue may follow. In patients with severe infection, life-threatening hemorrhage (dengue hemorrhagic fever) or shock may develop, along with liver failure, encephalopathy, and myocardial damage. This syndrome appears to be related to previous dengue viral infection, often of a different serotype. Common laboratory abnormalities include leukopenia, thrombocytopenia, and elevated serum aminotransferase levels. H

The diagnosis is based on clinical suspicion in a patient who traveled to an endemic area and presents with fever and other typical signs, symptoms, and laboratory abnormalities. Diagnosis is confirmed by serologic testing (IgM and IgG) or reverse transcriptase PCR. Therapy is supportive. A potential tetravalent dengue vaccine is undergoing trial. H

KEY POINT

- Dengue fever may cause acute febrile illness associated with frontal headache, retro-orbital pain, myalgia, and arthralgia, with or without minor spontaneous bleeding manifestations.

Hepatitis Virus Infection

Hepatitis A virus (HAV) is the most common cause of viral liver disease in the world. Infection often occurs though ingestion

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of contaminated food or water. Travel to Central and South America, Mexico, South Asia, and Africa poses the greatest risk for infection. Vaccination is recommended for persons traveling to developing countries and persons not already immune (see Table 29). Serum immune globulin is indicated for persons aged 12 months or younger and for those who decline vaccination or are allergic to its components. It has also been recommended for immunocompromised persons (who are less responsive to hepatitis A vaccine), patients with chronic liver disease, and those planning to depart within 2 weeks of their vaccination.

The risk for travel-associated acquisition of hepatitis B virus is low. Previously unvaccinated persons who have insufficient time before travel to receive the standard three-dose/6-month vaccination series can complete an accelerated vaccination schedule (0, 7, and 21 to 30 days); these persons require a booster dose at 12 months to ensure long-term protection. A combined hepatitis A/B vaccine is also available for this rapid three-dose schedule.

No vaccine prevents hepatitis C virus infection, and prophylactic immune globulin offers no protection. Avoidance of exposure to unscreened blood and nonsterile medical or injection practices is paramount in infection prevention. Tattooing and unprotected sexual practices may also pose an infection risk.

KEY POINTS

- Hepatitis A vaccine is available for travelers to endemic areas and should be administered 1 month before travel, with a second booster dose to be given 6 to 12 months later.
- An accelerated vaccination schedule for hepatitis B is available for persons who have insufficient time before planned travel to receive the standard 6-month dosing.

Rickettsial Infection

Rickettsial infection is transmitted by small vectors (fleas, lice, mites, and ticks). Outbreaks have been associated with war and natural disasters and are promoted by suboptimal hygiene conditions and tick infestation; travel is now well recognized as a risk for infection. *Rickettsia typhi* causes endemic or murine typhus, is transmitted by fleas from a rat reservoir and is prevalent in tropical and subtropical areas. *Rickettsia prowazeki*, the cause of epidemic or louse-borne typhus, is transmitted by human body lice and has a worldwide distribution.

Clinical presentation includes fever, headache, and malaise, often accompanied by a maculopapular, vesicular, or petechial rash. Extensive vasculitic-appearing lesions may occur. Infection with *Rickettsia africae* (African tick typhus) is second only to malaria as the reason for fever in travelers to Africa, especially South Africa. Following the bite of an infected tick or mite, an eschar with regional lymphadenopathy develops at the site of inoculation with *R. africae*, *Rickettsia conorii*, and *Orientia tsutsugamushi*.

Diagnosis is confirmed by PCR, immunohistochemical analysis of tissue samples, or culture during the acute stage of illness before antibiotics are initiated. Empiric therapy is warranted, however, when clinical suspicion of disease is high because these diagnostic tools are not readily available. Serologic tests for convalescent antibodies against many of the common rickettsial pathogens can confirm the diagnosis. The treatment of choice for all rickettsial infections is doxycycline.

KEY POINT

- Rickettsial infection presents with fever, headache, and malaise, often accompanied by a maculopapular, vesicular, or petechial rash.

Brucellosis

Brucellosis occurs by ingestion of unpasteurized dairy products or undercooked meat, by direct contact with fluids from infected animals through skin wounds or mucous membranes, or by inhalation of contaminated aerosols. *Brucella* species are present in animal reservoirs worldwide.

The Mediterranean basin, Indian subcontinent, Arabian Peninsula, and parts of Central and South America, Mexico, Asia, and Africa are high-prevalence areas. After a variable incubation period, patients develop fever, myalgia, arthralgia, fatigue, headache, and night sweats. Depression is frequent. Focal infection may occur, most commonly osteoarticular involvement. Infection with *B. melitensis* and *B. suis* causes the most severe disease. Hepatosplenomegaly and lymphadenopathy may be apparent on physical examination. Disease relapse and chronic infection occur in few patients, most often from persistent foci of infection or inadequate antibiotic treatment.

Diagnosis relies on isolating the organism from cultures of blood, bone marrow, other body fluids, or tissue. The serum agglutination test is the most widely used serologic test available. An initial elevated titer of 1:160 or greater or demonstration of a fourfold increase from acute to convalescent titers is considered diagnostic. The treatment of choice is a combination of doxycycline, rifampin, and streptomycin (or gentamicin), often given for several weeks.

KEY POINT

- Patients with brucellosis develop fever, myalgia, arthralgia, fatigue, headache, and night sweats, often with depression.

Travel-Associated Fungal Diseases

The endemic fungi are generally limited to specific geographic areas (**Table 34**). Unlike most other travel-related infections, disease may not become clinically evident until months or even years after returning from travel. Histoplasmosis and coccidioidomycosis are the most frequently reported travel-related fungal infections (see Fungal Infections chapter for a full discussion of these diseases).

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TABLE 34. Common Travel-Associated Acquired Fungal Infections

Organism	Geographic Distribution
Coccidioides species	Southwest United States
	Mexico
	Central and South America
Histoplasma species	Mississippi and Ohio River Valleys
	Mexico
	Central America
Penicillium marneffei	Southeast Asia
	Southern China

Other Important Diseases

Yellow Fever

Yellow fever is a flavivirus transmitted by the *Aedes* mosquito. Countries in tropical South America and sub-Saharan Africa are the geographic areas with the highest endemicity. After a 3- to 5-day incubation period, most patients present with fever, headache, myalgias, and backache. Serious multisystem disease (jaundice, hemorrhage, and shock) may develop. Immunization (see Table 29) is indicated for travelers to at-risk areas and to specific countries requiring proof of vaccination before entry.

Rabies

Rabies is found worldwide, except in Antarctica. Although dogs are the major source of infection in developing countries, specific enzootic hosts may predominate in various geographic areas. Preexposure vaccination (see Table 29) is recommended for those traveling to any high-risk international destination with the intention of a prolonged stay. Short-term travelers who may be at risk include adventure travelers and cave explorers. When determined that the bite poses a risk for rabies, two doses of rabies vaccine should be given to persons who have previously completed a preexposure vaccine series. Unvaccinated persons require rabies immune globulin followed by rabies vaccination.

Leptospirosis

The zoonosis leptospirosis is endemic worldwide. Infection occurs by direct exposure to urine or tissues of infected animals or indirectly through contaminated water or soil. Rodents and other small mammals are the most significant sources of human disease. Bacteria may be introduced through cuts and abrasions of the skin, mucous membranes or conjunctivae, or inhalation of aerosolized droplets. Acute systemic illness is manifested by high fever, headache, severe myalgias (especially in the lumbar region and calf muscles), conjunctival injection, abdominal pain, diarrhea, pharyngitis, and occasionally a pretibial rash. A second immune phase of illness is heralded by the production of antibodies and may include jaundice, kidney disease, pneumonitis, cardiac arrhythmia, hemorrhage, and aseptic meningitis.

Diagnosis relies on clinical suspicion and confirmatory serologic assays. Doxycycline is effective in treating mild disease, whereas intravenous penicillin or ceftriaxone is recommended for moderate to severe cases. Travelers at increased risk for infection may be given weekly chemoprophylaxis with doxycycline.

Q Fever

Coxiella burnetii is the causative bacterial agent of Q fever, a zoonotic illness acquired through inhalation of aerosols contaminated by the infected placenta of cattle, sheep, and goats. Travel to Middle Eastern and African countries poses the greatest risk. Most infections manifest as a self-limited febrile illness, although some patients develop an atypical pneumonia with hepatitis. The diagnosis is often confirmed serologically, and doxycycline is the treatment of choice.

Ebola

Ebola is a Filovirus associated with the viral hemorrhagic fever syndrome. Human outbreaks have sporadically occurred in regions of central Africa since 1976; however, the largest epidemic is ongoing in West African countries, which increases the risk for travel-associated disease. Infection can spread through direct contact with bodily fluids of symptomatic patients or improper infection control practices. Disease is often severe and manifested by abrupt fever, headache, prostration, coagulopathy, and multiorgan failure. Ill travelers at risk for Ebola infection must be rapidly identified and isolated when they present for care. Treatment consists of supportive measures. Potential antiviral medications are in trials. Artificial, passive immunity using antibodies from recovered patients has met with some success, and vaccine trials are ongoing.

Infectious Gastrointestinal Syndromes

Diarrhea (the passage of three or more unformed stools per day) is a common reason for acute medical evaluation. Diarrhea can be subclassified as acute (symptoms <14 days), subacute (14-30 days), or chronic (>30 days), with the duration of symptoms guiding appropriate testing. Most bacterial and viral gastrointestinal infections cause an acute diarrheal syndrome. Chronic diarrhea is unlikely to be infectious, with the exception of parasitic syndromes. Most infectious diarrhea is self-limited and resolves without directed intervention. Otherwise healthy patients with mild illness who present with less than 72 hours of symptoms can often be treated supportively, with no additional diagnostic evaluation or antimicrobial treatment. More severe presentations, including fever, significant abdominal pain, or dysentery (visible blood or mucus in

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stool), suggest inflammatory diarrhea caused by an invasive pathogen. Antimotility agents, such as loperamide, are discouraged for the treatment of inflammatory diarrhea or *Clostridium difficile* colitis but may relieve symptoms for patients with noninfectious diarrhea.

Patients with acute diarrhea who are immunocompromised, require hospitalization, or have inflammatory diarrhea should have stool cultures performed. Routine stool cultures can identify the most common bacterial pathogens causing diarrhea (**Table 35**); however, when enterotoxigenic *Escherichia coli*

TABLE 35. Causative Agents, Clinical Presentation, and Treatment of Infectious Colitis

Agent	Clinical Findings	Diagnosis	Antimicrobial Treatment[a]
Bacterial			
Campylobacter	Fevers, chills, diarrhea (watery or bloody), crampy abdominal pain	Standard stool culture	Azithromycin or erythromycin × 3-5 days
Shigella	Dysentery (fevers, abdominal cramps, tenesmus, bloody/mucusy stools)	Routine stool culture	Fluoroquinolone × 3 days; azithromycin × 3 days
Salmonella	Fever, chills, diarrhea (watery or bloody), cramps, myalgia; bacteremia in 10%-25% of cases	Routine stool culture; blood cultures (with moderate to severe illness)	Mild: none Underlying disease or severe illness: fluoroquinolone plus parenteral third-generation cephalosporin
STEC including *Escherichia coli* O157:H7	Bloody stools in >80% of cases; fever often absent or low grade; may be associated with HUS	*E. coli* O157:H7: stool culture with specialized media followed by serologic testing Other STEC: stool culture with specialized media followed by Shiga toxin serologic testing or PCR	None
ETEC (travelers' diarrhea)	Nonbloody, watery stools; constitutional symptoms rare	None	Fluoroquinolone × 3 days, azithromycin × 1 dose, or rifaximin × 3 days
Yersinia	Fever, diarrhea, right lower quadrant pain (may mimic appendicitis)	Routine stool culture	Fluoroquinolone × 3 days; trimethoprim-sulfamethoxazole × 3 days
Vibrio	Bloody stools (>25% of cases), fever, vomiting (>50% of cases)	Stool culture with specialized media	Fluoroquinolone × 3 days; azithromycin × 3 days
Clostridium difficile	Diarrhea, fever, abdominal pain/cramping, colonic distention (including toxic megacolon in severe cases), leukocytosis, sepsis; gross blood uncommon	PCR or stool EIA for toxin	Mild: metronidazole Severe: oral vancomycin
Viral			
Norovirus	Watery, noninflammatory diarrhea; vomiting in >50% of cases; short incubation period and high attack rate; fever rare	None (PCR for outbreak investigations)	None
Parasitic			
Giardia	Watery diarrhea, abdominal cramping, vomiting, steatorrhea, flatulence, weight loss	Stool O & P microscopy or stool antigen	Metronidazole × 5-10 days or tinidazole
Cryptosporidium	Watery diarrhea	Modified acid-fast stain, stool antigen	Supportive care
Amebiasis	Dysentery	Stool O & P microscopy, stool antigen	Tinidazole or metronidazole
Cyclospora	Watery diarrhea, bloating, flatulence, weight loss	Modified acid-fast stain	Trimethoprim-sulfamethoxazole

EIA = enzyme immunoassay; ETEC = enterotoxigenic *Escherichia coli*; HUS = hemolytic uremic syndrome; O & P = ova and parasites; PCR = polymerase chain reaction; STEC = shiga toxin-producing *E. coli*.

[a]Empiric treatment with final choice of antimicrobial guided by in vitro susceptibility testing.

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(ETEC, including *E. coli* O157:H7) or *Vibrio* infection is suspected, the laboratory should be notified because these organisms require special media for growth. Even with testing restricted to this select population, a pathogen is identified in less than 5% of all stool cultures. Molecular tests using a multiplex panel to identify common bacterial, viral, and parasitic organisms on a single stool sample are increasingly available and may have improved sensitivity but are costly. Diagnostic testing for *Clostridium difficile* should be performed in this subgroup of patients, regardless of a history of recent antibiotic use. Blood cultures should be obtained in patients requiring hospitalization or when *Salmonella* gastroenteritis is suspected.

KEY POINTS

- Most infectious diarrhea is self-limited and resolves without directed intervention; otherwise healthy patients with mild illness who present with less than 72 hours of symptoms can often be treated supportively, with no additional diagnostic evaluation or antimicrobial treatment.
- Diagnostic testing, including stool bacterial cultures, is appropriate for patients who are immunocompromised, sick enough to require hospitalization or those with inflammatory diarrhea.

Campylobacter Infection

Campylobacter gastroenteritis is primarily a foodborne illness particularly associated with consumption of undercooked poultry products. Person-to-person transmission is rare. Symptoms are indistinguishable from other causes of invasive diarrhea (see Table 35). Immunocompromised patients are at increased risk for associated sepsis and extraintestinal infections. Routine stool culture is typically diagnostic, and blood cultures may be positive with extraintestinal disease.

Antibiotic treatment guided by in vitro susceptibility testing is recommended to hasten resolution of symptoms when *Campylobacter* is isolated in stools. Empiric therapy is controversial because antibiotics are contraindicated for other causes of dysentery, such as Shiga toxin–producing *E. coli* (STEC), but is indicated in patients who are immunocompromised or severely ill. Because of increasing resistance to fluoroquinolones, macrolides are the preferred empiric treatment if *Campylobacter* infection is suspected. Often, symptoms have spontaneously improved by the time culture results are obtained, so no therapy is needed.

Diarrhea may persist for a prolonged duration in the absence of ongoing bacterial infection, suggesting a postinfective irritable bowel syndrome. *Campylobacter* is one of several enteric pathogens associated with reactive arthritis in patients positive for HLA-B27 antigen. The most serious postinfective complication is Guillain-Barré syndrome, which is thought to be caused by production of an antibody directed against the bacteria that cross-reacts with host neuronal tissue, causing peripheral nerve demyelination. Although Guillain-Barré syndrome can be linked to previous *Campylobacter* infection in numerous patients, the risk for neurologic complications after this infection is less than 1%.

KEY POINT

- Antibiotic treatment guided by in vitro susceptibility testing is recommended to hasten resolution of symptoms when *Campylobacter* is isolated in stools; if indicated, macrolides are the preferred empiric antibiotics for symptomatic patients suspected of having *Campylobacter* gastroenteritis.

Shigella Infection

Shigellosis is caused by one of four species of *Shigella*, with disease severity varying depending on the infecting organism. The number of ingested bacteria necessary to cause infection is low (<100 organisms), and person-to-person transmission through fecal-oral spread is common. Outbreaks of shigellosis are most frequent in settings with close contact and poor hygiene or inability to use a toilet, such as day care centers or nursing homes. Other routes of infection include ingestion of contaminated food or water and sexual transmission among men who have sex with men. The clinical presentation is summarized in Table 35. Vomiting is occasionally present. Reactive arthritis may be seen in up to 3% of patients with *Shigella flexneri* infection, but not with other species. *Shigella dysenteriae* produces a Shiga toxin similar to that of STEC and is a rare cause of hemolytic uremic syndrome (HUS).

Stool cultures should be obtained in all patients with significant illness or dysentery at presentation. *Shigella* infection can be diagnosed by standard stool cultures or molecular assay; the latter may be more sensitive. Blood cultures should be obtained in patients with severe disease or sepsis syndromes. Antibiotics reduce the duration of gastrointestinal symptoms. Empiric therapy (see Table 35) should be considered for patients with a compatible epidemiologic history (such as day care workers) or severe symptoms. In most cases, infection is self-limited and resolves without treatment; however, because asymptomatic shedding may be prolonged after infection, antibiotics are recommended for all patients with positive stool cultures to reduce the risk for secondary transmission.

KEY POINT

- Empiric therapy for *Shigella* infection should be considered for patients with a compatible epidemiologic history or severe symptoms and is recommended for all patients with positive stool cultures to reduce the risk for secondary transmission.

Salmonella Infection

Salmonella causes typhoidal (serotypes Typhi or Paratyphi) or nontyphoidal (all other serotypes) infections. Nontyphoidal serotypes are the leading cause of foodborne illness in the

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United States, with a broad array of implicated sources, including eggs, raw meat, dairy products, peanut butter, and fresh fruits and vegetables. Zoonotic infections associated with reptile exposure account for less than 5% of infections. Clinical manifestations of *Salmonella* gastroenteritis are summarized in Table 35. Occult blood is common, but grossly bloody stools are infrequent and suggest infection with *Shigella* or STEC.

Bacteremia occurs in 1% to 4% of immunocompetent patients with gastrointestinal salmonellosis and is significantly more common in older adults or immunocompromised patients. Bacteremia is associated with endothelial infection in 10% to 25% of patients, including aortitis, arteritis, or mycotic aneurysm. Vascular complications are associated with preexisting atherosclerosis, placing older adults at especially high risk. *Salmonella* osteomyelitis is an unusual complication seen primarily in patients with sickle cell disease.

Treatment decisions must consider the severity of the infection and the risk for extraintestinal disease (**Table 36**). Antibiotic treatment of otherwise healthy patients with mild symptoms does not hasten recovery and may lead to prolonged asymptomatic shedding of bacteria. However, treatment of patients with severe disease, characterized by high fever, sepsis syndrome, or hemodynamic instability, is associated with shorter duration of symptoms and is presumed to decrease the risk for extraintestinal spread. Patients who have underlying health conditions or use medications that place them at increased risk for bacteremia or endovascular infection should also be treated to prevent these life-threatening complications (see Table 36).

Fluoroquinolones remain the most reliably effective class of antibiotics for empiric therapy, although increasing resistance has been reported. Other agents that often have activity include amoxicillin, trimethoprim-sulfamethoxazole, and azithromycin. Patients with severe illness requiring hospitalization should be treated with a fluoroquinolone and a third-generation cephalosporin, pending in vitro susceptibility testing. Endovascular infections typically require surgical removal of prosthetic material or infected valves and a 6-week course of antibiotic treatment.

KEY POINTS

- Antibiotic treatment of otherwise healthy patients with mild symptoms does not hasten recovery and may lead to prolonged asymptomatic shedding of *Salmonella* bacteria.
- Treatment of patients with severe salmonellosis, characterized by high fever, sepsis syndrome, or hemodynamic instability, is associated with shorter duration of symptoms and is presumed to decrease the risk for extraintestinal spread.

Escherichia coli Infection

E. coli is universally present in the healthy intestinal microbiota; however, particular pathotypes are associated with diarrheal illnesses. Two pathotypes, STEC and ETEC, are particularly significant. STEC (also called enterohemorrhagic *E. coli*) infection is a significant cause of dysentery; clinical findings are provided in Table 35. The prototypical STEC agent is *E. coli* O157:H7, which has been associated with numerous foodborne outbreaks of diarrhea and HUS. STEC causes inflammation through production of Shiga toxin but does not invade the colonic mucosa. *E. coli* O157:H7 requires specialized media for culture. Diagnostic testing depends on laboratory protocol. Some laboratories routinely plate all stool samples on media capable of detecting *E. coli* O157:H7; other laboratories restrict testing to

TABLE 36. Antibiotic Treatment Considerations for Salmonellosis

Host	Clinical Presentation	Antibiotic Treatment[a]	Comments
Healthy adults age ≤50 years	Mild to moderate gastrointestinal symptoms	None	No significant decrease in duration of symptoms, potential for prolonged shedding
	Severe gastrointestinal symptoms, sepsis syndrome	Fluoroquinolone plus parenteral third-generation cephalosporin	Treatment in severely ill patients associated with decreased duration of symptoms
Healthy adults age >50 years	Mild to severe gastroenteritis	Fluoroquinolone	Increased risk for bacteremia
Vascular grafts or prosthetic material (including prosthetic heart valves)	Mild to severe gastroenteritis	Fluoroquinolone	Increased risk for endovascular infection
Prosthetic joint	Mild to severe gastroenteritis	Fluoroquinolone	Increased risk for secondary infection with bacteremia
Immunocompromised hosts[b]	Mild to severe gastroenteritis	Fluoroquinolone	Increased risk for bacteremia or extraintestinal infection
Any	Bacteremia	Fluoroquinolone plus parenteral third-generation cephalosporin	Evaluation for endovascular infection if prosthetic material or sustained bacteremia

[a]Empiric treatment, with final choice of antibiotic guided by in vitro susceptibility testing.

[b]Includes patients with HIV/AIDS, recent chemotherapy, use of immunosuppressing medications (such as glucocorticoids or tumor necrosis factor-α inhibitors), or hemoglobinopathies (such as sickle cell disease).

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only grossly bloody stools or to clinician request. Considering this variability, the laboratory should be notified when STEC is a concern to ensure appropriate testing is performed. When *E. coli* is isolated, confirmatory testing for the ●157:H7 antigen is performed reflexively. Other strains of STEC, such as *E. coli* O104:H4, which caused a large outbreak in Europe, are increasingly recognized as causing dysentery, and additional testing for Shiga toxin production may be pursued in these cases. Molecular tests of stool using a multiplex panel capable of detecting numerous pathogens causing dysentery, including STEC organisms, are increasingly being used for rapid diagnosis. Administration of antibiotics and antimotility medications for STEC infection has been associated with increased risk for HUS. Therefore, decisions about treatment of dysentery with empiric antibiotics should be made with caution, weighing the probability of STEC versus other causes of invasive colitis.

ETEC is the most frequent cause of travelers' diarrhea but is also increasingly recognized as a cause of foodborne illness in developed countries. Laboratory testing for this organism is lacking outside of research settings, so determining the incidence of ETEC is difficult. ETEC causes disease through toxin production, resulting in a secretory diarrhea. Clinical manifestations are outlined in Table 35. Even without treatment, illness lasts less than 1 week. Preemptive treatment aimed at shortening the duration of symptoms is common when travelers to a developing region develop diarrhea. Recommended agents include fluoroquinolones, azithromycin, and rifaximin.

KEY POINT

- Administration of antibiotics and antimotility medications for Shiga toxin–producing *Escherichia coli* infection has been associated with increased risk for hemolytic uremic syndrome.

Yersinia Infection

Enterocolitis due to *Yersinia* infection is uncommon. Most cases are associated with *Yersinia enterocolitica*, and infection usually occurs through ingestion of contaminated food products, especially undercooked pork. *Yersinia* infection causes acute inflammatory enteritis and is indistinguishable from other causes of inflammatory diarrhea. However, grossly bloody stools are uncommon. *Yersinia* is trophic for gastrointestinal lymphoid tissue. When mesenteric lymph nodes become infected, abdominal pain may localize to the right lower quadrant; this may mimic the presentation of appendicitis, so the diagnosis is often made at surgery. Postinfectious arthritis may occur in patients positive for HLA-B27. Stool culture is typically diagnostic; the organism may also be cultured from surgical specimens if appendectomy is performed. Treatment has not been clearly associated with improved clinical outcomes but does lead to more rapid eradication of bacteria from stool. Most strains are resistant to amoxicillin and macrolides but sensitive to fluoroquinolones and trimethoprim-sulfamethoxazole.

KEY POINT

- *Yersinia* is trophic for gastrointestinal lymphoid tissue, and infection can mimic the presentation of appendicitis.

Vibrio Infection

Non-cholera-causing species of *Vibrio*, particularly *Vibrio parahaemolyticus* and *Vibrio vulnificus*, are significant causes of foodborne gastrointestinal infections. These bacteria live in salt water, and human infection most commonly occurs through ingestion of raw or undercooked seafood, particularly shellfish. *Vibrio* gastroenteritis is indistinguishable from other bacterial causes. Clinical findings are outlined in Table 35. Severe infections may be seen in patients with hepatic dysfunction and heavy alcohol use. In this population, bloodstream infection with resultant sepsis is common, with a fatality rate approaching 30%. Skin and soft tissue infections caused by *Vibrio* usually occur through cutaneous exposure to contaminated water and not through ingestion. *Vibrio* does not grow well on routine stool cultures; specialized media with high saline content are required. Most isolates are sensitive to fluoroquinolones and macrolides.

KEY POINT

- Severe disease may occur in patients with *Vibrio* infection who have hepatic dysfunction and heavy alcohol use; bloodstream infection with resultant sepsis is common in this population, with a fatality rate approaching 30%.

Clostridium difficile Infection

Clostridium difficile infection (CDI) is the most common cause of health care–associated colitis. The incidence of this potentially devastating infection has more than doubled in the last decade. CDI is increasingly recognized as a significant cause of diarrhea outside of the hospital. National surveillance data identified half of all cases of CDI as community onset, and greater than 5% had no known previous health care or antibiotic exposure. Asymptomatic carriage of *C. difficile* is identified in more than 20% of patients hospitalized without diarrhea. These patients are an important source of secondary transmission in health care settings through fecal-oral spread of bacteria or spores. Antibiotic use is the strongest risk factor for CDI. It is most highly associated with antimicrobial agents that have activity against anaerobic colonic flora but are not effective against *C. difficile* (such as clindamycin). Antibiotic-associated diarrhea in these cases is thought to occur by suppression of the intestinal microbiota, with resultant overgrowth of *C. difficile* organisms and production of toxin (toxins A and B). Strains of *C. difficile* causing particularly fulminant infection have been identified, and disease in these cases is related to elevated production of toxins A and B and production of a novel binary toxin. These hypervirulent strains have been associated with severe or even fatal disease and may occur in patients without any known antibiotic use or health care exposure.

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The clinical presentation of CDI is broad (findings shown in Table 35). CDI frequently causes a pronounced leukemoid reaction and is identified in 25% of hospitalized patients with leukocyte counts of 30,000/μL (30×10^9/L) or more. Determination of CDI severity has prognostic and treatment ramifications. Features associated with severe infections are listed in **Table 37**.

Diagnosis relies on laboratory identification of *C. difficile* in stool samples; however, the presence of this organism does not necessarily imply disease because asymptomatic colonization may occur. Therefore, many laboratories perform testing only on unformed or liquid stool specimens. Enzyme immunoassays (EIAs) to detect toxin are specific, but sensitivity using a single stool sample is 75% to 85%. EIA results may be false negative when toxin production is low or if a strain does not produce the particular toxin the test is optimized to detect. Polymerase chain reaction (PCR) assays to detect the genes responsible for production of toxins A and B are increasingly used for diagnosis and allow improved sensitivity compared with EIAs. Considering the high sensitivity of PCR testing, repeat testing within 1 week of a negative result is unlikely to provide additional information; a negative result essentially rules out this infection. In patients with negative PCR results, an alternative cause should be considered. Stool cultures and cell culture cytotoxicity assays are not useful for clinical management. Visualization of colonic pseudomembranes may suggest CDI, but endoscopy is not recommended for purely diagnostic purposes.

TABLE 37. Clinical Features Associated with Severity of *Clostridium difficile* Infection

Variable	Mild to Moderate CDI	Severe CDI
Leukocytes (cells/μL [cells × 10^9/L])[a]	≤15,000 (15×10^9/L)	>15,000 (15×10^9/L)
Serum creatinine[a]	<1.5 times the baseline level	≥1.5 times the baseline level
Age (y)[a]	≤60	>60
Temperature (°C [°F])	≤38.3 (100.9)	>38.3 (100.9)
Serum albumin (g/dL [g/L])	≥2.5 (25)	<2.5 (25)
Endoscopic visualization of pseudomembranes	Absent	Present
Admission to ICU	No	Yes
Ileus or megacolon	No	Yes

CDI = *Clostridium difficile* infection.

[a]Factors noted as indicating severity of disease in Society for Healthcare Epidemiology of America/Infectious Diseases Society of America guidelines.

All patients with confirmed CDI require antimicrobial treatment, but optimal management depends on whether the episode represents the initial presentation or a recurrence and the severity of the illness (**Figure 20**). Oral metronidazole and vancomycin are equally effective in the treatment of

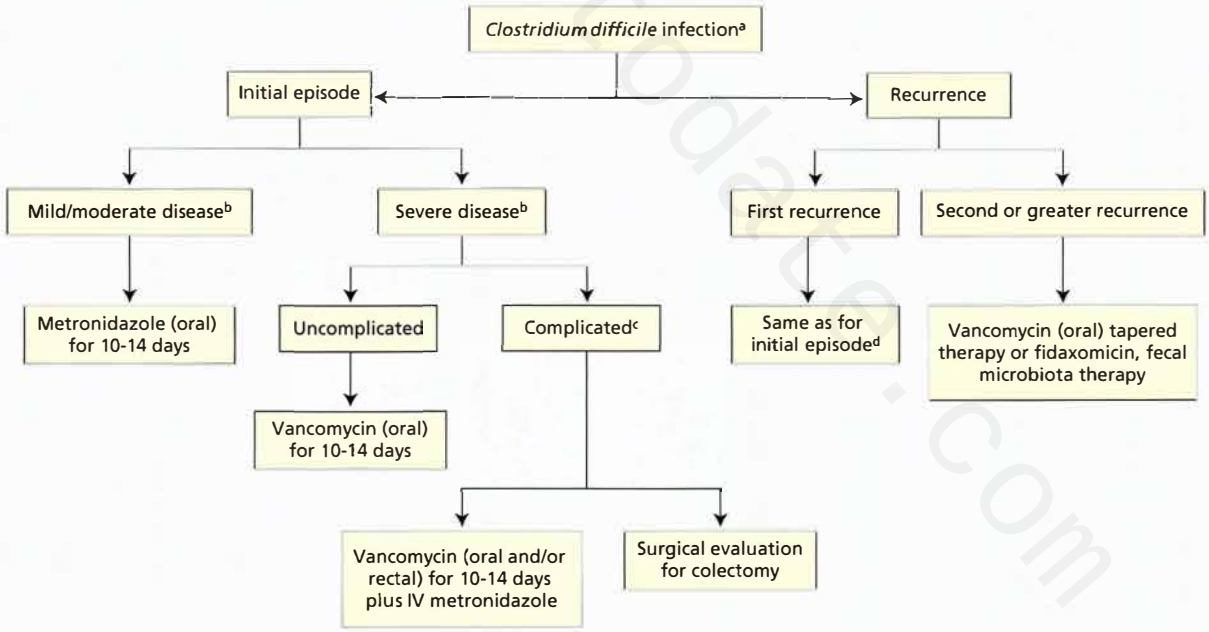

FIGURE 20. Treatment options for *Clostridium difficile* infection.

IV = intravenous.

[a]Defined as diarrhea with a confirmatory laboratory test.

[b]Severe disease is defined as any of the following: (1) leukocyte count >15,000/μL (15×10^9/L); (2) serum creatinine level ≥1.5 times baseline level; (3) age >60 years.

[c]Associated with ileus, megacolon, or hypotension.

[d]Based on disease severity at the time of recurrence (e.g., a mild-to-moderate first recurrence would be appropriately treated with the same regimen as for an initial mild-to-moderate case).

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mild-to-moderate CDI, with the former preferred because of its lower cost.

Relapse is seen in approximately 20% of patients regardless of antibiotic given. At initial relapse, a repeat course of the same medication may be used, assuming disease severity remains the same. In patients with a second relapse, treatment options include oral vancomycin given as a prolonged taper over more than 6 weeks or fidaxomicin, a nonabsorbable macrolide. Fidaxomicin has been associated with lower rates of subsequent relapses compared with oral vancomycin when used to treat the initial episode, but it is significantly more expensive. A terminal course of 2 weeks of rifaximin after pronged vancomycin pulsed taper (antibiotic given at the end of the course every other or every third day) has been beneficial in some case series.

Severe CDI is associated with significant medical costs, morbidity, and mortality. Oral vancomycin is superior to metronidazole in this subgroup and should be the initial treatment of choice. Ileus is frequently present, limiting colonic transit of orally dosed medications; therefore, a vancomycin enema through a rectal tube should be considered to maximize colonic luminal concentrations. Parenteral vancomycin does not penetrate intraluminally; however, intravenous metronidazole achieves detectable fecal levels and can be used in combination with oral or rectal vancomycin in critically ill patients. Fidaxomicin has not been well studied in severe CDI but may be indicated as salvage therapy in patients not responding to standard therapy. Surgical consultation for emergent colectomy is indicated in patients with toxic megacolon, colonic perforation, or severe sepsis.

Fecal microbiota transplant (FMT) has been advocated as a treatment approach for patients with multiple relapses of CDI. The rationale is that exogenous feces will restore the normal colonic microbiota. Numerous studies have documented improved outcomes in patients treated with FMT. Issues related to choice of donor, potential transmission of infectious agents in donor stool, method of administration, and logistics have limited the widespread implementation of FMT. Because of these challenges, increasing interest has focused on probiotic regimens to repopulate the bowel flora in patients with CDI. Probiotics have been effective in reducing the risk for CDI among patients prescribed antibiotics. The data on use of probiotics for treatment of CDI are less compelling; initial studies have not found a benefit in probiotics for treatment of CDI, but subsequent studies suggest some role for adjuvant probiotics in treatment of mild-to-moderate relapsing disease. Concern exists that use of probiotics in immunocompromised patients may be associated with development of extraintestinal infections.

C. difficile spores are stable for prolonged periods in the environment, which allows secondary spread of infection. This is a particular concern in health care settings. Alcohol-based hand gels are inferior to soap and water for eradication of spores, and hand washing is indicated for all health care workers interacting with infected patients. Hospitalized patients with CDI should be placed in contact isolation at least until diarrhea resolves. Documenting clearance of *C. difficile* through testing serial stool samples after an initial positive test result has no role in management.

KEY POINTS

- Enzyme immunoassays for *Clostridium difficile* infection have good specificity, but sensitivity using a single stool sample is only 75% to 85%; polymerase chain reaction assays to detect the genes responsible for production of toxins A and B are increasingly used for diagnosis with better sensitivity.
- Oral metronidazole and vancomycin are equally effective in treating mild-to-moderate *Clostridium difficile* infection, with the former preferred because of its lower cost; oral vancomycin is recommended for severe disease. **HVC**
- Fecal microbiota transplant is an effective treatment approach for patients with multiple relapses of *Clostridium difficile* infection and is effective in reducing the risk for this infection among patients prescribed antibiotics.
- Documenting clearance of *C. difficile* through testing serial stool samples after an initial positive test result has no role in management. **HVC**

Viral Gastroenteritis

Most cases of gastroenteritis are caused by viral pathogens. In immunocompetent patients, viral gastroenteritis is typically a mild, self-limited illness, and neither laboratory diagnosis nor directed treatment is indicated. The most significant viral cause of diarrhea in adults is norovirus, which has been associated with large outbreaks of gastrointestinal disease. Most cases are believed to be spread through fecal-oral transmission following ingestion of contaminated foods or water. Transmission via contact with contaminated surfaces is common. Clinical manifestations are outlined in Table 35. Diarrhea typically lasts less than 72 hours, which may distinguish viral from bacterial causes of gastroenteritis. Laboratory confirmation is indicated only for epidemiologic investigation of outbreaks. People with suspected infections should not handle food, and their clothing and bedding should be thoroughly washed.

KEY POINT

- Norovirus-caused viral gastroenteritis is most likely spread through ingestion of contaminated food or water.

Parasitic Infections

Parasitic gastrointestinal infections are most common in developing countries but can occur throughout the world.

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Protozoan infections cause subacute or chronic diarrhea. The yield of stool parasitic tests varies according to local prevalence, host immune status, history of travel, and duration of symptoms. In developed countries, stool microscopy has positive results in less than 10% of cases. Testing for parasites is not recommended for diarrhea lasting less than 7 days or for patients who develop diarrhea more than 3 days into a hospital stay.

Giardia Infection

Giardia is widespread in zoonotic reservoirs, and infections occur worldwide through ingestion of contaminated food and water. Excretion of cysts by beavers and other animals leads to contamination of natural water supplies, and persons who drink untreated fresh water are at particular risk for giardiasis. Infection is asymptomatic in up to two thirds of cases, but cysts may be shed for many months, with the potential for secondary spread. Clinical manifestations are outlined in Table 35. In many cases, symptoms resolve spontaneously without treatment, but a subset of patients will develop chronic symptoms with significant weight loss owing to malabsorption and anorexia. Hypogammaglobulinemia and IgA deficiency are risk factors for prolonged infection.

Because *Giardia* cysts are intermittently shed, stool microscopy is less sensitive than stool antigen testing. Treatment with metronidazole is curative in more than 85% of patients. Another nitroimidazole, tinidazole, is curative in approximately 90% of patients and offers the advantage of single-dose therapy. Occasionally, nitroimidazole resistance causes treatment failures with these agents; in this case, nitazoxanide may be effective. Infection in pregnant women is particularly problematic because nitroimidazoles are contraindicated during the first trimester. Paromomycin is an alternative. Even after eradication of the protozoa, diarrhea may persist because of infection-induced lactose intolerance, and diet modification in the months after treatment will minimize postinfective symptoms.

KEY POINTS

HVC
- Testing for parasites is not recommended for diarrhea lasting less than 7 days or for patients who develop diarrhea more than 3 days into a hospital stay.
- Treatment of giardiasis with metronidazole is curative in more than 85% of patients.

H *Cryptosporidium* Infection

Cryptosporidia infections are ubiquitous in the environment. Infection can occur in humans by close contact with infected animals, as can happen in petting zoos or through consumption of contaminated water or food. Immunocompromised patients, especially those with HIV/AIDS, are particularly susceptible to infection. Large community outbreaks following contamination of municipal water supplies have been reported. Infections in immunocompetent persons are usually asymptomatic or associated with a self-limited diarrheal illness. Among patients with AIDS, diarrhea may be prolonged and the large volume of stools may lead to dehydration and pronounced weight loss. Oocysts are not well visualized with conventional microscopy for ova and parasites but may be seen with modified acid-fast staining. Because oocytes may be shed intermittently, stool antigen testing is more sensitive than microscopy. Most immunocompetent patients do not require treatment, but nitazoxanide should be considered in symptomatic patients. Those with HIV often clear chronic infection with initiation of antiretroviral therapy. H

KEY POINT

- Immunocompromised patients, especially those with HIV/AIDS, are particularly susceptible to *Cryptosporidium* infection; in patients with AIDS, diarrhea may be prolonged, and the large volume of stools may lead to dehydration and pronounced weight loss.

Amebiasis

Entamoeba histolytica causes amoebic dysentery. Other species of *Entamoeba* may colonize the gastrointestinal tract but are not pathogenic and, when identified, do not mandate treatment. In developed countries, amebiasis is usually seen in immigrants or travelers returning from extended stays in endemic areas. Infections may be seen in institutional settings, where poor hygiene may predispose to spread of oocytes. Although most infected patients are asymptomatic, a subset develops dysentery with prolonged shedding in stool with visible blood or mucus. Stool microscopy for ova and parasites may detect the protozoa and is most sensitive if sequential samples are submitted, but stool antigen testing is more sensitive. Serum antibodies may also be useful in suggesting the diagnosis but cannot distinguish recent from remote infection. Tinidazole or metronidazole is effective as initial treatment, followed by a second agent, such as paromomycin, for eradication of intraluminal cysts.

KEY POINT

- Stool antigen testing is more sensitive than ova and parasite examination for the diagnosis of amebiasis.

Cyclospora Infection

Cyclospora species are widespread in the environment. Infections in the United States are most commonly associated with ingestion of contaminated fruits and vegetables imported internationally. Sporadic cases and outbreaks of cyclosporiasis have been identified. Symptoms are outlined in Table 35. Persons with HIV infection may have more severe illness associated with wasting. Modified acid-fast stains are required to visualize oocytes. Trimethoprim-sulfamethoxazole is the treatment of choice for symptomatic patients, with ciprofloxacin an alternative for patients intolerant to sulfa antimicrobials.

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KEY POINT

- Trimethoprim-sulfamethoxazole is the treatment of choice for *Cyclospora* infection in patients with symptoms; ciprofloxacin is an alternative for anyone intolerant of sulfa antimicrobial agents.

Infections in Transplant Recipients

Introduction

Rates of transplantation of solid organs or hematopoietic stem cells continue to rise in the United States, as do survival rates after transplantation. With increasing long-term survival, many of these patients are being integrated back into community medical settings, with regular medical care being transferred back to primary care providers. Consequently, all physicians are increasingly likely to be involved in the care of patients who have undergone transplantation, and an awareness of posttransplant complications, including infections, is increasingly important.

Antirejection Drugs in Transplant Recipients

Antirejection drugs are required after solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT). In general, the intensity of therapeutic immunosuppression is highest in the first few months after transplantation (induction therapy) to ensure initial graft survival and is then gradually decreased (maintenance therapy), although it may need to be increased later to manage episodes of rejection or graft-versus-host disease (GVHD). Additionally, some induction regimens include treatment with lymphocyte-depleting agents in association with lower doses of conventional immunosuppressants to further decrease the initial immune response to the transplant.

Because antirejection drugs work through suppression of different aspects of the immune system, various agents carry different risks for specific infections (**Table 38**). Glucocorticoids (such as prednisone) interfere with the immune response broadly, increasing the risk for infection from a wide range of organisms, including bacteria, viruses, and fungi. Lymphocyte-depleting agents also act broadly and are associated with increased risk for infection with cytomegalovirus (CMV), polyoma BK virus, *Pneumocystis* species, and other fungi. However, agents providing more focused T-cell suppression tend to have a narrower risk for infection. For example, mycophenolate regimens with lower glucocorticoid doses have a lower risk for *Pneumocystis* infection, whereas sirolimus is associated with lower rates of CMV disease but an increase in viral and bacterial respiratory infections.

TABLE 38. Immunosuppressive Agents Used in Transplantation

Class	Agents
Glucocorticoids	Prednisone, others
Cytotoxic agents (DNA synthesis inhibitors, antimetabolites)	Mycophenolate mofetil
	Mycophenolate sodium
	Azathioprine
	Methotrexate
	Cyclophosphamide
Calcineurin pathway inhibitors	Cyclosporine
	Tacrolimus
mTOR inhibitors	Sirolimus (rapamycin)
	Everolimus
Lymphocyte-depleting antibodies	
Polyclonal	Antithymocyte globulins
Monoclonal	Muromonab (anti-CD3)
	Basiliximab (anti-IL-2 receptor)
	Daclizumab (anti-IL-2 receptor)
	Rituximab (anti-CD20)
	Alemtuzumab (anti-CD52)

IL-2 = interleukin-2; mTOR = mammalian target of rapamycin.

Epstein-Barr virus (EBV)-associated posttransplant lymphoproliferative disease (PTLD) is also a potential complication with variable risk depending on specific immunosuppressive drug therapy. PTLD risk is higher in patients with a history of preexisting EBV infection treated with lymphocyte-depleting agents and in those receiving sirolimus and tacrolimus than in those receiving mycophenolate and cyclosporine.

Many immunosuppressive agents have significant drug interactions, which can be pharmacokinetic (affecting drug levels and metabolism) or pharmacodynamic (additive toxicity). Pharmacokinetic interactions are usually mediated through inhibition of, competition for, or induction of the cytochrome P-450 system (especially the 3A isoenzymes) or the membrane transporter P-glycoprotein. Additionally, individual genetic polymorphisms affect enzyme activity and can result in different rates of drug metabolism among patients. Pharmacokinetic interactions are very common and involve a long list of drugs; thus, possible interactions should be checked before any new drug is prescribed to a transplant recipient. Additive toxicity may result in nephrotoxicity or cytopenias and may also affect the risk for infection.

KEY POINT

- Pharmacokinetic interactions are very common and involve a long list of drugs, so possible interactions must be checked before any new drug is prescribed to a transplant recipient.

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Posttransplantation Infections

Infections after transplantation may present in atypical fashion and are more likely to disseminate. They may manifest with subtle signs and symptoms owing to altered anatomy associated with the transplant or to immunosuppression, so a high level of suspicion must be maintained. Additionally, noninfectious complications, such as graft rejection, GVHD, and drug toxicity, may present similarly to and be confused with infection.

Timeline and Type of Transplant

The risk for specific infections varies somewhat predictably with the type of transplant, the immunosuppressive regimen used, time after transplant, recipient and donor characteristics (such as seropositivity for certain microbes), and posttransplant complications, including GVHD or rejection. Before transplantation, donor and recipient should be evaluated for active infection and screened for CMV, EBV, hepatitis B and C viruses, HIV, and tuberculosis.

Risk for infection in patients with SOT can be divided into three time periods (**Table 39**). In the first month after transplantation, patients are at risk for surgical site and other nosocomial infections, which may include resistant bacteria or *Candida* species. Specific sites at highest risk for infection are usually related to the transplanted organ, for example urinary tract infection after kidney transplantation. With the intensive use of antimicrobials, *Clostridium difficile* colitis is an increasing problem in this group.

Between 1 and 6 months after SOT, the highest risk is for infection resulting from suppressed cell-mediated immunity. This is the most likely time for CMV reactivation and disease and other viruses (see Table 39). Opportunistic pathogens, such as *Pneumocystis* species, other fungi, and certain bacteria, also are relatively common in this time period.

Six months after SOT, opportunistic infections become less common unless episodes of rejection occur or need for high-level immunosuppression continues. In these instances (or with chronic allograft dysfunction), certain infections may present late (see Table 39). Patients may also present with more severe episodes of typical community-acquired infections.

Risk for infection after HSCT also follows a timeline (**Figure 21**). The most significant additional risk, compared with risk for infection after SOT, results from the significant period of neutropenia that occurs in the preengraftment phase after transplantation, with increased risk for bacterial (especially gram-negative and streptococcal) and invasive fungal disease.

TABLE 39. Timeline of Common Infections After Solid Organ Transplantation

Early Period (<1 Month after Transplantation)	Middle Period (1-6 Months after Transplantation)	Late Period (>6 Months after Transplantation)[a]
Staphylococcus aureus infection (including methicillin-resistant)	Cytomegalovirus infection	Epstein-Barr virus (including PTLD) infection
Nosocomial Gram-negative bacterial infection	Epstein-Barr virus (including PTLD) infection	Varicella-zoster virus infection
Clostridium difficile colitis	Herpes simplex virus infection	Community-acquired pneumonia
Candida infection	Varicella-zoster virus infection	Urinary tract infections
Aspergillus infection	Polyoma BK virus infection	Polyoma BK virus infection
Surgical site infections	*Pneumocystis jirovecii* infection	Cytomegalovirus infection
Nosocomial pneumonia	*Toxoplasma gondii* infection	*Listeria* infection
Catheter-related bacteremia	*Listeria* infection	*Nocardia* infection
Urinary tract infections	*Legionella* infection	
	Nocardia infection	
	Tuberculosis reactivation	
	Fungal infections	
	Hepatitis B and C	

PTLD = posttransplant lymphoproliferative disorder.

[a]For opportunistic infections in the late period, risk depends on level of immunosuppression.

KEY POINT

- The risk for specific infections varies somewhat predictably with the type of transplant, immunosuppressive regimen used, time after transplantation, recipient and donor characteristics (such as seropositivity for certain microbes), and posttransplant complications, including graft-versus-host disease or rejection.

Specific Posttransplantation Infections

Viral Infections

Although numerous viral infections can complicate transplantation, CMV is the most significant. The risk for reactivation is related to serologic status of the donor and recipient and is most likely in seronegative recipients from a seropositive donor; it is unlikely when donor and recipient are both negative. CMV disease after transplantation may manifest as a nonspecific febrile illness; may cause leukopenia and thrombocytopenia; or may cause specific organ disease, most often pneumonitis, colitis, esophagitis, or hepatitis. CMV is an immunomodulatory virus (active infection also results in nonspecific changes in immune system function), and CMV reactivation is associated with organ rejection, secondary infection and PTLD, and an increased risk for graft loss and death.

Other important viruses include EBV, human herpes virus (HHV) 6, and HHV-8, also known as Kaposi sarcoma herpes virus. The most significant consequence of EBV infection is PTLD resulting from B-lymphocyte proliferation. PTLD should be considered in any patient presenting with fever and

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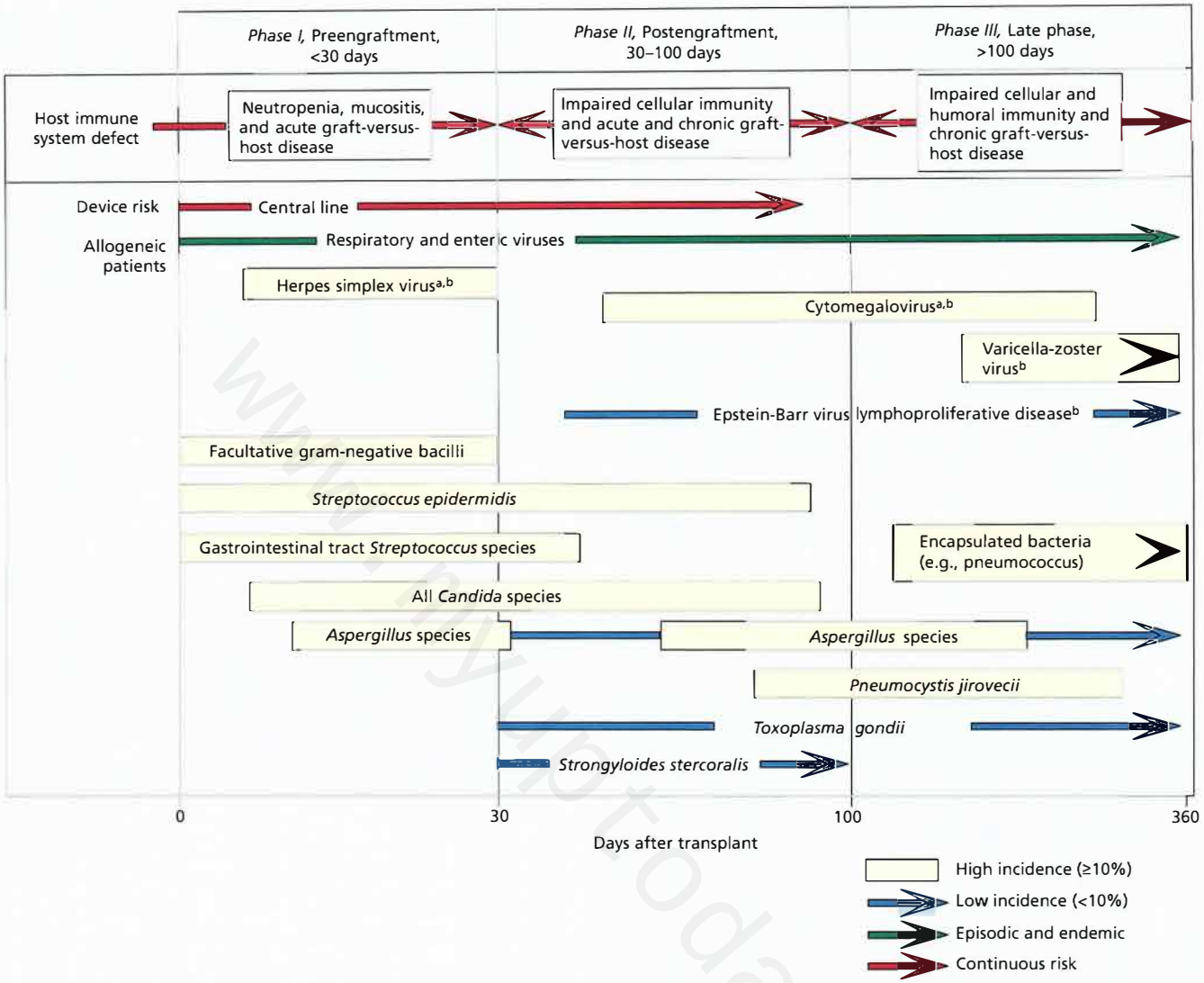

FIGURE 21. Phases of opportunistic infections in allogeneic hematopoietic stem cell transplant recipients.

[a]Without standard prophylaxis.

[b]Primarily among persons who are seropositive before transplantation.

Reprinted with permission from CDC, Infectious Diseases Society of America, and the American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Recommendations of CDC, the Infectious Diseases Society of America, and the American Society of Blood and Marrow Transplantation. Cytotherapy. 2001;3(1):41-54. [PMID: 12028843]

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lymphadenopathy or an extranodal mass; treatment includes reduction of immunosuppression and rituximab or other chemotherapy. HHV-6 reactivation is common after SOT and HSCT, although its correlation to specific disease is not always clear. Syndromes associated with HHV-6 include fever, myelosuppression, hepatitis, encephalitis, and pneumonitis. Recently, hepatitis E virus, previously thought to only cause acute hepatitis, has been shown to cause chronic hepatitis after SOT and may be associated with hepatic fibrosis and glomerulonephritis.

Bacterial Infections

Bacterial infections are common early after transplantation because of nosocomial and surgical infections after SOT and because of neutropenia after HSCT. Sites of infection are most often related to the specific organ after SOT. The most common causative agents for nosocomial infections are antibiotic-resistant staphylococci and gram-negative organisms. Pathogens may be present in the recipient before transplantation, including *Pseudomonas* and *Burkholderia* species in patients with cystic fibrosis receiving lung transplantation. *C. difficile* colitis is common considering the frequent and intense antibiotic use in these patients, especially in the second week after SOT, and in patients with GVHD after HSCT.

Even in the late period after HSCT, patients remain at risk for encapsulated organisms, such as *Streptococcus pneumoniae*. These and other community-acquired infections may be more severe than in patients without transplant. *Legionella*

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species cause a more extensive and rapidly progressive multilobar pneumonia in transplant recipients. *Listeria* species usually cause meningoencephalitis. *Nocardia* infection most commonly presents with lung nodules but may be disseminated at presentation, often to the brain. Tuberculosis usually occurs as a reactivation of latent infection after transplantation; all patients undergoing transplantation should be screened for latent tuberculosis and, if positive, treated for this before transplantation if feasible. In transplant recipients with tuberculosis, two thirds of cases occur in the first year, and 30% to 50% are extrapulmonary or disseminated at presentation. Treatment of tuberculosis after transplantation is complicated by increased risk for hepatotoxicity and drug interactions.

Fungal Infections

Fungal infections are common after transplantation, especially in the neutropenic phase after HSCT, or with GVHD. Early-phase fungal disease is most often due to invasive *Candida* infection or *Aspergillus* infection. Invasive aspergillosis is also more common after lung transplantation. Pulmonary aspergillosis may present with fever, dry cough, or chest pain, and may disseminate to the brain, causing headache, focal deficits, or mental status changes. With prophylaxis against these fungi, other molds are becoming increasingly common, such as *Mucor* species, which can present in a fashion similar to that of aspergillosis.

Meningitis due to *Cryptococcus neoformans* is most common in the later period after SOT and presents with subacute or chronic onset of fever, headache, and mental status changes. Infection with geographic fungi–*Histoplasma* in the Midwest and *Coccidioides* in the Southwest–may also occur late after SOT in their endemic areas in the United States, presenting with fever and pulmonary infection, although both may disseminate. *Blastomycosis* infection is not significantly increased in incidence or mortality in transplant recipients.

Pneumocystis jirovecii pneumonia can be significantly reduced by use of prophylaxis but may occur in the middle or late periods after transplant. In transplant recipients, *Pneumocystis* pneumonia is a more acute and rapidly progressive illness than is typical in those with AIDS.

Protozoa and Helminths

Toxoplasma gondii is a protozoan that can cause reactivation disease in the middle or late period after transplantation, most often with multiple brain abscesses with fever, headache, focal deficits and seizures, and multiple ring-enhancing lesions on brain imaging. Immunosuppression after transplantation can lead to a hyperinfection syndrome with *Strongyloides* species, which is associated with pneumonia, gram-negative bacteremia, and a high mortality rate. Trypanosomiasis and leishmaniasis can be seen in transplant recipients who are from endemic areas outside the United States.

KEY POINTS

- Cytomegalovirus infection after transplantation may manifest as a nonspecific febrile illness or may cause leukopenia and thrombocytopenia, pneumonitis, colitis, esophagitis, or hepatitis.
- The most significant consequence of Epstein-Barr virus infection is posttransplant lymphoproliferative disease resulting from B-lymphocyte proliferation.
- Bacterial infections are common early after transplantation because of nosocomial and surgical infections (after solid organ transplantation) and because of neutropenia (after hematopoietic stem cell transplantation).
- Early-phase fungal disease is most often due to invasive *Candida* infection or *Aspergillus* infection, *Cryptococcus neoformans* meningitis is most common in the later period, and *Pneumocystis* pneumonia may occur in the middle or late periods after transplant.

Prevention of Infections in Transplant Recipients

Prevention of infection after transplantation relies primarily on prophylactic antimicrobial agents and immunizations. Prophylaxis after SOT and HSCT can reduce incidence of bacterial and candidal infections in the early period. During neutropenia, prophylaxis usually includes an antifungal with mold activity, such as voriconazole, which is often continued for 3 months or longer if GVHD is present. Trimethoprim-sulfamethoxazole is the preferred agent for *Pneumocystis* prophylaxis and also has activity against some bacteria, including *Listeria* and *Nocardia* species, and *Toxoplasma* species. It is often continued for 12 months and sometimes longer.

Reducing the burden of CMV disease after transplantation remains important, usually through true prophylaxis (valganciclovir for those at risk on the basis of serologic results) or preemptive therapy (monitoring for reactivation by nucleic acid amplification testing and initiating therapy when results are positive). Both strategies are effective; prophylaxis is usually used for seronegative recipients of an organ from a seropositive donor (highest risk). If donor and recipient are both seronegative, CMV preventive therapy need not be given.

Immunizations are important for transplant recipients (**Table 40**). These are preferably given before patients undergo SOT. Because they receive myeloablative therapy, patients undergoing HSCT need revaccination with complete series after immune system reconstitution. Recommendations concerning pneumococcal vaccination have been revised, and immunocompromised patients should receive the 13-valent pneumococcal conjugate vaccine first followed by the 23-valent pneumococcal polysaccharide vaccine (see MKSAP 17 General Internal Medicine for complete recommendations). Live vaccines are typically contraindicated for patients receiving immunosuppression after transplantation.

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TABLE 40. Immunization Recommendations for Adult Recipients of Transplants[a]

Immunization	Recommendations for Solid Organ Transplantation	Recommendations for Hematopoietic Stem Cell Transplantation[b]
Pneumococcal	Before transplantation: PCV13 followed 8 weeks later by PPSV23	3-6 months after transplantation: 3-4 doses of PCV13
	5 years after transplantation: 1 dose PPSV23	12 months after transplantation: 1 dose of PPSV23
Influenza (inactivated only)	Annually	Annually
Tdap	Before transplantation: complete series, including Tdap booster	6 months after transplantation: 3 doses Tdap
MMR	Contraindicated after transplantation	24 months after transplantation: 1-2 doses, only if no GVHD or immune suppression
Inactivated polio	Before transplantation: complete series	6-12 months after transplantation: 3 doses
Haemophilus influenzae type B	No recommendation	6-12 months after transplantation: 3 doses
Meningococcal	Per recommendations for nontransplant patients	Per recommendations for nontransplant patients
Hepatitis B	Before transplantation: complete series if not already immune	6-12 months after transplantation: 3 doses if indications for nontransplant patients are met
Hepatitis A	Before transplantation: complete series if not already immune	Per recommendations for nontransplant patients
Varicella-zoster	>4 weeks before transplantation: varicella if not immune	>4 weeks before transplantation: varicella if not immune
	>4 weeks before transplantation: zoster if same indications as nontransplant patients are met	24 months after transplantation: 2 doses varicella if seronegative and only if no GVHD or immunosuppression
	Both contraindicated after transplantation	
Human papillomavirus	Before transplantation: per recommendations for nontransplant patients	Per recommendations for nontransplant patients

GVHD = graft-versus-host disease; MMR = measles, mumps, and rubella; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; Tdap = tetanus, diphtheria, and pertussis.

[a]See MKSAP 17 General Internal Medicine for more information on vaccination recommendations and schedules.

[b]For multiple-dose immunizations, the time period between doses is generally 1-2 months.

KEY POINTS

- Infection prevention after transplantation relies primarily on prophylactic antimicrobial agents and immunizations, although live vaccines are typically contraindicated for patients receiving immunosuppression.
- Patients undergoing hematopoietic stem cell transplantation require revaccination with complete series after immune system reconstitution, but live vaccines are contraindicated.

Health Care-Associated Infections

Epidemiology

Health care-associated infections are acquired while receiving care in a health care setting (hospital, dialysis center, ambulatory surgery center, long-term care facility). Hospital-acquired infections (HAIs) are a subset of health care-associated infections. An HAI is an infection that was neither present nor incubating upon admission to the hospital, usually defined as developing 48 hours after admission, depending on the implicated organism and the type of infection. HAIs are associated with the use of indwelling medical devices, surgery, invasive procedures, injections, transmission of organisms/infections between patients and health care personnel (HCP), and inappropriate use of antimicrobial agents. Bloodstream infections, pneumonia, surgical site infections, and urinary tract infections account for most HAIs. The Centers for Disease Control and Prevention estimates that 1 in 20 hospitalized patients will develop an HAI resulting in 1.7 million infections and 98,000 deaths per year. It is estimated that the direct costs of HAIs range from $35.7 billion to $45 billion annually, and, therefore, reduction of HAIs is a top health care priority. Approximately 65% to 70% of catheter-associated bloodstream infections and urinary tract infections and 55% of cases of ventilator-associated pneumonia and surgical site infections may be preventable. Hospitals have been challenged to eliminate preventable HAIs by aiming for 100% adherence to evidence-based practices and strategies shown to prevent these infections.

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KEY POINT

HVC
- Approximately 65% to 70% of catheter-associated bloodstream infections and urinary tract infections and 55% of ventilator-associated pneumonia cases and surgical site infections may be preventable.

Prevention

Hand hygiene remains the cornerstone for preventing infection. According to the World Health Organization, hand hygiene should be performed before clean/aseptic procedures and after bodily fluid exposure, touching a patient, and touching patient surroundings. Hand washing with soap and water should be performed for at least 15 seconds, being careful to cover all surfaces of the hands up to the wrists, between the fingers, and finger tips. Alcohol-based hand rubs are acceptable alternatives to soap and water, except after contact with patients who have *Clostridium difficile* infection or their environment. Standard precautions (wearing gloves, gowns, masks, eye protection) should be practiced in the care of every patient to protect HCP from exposure to bloodborne pathogens. All body fluids except sweat are potentially infectious, and HCP should use these barriers to protect themselves from anticipated exposure depending on the activity being performed. Transmission-based precautions (airborne, contact, droplet) are used in addition to standard precautions to prevent transmission of epidemiologically significant organisms (**Table 41**).

Appropriate and judicious device use, safe injection practices, following aseptic technique for invasive procedures and surgery, and maintaining a clean environment are important components of reducing HAIs. Many HAI prevention initiatives over the last decade have been successful, several of which have relied on bundling processes of care to improve outcomes. "Bundles" are usually three to five evidence-based processes of care that, when performed together, consistently have a greater effect on decreasing HAIs than individual components performed inconsistently. A multifaceted and multidisciplinary approach is required to prevent HAIs.

KEY POINT

- Hand hygiene remains the cornerstone for preventing infection and should be performed, at minimum, before and after every patient contact.

Catheter-Associated Urinary Tract Infections

General Information

Catheter-associated urinary tract infections (CAUTIs) account for the largest proportion of HAIs (40%). Urinary catheters are used in 15% to 25% of hospitalized patients and are associated with most hospital-acquired urinary tract infections (UTIs). Urinary catheters are often placed for inappropriate indications, and physicians are frequently unaware that their patients have a urinary catheter, leading to prolonged and unnecessary use. It is well established that the duration of catheterization is directly related to the risk for a UTI. With a catheter in place, the daily risk for a UTI ranges from 3% to 7%. CAUTI is the leading cause of secondary hospital-acquired bacteremia, and 17% of hospital-acquired bacteremias are from a urinary source (2.3% mortality). The pathogens most often associated with CAUTI are *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae/oxytoca*, *Candida albicans*, and *Enterococcus faecalis*. As with other HAIs, risk factors can be divided into modifiable and nonmodifiable categories (**Table 42**). Catheters should be used for appropriate indications only, which include urinary retention and bladder outlet obstruction, measurement of urinary output in critically ill patients, perioperative use for selected surgical procedures, assistance with healing of perineal or sacral wounds in patients with incontinence, use in patients requiring prolonged immobilization, and contribution to comfort at the end of life.

TABLE 41. Transmission-Based Precautions[a]

Precaution Type	Indications	Precaution	Examples
Airborne	Organisms transmitted from respiratory tract by small droplet nuclei (≤5 microns) that travel long distances on air currents	Airborne infection isolation room (negative-pressure room); HCP wear fit-tested N95 respirator	Chickenpox (plus contact precautions), tuberculosis, measles
Contact	Organisms transmitted by direct or indirect contact	Single room; gloves and gown for HCP entering room	Multidrug-resistant organisms (such as MRSA, VRE, ESBL-producing gram-negative organisms), *Clostridium difficile*, rotavirus
Droplet	Organisms transmitted from respiratory tract by large droplet nuclei (>5 microns) that travel less than 3 feet on air currents	Single room; HCP wear face/surgical mask when within 3 feet of patient	Influenza, *Bordetella pertussis*, *Neisseria meningitidis* for first 24 hours of therapy, mumps

ESBL = extended-spectrum β-lactamase; HCP = health care personnel; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

[a]Some organisms/infections require a combination of transmission-based precautions (adenovirus: contact and droplet; disseminated varicella zoster virus: airborne and contact).

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TABLE 42. Risk Factors for Catheter-Associated Urinary Tract Infection

Nonmodifiable
Female sex
Age >50 years
Diabetes mellitus
Severe underlying illness
Nonsurgical illness
Serum creatinine level >2.0 mg/dL (176.8 µmol/L)
Modifiable
Duration of catheterization
Nonadherence to aseptic technique (e.g., opening a closed system)
Less experienced catheter inserter

KEY POINT

HVC
- Urinary catheters are often placed for inappropriate indications in health care settings, and use is frequently prolonged and unnecessary, which increases the risk for urinary tract infection.

Diagnosis

Pyuria and bacteriuria are common in hospitalized patients with indwelling urinary catheters, even in those without infection; therefore, routine urinalysis and culture should not be performed in patients without symptoms or signs of infection. Patients considered to have a CAUTI are those with an indwelling urethral or suprapubic catheter, those in whom a catheter was removed in the 48 hours before symptom onset, or those undergoing intermittent catheterization who have signs and symptoms compatible with UTI (see Urinary Tract Infections), no other identifiable source, and bacteriuria (10^3 or more colony-forming units/mL of one or more bacterial species in a urine specimen). Patients with spinal cord injury may have increased spasticity or autonomic dysreflexia as symptoms related to a CAUTI. Bacteriuria in patients without signs or symptoms of UTI is called catheter-associated asymptomatic bacteriuria; most patients do not develop signs or symptoms of infection and generally do not require treatment, and the catheter may remain in place if still indicated.

KEY POINT

HVC
- Routine urinalysis and culture should not be performed for patients with indwelling urinary catheters without symptoms or signs of urinary tract infection.

Treatment

A urine specimen for culture should be obtained before antimicrobial treatment begins to guide definitive therapy based on culture results. Part of the treatment for CAUTI includes removing or replacing the urinary catheter, especially if it has been in place for 2 weeks or longer. The presence of biofilm on the catheter makes it difficult to eradicate bacteriuria or funguria and may lead to antimicrobial resistance if organisms cannot be eradicated. When culture data are available, therapy should be adjusted to the narrowest coverage spectrum possible. Treatment should be given for 7 days if symptoms resolve promptly and longer (10–14 days) for patients with delayed response (fever, unresolved symptoms after several days of therapy). CAUTIs caused by *Candida* species should be treated for 14 days; however, patients with candiduria alone do not require treatment.

KEY POINT

HVC
- When culture data are available, therapy for catheter-associated urinary tract infections should be adjusted to the narrowest coverage spectrum possible.

Prevention

Avoiding urinary catheter use, when possible, is the mainstay of CAUTI prevention. Condom catheters for men and intermittent catheterization are alternative strategies associated with a decreased risk for infection. An estimated 17% to 69% of CAUTIs may be preventable by following recommended infection prevention measures (**Table 43**). Antimicrobial or antiseptic coated catheters may be considered if the CAUTI rate is not decreasing after implementing, and complying with, core prevention strategies, including aseptic insertion and maintenance. The effect of these catheters in reducing CAUTIs and which patient populations may be most likely to benefit require further study. CAUTI prevention strategies are summarized by the acronym ABCDE: Adhere to general infection control principles, perform Bladder ultrasonography to potentially avoid catheterization, use Condom catheters or intermittent catheterization when appropriate, Do not use an indwelling catheter if criteria for use are not met, and remove catheters Early when they are no longer indicated using computerized reminders or nurse-driven removal protocols.

KEY POINT

HVC
- Avoiding urinary catheter use and considering alternatives are important components of catheter-associated urinary tract infection prevention.

Surgical Site Infections

General Information

An estimated 80 million surgical procedures are performed in the United States each year, 32 million of which are in ambulatory settings. The overall risk for a surgical site infection (SSI) after surgery is 1.9%. SSIs account for 23% of HAIs and add 7 to 10 days to hospital stays. The excess cost per patient is estimated to be from $10,443 to $25,546 and can be up to $90,000 when an antimicrobial-resistant organism or prosthetic joint implant is involved. The overall mortality rate associated with SSIs is 3%, with 75% of deaths directly attributable to the SSI.

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TABLE 43. Prevention of Catheter-Associated Urinary Tract Infection

Period	Preventive Measures
Before catheterization	Avoid catheterization whenever possible
	Insert catheter only for appropriate indications
	Consider alternatives, such as condom catheters and intermittent catheterization
At time of catheter insertion	Ensure that only properly trained persons insert and maintain catheters
	Adhere to hand hygiene practices and standard (or appropriate isolation) precautions according to CDC HICPAC/WHO guidelines
	Use proper aseptic techniques and sterile equipment when inserting the catheter (acute care setting)
After catheter insertion	Promote early catheter removal whenever possible
	Secure the catheter
	Use aseptic technique when handling the catheter, including for sample collection from the designated port (not collecting bag)
	Maintain a closed drainage system
	Avoid unnecessary system disconnections
	Maintain unobstructed urine flow
	Keep the collecting bag below the level of the bladder
	Empty the collecting bag regularly, using a separate collecting container for each patient

CDC = Centers for Disease Control and Prevention; HICPAC = Healthcare Infection Control Practices Advisory Committee; WHO = World Health Organization.

CONT.

Patient and procedure risk factors affect the overall SSI risk (**Table 44**), and surgical wound classification correlates with the infection rate. SSIs typically occur in the first 30 days after surgery and up to 90 days after surgery with implants or prosthetic joints. The major sources of organisms causing SSIs are from the patient's skin and possibly the alimentary tract or female genital tract depending on the type of surgery. The organism most often isolated is *Staphylococcus aureus* (30.4%), followed by coagulase-negative staphylococci (11.7%), *E. coli* (9.4%), *E. faecalis* (5.9%) and *P. aeruginosa* (5.5%).

KEY POINT

- *Staphylococcus aureus* is the organism most often responsible for surgical site infection.

Diagnosis

The clinical signs and symptoms vary by the site and type of SSI and the implicated organism. Inflammatory changes at the surgical site (signs and symptoms of pain/tenderness, warmth, swelling, erythema) and the presence of

TABLE 44. Risk Factors for Surgical Site Infection

Endogenous	Exogenous (usually modifiable)
Diabetes mellitus	Prolonged preoperative stay
Advanced age	Preoperative hair removal by shaving
Obesity	Inadequate surgical scrub/antiseptic skin preparation
Smoking	Length of operation
Malnutrition, recent weight loss	Surgical technique
Cancer	Prophylactic antimicrobials and timing
Immunosuppression (glucocorticoid use, chemotherapy, radiation therapy)	Hypothermia
Remote site of infection	Hypoxia
Wound class[a]	Hyperglycemia
	Blood transfusion

[a]Surgical wound classification is based on risk for infection: Clean: does not enter a hollow organ (gastrointestinal [GI], genitourinary [GU], respiratory tract), no inflammation at surgical site, site closed at end of surgery (infection rate <2%); Clean contaminated: hollow organ(s) (GI, GU, respiratory tract) entered, area appropriately prepared before surgery, no unusual events leading to additional risk for contamination, minimal spillage, no infected bile or urine (infection rate <10%); Contaminated: significant break in sterile technique (minor break during clean procedure), entry into infected hollow organ, gross spillage from GI tract, infected urine or bile encountered, inflammation (nonpurulent) at surgical site, penetrating trauma (<4 hours old) (infection rate 20%); Dirty/infected: surgical site grossly contaminated, preexisting infection (purulent inflammation, perforation of an unprepared hollow viscus, chronic open wound to be grafted/covered, penetrating trauma (>4 hours old) (infection rate 30%-40%).

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CONT.

purulent drainage suggest a superficial incisional infection. Deep incisional SSIs may have more extensive tenderness, including outside the area of erythema, and more systemic signs of infection, such as fever and leukocytosis. A deep incisional SSI also should be considered with wound dehiscence or if the surgeon deliberately opens the incision, unless the wound/drainage culture is negative. Organ/deep space SSIs generally present with more systemic signs of infection and local symptoms related to a deep abscess or infected fluid collection. When organ/deep space SSIs are suspected, CT imaging is helpful to localize the infection and determine the best approach to for drain the fluid/abscess. When an SSI is suspected, wound drainage fluid, purulent fluid, or infected tissue should be obtained and sent for culture. Deep tissue or wound cultures are preferable to superficial wound swab cultures, which are more likely to reflect skin or wound colonization and not necessarily yield the causative pathogen (sensitivity, <30%).

KEY POINT

- When a surgical site infection is suspected, wound drainage material, purulent fluid, or infected tissue should be obtained and sent for culture.

Treatment

The choice of antimicrobial agent should be guided by culture results; the duration of treatment varies by the anatomic site of infection and the depth of the infection. Patients with signs of sepsis may require empiric therapy pending culture results, with antibiotics chosen to cover the most likely pathogens based on surgical type and site. Therapy should be revised after culture results are available. Superficial incisional infections can usually be managed with antimicrobial agents without tissue debridement. Treatment of deep incisional and organ/deep space SSIs generally requires a combination of surgical debridement to remove necrotic tissue or drain abscesses or infected fluid and specific antimicrobial therapy. Surgical debridement or drainage of infected fluid and abscess material may need to be repeated for the infection to be controlled and resolved, even with appropriate antimicrobial therapy. When an SSI involves an implant, removing the implant should be considered. However, depending on the patient and the site, organism, and severity of infection, a trial of antimicrobial therapy may be appropriate before implant removal.

KEY POINT

- Treatment of deep incisional and organ or deep space surgical site infections generally requires a combination of specific antimicrobial therapy and surgical debridement to remove necrotic tissue or drain abscesses or infected fluid.

Prevention

Preventing SSIs can be divided into preoperative, intraoperative, and postoperative measures. Although many host risk factors for SSIs are not modifiable, several are and should be optimized before surgery. Hyperglycemia should be controlled, doses of immunosuppressive agents should be lowered as much as possible or stopped completely if feasible, patients who are obese should be encouraged to lose weight, and patients who smoke should cease tobacco use. Patients should shower with soap or an antiseptic agent the night before surgery. Hair around the planned incision site should be clipped, not shaved, if it must be removed. Skin preparation at the planned incision site should be performed at the time of surgery using an alcohol-based antiseptic; studies support the efficacy of alcohol combined with either chlorhexidine or povidone iodine–based antiseptics. If antimicrobial prophylaxis is indicated, the correct agent should be given at the correct dose at the correct time (for example, in the 60 minutes before incision or 2 hours before incision for vancomycin or fluoroquinolones, respectively) and discontinued within 24 hours after surgery. Continuing antimicrobial agents postoperatively has not shown benefit, even in cases of intraoperative spillage of gastrointestinal contents. During surgery, patient normothermia and adequate volume replacement help maximize tissue oxygen delivery. Perioperative blood glucose levels should be maintained at less than 200 mg/dL (11.1 mmol/L). A primarily closed incision should remain covered with a sterile dressing for 24 to 48 hours.

KEY POINT

- Continuing prophylactic antimicrobial agents postoperatively has not shown benefit in preventing surgical site infections. HVC

Central Line-Associated Bloodstream Infections

Central line–associated bloodstream infections (CLABSIs) originate from a central venous catheter (including peripherally inserted central catheters) without another recognizable source of infection and cause bacteremia. Approximately 250,000 CLABSIs occur in the United States every year, with 80,000 occurring in the intensive care unit (ICU). CLABSIs increase length of hospital stay up to 24 days and have an attributable mortality rate of 35%. Approximately 55% of patients in the ICU and 24% of those in other units have a central line. Antimicrobial resistance is a problem for most CLABSI-associated pathogens. CLABSI risk factors are shown in **Table 45**.

Diagnosis

A CLABSI should be suspected in patients with a central line who do not have an obvious source of bacteremia due to an infection at another site. At least two sets of blood cultures

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TABLE 45. Risk Factors for Central Line-Associated Bloodstream Infections

Nonmodifiable (Intrinsic) Risk Factors
Age (highest risk in neonates)
Male sex
Underlying diseases or conditions (for example, hematologic and immunologic deficiencies)
Neutropenia
Modifiable (Extrinsic) Risk Factors
Prolonged hospitalization before catheterization
Prolonged catheterization
Multiple CVCs
Multilumen CVC
Heavy microbial colonization at insertion site and catheter hub
Femoral vein (followed by internal jugular vein) catheterization
Lack of maximal sterile barriers for insertion and breaks in aseptic technique
Emergent insertion
Total parenteral nutrition
Poor catheter care and maintenance

CVC = central venous catheter.

CONT.

should be obtained (at least one peripherally) from different sites after appropriate skin disinfection and before starting antimicrobial therapy. Primary CLABSI pathogens include coagulase-negative staphylococci, *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]), *E. faecalis*, other *Candida* species, *K. pneumoniae* and *Klebsiella oxytoca*, *Enterococcus faecium*, *C. albicans*, *Enterobacter* species, *E. coli*, and *P. aeruginosa*. Blood cultures from central lines have a higher rate of false positivity; they may falsely identify a CLABSI by surveillance data definitions that are different from clinical definitions. However, negative cultures from central lines have a high negative predictive value for infection.

KEY POINT

- A central line–associated bloodstream infection should be suspected in patients with a central line who do not have an obvious source of bacteremia due to an infection at another site.

Treatment

The infected central line should be removed, especially when *S. aureus*, *P. aeruginosa*, or a *Candida* species is involved. Most cases of uncomplicated CLABSI are treated for 7 to 14 days (**Table 46**); *S. aureus* CLABSI may require treatment for 4 to 6 weeks after catheter removal. Shorter therapy durations (14 days) may be considered in select patients with *S. aureus* CLABSI whose catheters have been removed and do not have diabetes mellitus, are not immunosuppressed, have no implanted prosthetic devices, have no evidence of endocarditis by echocardiography (preferably transesophageal), and have no evidence of infected thrombophlebitis ; whose fever and bacteremia resolve within 72 hours of starting appropriate therapy; and whose physical examination and/or diagnostic tests do not suggest the presence of metastatic infection. Blood cultures should become negative after removal of the central line and appropriate antimicrobial therapy is given in all cases of CLABSI. When bacteremia persists, evaluation for

TABLE 46. Management of Central Venous Catheter-Related Bloodstream Infection Based on Pathogen[a]

Organism	Treatment
Uncomplicated[b]	
Coagulase-negative staphylococci	Remove catheter, antimicrobial therapy 5-7 days If catheter is not removed, systemic antimicrobials and antimicrobial lock treatment[c] 10-14 days
Staphylococcus aureus (no active malignancy or immunosuppression)	Remove catheter, antimicrobials ≥14 days
Enterococcus species	Remove catheter, antimicrobials 7-14 days
Gram-negative bacilli	Remove catheter, antimicrobials 7-14 days
Candida species	Remove catheter, antifungal agent 14 days after first negative blood culture
Complicated	
Suppurative thrombophlebitis, endocarditis, osteomyelitis, other site of metastatic or deep-seated infection	Remove catheter, antimicrobials 4-6 weeks (6-8 weeks for osteomyelitis)

[a]Short-term catheters.

[b]Bloodstream infection and fever resolves in 72 hours, no intravascular hardware, no endocarditis or suppurative thrombophlebitis.

[c]For detailed information on this procedure, refer to Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America [errata in Clin Infect Dis. 2010 Apr 1;50(7):1079; Clin Infect Dis. 2010 Feb 1;50(3):457]. Clin Infect Dis. 2009 Jul 1;49(1):1-45. [PMID: 19489710]

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CONT. a deeper source of infection, including endocarditis, should be performed.

KEY POINT

- The first step in treating a central line–associated bloodstream infection is to remove the infected central line, followed by appropriate antimicrobial therapy.

Prevention

Preventing CLABSIs begins with inserting and accessing central lines only when absolutely necessary and removing them as soon as possible. Hospitalized patients with central lines should be assessed daily to determine whether the line can be removed. Basic catheter insertion techniques should be followed, including hand hygiene, chlorhexidine skin antisepsis following recommended application methods and contact time for maximal effect, maximal barrier precautions, and optimal catheter site selection (with a subclavian site preferred and femoral sites avoided). Insertion techniques, checklists, and staff education significantly reduce CLABSIs. Although most prevention efforts and research have focused on CLABSIs occurring in ICUs, similar prevention strategies and precautions should be applied for all central lines.

KEY POINT

HVC
- Hospitalized patients with central lines should be assessed daily to determine whether the line can be removed.

Staphylococcus aureus Bacteremia

S. aureus is a leading cause of hospital-acquired bacteremia. Source control, with removal or drainage of the focus of infection (such as an infected central venous access catheter, a foreign body, or an abscess), is important for treatment success. Bacteremia that persists longer than 72 hours after the start of appropriate antimicrobial therapy suggests a complicated *S. aureus* infection and requires additional evaluation and a longer course of therapy. Endocarditis and vertebral osteomyelitis are two important complications of *S. aureus* bacteremia. Patients with complicated bacteremia should undergo evaluation for endocarditis with echocardiography, preferably transesophageal. Additionally, when bacteremia is related to an infected central line, 71% of patients have thrombosis of the affected vein and require a longer course of antimicrobial therapy to clear the infection. Complicated *S. aureus* bacteremia should be treated for 4 to 6 weeks with an appropriate antimicrobial agent. Blood cultures should be repeated every 2 to 4 days until they are negative in order to document clearance of bacteremia. Bacteremia caused by methicillin-sensitive *S. aureus* (MSSA) should be treated with a penicillinase-resistant semisynthetic penicillin (nafcillin) or a first-generation cephalosporin (cefazolin) given at maximal doses. Vancomycin leads to higher rates of relapse and microbiologic failure in the treatment of MSSA bacteremia because it has slow bactericidal activity compared with β-lactam antibiotics.

For complicated bacteremia with MRSA, vancomycin and daptomycin are the preferred antimicrobial agents for treatment. Vancomycin trough concentrations of 15 to 20 μg/mL are recommended. For isolates with a vancomycin minimum inhibitory concentration (MIC) of 2 μg/mL or less, the patient's clinical response determines whether to continue vancomycin or change to an alternate agent, independent of the MIC. An alternative to vancomycin should be considered if no clinical or microbiologic (such as persistent bacteremia) response occurs despite adequate source control. Bacteremia may persist owing to the slow bactericidal activity of vancomycin, inadequate dosing, or poor tissue penetration. Vancomycin should not be used when the isolate has an MIC greater than 2 μg/mL; daptomycin is an acceptable alternative if the isolate is susceptible, although resistance has developed in patients taking daptomycin. Some experts recommend trying high-dose daptomycin (8–10 mg/kg per day) if bacteremia persists despite adequate source control. The median time to clearance of MRSA bacteremia is 7 to 9 days.

Management of persistent MSSA and MRSA bacteremia includes a search for, and removal of, all foci of infection, including surgical debridement of infected wounds and abscess drainage. It is important to remember that foci of infection not present on initial evaluation may develop with persistent bacteremia. Combination antimicrobial agents (for example, β-lactams and aminoglycosides, vancomycin and rifampin) to enhance bacterial killing do not improve outcomes and should not be given. Daptomycin should not be used in patients with concomitant *S. aureus* pneumonia because it is inactivated by surfactant.

KEY POINTS

- Bacteremia caused by methicillin-sensitive *Staphylococcus aureus* should be treated with a penicillinase-resistant semisynthetic penicillin (nafcillin) or a first-generation cephalosporin (cefazolin); for complicated bacteremia caused by methicillin-resistant *S. aureus*, vancomycin and daptomycin are the preferred antimicrobial agents for treatment.
- The median time to clearance of methicillin-resistant *Staphylococcus aureus* bacteremia is 7 to 9 days.

Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

General Information

Hospital-acquired pneumonia (HAP) is defined as pneumonia occurring more than 48 hours after admission that was not incubating at admission. Ventilator-associated pneumonia (VAP) is defined as pneumonia developing 48 hours after endotracheal intubation. HAP accounts for 15% of HAIs (the second most common HAI) and has an estimated attributable

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CONT.

mortality rate of 27% to 50%. It increases hospital length of stay by 7 to 9 days at an additional cost of $40,000. Risk factors for developing HAP are listed in **Table 47**. The most significant risk factor is intubation and mechanical ventilation. In patients receiving mechanical ventilation, the incidence of HAP increases 6-fold to 21-fold. VAP is the most common HAI in critically ill patients and occurs in 5% to 15% of patients using ventilators. Bacteria are the most commonly isolated pathogens. Viral and fungal pathogens also play a role, primarily in immunocompromised patients. Early onset (<5 days after admission/intubation) generally results from antimicrobial sensitive organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *S. aureus*, and antibiotic susceptible gram-negative bacteria); late onset (≥5 days after admission/intubation) is more likely with multidrug resistant organisms (MDROs), including *P. aeruginosa*, *K. pneumoniae*, *Acinetobacter* species, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, and MRSA.

KEY POINT

- The most significant risk factor for hospital-acquired pneumonia is intubation and mechanical ventilation.

Diagnosis

Diagnosing HAP and VAP can be difficult because no reliable tests exist to make a definitive diagnosis. Instead, diagnosis is based on clinical, radiologic, and microbiologic findings. Clinical findings include temperature greater than 38.0 °C (100.4 °F), leukocytosis or leukopenia, purulent sputum, and a decrease in arterial oxygen saturation. A new or progressing lung infiltrate on chest radiograph is also required; if clinical findings are present without radiographic findings, tracheobronchitis should be considered. A specimen from the lower respiratory tract should be obtained before starting antimicrobial therapy; however, inability to obtain a specimen should not delay therapy in critically ill patients. Alternatively, quantitative cultures of specimens obtained by bronchoalveolar lavage can be used to diagnose VAP (and confirm the microbiology of the infection). Bronchoalveolar lavage is similar to diagnosis by clinical findings in terms of antimicrobial use and outcomes.

TABLE 47. Risk Factors for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

Modifiable Risk Factors	Nonmodifiable Risk Factors
Depressed level of consciousness	Age >70 years
Enteral nutrition	Immunosuppression
Malnutrition	Thoracic or abdominal surgery
Mechanical ventilation	Underlying chronic lung disease
Oropharyngeal colonization	
Reintubation	
Stress ulcer prophylaxis	
Supine position	

KEY POINT

- Clinical findings of ventilator-associated pneumonia include temperature greater than 38.0 °C (100.4 °F), leukocytosis or leukopenia, purulent sputum, and a decrease in arterial oxygen saturation.

Treatment

Therapy should be started promptly when HAP is suspected. Empiric treatment guidelines depend on whether HAP is early or late onset. Combination antimicrobial therapy may be considered for empiric therapy to provide a broader spectrum of coverage when MDROs are possible pending microbiologic testing results. No evidence indicates that HAP or VAP caused by *Pseudomonas* species requires combination therapy or that a synergistic combination improves outcomes. If a patient had a witnessed aspiration event or recent surgery, antimicrobial coverage for oral anaerobes may be considered. Cephalosporins should be avoided as monotherapy in situations in which extended spectrum β lactamase (ESBL)-producing gram-negative organisms (such as *K. pneumoniae*) are prevalent; a carbapenem may be a more appropriate empiric antimicrobial choice in such settings. All patients should be re-evaluated for clinical improvement and review of microbiologic results at 48 to 72 hours and considered for de-escalation (changing to narrow spectrum or oral therapy) or discontinuation of antimicrobial therapy when the diagnosis is in doubt. De-escalation of antimicrobial therapy is considered when culture results are available and the patient has stabilized (clinical improvement usually takes 48–72 hours) to prevent the emergence of antimicrobial resistance. The duration of therapy for HAP and VAP is generally 7 to 8 days except in cases caused by *P. aeruginosa* or *Acinetobacter* species, for which treatment should continue for 14 days. Patients who do not improve within 72 hours of appropriate antimicrobial therapy initiation should be evaluated for infectious complications, an alternate diagnosis, or another site of infection to explain the clinical picture. (For example, a patient with moderate to large pleural effusions should be evaluated for infection with a diagnostic thoracentesis.)

KEY POINTS

- No evidence indicates that hospital-acquired pneumonia or ventilator-associated pneumonia caused by *Pseudomonas* species requires combination therapy or that a synergistic combination improves outcomes. HVC
- Patients suspected of having hospital-acquired or ventilator-associated pneumonia who do not improve within 72 hours of appropriate antimicrobial therapy initiation should be evaluated for infectious complications, an alternate diagnosis, or another site of infection to explain the clinical picture.

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Prevention

Avoiding intubation, if possible, and using noninvasive positive-pressure ventilation as an alternative, when feasible, can decrease the risk for HAP. Sedation should be minimized and interrupted once daily if not clinically contraindicated in patients who are mechanically ventilated, and patients should be assessed for readiness for extubation using spontaneous breathing trials. This practice has been shown to decrease the duration of intubation by 1 to 2 days. The head of the bed should be elevated 30 to 45 degrees; a supine position, particularly in patients receiving enteral nutrition, increases the risk for VAP. Daily oral care with chlorhexidine may benefit some patients. Additional components of commonly used ventilator guidelines include subglottic suctioning, peptic ulcer disease and deep venous thrombosis prophylaxis, and avoiding gastric overdistention. One study showed that using a multifaceted intervention and ventilator guidelines decreased VAP rates by 71%.

KEY POINT

HVC
- Avoiding intubation (if possible) and using noninvasive positive-pressure ventilation as an alternative (when feasible) can significantly decrease the risk for hospital-acquired pneumonia.

Hospital-Acquired Infections Caused by Antimicrobial-Resistant Organisms

Up to 75% of HAIs are associated with organisms resistant to first-line antimicrobial agents. Infections with MDROs are associated with increased morbidity, mortality, and cost (up to $20 billion per year). Antimicrobial resistance has been noted in nearly all bacterial pathogens. However, antimicrobial resistance has dramatically increased among gram-negative organisms in the last 10 years. ESBL-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae (production of *K. pneumoniae* carbapenemase enzyme is most common in the United States), and pan-resistant strains of *P. aeruginosa* and *Acinetobacter* species are particularly concerning. Among gram-positive organisms, more than two thirds of *E. faecium* isolates in the United States are vancomycin resistant. Vancomycin-intermediate *S. aureus* is a global concern. Vancomycin-resistant *S. aureus* remains rare. Infections caused by these organisms are particularly difficult and challenging to treat and are associated with mortality rates estimated to be up to four times higher than mortality seen with infections caused by non–antimicrobial-resistant strains. Resistance to antimicrobial agents is not limited to the hospital setting. It occurs in other health care settings and to a lesser extent in the community (such as community-associated MRSA). Limiting transmission of these organisms in any health care setting must be a priority and is best accomplished by full compliance with hand hygiene protocols and contact precautions, cleaning and disinfecting the environment and patient care equipment before it is used for another patient, and judicious use of antimicrobial agents. Although *C. difficile* is not technically an MDRO, it is often listed with MDROs as a problematic pathogen in health care settings.

KEY POINT

HVC
- Limiting transmission of antimicrobial-resistant organisms in health care settings is best accomplished by full compliance with hand hygiene protocols and contact precautions, cleaning and disinfecting the environment and patient care equipment before it is used for another patient, and judicious use of antimicrobial agents.

HIV/AIDS

Epidemiology and Prevention

More than 33 million persons worldwide are estimated to be infected with the retrovirus HIV-1, including more than 1 million persons in the United States. More than 50,000 persons are newly infected each year in the United States. HIV-2 is another retrovirus infecting humans, but almost all HIV-2 infections to date have been acquired in Africa; infection with HIV-2 remains uncommon in the United States. Although infection with HIV-2 can cause a positive result on screening serologic tests, the HIV-1/HIV-2 antibody differentiation immunoassay now recommended for HIV testing will differentiate HIV-2 from HIV-1 infection (see following section on Screening and Diagnosis). Because the remainder of this chapter deals specifically with HIV-1, the term *HIV* is used throughout.

HIV is spread by sexual contact (estimated to be responsible for >80% of all infections), by contact with infected blood (transfusions, shared needles, occupational exposures), or perinatally. Transmission can be reduced by use of condoms and clean needle exchange programs. Transmission is also reduced (although not to zero) with attainment of undetectable viral load levels in the blood of infected patients. Treatment of a pregnant woman significantly reduces perinatal transmission. Prophylaxis with antiretroviral agents can reduce HIV infection in the postexposure and preexposure settings.

KEY POINT

- HIV is spread by sexual contact or by contact with infected blood, such as transfusions, shared needles, occupational exposures, or perinatal transmission.

Pathophysiology and Natural History

HIV can infect numerous cell types, most significantly CD4 T-helper lymphocytes. HIV integrates into the host cell

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genome, and long-lived cells can serve as a reservoir of virus, which contributes to the challenge of developing a cure for HIV infection. Replication of HIV contributes to early death of T cells, depletion of CD4 cells, and immunocompromise, resulting in increased risk for opportunistic infections and development of AIDS.

Acute HIV Infection

Most persons who develop HIV infection experience an acute symptomatic illness, referred to as acute retroviral syndrome, within a few weeks of acquiring the infection. Severity varies, but presentation is most often consistent with an infectious mononucleosis syndrome. Signs and symptoms and their frequency are listed in **Table 48**. Differential diagnosis includes acute infection with Epstein-Barr virus, cytomegalovirus, influenza, and a hepatitis virus and syphilis. Patients with acute infection may not yet be producing antibodies against HIV antigen (the "window period"), which results in negative results on traditional HIV serologic testing. Therefore, diagnosis of acute HIV infection during this time period relies on detecting the virus by RNA polymerase chain reaction or p24 antigen testing. Because levels of virus are usually very high in patients with acute infection, treatment is recommended to reduce the rate of transmission and possibly to reduce the progression of disease.

KEY POINT

- Diagnosis of acute HIV infection relies on detecting the virus by RNA polymerase chain reaction or p24 antigen testing.

Chronic HIV Infection and AIDS

Whether patients with acute HIV infection are treated or not, signs and symptoms of infection resolve and the disease enters a chronic stage. Although patients may be asymptomatic for years, active viral replication and destruction of CD4 T-helper lymphocytes continue. Signs and symptoms of chronic HIV infection include the following:

- Lymphadenopathy
- Fever, night sweats
- Fatigue
- Weight loss
- Chronic diarrhea
- Seborrheic dermatitis, psoriasis, tinea, onychomycosis
- Oral aphthous ulcers, oral hairy leukoplakia, gingivitis/periodontitis
- Peripheral neuropathy
- Leukopenia, anemia, thrombocytopenia
- Nephropathy

AIDS is diagnosed when certain indicator opportunistic infections or malignancies develop or when the CD4 cell count falls below 200/μL. Even before reaching this cell count level, however, patients may develop recurrent or refractory infections, such as vaginal candidiasis, oral or genital herpes simplex virus infection, pneumococcal pneumonia, and herpes zoster.

KEY POINT

- In patients with chronic HIV infection, AIDS is diagnosed when certain indicator opportunistic infections or malignancies develop or when the CD4 cell count falls below 200/μL.

TABLE 48. Signs and Symptoms of Acute HIV Infection (Acute Retroviral Syndrome)

Sign/Symptom	Frequency (%)
Fever	96
Lymphadenopathy	74
Pharyngitis	70
Rash	70
Myalgia/arthralgia	54
Diarrhea	32
Headache	32
Nausea/vomiting	27
Hepatosplenomegaly	14
Weight loss	13
Thrush	12
Neurologic symptoms	12

Screening and Diagnosis

The recommended algorithm for diagnosing HIV infection has changed significantly with the recent implementation of the fourth-generation HIV test. This test combines an immunoassay for HIV antibody with a test for HIV p24 antigen (**Figure 22**). This improves the ability of the test to detect early HIV infection because p24 antigen becomes detectable a week before antibody in acute infection. Detection of antigen may help diagnose patients as early as 2 weeks after infection. Western blot testing is no longer recommended. Combined antibody/antigen testing with the approved assay has a specificity of 99.6% but must be confirmed with additional testing.

A positive result on HIV-1/2 antigen/antibody combination assay is followed by testing of the sample with the HIV-1/HIV-2 antibody differentiation immunoassay. Detection of HIV-1 or HIV-2 antibody confirms the diagnosis. Samples negative on the antibody differentiation immunoassay are tested with an HIV-1 nucleic acid amplification test (NAAT); if the NAAT result is positive with a negative antibody, then acute HIV infection is diagnosed. Specimens positive on the initial antigen/antibody combination immunoassay but negative on the antibody differentiation immunoassay and NAAT represent false-positive results. Although false-positive findings are rare, in a population with low pretest probability (such as in

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TABLE 51. Prophylaxis against Opportunistic Infections in HIV/AIDS[a]

Opportunistic Infection	Indication	Preferred Drug
Pneumocystis jirovecii	CD4 cell count <200/μL	TMP-SMX, double-strength tablet once daily or three times weekly
Toxoplasmosis	CD4 cell count <100/μL and positive serologic results	TMP-SMX, double-strength tablet once daily
Mycobacterium avium complex	CD4 cell count <50/μL	Azithromycin, 1200 mg/week
Tuberculosis	TST >5 mm or positive IGRA results	INH, 300 mg/d for 9 months

IGRA = interferon-γ release assay; INH = isoniazid; TMP-SMX = trimethoprim-sulfamethoxazole; TST = tuberculin skin test.

[a]Also recommended are the 23-valent pneumococcal polysaccharide vaccine and 13-valent pneumococcal conjugate vaccine, influenza vaccine annually, hepatitis B vaccine in susceptible persons, and hepatitis A vaccine for persons at high risk.

KEY POINTS *(continued)*

- Before treatment for latent tuberculosis or prophylaxis against *Mycobacterium avium* complex (MAC) infection begins, active tuberculosis infection must be ruled out in patients with a positive tuberculin skin test result or a positive result on interferon-γ release assay; active MAC infection must be ruled out in patients with a CD4 cell count less than 50/μL.

Complications of HIV Infection in the Antiretroviral Therapy Era

Metabolic Disorders

Management of metabolic disorders, including hyperlipidemia and diabetes mellitus, is of increasing importance in treating patients with HIV infection. This is partly for the same reasons that metabolic disorders are increasing in the general population and partly related to HIV infection and treatment. HIV infection is associated with decreases in serum total cholesterol, HDL cholesterol, and LDL cholesterol levels and increases in serum triglyceride levels. Treatment of HIV infection leads to increases in total cholesterol and LDL cholesterol levels. Additionally, certain antiretroviral agents, including some protease inhibitors, directly contribute to further increases in cholesterol and triglyceride levels. Although some antiretroviral agents, notably certain protease inhibitors, may contribute directly to insulin resistance, HIV treatment often leads to regaining of weight lost before the start of therapy; thus, it contributes to impaired fasting plasma glucose levels or development of diabetes. Results of lipid panels and fasting plasma glucose or hemoglobin A_{1c} measurements should therefore be monitored periodically as part of treatment.

Older antiretroviral agents are also associated with lipodystrophy, which refers to changes in fat distribution causing lipoatrophy in the face and extremities and fat accumulation centrally. Lipodystrophy is associated with adverse cosmetic and metabolic effects. Nucleoside analogues are also associated with mitochondrial toxicity, which can lead to lactic acidosis and may be fatal if not recognized. Avoidance of the nucleoside analogues stavudine and zidovudine has decreased the occurrence of lipodystrophy and mitochondrial toxicity.

Osteopenia and osteoporosis are increased in patients with HIV infection; however, the role of specific antiretroviral agents, such as tenofovir, in these conditions is unclear. Bone densitometry assessment should be considered in specific patients with HIV infection (postmenopausal women, men older than 50 years, and all patients with other risk factors for osteopenia or osteoporosis).

Kidney dysfunction is increasingly being diagnosed in patients with HIV infection. Although HIV can cause associated nephropathy and chronic kidney disease, other factors contributing to kidney dysfunction include diabetes and certain antiretroviral agents, most notably tenofovir. Because proteinuria is usually the first manifestation of tenofovir nephrotoxicity, patients receiving tenofovir require urinalysis every 6 to 12 months. Additionally, certain agents used in antiretroviral regimens, notably cobicistat and dolutegravir, inhibit tubular secretion of creatinine. This can cause measured serum creatinine to increase without any true change in glomerular filtration rate and should not be mistaken for actual kidney dysfunction. Dialysis or kidney transplantation is an option for selected patients with HIV infection and end-stage kidney disease.

All patients with HIV infection should be evaluated for active hepatitis B and C because coinfection is associated with increased risk for progression and worse prognosis. Hepatitis C should be tested for annually. HIV infection and hepatitis B can both be treated with tenofovir, emtricitabine, and lamivudine, and including two of these agents in the medication regimen is crucial for managing coinfection. Treatment of hepatitis C (previously difficult because of overlapping toxicities of regimens for the two viruses) has become less problematic as a result of the new hepatitis C agents (sofosbuvir, simeprevir, ledipasvir, ombitasvir, paritaprevir, dasabuvir) (see MKSAP 17 Gastroenterology and Hepatology), although drug interactions between agents in both regimens will still require monitoring.

KEY POINTS

- HIV infection and its management are associated with increased incidence of hyperlipidemia, glucose intolerance, and diabetes mellitus.
- All patients with HIV infection should be evaluated for active hepatitis B and C because coinfection is associated with increased risk for progression and worse prognosis.

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Cardiovascular Disease

As patients with HIV infection age and develop metabolic risks, such as hyperlipidemia and diabetes, the incidence of cardiovascular disease increases. HIV infection is also associated with an increased risk for cardiovascular disease, which is thought to be caused by chronically high levels of inflammatory markers. Interrupting HIV therapy is associated with an increase in cardiovascular events and death, as well as more infectious complications. Therefore, even if HIV treatment regimens contribute to unfavorable metabolic effects, the net effect of antiretroviral therapy on risk for cardiovascular disease is very favorable because of benefits thought to be related to decreased inflammation. In patients with HIV infection, attention to the usual modifiable risk factors for cardiovascular disease is as important as, or more important than, in the general population.

KEY POINT

- Interrupting HIV therapy is associated with an increase in cardiovascular events and death, as well as more infectious complications.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) may develop in the first few months after initiation of antiretroviral therapy, most often in patients whose baseline CD4 cell count was low. IRIS is due to a vigorous inflammatory response, made possible by reconstitution of the immune system, to an infection that was already present, either known and receiving treatment or undiagnosed and asymptomatic. Patients may paradoxically appear to be presenting with a new infection or worsening of a previously diagnosed infection after undergoing successful treatment with antiretroviral agents. IRIS is associated with various infections but is most likely to be caused by infection with mycobacteria or fungi (such as cryptococcal meningitis). Therapy usually includes continued antiretroviral agents along with treatment of the specific infection. Adjuvant glucocorticoid therapy is sometimes needed to modulate the overactive inflammatory response.

KEY POINT

- Immune reconstitution inflammatory syndrome may develop in the first few months after initiation of antiretroviral therapy and is due to a vigorous inflammatory response, made possible by reconstitution of the immune system, to an infection that was already present, either known and being treated or undiagnosed and asymptomatic.

Opportunistic Infections

In patients with untreated HIV infection, decreasing CD4 cell counts predispose them to infections that do not usually occur in persons with an intact immune system. These opportunistic infections usually develop when the CD4 cell count is less than 200/μL and become even more likely when the count is lower. However, mucocutaneous *Candida* infection can develop with CD4 cell counts greater than 200/μL. Oral candidiasis (thrush) most often can be treated with topical agents such as clotrimazole troches. Dysphagia or other swallowing symptoms indicate esophageal involvement, and treatment of esophageal candidiasis requires a systemic agent such as fluconazole.

Cryptococcus infection may be isolated to the lung but usually has disseminated before diagnosis and manifests as subacute or chronic meningitis. Cryptococcal meningitis is diagnosed by cerebrospinal fluid culture or by antigen testing of cerebrospinal fluid or serum. Treatment includes antifungal agents and control of increased intracranial pressure by serial lumbar punctures or shunting.

Pneumocystis jirovecii pneumonia is a common complication in patients with HIV infection who have not received prophylaxis. Patients present with subacute onset of fever, dyspnea, and dry cough, and chest radiographs most commonly show diffuse interstitial or alveolar infiltrates (**Figure 23**). Although the microorganisms may be found in induced sputum, diagnosis usually requires stains of bronchoalveolar lavage fluid. High-dose trimethoprim-sulfamethoxazole is the treatment of choice. During treatment, an immune response to dying microorganisms may actually worsen disease in the first few days. Adjunctive glucocorticoids are beneficial and should be used in patients with an arterial partial pressure of oxygen (breathing ambient air) of less than 70 mm Hg (9.31 kPa) or an alveolar-arterial gradient of greater than 35 mm Hg (4.66 kPa).

Toxoplasma gondii can cause encephalitis in patients with CD4 cell counts less than 100/μL. Diagnosis is typically

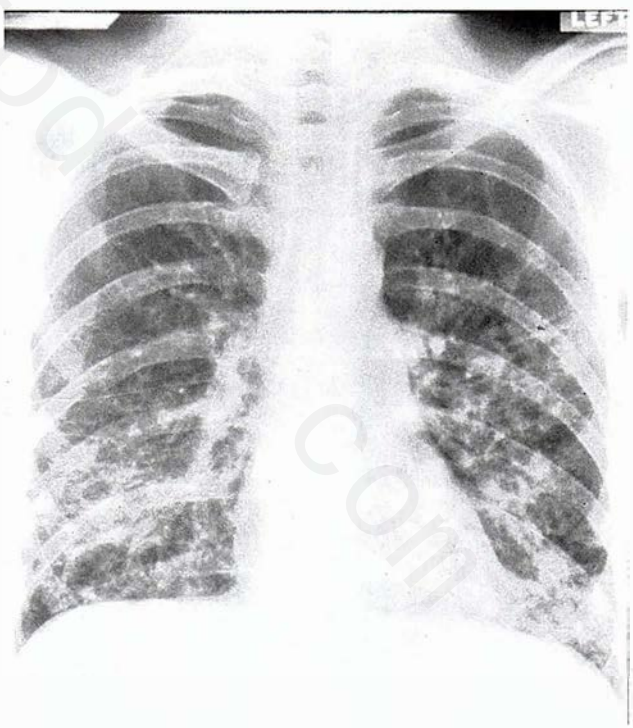

FIGURE 23. The chest radiograph for *Pneumocystis* pneumonia in a patient with AIDS typically shows diffuse bilateral interstitial or alveolar infiltrates. Diagnosis can be confirmed by identification of stains of the organism in sputum or bronchoalveolar lavage fluid.

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CONT.

based on signs and symptoms and imaging findings. Patients present with headache, fever, focal neurologic deficits, and possibly seizures. Multiple ring-enhancing lesions are seen on imaging studies (**Figure 24**). MRI is preferred to CT because of higher sensitivity. Toxoplasmosis in patients with AIDS is almost always a reactivation disease; therefore, results of serologic testing for anti-*Toxoplasma* IgG antibodies are usually positive. After presumptive treatment (with pyrimethamine plus either sulfadiazine or clindamycin), patients should be assessed for response within 1 or 2 weeks of starting therapy.

Tuberculosis and MAC infection are the most common mycobacterial infections in patients with AIDS. Tuberculosis may present at any CD4 cell count, is more likely to be extrapulmonary at presentation, and may not have the classic chest radiographic findings. Treatment of tuberculosis and HIV coinfection must take into account drug interactions between the rifamycins and many antiretroviral agents. MAC infection in patients with AIDS is usually disseminated at presentation and develops at CD4 cell counts less than 50/μL. Clinical features include fever, sweats, weight loss, lymphadenopathy, hepatosplenomegaly, and cytopenias. Treatment involves a multidrug regimen with clarithromycin or azithromycin as the cornerstone of therapy.

Cytomegalovirus (CMV) infection in patients with AIDS usually presents with specific end-organ dysfunction rather than a nonspecific systemic illness. The most common manifestations are retinitis, esophagitis or colitis, and polyradiculitis or encephalitis. The diagnosis may be made clinically or by demonstrating CMV by histopathologic studies or NAAT. Initial treatment of CMV infection is oral valganciclovir or intravenous ganciclovir.



FIGURE 24. This patient with AIDS has cerebral toxoplasmosis characterized by a ring-enhancing brain lesion associated with edema and mass effect.

Molluscum contagiosum is a poxvirus infection that most commonly causes multiple small papules on the face and trunk; it usually responds to immune reconstitution after treatment of the HIV infection. *Bartonella* infection causes bacillary angiomatosis and is characterized by skin lesions that resemble Kaposi sarcoma (KS). KS is caused by a herpes family virus (human herpesvirus 8) and presents with lesions that may vary in color from red to purple to brown and may be macules, papules, plaques, or nodules. KS is most often found on the skin but may also occur on mucous membranes of the respiratory and gastrointestinal tracts.

KEY POINTS

- In patients with untreated HIV infection, opportunistic infections usually develop when the CD4 cell count is less than 200/μL.
- Diagnosis of *Pneumocystis jirovecii* pneumonia usually requires stains of bronchoalveolar lavage fluid.
- The most common manifestations of cytomegalovirus infection are retinitis, esophagitis or colitis, and polyradiculitis or encephalitis.
- In patients with AIDS, Kaposi sarcoma presents with lesions that may vary in color from red to purple to brown and may be macules, papules, plaques, or nodules.

Management of HIV Infection

When to Initiate Treatment

Recommendations regarding when to start treatment for HIV infection have changed over the years as new data and new regimens become available. Current recommendations from the U.S. Department of Health and Human Services are updated regularly and are available at the National Institutes of Health AIDSInfo Web site (www.aidsinfo.nih.gov). Newer regimens are better tolerated and easier to adhere to (with many single-pill options available). With the additional benefits of fewer complications and reduced transmission, the threshold for starting treatment is now earlier in the disease process and at higher CD4 cell counts. Guidelines recommend treatment for all patients with HIV who are ready to start treatment; the strength of the recommendation varies by CD4 cell count and is based on randomized controlled trials for patients with cell counts less than 350/μL, on cohort studies for those with cell counts between 350 and 500/μL, and on expert opinion for those with cell counts greater than 500/μL. Randomized controlled trials in patients with normal cell counts are in progress.

KEY POINTS

- Newer antiretroviral regimens are better tolerated and easier to adhere to, so the threshold for starting treatment is now earlier in the disease process and at higher CD4 cell counts.
- Antiretroviral treatment is recommended for all persons with HIV who are ready to start treatment.

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Antiretroviral Regimens

The most important principle in treating HIV infection is that treatment must fully suppress viral replication to prevent the development of viral drug resistance. Generally, this involves treatment with three drugs from two different classes (**Table 52**). The effectiveness of therapy is determined by monitoring viral load levels, which should fall quickly and progressively within the first few weeks of treatment and reach undetectable levels within a few months. Viral loads should remain undetectable while the patient is receiving antiretroviral therapy, and any persistent detectable levels of virus should be considered as treatment failure. Such treatment requires a level of adherence that may be difficult to maintain for some patients, and adherence must be addressed before therapy begins and at every follow-up visit. The availability of single-pill, once-daily combination regimens has greatly simplified adherence.

Dosing frequency has also been reduced with the use of the pharmacologic "booster" drugs ritonavir and cobicistat. These drugs are not used as antiretroviral agents. Instead, they inhibit the metabolism of other drugs and improve therapeutic drug levels while requiring less frequent dosing. Cobicistat is coformulated with elvitegravir, an integrase inhibitor, and with the protease inhibitors darunavir and atazanavir. Ritonavir is given with most protease inhibitors. Many antiretroviral agents, and pharmacologic boosters especially, affect levels of many other drugs that are metabolized by the same pathways. Drug interactions are increasingly a concern, given the aging population with HIV infection and the increasing frequency in this population of other medical conditions that require treatment. Possible interactions must always be checked before any new drug is started (http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/32/drug-interactions).

TABLE 52. Antiretroviral Agents Used in the United States to Treat HIV Infection

Class	Agent[a]	Adverse Effects
Nucleoside RTIs	Abacavir	Hypersensitivity (test for and rule out HLA B5701 before prescribing)
	Didanosine	Nausea, neuropathy, pancreatitis, lactic acidosis
	Emtricitabine	Minimal toxicity, HBV activity
	Lamivudine	Minimal toxicity, HBV activity
	Stavudine	Neuropathy, lipodystrophy, lactic acidosis, dyslipidemia
	Tenofovir	Nausea, kidney disease and Fanconi syndrome, decreased bone density, HBV activity
	Zidovudine	Nausea, headache, anemia, leukopenia, lactic acidosis, lipodystrophy, myopathy
Nonnucleoside RTIs	Efavirenz	Neuropsychiatric symptoms (dizziness, somnolence, sleep disturbance, vivid dreams, mood changes), rash, dyslipidemia
	Etravirine	Nausea, rash
	Nevirapine	Hypersensitivity, rash, hepatitis
	Rilpivirine	Rash, headache, insomnia; requires food and gastric acid (no concomitant PPI use) for absorption
Protease inhibitors	Atazanavir	Nausea, hyperbilirubinemia, nephrolithiasis, rash; requires food and gastric acid (no concomitant PPI use) for absorption
	Darunavir	Nausea, diarrhea, rash
	Fosamprenavir	Nausea, diarrhea, rash
	Lopinavir	Nausea, diarrhea, hyperlipidemia, insulin resistance
	Saquinavir	Nausea, diarrhea, hyperlipidemia, QT prolongation
	Tipranavir	Nausea, diarrhea, hyperlipidemia, rash, hepatitis, intracranial hemorrhage
CCR5 antagonist	Maraviroc	Hypersensitivity, hepatitis
Integrase inhibitors	Dolutegravir	Elevated creatinine (decrease in tubular secretion, not GFR), insomnia, headache (otherwise well tolerated)
	Elvitegravir	Nausea, diarrhea (otherwise well tolerated)
	Raltegravir	Rash, myopathy (otherwise well tolerated)
Pharmacokinetic boosters	Cobicistat	Elevated creatinine (decrease in tubular secretion, not GFR), not recommended if CrCl <70 mL/min
	Ritonavir	Nausea, diarrhea, hyperlipidemia, insulin resistance, lipodystrophy

CrCl = creatinine clearance; GFR = glomerular filtration rate; HBV = hepatitis B virus; PPI = proton-pump inhibitor; RTIs = reverse transcriptase inhibitors.

[a]Many agents are also available as components of combination medications.

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Recommendations for initial HIV treatment include use of tenofovir and emtricitabine or abacavir and lamivudine as the dual nucleoside reverse transcriptase inhibitor "backbone." Options for a third agent to complete the regimen include the ritonavir-boosted protease inhibitor darunavir or the integrase inhibitors raltegravir, dolutegravir, or cobicistat-boosted elvitegravir. These regimens are effective and are associated with low toxicity. The choice between them is often based on patient preference and small differences in potential adverse effects.

KEY POINTS

- The most important principle in treating HIV infection is that the antiretroviral regimen must fully suppress viral replication to prevent the development of viral drug resistance.
- With effective antiretroviral therapy, viral load levels decrease quickly and progressively within the first few weeks of treatment, reach undetectable levels within a few months, and remain undetectable while therapy continues.
- Cobicistat and ritonavir are pharmacologic "booster" drugs that inhibit the metabolism of other drugs and improve therapeutic drug levels while requiring less frequent dosing.
- Recommendations for initial HIV treatment include three drugs from two different classes, usually two nucleoside reverse transcriptase inhibitors as a "backbone" plus a third agent, most commonly a protease inhibitor or an integrase inhibitor.

Resistance Testing

Testing for HIV drug resistance can be genotypic (looking for specific mutations associated with resistance to specific drugs) or phenotypic (assessing whether HIV can replicate in the presence of achievable levels of specific drugs). Genotypic testing is cheaper and faster, but phenotypic test results may be easier to interpret, especially for drugs such as protease inhibitors that have complicated patterns of resistance involving multiple mutations. Resistance testing should always be done before an initial drug regimen is chosen and when treatment failure occurs, as indicated by failure to suppress viral load or an increase in viral load that was previously suppressed. Resistance testing should be done while the patient is still receiving the ineffective regimen because testing after therapy is discontinued may allow wild-type virus to outgrow the resistant virus population so that resistance will not be detected. A viral load level greater than 500 copies/mL is usually necessary to successfully perform resistance testing.

KEY POINTS

- Resistance testing should always be done when antiretroviral therapy is initiated and when treatment failures occur.
- Resistance testing should be done while the patient is still receiving the ineffective regimen.

Management of Pregnant Patients with HIV Infection

All pregnant women should be tested for HIV infection; all those with HIV should be treated with antiretrovirals. Treatment for HIV infection during pregnancy will reduce the risk for perinatal transmission to the newborn from about 25% to less than 2%. About one third of transmissions occur in utero and about two thirds at delivery. Because the virus is also transmissible in breast milk, breast-feeding should be avoided in women with HIV infection, even those with undetectable viral load, if an alternative is available. Treatment of the mother after delivery is the same as in a nonpregnant patient with HIV infection.

KEY POINTS

- All pregnant women should be tested for HIV infection.
- All pregnant women with HIV infection should receive antiretroviral therapy to reduce perinatal transmission.

Postexposure Prophylaxis and Preexposure Prophylaxis

Postexposure prophylaxis for HIV infection after an occupational exposure has been used since the 1990s. Antiretroviral agents must be started as soon as possible after exposure to maximize likelihood of successful prevention; treatment is continued for 4 weeks. Exposed workers should be counseled on transmission, symptoms of acute infection, and toxicity of the medications being prescribed. Testing for HIV should be done immediately and at follow-up in 6 weeks, 12 weeks, and 6 months. Prophylaxis should always include at least three drugs. Drug selection may depend on the history of viral resistance in the source patient, but the recommended regimen is tenofovir, emtricitabine, and raltegravir.

Prophylaxis against significant nonoccupational exposures is also recommended by the Centers for Disease Control and Prevention. Table 53 outlines the risk for HIV transmission

TABLE 53. Risk for Transmission of HIV per Single Exposure

Exposure	Risk (%)
Occupational—needlestick	0.3
Occupational—mucous membrane	0.09
Needle-sharing injection drug use	0.7
Receptive anal intercourse	0.5
Receptive vaginal intercourse	0.1
Insertive anal intercourse	0.07
Insertive vaginal intercourse	0.05
Oral sex	0.01

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CONT.

associated with each type of single exposure. Prophylaxis is recommended for persons presenting with an exposure within the previous 72 hours. Counseling, recommended antiretroviral regimen, and testing are the same as for occupational exposure.

Data also support the use of preexposure prophylaxis (PrEP) in certain populations with ongoing high risk for infection, such as sexual partners of infected persons. Studies have shown benefit in heterosexual partners of infected persons, men who have sex with men, and injection drug users, and consideration of PrEP is recommended for persons in such groups who can adhere to the daily regimen. Efficacy has varied depending on adherence to the regimen; rates of reduction in new infection ranged from 42% to 75% and as high as 92% in patients whose adherence was documented by monitoring blood levels of the drugs. The FDA-approved regimen for PrEP is combination tenofovir-emtricitabine taken once daily. Patients should be counseled regarding possible drug toxicity, the need for strict adherence to the regimen, and the need for continued barrier precautions during sex because the effectiveness of this regimen is less than 100%. They should also be tested for HIV infection, hepatitis B, and other sexually transmitted infections before initiating preventive therapy. Women also require a pregnancy test before starting any regimen. While receiving prophylaxis, patients should be monitored for HIV infection and kidney function (and pregnancy in women) every 2 to 3 months.

KEY POINTS

- Postexposure prophylaxis for HIV infection after an occupational exposure or a significant nonoccupational exposure must be started as soon as possible; prophylaxis should always include three drugs taken for 4 weeks.
- The FDA-approved regimen for preexposure prophylaxis is combination tenofovir-emtricitabine taken once daily.

Viral Infections

Influenza Viruses

Overview

The influenza virus group consists of three enveloped RNA members of the family Orthomyxoviridae: influenza A, B, and C. Influenza A viruses are further classified into hemagglutinin (H) and neuraminidase (N) subtypes based on activity of their surface envelope glycoproteins. Influenza A viruses infect humans and other animal (for example, avian and swine) hosts. Influenza B viruses infect only humans. Influenza C viruses are rarely recognized in humans.

H and N surface envelope glycoproteins (antigenic variation) change frequently. Minor changes (antigenic drift) are partly responsible for seasonal outbreaks or epidemics that occur almost yearly. Major changes (antigenic shift) are alterations in the virus caused by reassortment of genes between human and animal influenza A strains. Emergence of a new influenza virus for which humans have no previous protective immunity may result in severe worldwide pandemics.

Influenza A outbreaks generally occur in winter, with attack rates of 10% to 20%. Seasonal influenza disproportionately affects persons 65 years of age or older. Very old persons, very young children, persons with chronic medical conditions, and pregnant women often develop severe disease, which accounts for most hospitalizations and deaths attributable to this infection. In pandemics, disease extends beyond the usual season with higher attack rates and increased mortality in all age groups, especially otherwise healthy young adults. The highly pathogenic H5N1 avian influenza virus predominantly affects children and young adults recently exposed to infected birds and poultry in Europe and Asia. Person-to-person human transmission appears to be limited. The novel H7N9 influenza virus in China is also believed to result from exposure to infected poultry or contaminated environments. To date, no evidence of sustained person-to-person spread has been found.

KEY POINT

- Seasonal influenza disproportionately affects persons 65 years or older; more severe infection often develops in very old persons, very young children, persons with chronic medical conditions, and pregnant women.

Clinical Features and Evaluation

Influenza virus is transmitted by sneezing and coughing. After an incubation period of 1 to 4 days, patients develop fever, headache, myalgia, pharyngeal irritation, and respiratory symptoms (dry cough and nasal discharge). Mild or asymptomatic infections occur, particularly with influenza B. Viral shedding begins 24 to 48 hours before symptom onset and may continue for 5 to 10 days. Patients with uncomplicated infection improve within 2 to 5 days. The most common complications are primary influenza pneumonia and secondary bacterial pneumonia, which are mainly responsible for increased morbidity and mortality in patients aged 65 years and older (see Community-Acquired Pneumonia).

During a confirmed local influenza outbreak, infection can be reliably diagnosed on the basis of clinical criteria alone. When confirmation is needed, rapid antigen tests of respiratory samples from nasopharyngeal swabs detect both influenza A and B. Positive test results are highly specific. However, sensitivity ranges from 40% to 80%. Detection of viral nucleic acid by polymerase chain reaction (PCR) is rapid, has high sensitivity and specificity, and can determine the type and subtype of influenza virus. Serologic assays are useful only for diagnosing infection retrospectively. Whether to test is based on how the result will influence management; testing is generally reserved for patients at high risk for complications, including adults older than 65 years, immunocompromised patients, pregnant and postpartum women, and health care workers.

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CONT. HSV eye infections. Intravenous acyclovir is required to treat HSV encephalitis. No studies of efficacy of systemic antiviral therapy for HSV aseptic meningitis exist.

KEY POINTS

- Primary infection with herpes simplex virus 1 most frequently manifests as gingivostomatitis and pharyngitis.
- Infection with herpes simplex virus 2 is a common cause of genital ulcer disease worldwide.
- Acyclovir, valacyclovir, and famciclovir are effective for treating episodic herpes simplex virus infections and suppressing recurrent infections.

Varicella-Zoster Virus

Overview

Varicella-zoster virus (HHV-3) causes a primary infection (varicella, or chickenpox) and a reactivation disorder (herpes zoster, or shingles). VZV establishes lifelong latency after the initial infection. Widespread pediatric varicella immunization has led to a 90% reduction in this once predominantly childhood disease. Varicella in adults and immunocompromised persons of any age is associated with greater morbidity and occasional mortality. Contact and airborne precautions should be used for hospitalized patients with varicella.

Herpes zoster occurs most often in persons older than 60 years. Up to 4% of persons who have had one episode of herpes zoster will experience a second episode; recurrence rates are increased in immunocompromised patients. Herpes zoster cannot be transmitted by contact with a person who has active herpes zoster lesions. However, persons lacking VZV immunity may develop varicella from close contact with viral particles in herpes zoster lesions. Hospitalized patients with herpes zoster must be placed in contact isolation; airborne isolation is required for patients who are immunocompromised.

Clinical Features and Diagnosis

Varicella develops after an incubation period of 10 to 21 days following exposure. Fever, malaise, and rash (often pruritic) subsequently develop. Classically, the exanthem begins on the face and trunk and spreads centrifugally to the extremities. Oropharyngeal mucosa may also be involved. Characteristic lesions consist of macules, papules, vesicles, and scabs in different stages of development at the same time (**Figure 26A**).

Most infections resolve within 1 to 2 weeks. Complications, most often in adults, include pneumonitis, acute cerebellar ataxia, encephalitis, hepatitis, and secondary bacterial skin infections. Nonimmune pregnant women are especially prone to varicella pneumonitis during the second and third trimesters, and perinatal infection may occur if infection presents approximately 5 days before and up to 2 days after delivery.

Herpes zoster presents with pain or paresthesias in a specific dermatome; the characteristic rash develops several days later (**Figure 26B**). In order of frequency, the thoracic, trigeminal, lumbar, and cervical cutaneous dermatomes are most often involved. Lesions are similar to varicella, and the rash does not cross the midline. Scattered lesions may occur outside the affected dermatome, more commonly in immunocompromised patients.



FIGURE 26. (*A*) Varicella (chickenpox) exanthem showing characteristic macules, papules, vesicles, and scabs in different stages of development at the same time. (*B*) Dermatomal herpes zoster showing vesicles and pustules on an erythematous base. (*C*) Trigeminal herpes zoster with nasociliary nerve involvement.

Pain due to acute neuritis and postherpetic neuralgia is the most debilitating complication. Postherpetic neuralgia refers to pain that continues for more than 1 month after resolution of the rash. More than 50% of cases occur in persons older than 60 years. Herpes zoster ophthalmicus is a potentially serious sight-threatening condition that may develop when the first branch of the trigeminal nerve is involved (**Figure 26C**). Involvement of the geniculate ganglion may cause Ramsay Hunt syndrome (pain and vesicles in the external ear canal, ipsilateral peripheral facial palsy, and altered or absent taste). Other extracutaneous complications include central nervous system involvement (meningoencephalitis or encephalitis, transverse myelitis, Guillain-Barré syndrome, and stroke), visceral disease (pneumonitis and hepatitis), and secondary bacterial skin infections.

Diagnosis of varicella is clinical and is based on characteristic skin lesions. The lesions may sometimes be confused with disseminated HSV or enteroviral infections; direct fluorescent antibody tests or PCR of samples from active vesicular lesions may be useful in differentiating the infection. Serologic assays detecting IgG antibodies to VZV confirm both previous infection and immunity.

Management

Acyclovir, valacyclovir, and famciclovir, if started within 72 hours of onset of VZV rash, accelerate the resolution of lesions, decrease new lesion formation and viral shedding, and lessen the severity of acute zoster pain. Valacyclovir and famciclovir also decrease the duration of postherpetic neuralgia. Intravenous acyclovir is indicated for hospitalized, immunocompromised patients and for patients with severe neurologic complications. The addition of glucocorticoids to antiviral therapy is controversial.

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Primary prevention of VZV infection involves avoidance of close contact with actively infected persons, routine childhood vaccination, and vaccination for adults who lack a history or serologic evidence of previous VZV infection. Vaccination within 3 to 5 days of exposure is also recommended for postexposure prophylaxis in susceptible immunocompetent persons. Varicella-zoster immune globulin, given within 4 to 10 days of exposure, is recommended for postexposure prophylaxis of immunocompromised adults and pregnant women without evidence of VZV immunity. A zoster vaccine is available and recommended for immunocompetent persons aged 60 years and older that reduces the incidence and severity of herpes zoster and postherpetic neuralgia. The vaccine may also be given to persons with a previous episode of herpes zoster.

KEY POINTS

- Acyclovir, valacyclovir, and famciclovir, if started within 72 hours of onset of varicella-zoster virus rash, accelerate the resolution of lesions, decrease new lesion formation and viral shedding, and lessen the severity of acute zoster pain.
- A zoster vaccine is available for immunocompetent persons aged 60 years and older that reduces the incidence and severity of herpes zoster and postherpetic neuralgia.

Epstein-Barr Virus

Epstein-Barr virus (EBV) (HHV-5) infects oropharyngeal B-cell lymphocytes; latency is established locally and in lymphatic tissue throughout the body. Primary infection mainly occurs when asymptomatic persons shedding EBV in saliva have intimate contact with previously uninfected persons. Most often, infection is asymptomatic and transpires in children and adolescents; antibodies to EBV are present in 95% of adults worldwide. EBV is the most common cause of infectious mononucleosis, characterized by an exudative pharyngitis, fever, and lymphadenopathy (mostly cervical). Splenomegaly is present in approximately 50% of patients. Other, less frequent findings include jaundice, hepatomegaly, and an erythema multiforme–like rash. In most cases, disease spontaneously resolve within 2 to 3 weeks; however, subsequent asthenia may persist for variable periods. EBV is associated with the development of certain malignancies in immunosuppressed and immunocompetent hosts (see Table 54).

Diagnosis can be confirmed by the presence of EBV heterophile (Monospot) antibodies or by the detection of EBV-specific antibodies, particularly IgM, to the EBV viral capsid antigen. With mononucleosis, a lymphocytosis typically exists, classically consisting of atypical lymphocytes. Thrombocytopenia, elevated hepatocellular enzymes, lactate dehydrogenase, and bilirubin are other commonly found laboratory abnormalities.

Acyclovir and other antiviral agents have not proven beneficial in the treatment of infectious mononucleosis or EBV malignancies. Glucocorticoids should be reserved for complications of EBV, such as a compromised airway or autoimmune hemolytic anemia but in general are not recommended for the treatment of mononucleosis.

KEY POINTS

- Epstein-Barr virus is the most common cause of infectious mononucleosis, characterized by exudative pharyngitis, fever, and lymphadenopathy.
- Glucocorticoids should be reserved for complications of Epstein-Barr virus but in general are not recommended for the treatment of mononucleosis.

Human Cytomegalovirus

Most cases of cytomegalovirus (CMV) infection (HHV-5) are asymptomatic, and the virus remains latent afterward. Serologic evidence of CMV is present in 60% to 100% of adults worldwide. CMV may spread by close contact through saliva, blood transfusion, organ transplantation, and breastfeeding. Disease acquisition can also occur through congenital or sexual transmission. Symptomatic primary infection usually manifests as a mononucleosis-like syndrome. Compared with patients who have EBV mononucleosis, patients are usually older and have pharyngitis less often. Fever alone may predominate, making CMV a consideration in persons with fever of unknown origin. The lung, liver, heart, and hematologic and central nervous systems may be involved during primary infection. Latent CMV frequently reactivates in immunocompromised patients. Manifestations of secondary infection include fever, retinitis, pneumonitis, hepatitis, esophagitis, gastritis, colitis, and meningoencephalitis.

Diagnosis relies on isolation of the virus from body fluids, such as urine; detection of CMV pp65 antigen in leukocytes; cytopathic demonstration of "owl's eye" intracellular inclusions; PCR; and serologic assays. Antiviral treatment is typically indicated in cases of disease reactivation in immunocompromised patients and occasionally in immunocompetent hosts with severe disease. Ganciclovir and valganciclovir are first-line agents and are also used as prophylaxis or preemptive therapy in certain transplant patients. Foscarnet and cidofovir are second-line agents.

KEY POINTS

- Most cases of cytomegalovirus infection are asymptomatic; symptomatic primary infection usually manifests as a mononucleosis-like syndrome.
- Ganciclovir is typically indicated in cases of cytomegalovirus reactivation in immunocompromised patients.

New Topics in Anti-infective Therapy

Introduction

There is a critical shortage of new antimicrobial agents active against multidrug-resistant organisms, often referred to as the ESKAPE pathogens: *Enterococcus faecium*,

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Staphylococcus aureus, *Klebsiella pneumoniae*, *Acinetobacter* species, *Pseudomonas aeruginosa*, and *Enterobacter* species. Few new agents address the growing problem of gram-negative antimicrobial resistance. Therefore, older antimicrobial agents with in vitro activity against resistant organisms are being used to address these therapeutic challenges.

Newer Antibacterial Drugs

Lipopeptides and Glycolipopeptides

Daptomycin is active in vitro against gram-positive organisms, such as *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]), streptococci, and enterococci (including vancomycin-resistant *E. faecium* [VRE] but not vancomycin-resistant *Enterococcus faecalis*). It is an alternative for *S. aureus* bacteremia organisms with vancomycin minimum inhibitory concentrations of 2 µg/mL or more. Resistance to daptomycin occurs but is rare.

Telavancin is active in vitro against aerobic gram-positive organisms, such as *S. aureus* (including MRSA), streptococci, and vancomycin-susceptible *E. faecalis*. New or worsening kidney dysfunction may occur during telavancin therapy, so kidney function should be monitored and the dose adjusted as needed.

Dalbavancin and oritavancin are new agents (approved in 2014) that have pharmacokinetics allowing administration once per week. Both are approved only for the treatment of skin and soft-tissue infections.

Refer to **Table 55** for expanded information on each of the newer antibacterial drugs discussed throughout this section.

KEY POINTS

- Daptomycin is approved for gram-positive complicated skin and soft tissue infections, *Staphylococcus aureus* bacteremia, and right-sided endocarditis.
- Telavancin is approved for complicated skin and soft tissue infections caused by aerobic gram-positive organisms (including methicillin-resistant *S. aureus*) and *S. aureus* hospital-acquired pneumonia.
- Dalbavancin and oritavancin are newly approved medications for the treatment of acute bacterial skin and skin structure infections and can be administered once per week.

Oxazolidinones

Oxazolidinone antibiotics exert a bacteriostatic effect. Linezolid has excellent bioavailability and is active in vitro against gram-positive aerobic organisms (including MRSA and VRE). Linezolid should not be used in patients taking monoamine oxidase inhibitors. Tedizolid is a new oxazolidinone that is more potent than linezolid against gram-positive organisms and has activity against linezolid-resistant *S. aureus*. It presents a lower risk for thrombocytopenia, lower potential for monoamine oxidase interaction, and shorter duration of treatment for skin and soft tissue structure infection (6 days versus 10 days) compared with linezolid.

KEY POINT

- Tedizolid is a new oxazolidinone that is more potent against gram-positive organisms than linezolid, and has activity against linezolid-resistant *Staphylococcus aureus* and a lower risk for thrombocytopenia.

β-Lactam Antibiotics

Ceftaroline is an advanced-generation bactericidal cephalosporin with activity against MRSA (unique for β-lactam antibiotics), multidrug-resistant *Streptococcus pneumoniae*, and *S. aureus* (vancomycin-intermediate, linezolid-resistant, daptomycin-nonsusceptible strains). It has gram-negative activity similar to that of ceftriaxone and is not active against *P. aeruginosa* or extended-spectrum β-lactamase–producing or carbapenemase-producing Enterobacteriaceae species. Ceftolozane-tazobactam, a combination novel cephalosporin and well-established β-lactamase inhibitor, is approved to treat complicated urinary tract infection (including pyelonephritis) and complicated intra-abdominal infections (in combination with metronidazole). This new agent is active against multidrug-resistant strains of *Pseudomonas* and extended-spectrum β-lactamase producing *Escherichia coli*.

KEY POINTS

- Ceftaroline is active against methicillin-resistant *Staphylococcus aureus*; multidrug-resistant *Streptococcus pneumoniae*; and vancomycin-intermediate, linezolid-resistant, daptomycin-nonsusceptible strains of *S. aureus* and has gram-negative activity similar to that of ceftriaxone.
- Ceftolozane-tazobactam is active against multidrug-resistant strains of *Pseudomonas* and extended-spectrum β-lactamase–producing *Escherichia coli*.

Glycylcyclines

Tigecycline is active in vitro against aerobic gram-positive organisms (including MRSA, VRE, and penicillin-resistant *S. pneumoniae*); many gram-negative organisms, including *Enterobacter cloacae*, carbapenem-resistant Enterobacteriaceae, and *Acinetobacter baumannii* (but not *P. aeruginosa* or *Proteus mirabilis*); anaerobes, including *Bacteroides fragilis*; and some atypical organisms (*Mycoplasma*).

KEY POINT

- Tigecycline is a broad-spectrum antibiotic that should be used only when alternative treatments are not available. HVC

Newer Uses for Older Antimicrobial Agents

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-SMX) is used to treat *Pneumocystis jirovecii*, *Stenotrophomonas maltophilia*,

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TABLE 55. Newer Antimicrobial Agents

Agent (class)	Adverse Events	Issues/Limitations	FDA Indications	Relative Cost
Ceftaroline (cephalosporin)	Similar to other cephalosporins	Limited clinical experience for MRSA outside of skin infections	Community-acquired pneumonia (not caused by MRSA, clinical trial data lacking), ABSSSI caused by susceptible organisms (including MRSA)	$$
Ceftolozane-tazobactam (combination cephalosporin–β-lactamase inhibitor)	Similar to other cephalosporins	Approved at the end of 2014, so limited clinical experience	Complicated UTI (including pyelonephritis) and complicated intra-abdominal infections (in combination with metronidazole)	$$$
Dalbavancin and oritavancin (glycolipopeptide)	Nausea, headache, diarrhea	Red man syndrome, elevated liver enzymes, cost	ABSSSIs caused by susceptible strains of gram-positive microorganisms (*Staphylococcus aureus* including MRSA, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group)	$$$$
Daptomycin (lipopeptide)	Creatinine kinase elevation	Inactivated by lung surfactant, not effective for pneumonia	Gram-positive complicated skin and soft tissue infections, *S. aureus* (including MRSA) bacteremia, and right-sided endocarditis	$$
Linezolid (oxazolidinone)	Reversible myelosuppression (most commonly thrombocytopenia) after 2 weeks, neuropathies after 28 days	SSRI interaction	Hospital- and community-acquired pneumonia (good lung penetration); uncomplicated and complicated skin and soft tissue infections, including diabetic foot infections without osteomyelitis; and vancomycin-resistant *Enterococcus* infections	$$$
Tedizolid (oxazolidinone)	Nausea, headache, diarrhea	Patients taking SSRIs were excluded from clinical trials	ABSSSI caused by susceptible gram-positive organisms (methicillin-sensitive and resistant *S. aureus*, linezolid-resistant *S. aureus*, *S. pyogenes*, *S. agalactiae*, *S. anginosus* group, *Streptococcus intermedius*, *Streptococcus constellatus*, *Enterococcus faecalis*)	$$
Telavancin (glycolipopeptide)	Nephrotoxicity	Interaction with coagulation tests, decreased efficacy in preexisting chronic kidney disease (estimated glomerular filtration rate <90 mL/min per 1.73 m^2)	Complicated skin and soft tissue infections caused by susceptible organisms and *S. aureus* (including MRSA) hospital-acquired pneumonia	$$$
Tigecycline (glycylcycline)	Diarrhea, nausea, vomiting	Black box warning (2013): increased risk for death; should be used only in situations in which alternative treatments are not available	Complicated skin and soft tissue infections, complicated intra-abdominal infections, community-acquired bacterial pneumonia caused by susceptible organisms	$$$

ABSSSI = acute bacterial skin and skin structure infections; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; SSRI = selective serotonin reuptake inhibitor; UTI = urinary tract infection.

CONT.

Enterobacter species, and *Nocardia* infections. TMP-SMX has come into wider use with the emergence of community-associated MRSA. It has broad aerobic, gram-positive (including MRSA), and gram-negative (excluding *P. aeruginosa*) activity. The most common adverse reactions associated with TMP-SMX are urticaria and rash. Hyperkalemia is an adverse effect of treatment, regardless of dosage. Reversible decreases in creatinine clearance also occur, and TMP-SMX may interfere with accurate measurement of creatinine, leading to falsely elevated levels.

KEY POINT

- Trimethoprim-sulfamethoxazole has broad aerobic, gram-positive, and gram-negative activity and is active against community-associated methicillin-resistant *Staphylococcus aureus*.

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Polymyxins

Colistin (polymyxin E), a bactericidal agent used to treat multidrug- and pan-resistant, aerobic, gram-negative infections, is active against many aerobic gram-negative bacteria, including *P. aeruginosa*, *K. pneumoniae*, *A. baumannii*, and carbapenem-resistant Enterobacteriaceae species. *Burkholderia cepacia* and *Proteus*, *Providencia*, and *Serratia* species are resistant. Colistin, usually formulated as colistimethate sodium, can be administered by nebulized aerosol to treat pan-resistant, gram-negative pneumonia or intraventricularly for multidrug-resistant, gram-negative meningitis (usually hospital acquired). Kidney function should be monitored because of colistin's dose-dependent nephrotoxic effects (mainly acute tubular necrosis) and used with caution in patients with preexisting kidney insufficiency. Transient neurologic dysfunction may be alleviated by decreasing the dose. H

KEY POINT

- When colistin is used, kidney function should be monitored because of its dose-dependent nephrotoxic effects; it should be used with caution in patients with preexisting kidney insufficiency.

Fosfomycin

Fosfomycin is a bactericidal agent available as an oral formulation that has gram-negative and gram-positive activity (including against MRSA and VRE). It has 30% to 37% bioavailability with good distribution into the kidneys, bladder, and prostate, achieving high urine levels for up to 48 hours after a single dose. It is an option for treating lower urinary tract infections caused by VRE and other multidrug-resistant uropathogens. Because of rapid clearance from serum, fosfomycin should not be used in bacteremia; because it does not achieve adequate levels in kidney tissue, it should not be used to treat pyelonephritis. H

KEY POINT

- Fosfomycin can be used to treat lower urinary tract infections caused by vancomycin-resistant *Enterococcus faecium* and other multidrug-resistant uropathogens but should not be used to treat bacteremia or pyelonephritis.

Aminoglycosides

Aminoglycosides, rapidly bactericidal agents with aerobic gram-negative activity, are generally not used alone because other antimicrobial options are easier to use and do not require monitoring of serum levels to avoid associated nephrotoxicity and ototoxicity. Aminoglycosides may be used to broaden empiric antimicrobial coverage or for synergy to enhance bactericidal activity in the treatment of some gram-positive infections (enterococcal endocarditis). Aminoglycosides remain active against some problem pathogens (*A. baumannii*, *P. aeruginosa*, carbapenem-resistant Enterobacteriaceae species). Extended-interval dosing is associated with less nephrotoxicity and has replaced traditional aminoglycoside dosing in many clinical situations. H

KEY POINT

- Aminoglycosides require monitoring of serum levels to avoid associated nephrotoxicity and ototoxicity, but extended-interval dosing creates less nephrotoxicity and has replaced traditional dosing in many clinical situations.

Rifamycins H

Rifamycins include rifampin (most common), rifapentine, and rifabutin. Rifampin is a bactericidal agent used against staphylococci, including MRSA, but is not used as monotherapy because resistance develops. Rifampin may be used with other antimicrobial agents, especially to treat prosthetic or indwelling foreign-body staphylococcal infections. Rifampin has excellent bioavailability and distributes widely in body tissues and fluids, including cerebrospinal fluid. Rifampin induces hepatic microsomal enzymes, causing multiple drug-drug interactions, and other medication doses should be adjusted as necessary. Hepatitis is the most serious potential adverse effect related to rifampin. H

KEY POINT

- Rifampin, the most commonly used rifamycin, is not used as monotherapy because resistance develops; it may be used with other antimicrobial agents and has excellent bioavailability, distributing widely through body tissues and fluids, including cerebrospinal fluid.

Antimicrobial Stewardship H

Suboptimal use of antimicrobial agents drives the emergence of antimicrobial resistance, leads to poor outcomes, and increases adverse events (5% risk per patient) and costs. Suboptimal use may include inappropriate use of antimicrobial agents when not indicated and incorrect antimicrobial choice, dose, route of administration, or duration of therapy. Antimicrobial stewardship programs promote responsible antimicrobial use by monitoring and giving advice on high-risk, high-cost agents; combination therapy; intravenous-to-oral conversion; streamlining; de-escalation; and duration of therapy.

Combination therapy has not been clinically shown to minimize the emergence of resistance but may be used as empiric therapy to broaden the spectrum of activity, provide coverage for potential antimicrobial-resistant organisms pending culture and in vitro susceptibility results, or for synergy (more rapid killing) in specific situations such as enterococcal endocarditis. Conversion from an intravenous to an oral antimicrobial agent should be considered whenever possible to limit the need for intravenous catheter access and the risk for a catheter-related bloodstream infection. Considerations include a temperature less than 38.0 °C

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CONT. (100.4 °F) or clinical improvement over 24 hours, an improving leukocyte count, improving signs and symptoms related to infection with the patient clinically stable, a functional gastrointestinal tract with the ability to swallow medications (or having a nasogastric tube in place), no diagnostic indication for intravenous therapy (such as endocarditis, central nervous system infection, *S. aureus* bacteremia), and having a suitable oral alternative available with good oral bioavailability (including fluoroquinolones, oxazolidinones, metronidazole, clindamycin, trimethoprim-sulfamethoxazole, fluconazole, and voriconazole).

KEY POINT

HVC
- Suboptimal use of antimicrobial agents drives the emergence of antimicrobial resistance, leads to poor outcomes, and increases adverse events and costs.

Outpatient Parenteral Antimicrobial Therapy

Outpatient parenteral antimicrobial therapy (OPAT) allows patients to complete intravenous antimicrobial treatment safely and effectively in an outpatient setting. Common infections considered for OPAT include cellulitis and soft tissue infections, bone and joint infections, infective endocarditis (after an initial period of hospital care and clinical stabilization), antimicrobial-resistant infections in which parenteral therapy is the only option (such as urinary tract infection), and central nervous system infections (including meningitis, brain abscess, encephalitis after initial hospital care and clinical stabilization). In choosing an OPAT regimen, it may be necessary to consider an agent other than the one being used in the hospital to minimize the number of daily doses needed (by choosing agents with a long half-life to maximize the required dosing interval), required monitoring, and the potential for adverse effects that would require closer observation. All patients receiving OPAT should be followed closely by a physician to ensure the appropriate therapy is received, the monitoring plan (antibiotic levels, complete blood count, creatinine level, liver function tests, coagulation tests as appropriate for the antibiotic) is being followed, and the antibiotic dose and timing are adjusted as needed or stopped if adverse effects are encountered. Additionally, patient education regarding signs and symptoms of early intravenous line infection and how to report such concerns is important. OPAT is not appropriate if the patient's medical needs would be better met in the hospital. It is being increasingly used without initial hospitalization, which makes a thorough medical assessment even more important.

KEY POINT

HVC
- Outpatient parenteral antimicrobial therapy provides appropriately selected patients the ability to complete antimicrobial treatment in an outpatient setting.

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 33-year-old woman is evaluated in the emergency department for a 2-month history of fever, lethargy, weight loss, and headache. She moved to the United States from India 4 years ago. Her father died of tuberculosis 20 years ago. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, temperature is 38.6 °C (101.5 °F), blood pressure is 114/70 mm Hg, pulse rate is 94/min, and respiration rate is 18/min. BMI is 20. Except for lethargy, neurologic examination is unremarkable. No abnormalities are noted on ophthalmologic, cardiac, or pulmonary examinations or in the remainder of the physical examination.

Cerebrospinal fluid (CSF) studies:

Leukocyte count	275/μL (275×10^6), with 98% lymphocytes
Glucose	30 mg/dL (1.7 mmol/L)
Protein	250 mg/dL (2500 mg/L)
CSF opening pressure	150 mm H_2O

The remainder of a complete blood count and comprehensive metabolic panel are normal. Acid fast bacilli smear of CSF is negative, but polymerase chain reaction is positive for *Mycobacterium tuberculosis*.

Minimal basilar meningeal enhancement is seen on CT scan of the head without any evidence of cisternal or ventricular abnormalities, midline shift, or mass lesion.

In addition to four-drug antituberculous therapy, which of the following is the most appropriate additional treatment?

(A) Acetazolamide
(B) Dexamethasone
(C) Furosemide
(D) Ventriculoperitoneal shunt

Item 2

A 33-year-old man is admitted to the hospital after experiencing a generalized tonic-clonic seizure. He has also had increasing weakness of the left hand and arm, headaches, and fever of 1 week's duration. Medical history is significant for AIDS, without opportunistic infections in the past several years. His last clinic visit was more than 2 years ago, and his family reports that he has been taking his antiretroviral therapy (ART) only intermittently since around that time.

On physical examination, temperature is 37.3 °C (99.1 °C), blood pressure is 142/92 mm Hg, pulse rate is 96/min, and respiration rate is 14/min. He is somnolent and slightly confused. His general medical examination is normal. On neurologic examination, there is no nuchal rigidity. Left upper extremity weakness is noted, but the examination is otherwise unremarkable.

Laboratory studies:

CD4 cell count	66/μL
Leukocyte count	4400/μL (4.4×10^9/L) (differential: 80% polymorphonuclear cells, 12% lymphocytes, 5% eosinophils, 3% monocytes)
Cryptococcal antigen, serum	Negative
Toxoplasma gondii	IgG positive, IgM negative

Noncontrast head CT shows a single lesion in the right parietal area. Brain MRI with contrast confirms this lesion with additional smaller lesions in the left frontal, basal ganglia, and cerebellar areas; all show a small surrounding area of enhancement without edema. No meningeal enhancement is seen.

Which of the following is the most likely diagnosis?

(A) Central nervous system lymphoma
(B) Cryptococcosis
(C) Progressive multifocal leukoencephalopathy
(D) Toxoplasmosis

Item 3

A 59-year-old man is evaluated in the ICU for fever and leukocytosis. He was admitted to the ICU 13 days ago with respiratory failure resulting from Guillain-Barré syndrome and was intubated and mechanically ventilated. On hospital day 9, he developed fever without an increase in secretions or change in oxygenation. A new left lower-lobe infiltrate was seen on chest radiograph, and his leukocyte count was 17,500/μL (17.5×10^9/L). Sputum culture grew methicillin sensitive *Staphylococcus aureus*. Nafcillin was started, with temporary resolution of the fever within 48 hours. Medical history is otherwise unremarkable. Medications are nafcillin and intravenous immune globulin.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 132/84 mm Hg, pulse rate is 94/min, and respiration rate is 18/min. Pulmonary examination reveals decreased breath sounds in the left lower lung field. The remainder of the examination is noncontributory.

Laboratory studies show a leukocyte count of 17,300/μL (17.3×10^9/L). Sputum Gram stain reveals 1+ leukocytes and 1+ gram-positive cocci in clusters.

A new moderate left pleural effusion, but no increase in the left lower lobe infiltrate, is seen on chest radiograph. CT scan shows left lower lobe consolidation with air bronchograms and a moderate left pleural effusion.

Which of the following is the most appropriate next step in management?

(A) Add gram-negative antimicrobial coverage
(B) Change nafcillin to vancomycin
(C) Perform bronchoscopy with bronchoalveolar lavage
(D) Perform thoracentesis

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Item 4

A 42-year-old woman undergoes evaluation after being admitted to the hospital 2 days ago with fever; chills; and redness, pain, and swelling over the left mid-anterior shin to just below the knee. She reports falling 5 days before admission and abrading her shin. Empiric vancomycin was started on admission. Medical history is notable for type 2 diabetes mellitus controlled by diet. She takes no other medications.

On physical examination, temperature is 38.7 °C (101.7 °F), blood pressure is 112/74, pulse rate is 110/min, and respiration rate is 20/min. On cardiopulmonary examination, the lungs are clear, and no murmur is heard. A large area of erythema, tense edema, and diffuse tenderness is observed over the left anterior shin without signs of lymphangitic spread.

Laboratory studies show a leukocyte count of 14,500/μL (14.5×10^9/L) and serum vancomycin trough level of 17 μg/mL. Blood cultures obtained at admission grow methicillin-resistant *Staphylococcus aureus* with a vancomycin minimum inhibitory concentration of 4 μg/mL.

Which of the following is the most appropriate management of this patient's antimicrobial regimen?

(A) Add rifampin
(B) Continue current vancomycin dose
(C) Increase vancomycin dose
(D) Switch vancomycin to daptomycin

Item 5

A 40-year-old woman is evaluated for a 1-month history of cough, fever, night sweats, and weight loss. Pulmonary tuberculosis is strongly suspected, and the community has no reported cases of drug-resistant tuberculosis. She takes no medications.

On physical examination, temperature is 37.9 °C (100.2 °F), blood pressure is 130/70 mm Hg, pulse rate is 95/min, and respiration rate is 15/min. BMI is 21. Crackles are heard in the lung apices bilaterally.

Chest radiograph shows bilateral apical fibrocavitary disease.

A sputum smear reveals acid-fast bacilli.

The initial phase of four-drug tuberculosis therapy with isoniazid, rifampin, pyrazinamide, and ethambutol is planned.

In addition to liver function testing, which of the following baseline studies should be obtained in this patient as part of monitoring for potential adverse drug effects?

(A) Audiogram
(B) CD4 cell count
(C) Vestibular testing
(D) Visual acuity and color vision

Item 6

A 19-year-old woman is hospitalized for a 3-day history of fever. She has removed several embedded ticks from her skin in the last month. One day before admission, she noted onset of a bilateral temporal headache. On the day of admission, she noted neck stiffness, photophobia, and a new skin eruption.

On physical examination, temperature is 39.4 °C (102.9 °F), blood pressure is 130/58 mm Hg, pulse rate is 115/min, and respiration rate is 24/min. She is ill-appearing and resists passive flexion of the neck. Findings on neurologic examination are normal.

A typical representation of the skin rash on the trunk and extremities, including the palms and soles of her feet, is shown.



Laboratory studies:

Leukocyte count	14,900/μL (14.9×10^9/L)
Platelet count	36,000/μL (36×10^9/L)
Alanine aminotransferase	95 U/L
Aspartate aminotransferase	116 U/L
Cerebrospinal fluid (CSF) leukocyte count	173 (173×10^6/L) (45% polymorphonucleocytes, 52% lymphocytes, 3% eosinophils)
CSF Gram stain	Negative for organisms
Urine pregnancy test	Negative

Dexamethasone, ceftriaxone, vancomycin, and doxycycline are initiated. Within 48 hours, her fever has resolved, and her platelet count has normalized. Laboratory tests sent at admission reveal no growth on CSF bacterial cultures, and results on serologic testing for Rocky Mountain spotted fever are negative.

Which of the following is the most likely diagnosis?

(A) Enterovirus
(B) Heartland virus
(C) Lyme disease
(D) Rocky Mountain spotted fever
(E) West Nile virus

Item 7

A 52-year-old woman admitted 5 days ago with severe community-acquired pneumonia is evaluated for new onset of acute diarrhea. She has been treated with empiric antibiotic therapy, consisting of ceftriaxone and azithromycin. She has had five liquid bowel movements in the last 24 hours.

On physical examination, temperature is 37.9 °C (100.2 °F), blood pressure is 122/64 mm Hg, pulse rate is 90/min, and respiration rate is 18/min. There are crackles at the right lung base. Abdominal examination reveals normal bowel sounds and no tenderness to palpation.

Leukocyte count is 10,300/μL (10.3×10^9/L). The result of *Clostridium difficile* toxin polymerase chain reaction assay on stool sample is negative.

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Which of the following is the most appropriate management? CONT.

(A) Order stool bacterial cultures
(B) Prescribe an antimotility agent
(C) Prescribe metronidazole
(D) Repeat stool *Clostridium difficile* toxin polymerase chain reaction test

Item 8

A 40-year-old woman is admitted to the hospital for a 1-month history of diffuse abdominal pain, fever, sweats, fatigue, and weight loss. She reports no swallowing or other focal symptoms. Medical history is significant for AIDS, for which she began antiretroviral therapy and opportunistic infection prophylaxis 2 months ago. At that time, CD4 cell count was 23/μL and HIV viral load was 320,875 copies/mL. Medications are abacavir-lamivudine, ritonavir, darunavir, azithromycin, and trimethoprim-sulfamethoxazole.

On physical examination, temperature is 37.9 °C (100.2 °F), blood pressure is 122/76 mm Hg, pulse rate is 88/min, and respiration rate is 14/min. BMI is 22. The oropharynx is clear. Cervical, axillary, and inguinal 1-cm lymph nodes are palpated bilaterally. Lungs are clear. Heart examination is normal. The liver edge extends 2 cm below the right costal margin, and the spleen tip is palpable. No rash is noted, and the neurologic examination is normal.

Laboratory studies:

CD4 cell count	56/μL
HIV viral load	5140 copies/mL
Hemoglobin	9.2 g/dL (92 g/L)
Leukocyte count	3600/μL (3.6×10^9/L)
Alkaline phosphatase	349 U/L

Serum aminotransferases, bilirubin, and kidney function are normal.

Chest radiograph is normal. Abdominal CT shows retroperitoneal lymphadenopathy; diffuse hepatic and splenic enlargement without focal lesions; and normal stomach, small and large bowel, and kidneys.

Which of the following is the most likely diagnosis?

(A) Cytomegalovirus infection
(B) Disseminated candidal infection
(C) Disseminated *Mycobacterium avium* complex infection
(D) Medication toxicity

Item 9

A 28-year-old woman is admitted to the hospital with fever, vomiting, and change in mental status over the past 2 days. Her family reports that she has reported a headache for the past 4 weeks and that her symptoms have been progressively worsening. Medical history is significant for type 1 diabetes mellitus. Her only medication is insulin. She does not smoke, drink, or use drugs. She resides in Arizona.

On physical examination, temperature is 38.9 °C (102.0 °F), blood pressure is 110/80 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. BMI is 22. Oxygen saturation breathing ambient air is 97%. She is oriented to person but not place or time. The general medical examination is unremarkable. On neurologic examination, nuchal rigidity is noted, but no additional focal findings are present.

Laboratory studies show a cerebrospinal fluid (CSF) leukocyte count of 1500/μL (1500×10^6/L) with a predominant lymphocytosis but also presence of eosinophils, glucose level of 30 mg/dL (1.7 mmol/L), and protein level of 90 mg/dL (900 mg/L). CSF IgG complement fixation is positive for *Coccidioides immitis*.

MRI of the brain shows generalized leptomeningeal enhancement.

Which of the following is the most appropriate treatment?

(A) Caspofungin
(B) Fluconazole
(C) Intrathecal amphotericin B
(D) Itraconazole

Item 10

A 74-year-old woman is evaluated for positive syphilis serologic results. She is being evaluated for progressive difficulty with memory. She reports no known history of syphilis but lists several risk factors for possible infection in the past. Medical history is significant for hypertension and type 2 diabetes mellitus. Medications are enalapril, amlodipine, and metformin.

On physical examination, vital signs are normal. The general physical examination is normal, and her neurologic examination is unremarkable.

Cognitive testing is notable for a score of 19/30 on the Mini-Mental State Examination. Findings on serum rapid plasma reagin testing are positive, with a titer of 1:4. Results of confirmatory fluorescent treponemal antibody absorption testing are positive.

Which of the following is the most appropriate next step in management?

(A) Cerebrospinal fluid analysis
(B) Intramuscular benzathine penicillin
(C) Intravenous penicillin
(D) Serum VDRL test

Item 11

A 47-year-old man is evaluated in follow-up for a diagnosis of pulmonary tuberculosis 2 months ago. He is now completing the initial 2-month treatment phase consisting of rifampin, isoniazid, and ethambutol. Pyrazinamide was withheld owing to acute gouty arthritis at initial presentation. His isolate of *Mycobacterium tuberculosis* is susceptible to all first-line antituberculous agents. Medical history is remarkable for hypertension and gout, including recurrent acute gouty attacks and chronic tophaceous gout. Other medications are lisinopril and allopurinol.

On physical examination, vital signs are normal. The knees and several joints on the hands bilaterally show gouty changes, and tophi are noted at the elbows. The remainder of the examination is normal.

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Chest radiography reveals no cavitary lesions. Current sputum acid-fast smears are negative.

Which of the following is the most appropriate duration for the continuation phase of this patient's tuberculosis treatment with isoniazid and rifampin?

(A) 4 months
(B) 7 months
(C) 10 months
(D) 12 months

Item 12

A 33-year-old man is seen to establish ongoing care. He underwent kidney transplantation 3 years ago and has been stable since then, with no episodes of rejection or infection. A review of his immunizations indicates he received the scheduled childhood vaccinations, and his pretransplantation immunizations included the hepatitis A and B and the pneumococcal conjugate and polysaccharide vaccines. He has never received the varicella vaccine, and he was last administered a diphtheria-tetanus immunization following an accidental laceration 8 months ago. Medical history is significant for postinfectious glomerulonephritis as a child resulting in end-stage kidney disease requiring transplantation. Medications are cyclosporine, prednisone, and mycophenolate mofetil.

On physical examination, vital signs are normal. A well-healed abdominal incision is noted, but the examination is otherwise unremarkable.

Which of the following immunizations should be given now?

(A) 13-Valent pneumococcal conjugate vaccine
(B) 23-Valent pneumococcal polysaccharide vaccine
(C) Tetanus-diphtheria-acellular pertussis vaccine
(D) Varicella vaccine

Item 13

A 28-year-old man is evaluated after being informed his roommate at a homeless shelter was diagnosed with pulmonary tuberculosis. He reports no fever, cough, night sweats, or weight loss. Medical history is significant for injection drug use, most recently 2 weeks ago, although he reports no known infectious complications in the past. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. BMI is 22. Track marks secondary to injection drug use are present bilaterally on the antecubital fossa, without tenderness, warmth, erythema, or fluctuance. Cardiopulmonary examination and all other examination findings are normal.

A tuberculin skin test induces 7-mm induration.

Chest radiograph is normal.

Which of the following is the most appropriate next step in the management of this patient?

(A) Chest CT
(B) Isoniazid
(C) Isoniazid, rifampin, pyrazinamide, and ethambutol
(D) No further intervention

Item 14

A 30-year-old woman is evaluated for a 2-day history of increasing pain in the right antecubital fossa and biceps. She reports daily injection drug use. Medical history is otherwise unremarkable, and she takes no prescription medications.

On physical examination, temperature is 39.7 °C (103.5 °F), blood pressure is 90/56 mm Hg, pulse rate is 120/min, and respiration rate is 28/min. BMI is 28. She appears ill. No lymphangitis or right axillary or epitrochlear lymphadenopathy is evident. The right biceps area is extremely tender and warm, with multiple track marks, woody induration, edema, and overlying ecchymotic bullous lesions.

Laboratory studies:

Leukocyte count	23,000/μL (23×10^9/L) (80% neutrophils, 12% band forms, 8% lymphocytes)
Aspartate aminotransferase	55 U/L
Bilirubin, total	2.0 mg/dL (34.2 μmol/L)
Creatinine	1.7 mg/dL (150 μmol/L)
Electrolytes:	
Sodium	135 mEq/L (135 mmol/L)
Potassium	4.2 mEq/L (4.2 mmol/L)
Chloride	95 mEq/L (95 mmol/L)
Bicarbonate	16 mEq/L (16 mmol/L)

No gas or foreign body is seen on plain radiographs of the right arm and shoulder.

In addition to emergent surgical evaluation, which of the following is the most appropriate empiric treatment?

(A) Ceftriaxone plus metronidazole
(B) Doxycycline plus ciprofloxacin
(C) Penicillin plus clindamycin
(D) Vancomycin plus piperacillin-tazobactam

Item 15

A 50-year-old woman is evaluated in the hospital for persistent fever and flank pain. She was admitted 3 days ago for treatment of pyelonephritis because of nausea and vomiting. Her fever is persistent after 72 hours of treatment. Medical history is unremarkable. Her only medication is intravenous ceftriaxone.

On physical examination, temperature is 39.0 °C (102.2 °F), blood pressure is 110/60 mm Hg, pulse rate is 110/min, and respiration rate is 18/min. BMI is 26. Right costovertebral angle tenderness is noted on abdominal examination. The remainder of the examination is noncontributory.

Urinalysis and culture on admission revealed greater than 100,000 colony-forming units/mL of *Escherichia coli* susceptible to ceftriaxone. Blood culture is negative.

Which of the following is the most appropriate management?

(A) Kidney imaging
(B) Repeat urine culture
(C) Switch to gentamicin
(D) Continued observation

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Item 16

A 35-year-old man undergoes consultation for concerns of a possible HIV exposure. He reports that the condom broke the previous night during receptive anal intercourse with a partner who has HIV. He states that his partner is reliably taking antiretroviral therapy and is healthy. Medical history is notable for a negative HIV test result 6 months ago. He takes no medications.

On physical examination, vital signs are normal, as is the remainder of the physical examination.

An HIV antigen/antibody combination immunoassay is ordered.

Which of the following is the most appropriate next step in management?

(A) Determine partner's viral load
(B) Start combination tenofovir-emtricitabine
(C) Start combination tenofovir-emtricitabine and raltegravir
(D) Await results of HIV testing

Item 17

A 65-year-old woman is hospitalized for fever and altered mental status. Four days ago, she experienced headaches and had a temperature of 39.0 °C (102.2 °F). Today she developed aphasia, prompting hospital admission. Her medical history is otherwise noncontributory, and she takes no medications.

On physical examination, temperature is 39.3 °C (102.7 °F), blood pressure is 122/64 mm Hg, pulse rate is 98/min, and respiration rate is 18/min. The patient is unresponsive and grimaces to sternal rub. The neck is resistant to passive flexion. All extremities move spontaneously. There is no rash.

Cerebrospinal fluid (CSF) studies:

Leukocyte count	150/μL (150 × 10^6/L); 38% lymphocytes, 34% neutrophils, 28% monocytes
Erythrocyte count	0/μL (0 × 10^6/L)
Glucose	54 mg/dL (3.0 mmol/L)
Protein	137 mg/dL (1370 mg/L)
Pressure (opening)	150 mm H_2O
Gram stain	No organisms

Brain MRI shows no focal abnormality or hydrocephalus.

The patient is administered empiric therapy with dexamethasone, vancomycin, ceftriaxone, ampicillin, and acyclovir pending additional test results.

Which of the following is the most appropriate next step in management?

(A) Monitor intracranial pressure
(B) Perform transcranial Doppler ultrasonography
(C) Perform electroencephalography
(D) Start mannitol

Item 18

A 22-year-old man is admitted to the hospital for a 1-day history of severe headache, photophobia, and neck stiffness. He had noted fever starting 2 days before admission. Medical history is significant for an episode of meningococcal meningitis 5 years ago but is otherwise unremarkable. He takes no medications.

On physical examination, temperature is 38.8 °C (101.8 °F), blood pressure is 100/60 mm Hg, pulse rate is 110/min, and respiration rate is 18/min. BMI is 20. Nuchal rigidity is noted. Extraocular movements are intact, and the eye examination is unremarkable with no papilledema or retinal findings. The general medical examination is otherwise normal except for a petechial rash across the trunk and lower extremities.

Cerebrospinal fluid Gram stain is positive for gram-negative diplococci.

Ceftriaxone is started.

Which of the following is the most likely diagnosis?

(A) Selective IgA deficiency
(B) Common variable immunodeficiency
(C) Late complement component deficiency
(D) Classical complement pathway deficiency

Item 19

A 42-year-old woman is evaluated for headache of 4 days' duration. The headache is nonlocalizing and without apparent triggers. She reports no recurrent headaches and has no history of migraine. She has had untreated dental caries for 2 months and has noticed jaw swelling in the left mandibular region for the past 3 days. She takes no medications.

On physical examination, the patient is awake, alert, and oriented but appears uncomfortable. Vital signs, including temperature, are normal. Neck stiffness is present. Oral examination reveals several broken teeth and generally poor dentition, with the left upper molars showing evidence of dental caries. Neurologic examination reveals impaired extraocular movements, but mental status is normal. The remainder of the physical examination is unremarkable.

A CT scan of the head shows a small ring-enhancing lesion in left temporoparietal junction, approximately 1 cm in diameter.

CT guided stereotactic aspiration of the abscess is planned.

Which of the following is the most appropriate empiric antibiotic to administer intravenously?

(A) Meropenem
(B) Penicillin and metronidazole
(C) Trimethoprim-sulfamethoxazole
(D) Vancomycin

Item 20

A 31-year-old woman is evaluated for a 5-day history of a nonpainful cutaneous lesion on the back of her left hand. She works as a packer in a parcel distribution center. She does not recall injury to this area and reports no unusual employment or recreational exposures. She has not had

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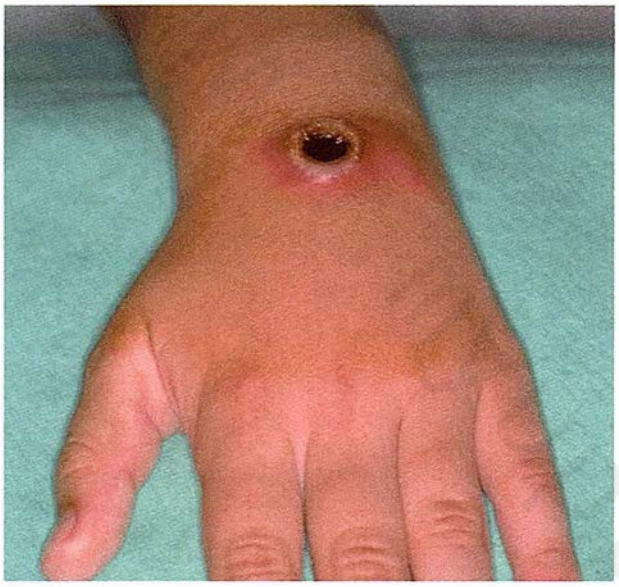
fever, cough, shortness of breath, headache, chest discomfort, or gastrointestinal symptoms. Yesterday, two coworkers were evaluated for similar lesions. Her husband has recently been prescribed an antibiotic after being diagnosed with a "boil" from which methicillin-resistant *Staphylococcus aureus* was cultured. Her only medication is an oral contraceptive pill.

On physical examination, vital signs are normal. Other than the lesion on the proximal dorsal surface of her left hand, the physical examination is normal.

The hand lesion is shown.



Which of the following is the most appropriate management?

(A) Begin doxycycline, imipenem, and rifampin
(B) Begin ciprofloxacin
(C) Begin trimethoprim-sulfamethoxazole
(D) Obtain biopsy and culture prior to initiating therapy

Item 21

A 22-year-old woman is evaluated during a routine office visit. She is pregnant at 38 weeks' gestation. She reports no dysuria, urgency, fever, or chills. Medical history is unremarkable. Her only medication is a prenatal vitamin.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 100/70 mm Hg, pulse rate is 80/min, and respiration rate is 16/min. Abdominal examination is consistent with her stage of pregnancy; no costovertebral angle tenderness is noted. The remainder of the examination is unremarkable.

Urine dipstick is positive for nitrites and leukocyte esterase. Urine culture grows greater than 100,000 colony-forming units/mL of *Escherichia coli* susceptible to ampicillin, nitrofurantoin, and trimethoprim-sulfamethoxazole.

Which of the following is the most appropriate treatment?

(A) Amoxicillin
(B) Nitrofurantoin
(C) Trimethoprim-sulfamethoxazole
(D) No treatment

Item 22

A 30-year-old woman is requesting HIV testing. She is asymptomatic and reports no known exposure to a person with HIV. She has had multiple lifetime sexual partners, all of whom are men, and none of whom were men known to have sex with other men. She reports no intravenous drug use by a sexual partner or herself. She does not use condoms and has been in a monogamous relationship for the past 6 months. Medical history is negative for any opportunistic infections or sexually transmitted infections. Her only medication is an oral contraceptive pill.

On physical examination, vital signs are normal. BMI is 23. The remainder of the evaluation is normal.

The HIV-1/2 antigen/antibody combination immunoassay is reactive. Result on a subsequent HIV-1/HIV-2 antibody differentiation immunoassay is negative, as is result on an HIV-1 nucleic acid amplification test.

Which of the following is the most appropriate next step in management?

(A) Repeat HIV-1/2 antigen/antibody combination immunoassay in 6 weeks
(B) T-cell subset testing
(C) Western blot HIV-1 antibody testing
(D) No further testing

Item 23

A 31-year-old man is evaluated for a recent exposure to chickenpox. He visited his sister's home last week. His nephew was subsequently developed a rash and was diagnosed with chickenpox 1 day after he left. He has no symptoms and states that he feels well. He never had chickenpox as a child and has not been immunized against varicella. Medical history is notable for psoriatic arthritis. His only medication is etanercept.

On physical examination, vital signs are normal. No skin rash is present. The remainder of the examination is normal.

The result of a serologic assay for antibodies against varicella-zoster virus is negative.

Which of the following is the most appropriate management?

(A) Acyclovir therapy
(B) Varicella vaccine
(C) Varicella-zoster immune globulin
(D) Varicella vaccine and varicella-zoster immune globulin
(E) Observation for 21 days after exposure

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Item 24

A 34-year-old woman is evaluated following elective cholecystectomy 2 weeks ago. She notes mild pain, redness, and swelling at the incision site with some "cloudy" drainage that started 3 days ago. She reports no fever or chills. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, temperature is 36.7 °C (98.1 °F), blood pressure is 110/72 mm Hg, pulse rate is 76/min, and respiration rate is 14/min. BMI is 30. She has erythema and mild tenderness around the incision site with a small amount of pinkish drainage. The remainder of the examination is noncontributory.

Laboratory studies show a leukocyte count of 6700/μL (6.7×10^9/L).

Which of the following is the most appropriate diagnostic test to perform next?

(A) Blood cultures
(B) Gram stain and culture of fluid drainage
(C) Opening of incision site for tissue Gram stain and culture
(D) Ultrasonography of incision site

Item 25

A 57-year-old woman is evaluated in the emergency department for a 2-day history of severe headache. She also reports nausea without vomiting and difficulty tolerating bright lights. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 136/86 mm Hg, pulse rate is 110/min, and respiration rate is 14/min. BMI is 24. The general medical examination is unremarkable. On neurologic examination, she shows photophobia, and a nondilated funduscopic examination shows no papilledema. The remainder of the examination is nonfocal.

A lumbar puncture is performed.

Cerebrospinal fluid (CSF) profile:

Leukocyte count	2235/μL (2235×10^6/L) with neutrophilic predominance
Glucose	24 mg/dL (1.3 mmol/L)
Pressure (opening)	410 mm H_2O
Protein	468 mg/dL (4680 mg/L)

CSF Gram stain and culture results are pending.

In addition to dexamethasone, which of the following is the most appropriate intravenous empiric antibiotic treatment?

(A) Ampicillin, ceftriaxone, and vancomycin
(B) Ceftazidime and vancomycin
(C) Meropenem
(D) Moxifloxacin

Item 26

A 22-year-old woman is evaluated for a 4-day history of vaginal discharge. The discharge is thick and yellow. She has no abdominal pain. She is sexually active. Medical history is unremarkable, with no drug allergies.

On physical examination, vital signs are normal. Pelvic examination reveals an inflamed and friable cervix. Mucopurulent discharge is noted from the cervical os. No cervical motion, adnexal, or uterine tenderness is noted. The vaginal mucosa and vulvar area are normal in appearance. Wet mount shows only numerous leukocytes. The pH of the vaginal secretions is 5. Result of the whiff test is negative, and no fungal elements are seen on examination of the potassium hydroxide preparation.

Which of the following is the most appropriate treatment?

(A) Cefotetan and doxycycline
(B) Ceftriaxone and azithromycin
(C) Fluconazole
(D) Metronidazole

Item 27

A 27-year-old man is hospitalized for a 2-day history of fever and headaches and a 1-day history of left lower-extremity weakness. Ten days earlier he had returned from a 1-week trip to Idaho, which involved rafting and sleeping outdoors. He reports no known tick bite.

On physical examination, temperature is 39.1 °C (102.4 °F), blood pressure is 122/72 mm Hg, pulse rate is 118/min, and respiration rate is 28/min. The patient is oriented to person, place, and time. He has mild nuchal rigidity limiting neck flexion. He has left lower-extremity weakness with inability to flex or extend the knee or ankle. Deep tendon reflexes are absent. Sensation is intact. No rash is present.

Cerebrospinal fluid (CSF) studies:

Erythrocyte count	17/μL (17×10^6/L)
Leukocyte count	256/μL (256×10^6/L)
Glucose	55 mg/dL (3.1 mmol/L)
Protein	299 mg/dL (2990 mg/L)

MRI of the brain shows no focal abnormalities.

Which of the following is the most appropriate CSF laboratory test to perform next?

(A) Eastern equine encephalitis virus antibody
(B) La Crosse encephalitis virus antibody
(C) Powassan virus antibody
(D) West Nile virus antibody

Item 28

A 63-year-old woman is evaluated in the hospital for decompensated heart failure. She presented to the emergency department with increased shortness of breath and pedal edema yesterday. An indwelling urinary catheter was placed, intravenous diuretics were given, and she was admitted for further treatment. Medical history is notable for hypertension, type 2 diabetes mellitus, and chronic kidney disease. Medications are aspirin, carvedilol, insulin, lisinopril, rosuvastatin, spironolactone, and as-needed furosemide.

On physical examination, temperature is 36.8 °C (98.2°F), blood pressure is 124/72 mm Hg, pulse rate is

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100/min, and respiration rate is 18/min. Bibasilar crackles are heard on pulmonary examination, and cardiac examination is significant for an S_3. Bilateral lower-extremity edema to the mid-calf is noted. The urinary catheter is draining clear urine.

Laboratory study results show a serum creatinine level of 2.8 mg/dL (248 µmol/L) (baseline, 2.2 mg/dL [194 µmol/L]).

Which of the following is the most appropriate management of this patient's urinary catheter?

(A) Change catheter after 3 days
(B) Change catheter now
(C) Remove catheter now
(D) Remove catheter when kidney function returns to baseline

Item 29

A 57-year-old woman is evaluated for blood cultures growing yeast during long-term intravenous antibiotic therapy. She has completed 4 weeks of a planned 6-week course of intravenous antibiotics for methicillin-sensitive *Staphylococcus aureus* infective endocarditis. A peripherally inserted central venous catheter (PICC) was placed at the beginning of her treatment. She developed a high fever 3 days ago, and blood cultures drawn peripherally and through the catheter at that time grew *Candida* species; further identification is pending. Medical history is otherwise negative, and her only medication is nafcillin.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 126/80 mm Hg, pulse rate is 82/min, and respiration rate is 16/min. The eye grounds are clear. Chest examination is unremarkable. Cardiac auscultation reveals a grade 2/6 crescendo-decrescendo murmur at the right upper sternal border. She has no spinal tenderness. The right brachial PICC site is without erythema, drainage, or tenderness.

In addition to continuing intravenous antibiotic therapy, which of the following is the most appropriate management?

(A) Continue PICC use
(B) Continue PICC use and add antifungal therapy
(C) Remove PICC
(D) Remove PICC and add antifungal therapy

Item 30

A 23-year-old man is evaluated in the emergency department for a 5-day history of malaise and an erythematous macular and papular rash that began on the chest and spread to involve the extremities. The rash is not pruritic. The patient is sexually active with men; he has a new sexual partner and does not use condoms. He takes no medications and has no known allergies.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 110/65 mm Hg, pulse rate is 90/min, and respiration rate is 12/min. A generalized rash is noted. Cervical, axillary, and inguinal lymph nodes are freely movable and nontender on palpation. No genital or mucosal lesions are present.

Rash of the palm is shown.



Which of the following is the most appropriate treatment?

(A) Azithromycin
(B) Benzathine penicillin
(C) Ceftriaxone
(D) Methylprednisolone

Item 31

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A 46-year-old woman is admitted to the hospital with abdominal pain, worsening diarrhea, and intermittent low-grade fever of 1 week's duration. She reports no nausea, vomiting, or swallowing symptoms; no melena or hematochezia; and no rash. She underwent kidney transplantation 4 months ago. She is cytomegalovirus seropositive and received an organ from a cytomegalovirus seronegative donor; she received valganciclovir for 3 months after transplantation with no clinical or laboratory evidence of cytomegalovirus disease. Medical history is significant for autosomal-dominant polycystic kidney disease. Medications are tacrolimus, prednisone, mycophenolate mofetil, and trimethoprim-sulfamethoxazole.

On physical examination, temperature is 37.3 °C (99.1 °F), blood pressure is 144/90 mm Hg, pulse rate is 104/min, and respiration rate is 16/min. BMI is 23. Mucous membranes are dry. The abdomen is soft with mild tenderness in lower quadrants, bowel sounds are normal, and no rebound or guarding is noted. No skin rash is noted, and the remainder of the examination is unremarkable.

Stool culture is positive for *Candida albicans*. Results on *Clostridium difficile* toxin nucleic acid testing are negative.

Plain radiograph of the abdomen is unremarkable and shows a normal bowel gas pattern without free air.

Which of the following is the most likely cause for the patient's diarrhea?

(A) *Candida albicans*
(B) *Clostridium difficile*
(C) Cytomegalovirus
(D) Mycophenolate toxicity
(E) Polyoma BK virus

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Item 32

A 78-year old man is evaluated in the emergency department for confusion. He is a retiree living in an assisted-living facility. Five weeks ago, he underwent outpatient debridement of a right foot plantar bunion. He ambulates with the assistance of a walker because of poor balance following a cerebral vascular accident. Medical history is also significant for type 2 diabetes mellitus, hypertension, remote smoking history, and amputation of the left great toe because of infection. Medications are insulin, lisinopril, simvastatin, hydrochlorothiazide, and aspirin.

On physical examination, temperature is 38.8 °C (101.8 °F), blood pressure is 106/66 mm Hg, pulse rate is 98/min, and respiration rate is 14/min. BMI is 25. The patient is lethargic and confused. His right foot is edematous and erythematous, with a palpable dorsalis pedis pulse. A 2.5- × 3.1-cm ulceration is located beneath the fifth metatarsal-phalangeal joint with malodorous drainage. Metal probe detects bone. The proximal leg is unremarkable.

Laboratory studies reveal a leukocyte count of 17,400/μL (17.4×10^9/L) with 15% band forms, a serum creatinine level of 1.5 mg/dL (132.6 μmol/L), normal electrolytes, and serum glucose level of 249 mg/dL (13.8 mmol/L).

Plain radiography of the foot reveals edema over the fifth metatarsal-phalangeal joint but no gas or obvious osteoarticular destruction.

Which of the following is the most appropriate management?

(A) Cefazolin and metronidazole
(B) Clindamycin and gentamicin
(C) Vancomycin and piperacillin-tazobactam
(D) Hold antibiotic therapy pending bone biopsy

Item 33

A 54-year-old man is hospitalized for a 5-day history of fever, frontal headache, back pain, and rash. He recently returned from a 10-day vacation on the Caribbean island of Martinique. Six days after returning, he suddenly developed fever; generalized body, lower back, and joint achiness; and a headache localized behind his eyes. Yesterday he developed a rash on his chest and inner arms.

On physical examination, temperature is 39.6 °C (103.3 °F), blood pressure is 112/68 mm Hg, pulse rate is 118/min, and respiration rate is 16/min. BMI is 31. A maculopapular rash is present on the flexor surfaces of the arms and chest wall. He has discomfort of wrists, elbows, and knees with passive flexion and extension. The remainder of the examination is normal.

Laboratory studies:

Hemoglobin	15.2 g/dL (152 g/L)
Leukocyte count	3210/μL (3.2×10^9/L); 38% polymorphonuclear cells, 58% lymphocytes, 4% monocytes
Platelet count	87,000/μL (87×10^9/L)
Alanine aminotransferase	226 U/L
Aspartate aminotransferase	138 U/L
Bilirubin, total	0.7 mg/dL (12.0 μmol/L)

Peripheral blood smear is normal.

Which of the following is the most likely diagnosis?

(A) Anaplasmosis
(B) Chikungunya
(C) Dengue fever
(D) Leptospirosis

Item 34

A 68-year-old man was admitted to the hospital 4 days ago for community-acquired pneumonia. He has COPD and presented with a 2-week history of fever and increasing shortness of breath, but no increase in his baseline cough. He was hypoxic, and a chest radiograph showed new patchy infiltrates in addition to his underlying interstitial changes but no pleural effusions. Empiric antibiotics were initiated, and blood and sputum cultures have shown no growth. His dyspnea and oxygenation have not improved significantly since admission. Medical history is otherwise unremarkable. He has a 45-pack-year smoking history and continues to smoke. Medications are tiotropium, fluticasone-salmeterol, and as-needed albuterol metered dose inhalers and intravenous cefotaxime and azithromycin.

On physical examination, temperature is 38.6 °C (101.5 °F), blood pressure is 128/55 mm Hg, heart rate is 97/min, and respiration rate is 33/min. Oxygen saturation is 92%, with the patient breathing 6 L/min of oxygen by nasal cannula. BMI is 28. Pulmonary examination shows decreased air movement and scattered rhonchi throughout both lung fields, unchanged from admission. Cardiac and abdominal examinations are unremarkable, and no lower extremity edema is present.

Laboratory studies show a leukocyte count of 13,500/μL (13.5×10^9/L) (14,700/μL [14.7×10^9/L] on admission). Metabolic studies are normal.

Chest radiograph continues to show multilobar, patchy infiltrates and increased interstitial markings without pleural effusions, unchanged from admission.

Which of the following is the most appropriate next step in management?

(A) Bronchoscopy
(B) Chest CT
(C) Chest ultrasonography
(D) Thoracoscopic lung biopsy

Item 35

An 82-year-old man is evaluated for a 2-month history of progressive fatigue and midline lower back pain that has increased in severity. He reports no trauma to the area. Medical history is significant for elective coronary artery bypass surgery 3 months ago. While hospitalized, he developed a central line–associated bloodstream infection with *Staphylococcus aureus* and a catheter-associated urinary tract infection with *Proteus mirabilis*. Medications are aspirin, metoprolol, and simvastatin. He is allergic to penicillin.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 110/72 mm Hg, pulse rate is 68/min, and respiration rate is 14/min. BMI is 26. Cardiopulmonary examination is normal. He has moderate point tenderness

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over the third lumbar vertebrae. Lower-extremity evaluation reveals normal motor strength and sensation with symmetrical patellar deep tendon reflexes.

Laboratory studies reveal an erythrocyte sedimentation rate of 110 mm/h, leukocyte count of 10,200/μL (10.2 × 10^9/L), and serum creatinine of 1.2 mg/dL (106.1 μmol/L). A blood culture is positive for *Corynebacterium* species, but subsequent cultures are negative.

Findings of MRI of the lumbar spine, with contrast, are consistent with osteomyelitis of the L4 and adjacent L5 vertebral bodies, abnormality in the intervening disc space, and no evidence of an epidural collection.

Which of the following is the most appropriate management?

(A) Antimicrobial therapy with vancomycin and ciprofloxacin
(B) CT-guided biopsy of the lumbar disc space
(C) Echocardiography
(D) Three-phase nuclear bone scan

Item 36

A 30-year-old woman is evaluated in follow-up after being recently diagnosed with HIV infection. She is asymptomatic. Medical history is unremarkable, and she takes no medications; she has not yet started antiretroviral therapy. She received all scheduled childhood immunizations.

On physical examination, vital signs are normal. She has shotty cervical lymphadenopathy, but the examination is otherwise unremarkable.

Laboratory studies:

Absolute CD4 cell count	461/μL
HIV viral load	44,874 copies/mL
Hepatitis A IgG antibody	Negative
Hepatitis B surface antibody	Positive
Hepatitis B surface antigen	Negative
Hepatitis C antibody	Negative

Which of the following immunizations should this patient receive today?

(A) Hepatitis A vaccine
(B) Hepatitis B vaccine
(C) Human papillomavirus vaccine
(D) Pneumococcal conjugate vaccine
(E) Pneumococcal polysaccharide vaccine

Item 37

A 62-year-old woman is admitted to the hospital for management of varicella-zoster infection. She developed pain and tingling over the right posterior flank area 3 days ago, followed by the development of vesicular lesions. She reports fever without chills and no cough. She is undergoing immunosuppressive chemotherapy for breast cancer and received her last dose 10 days ago. Medical history is otherwise unremarkable, and her only medication is valacyclovir.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 126/84 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. A vesicular rash is present over the right flank that does not cross the midline, with vesicles in various stages of development with no crusting and no purulent drainage.

Which of the following is the most appropriate in-hospital precaution for preventing spread of infection?

(A) Airborne
(B) Airborne and contact
(C) Contact
(D) Contact and droplet
(E) Droplet

Item 38

A 25-year-old woman e-mails her internist from Mexico with a report of diarrhea for 2 days. She is travelling and reports three to four loose bowel movements per day. She has been dining in the hotel restaurants but has also consumed foods and bottled soft drinks served with ice from local food vendors. She feels urgency to move her bowels but no tenesmus. She has mild abdominal cramping without pain, vomiting, or fever. Stools are described as watery without mucus or blood. Although she is uncomfortable, she has not had to alter her travel plans. Medical history is unremarkable and she takes no medications. She was given levofloxacin and loperamide to take with her on her trip.

In addition to encouraging oral hydration, which of the following is the most appropriate treatment recommendation for this patient?

(A) Begin levofloxacin and loperamide now
(B) Begin levofloxacin now and start loperamide 24 hours later
(C) Begin loperamide now
(D) No further treatment unless symptoms worsen

Item 39

A 55-year-old man is evaluated in the hospital for pulmonary tuberculosis. He was admitted 10 days ago with cough, fever, and night sweats. A chest radiograph showed bilateral, apical fibronodular disease without cavities. Findings on sputum evaluation were positive for *Mycobacterium tuberculosis*. Because drug-resistant tuberculosis had not been reported in the community, a four-drug antituberculous regimen was started. Since the patient began therapy, his initial symptoms have resolved. Medical history is otherwise unremarkable. Medications are isoniazid, rifampin, pyrazinamide, and ethambutol.

On physical examination, vital signs are normal. Lungs are clear to auscultation. The remainder of the examination is otherwise unremarkable.

His three most recent acid-fast bacilli sputum smears have been negative.

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Which of the following additional criteria is required for this patient to be considered noncontagious?

(A) Absence of a cavity on initial chest radiograph
(B) Adequate tuberculosis treatment for at least 2 weeks
(C) Negative tuberculin skin test result
(D) Normal leukocyte count

Item 40

A 72-year-old man is admitted to the hospital with fever and chills of 2 days' duration. He underwent left hemicolectomy 12 days ago for diverticular disease, which was complicated by methicillin-resistant *Staphylococcus aureus* bacteremia. A planned, 14-day course of vancomycin was started through a central venous catheter, and he was afebrile with negative blood cultures and normal leukocyte count at the time of hospital discharge 1 week ago. Medical history is otherwise significant for hypertension, diabetes mellitus, and chronic kidney disease. Medications are vancomycin, losartan, and insulin.

On physical examination, temperature is 39.2 °C (102.6 °F), blood pressure is 130/70 mm Hg, pulse rate is 100/min and regular, and respiration rate is 16/min. The patient has a right subclavian central venous catheter. His abdominal surgical site is clean and dry. The remainder of the examination is normal.

Laboratory studies reveal a leukocyte count of 16,000/μL (16×10^9/L); a serum creatinine level of 2.1 mg/dL (186 μmol/L), which is unchanged from his baseline; and a therapeutic vancomycin level. Two sets of blood cultures are positive for budding yeast.

The central venous catheter is removed.

Which of the following is the most appropriate treatment?

(A) Amphotericin B deoxycholate
(B) Fluconazole
(C) Liposomal amphotericin B
(D) Micafungin

Item 41

A 42-year-old man is admitted to the hospital for a 1-month history of high fever and 6.8-kg (15-lb) weight loss. Medical history is significant for AIDS diagnosed 10 years ago after an episode of pneumocystis pneumonia. He recently immigrated to the United States from Central America. Medical history is otherwise unremarkable. He is taking no antiretroviral or prophylactic therapy.

On physical examination, temperature is 39.9 °C (103.8 °F), blood pressure is 90/60 mm Hg, pulse rate is 120/min, and respiration rate is 18/min. Diffuse crackles are heard in the lungs. Abdominal examination reveals hepatosplenomegaly. No skin rash is present.

Laboratory studies:

Hemoglobin	8 g/dL (80 g/L)
Leukocyte count	1800/μL (1.8×10^9/L)
Platelet count	90,000/μL (90×10^9/L)
CD4 cell count	5/μL (0.005×10^9/L)

Small yeast forms within neutrophils are seen on a peripheral blood smear.

A chest radiograph shows a diffuse reticular pattern.

Which of the following is the most likely diagnosis?

(A) Blastomycosis
(B) Candidiasis
(C) Coccidioidomycosis
(D) Histoplasmosis

Item 42

A 28-year-old woman was admitted to the hospital 3 days ago with fever, chills, dysuria, flank pain, and nausea. Empiric ceftriaxone was initiated for pyelonephritis. She reports her nausea is improved, and she has no vomiting. Medical history is unremarkable, and she takes no other medications.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 106/70 mm Hg, pulse rate is 78/min, and respiration rate is 16/min. She has minimal left costovertebral angle tenderness. Bowel sounds are normal.

Laboratory studies show a leukocyte count of 9300/μL (9.3×10^9/L) and serum creatinine level of 0.7 mg/dL (61.9 μmol/L). Urine and blood cultures grow *Escherichia coli* sensitive to ampicillin, ceftriaxone, trimethoprim-sulfamethoxazole, and ciprofloxacin. The organism was also sensitive to nitrofurantoin on the urine panel.

Which of the following is the most appropriate treatment for this patient at this time?

(A) Intravenous ciprofloxacin
(B) Oral nitrofurantoin
(C) Oral trimethoprim-sulfamethoxazole
(D) Intravenous ceftriaxone

Item 43

A 30-year-old woman is evaluated for a reactive tuberculin skin test (TST). She developed 6-mm induration 48 hours after the test was performed. She has no fever, weight loss, or cough, and cannot recall any exposure to tuberculosis. Medical history is notable for psoriasis diagnosed 10 years ago. Her only medication is infliximab. A TST result was negative before initiation of therapy.

On physical examination, vital signs are normal. Stable plaque psoriasis is noted. The lungs are clear, and the remainder of the examination is normal.

Which of the following is the most appropriate next step in the management of this patient?

(A) Chest radiography
(B) Interferon-γ release assay
(C) Rifampin, isoniazid, pyrazinamide, and ethambutol
(D) No further intervention

Item 44

A 27-year-old woman is evaluated for a 4-day history of painful vulvar lesions accompanied by fatigue and malaise. The patient reports dysuria but no urgency or frequency and no vaginal discharge. She has been sexually active with a single male partner for the past 2 years. She has no history of genital lesions or sexually transmitted infections.

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On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 120/70 mm Hg, pulse rate is 90/min, and respiration rate is 12/min. Multiple shallow ulcers on an erythematous base are located over the labia majora and minora, consistent with herpes simplex virus infection. Palpation reveals bilateral inguinal lymphadenopathy.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Direct fluorescent antibody testing of lesion specimen
(B) Polymerase chain reaction of lesion specimen
(C) Type-specific serum antibody testing
(D) Tzanck smear of lesion specimen

Item 45

A 27-year-old male park ranger is evaluated for a 3-week history of diarrhea and weight loss. He notes four to seven pale, greasy, and foul-smelling bowel movements per day, with an oily sheen. He reports no visible blood or mucus. He has no fever but does have abdominal bloating and increased flatulence. He states he has lost 10 pounds since the onset of symptoms. In the last 2 months, he has been clearing trails in the backcountry and camping in primitive sites. He admits to drinking from freshwater streams but uses chlorine water purification tablets for disinfection.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 132/68 mm Hg, pulse rate is 56/min, and respiration rate is 18/min. The patient has a mildly bloated abdomen with tenderness to palpation but no peritoneal signs.

Laboratory studies show a leukocyte count of 7400/μL (7.4×10^9/L). The stool is negative for occult blood and fecal leukocytes.

Which of the following is the most appropriate diagnostic stool test?

(A) *Entamoeba* antigen testing
(B) *Giardia* antigen testing
(C) Microscopy for ova and parasites
(D) Modified acid-fast staining

Item 46

A 33-year-old woman is evaluated during tuberculosis screening. She reports no cough, weight loss, or any other symptoms. She uses heroin daily and is transiently homeless. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. BMI is 20. Other than needle marks without evidence of infection, the examination is normal.

Which of the following is the preferred method of tuberculosis screening in this patient?

(A) Chest radiography
(B) Induced sputum examination
(C) Interferon-γ release assay
(D) Tuberculin skin test

Item 47

A 44-year-old man is evaluated after a new diagnosis of HIV infection. He is asymptomatic and reports no fever, chills, sweats, weight loss, cough, chest pain, dyspnea on exertion, diarrhea, or difficulty swallowing. He reports no history of opportunistic infections, and he has had no known exposure to tuberculosis. Medical history is otherwise unremarkable. He has just started taking tenofovir-emtricitabine and raltegravir.

On physical examination, vital signs are normal. He has erythematous, scaly patches on his face consistent with seborrheic dermatitis. No thrush or oral lesions are observed. Mild lymphadenopathy is noted in cervical, axillary, and inguinal areas. The lungs are clear throughout. No hepatosplenomegaly, masses, or tenderness is noted on abdominal examination.

Laboratory studies:

Absolute CD4 cell count	41/μL
HIV viral load	108,522 copies/mL
Cytomegalovirus IgG antibody	Positive
Toxoplasma IgG antibody	Positive
Tuberculosis interferon-γ release assay	Indeterminate

In addition to trimethoprim-sulfamethoxazole, which of the following should be started now?

(A) Azithromycin
(B) Fluconazole
(C) Isoniazid and vitamin B_6
(D) Pyrimethamine and leucovorin
(E) Valganciclovir

Item 48

A 44-year-old man is evaluated for acute rejection of a transplanted kidney. Medical history is significant for autosomal-dominant polycystic kidney disease requiring transplantation 18 months ago. He and his donor were both seronegative for cytomegalovirus, and the patient received standard prophylaxis. His posttransplantation course has been remarkable for previous episodes of rejection, the last of which was approximately 6 months ago. He also has hypertension. Current medications are amlodipine, tacrolimus, prednisone, and mycophenolate mofetil. He is scheduled to have his level of immunosuppression increased significantly for the current episode of rejection.

Physical examination findings are unremarkable.

Laboratory studies show a leukocyte count of 4500/μL (4.5×10^9/L) with 88% polymorphonuclear cells and 8% lymphocytes and a serum creatinine level of 1.8 mg/dL (159 μmol/L).

For which infection should this patient receive prophylaxis at this time?

(A) Aspergillus
(B) Cytomegalovirus
(C) *Pneumocystis jirovecii*
(D) *Mycobacterium avium* complex

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Item 49

A 61-year-old woman is evaluated for immunization before traveling. She plans to travel to Cambodia in 2 weeks and will spend 4 weeks in rural areas. Medical history is significant for controlled rheumatoid arthritis. She has been provided all adult immunizations recommended by the Advisory Committee on Immunization Practices but has not previously received any hepatitis A immunization. Medications are infliximab and methotrexate.

On physical examination, vital signs are normal. No active inflammatory joint disease is evident, and the remainder of the examination is unremarkable.

Which of the following is the most appropriate hepatitis A prophylaxis regimen for this patient?

(A) Hepatitis A vaccine now
(B) Hepatitis A vaccine and immune globulin now
(C) Immune globulin now
(D) Immune globulin now and hepatitis A vaccine upon return

Item 50

A 77-year-old woman is evaluated for a 5-day history of diarrhea. She has been diagnosed with *Clostridium difficile* colitis twice in the last 3 months and both times was successfully treated with metronidazole. This is her third episode. She has four to six liquid bowel movements per day. She reports no fevers, abdominal pain, nausea, or vomiting.

On physical examination, the patient is afebrile, blood pressure is 150/82 mm Hg, pulse rate is 106/min, and respiration rate is 18/min. The patient's abdomen is soft and nontender with positive bowel sounds.

Laboratory studies reveal a leukocyte count of 8800/μL (8.8×10^9/L) and serum creatinine of 0.8 mg/dL (70.7 μmol/L). Stool polymerase chain reaction assay is positive for *C. difficile* toxin.

Which of the following is the most appropriate oral treatment?

(A) Metronidazole for 14 days
(B) Metronidazole for 6 weeks
(C) Rifaximin for 14 days
(D) Vancomycin for 14 days
(E) Vancomycin for 6 weeks

Item 51

A 74-year-old man was admitted to the hospital 3 days ago for treatment of community-acquired pneumonia. Supplemental oxygen and empiric intravenous ceftriaxone and azithromycin were initiated; blood and sputum cultures showed no growth. He reports feeling much better, with decreased shortness of breath and cough; he has been afebrile since the second hospital day. Medical history is unremarkable. Medications are intravenous ceftriaxone and azithromycin.

On physical examination, temperature is 37.7 °C (99.9 °F), blood pressure is 120/75 mm Hg, pulse rate is 92/min, and respiration rate is 18/min. Oxygen saturation is 94% breathing ambient air. He is breathing comfortably. Pulmonary examination reveals decreased breath sounds at both lung bases but no dullness to percussion. Cardiac and abdominal examinations are unremarkable, and no lower extremity edema is present.

Laboratory studies show a leukocyte count of 13,500/μL (13.5×10^9/L) (18,300/μL [18.3×10^9/L] on admission) and an otherwise normal complete blood count. A comprehensive metabolic profile, including kidney function, is normal.

Which of the following is the most appropriate management of this patient's antibiotic therapy?

(A) Continue current intravenous antibiotic therapy
(B) Switch to oral antibiotic and discharge
(C) Switch to oral antibiotic and observe for 24 hours
(D) Switch to oral antibiotic and overlap with intravenous therapy for 24 hours

Item 52

A 40-year-old woman is admitted to the hospital for significant hypoxemia. She reports a 3-day history of fever, fatigue, headache, dry cough, and pleuritic chest pain. She also notes several tender, raised soft tissue "lumps" on her legs. Four weeks before symptom onset, she traveled to Arizona to participate in an outdoor art convention. Medical history is significant for well-controlled Crohn disease, and results of surveillance testing for *Mycobacterium tuberculosis* have been negative. Her only medication is infliximab.

On physical examination, temperature is 38.7 °C (101.7 °F), blood pressure is 102/82 mm Hg, pulse rate is 98/min, and respiration rate is 22/min. BMI is 26. Oxygen saturation is 96% with 5 L/min of oxygen via nasal cannula. No lymphadenopathy is palpable. Coarse crackles and scattered rhonchi are heard in all lung fields with dullness to percussion at the bases. Cardiac examination reveals no murmurs. No hepatosplenomegaly is noted. She has four to five discrete, tender, 1- to 2-cm erythematous nodules on both anterior lower extremities.

Laboratory studies show a leukocyte count of 4500/μL (4.5×10^9/L) (40% polymorphonuclear cells, 50% lymphocytes, 4% monocytes, 6% eosinophils). Results of pneumococcal and *Legionella* urine antigen assays are negative, and a serum mycoplasma IgM antibody assay is reactive.

Chest radiography shows bilateral airspace opacities, small bilateral pleural effusions, and enlarged right-sided hilar lymphadenopathy.

Which of the following is the most likely diagnosis?

(A) Blastomycosis
(B) Coccidioidomycosis
(C) Histoplasmosis
(D) *Mycoplasma* pneumonia

Item 53

An 85-year-old man is being treated in the ICU for bacteremia secondary to a urinary tract infection. He was evaluated 2 days ago for intermittent confusion, weakness,

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bladder pain, and hematuria. Because of hemodynamic instability, he was admitted to the ICU. Intravenous fluids were given, and empiric meropenem was started, with resolution of his hypotension and fever. Medical history is otherwise noncontributory. He takes no other medications.

On physical examination, temperature is 37.7 °C (99.9 °F), blood pressure is 118/84 mm Hg, pulse rate is 96/min, and respiration rate is 18/min. Cardiac examination is normal. He has no flank or abdominal tenderness.

Urine culture is now reported to be growing more than 10^5 colony-forming units of *Enterococcus faecalis*. Blood culture grows *E. faecalis* sensitive to ampicillin, vancomycin, and gentamicin.

Which of the following is the most appropriate treatment?

(A) Switch to ampicillin
(B) Switch to ampicillin and gentamicin
(C) Switch to vancomycin
(D) Switch to vancomycin and gentamicin
(E) Continue meropenem

Item 54

A 52-year-old man is admitted to the hospital for a 2-day history of right maxillary sinus pain and exophthalmos of the right eye with fever. Empiric cefepime is initiated. Medical history is significant for acute myelogenous leukemia, for which he recently completed induction chemotherapy.

On physical examination, temperature is 38.8 °C (101.8 °F), blood pressure is 100/70 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. Exophthalmos of the right eye is noted, with ecchymosis around the eye and right nostril and bloody nasal discharge. The remainder of the examination is unremarkable.

Laboratory studies show an absolute neutrophil count of 100/μL (0.1×10^9/L). The result of a serum galactomannan antigen immunoassay is positive.

Septate hyphae with acute angle branching are noted in tissue from sinus debridement.

CT of the head and sinuses reveals right maxillary sinusitis, right ethmoid sinusitis, and right eye retroorbital inflammation.

Which of the following is the most likely diagnosis?

(A) *Aspergillus* rhinosinusitis
(B) *Candida* rhinosinusitis
(C) Cryptococcal rhinosinusitis
(D) *Pseudomonas* rhinosinusitis

Item 55

A 35-year-old woman is evaluated for intermittent fever, sweats, fatigue, and dull midchest pain of 2 weeks' duration. Medical history is significant for liver transplantation 6 months ago for primary biliary cirrhosis; she was seronegative for cytomegalovirus and Epstein-Barr virus, and her donor was positive for both. Results of pretransplant testing for tuberculosis were negative. She received valganciclovir prophylaxis for 3 months after transplantation. Medications are tacrolimus, prednisone, mycophenolate mofetil, and trimethoprim-sulfamethoxazole.

On physical examination, temperature is 37.7 °C (99.9 °F), blood pressure is 142/88 mm Hg, pulse rate is 92/min, and respiration rate is 14/min. Oropharynx has whitish plaques on the palate and buccal mucosa. No enlarged lymph nodes are palpable. Cardiopulmonary examination is normal. Abdomen is soft and nontender without hepatosplenomegaly. Extremities are without edema. No skin lesions are noted.

Laboratory studies are significant for a leukocyte count of 5200/μL (5.2×10^9/L) and hematocrit of 33%. Liver and kidney function are normal. Bacterial and fungal blood cultures show no growth.

Chest radiograph shows clear lung fields but left hilar enlargement. Chest CT confirms an enlarged, 3-cm left hilar lymph node; the liver and spleen are unremarkable.

Which of the following is the most likely cause of her clinical findings?

(A) Cytomegalovirus infection
(B) Invasive candidal infection
(C) Posttransplant lymphoproliferative disease
(D) Reactivation tuberculosis

Item 56

A 22-year-old woman is evaluated for a dog bite to the right arm. The dog is reported to be up to date on all vaccinations. Medical history is notable for Crohn disease, and she is up to date on all immunizations, with a tetanus-diphtheria-acellular pertussis vaccine administered 3 years ago. Her only medication is infliximab.

On physical examination, vital signs are normal. No epitrochlear or axillary lymphadenopathy is noted. The right forearm has several minor punctures and tears, with a small amount of erythema and minimal tenderness. No warmth, edema, or purulence is present.

Plain radiograph of the right forearm shows no evidence of fracture, gas, or foreign body.

Which of the following is the most appropriate next step in the management of this patient?

(A) Amoxicillin-clavulanate
(B) Metronidazole
(C) Tetanus immunization
(D) No additional evaluation or therapy

Item 57

A 48-year-old woman is evaluated for a skin rash located on her left buttock. She describes the rash as irritating but not painful or associated with any systemic symptoms. She has had a similar rash approximately four times over the past year in the same area. She reports that when the rash has occurred before, the lesions last approximately 6 days, then crust over and resolve. On multiple occasions, she noticed a severe headache lasting 2 to 3 days when she had the rash. Medical history is unremarkable, and she takes no medications. She is married, and her husband has not had

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any similar symptoms. Her only medication is naproxen for menstrual cramps.

On physical examination, temperature is 36.9 °C (98.4 °F), blood pressure is 126/68 mm Hg, pulse rate is 72/min, and respiration rate is 12/min. BMI is 22. She appears well. Pelvic examination is unremarkable.

The rash, located at the mid-lower sacral area lateral to the gluteal crease, is shown.



Which of the following is the most likely cause of this patient's rash?

(A) Dermatitis herpetiformis
(B) Fixed drug eruption
(C) Herpes simplex virus 2 infection
(D) Localized herpes zoster

Item 58

A 29-year-old woman is evaluated for a 1-day history of diarrhea. She notes liquid stools with no mucus or visible blood. She has mild abdominal cramping relieved by defecation. She reports no nausea or vomiting. Three days ago, she ate almond butter from a manufacturer that posted a voluntary recall of the product due to contamination with *Salmonella braenderup*.

On physical examination, temperature is 37.9 °C (100.2 °F), blood pressure is 116/52 mm Hg, pulse rate is 90/min, and respiration rate is 18/min. The patient's abdomen is soft and mildly tender, with hyperactive bowel sounds.

Laboratory studies reveal a leukocyte count of 9700/μL (9.7×10^9/L).

Which of the following is the most appropriate treatment?

(A) Azithromycin
(B) Ciprofloxacin
(C) Loperamide
(D) Probiotics
(E) No therapy

Item 59

A 46-year-old man is evaluated for fever, dysuria, and urinary frequency of 1 day's duration. He also notes a sensation of deep pelvic pain near the rectum. He has no urethral discharge or testicular pain. He states that he felt well before the current illness and has no other symptoms. Medical history is unremarkable. He is not sexually active. He takes no medications.

On physical examination, temperature is 38.8 °C (101.8 °F), blood pressure is 130/80 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. Rectal examination reveals a tender and tense prostate.

Blood and urine cultures are pending. Urine dipstick is positive for leukocyte esterase and nitrites.

Which of the following is the most appropriate treatment?

(A) Ampicillin
(B) Ceftriaxone (single dose) and doxycycline
(C) Ciprofloxacin
(D) Meropenem

Item 60

A 58-year-old man is evaluated in January during a recent outbreak of influenza virus in the assisted-living facility, where he works as a patient care aide. He reports declining influenza immunization offered in the autumn months because his sister told him that a friend developed a neurologic illness after receiving the vaccine. He is worried about possibly becoming ill and cannot afford to miss work. Medical history is significant for asthma, and his only medication is inhaled albuterol as needed.

On physical examination, vital signs are normal. The remainder of the examination is unremarkable.

Which of the following is the most appropriate influenza prophylaxis regimen to recommend to this patient?

(A) Amantadine chemoprophylaxis
(B) Oseltamivir chemoprophylaxis
(C) Oseltamivir chemoprophylaxis and inactivated influenza vaccine
(D) Oseltamivir chemoprophylaxis and live-attenuated influenza vaccine

Item 61

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A 73-year-old woman is hospitalized for a 1-day history of altered mental status and fever. Her family notes that yesterday she seemed confused and had trouble getting dressed. This morning, she was unable to be roused, and she was transported to the hospital by ambulance.

On physical examination, temperature is 39.1 °C (102.4 °F), blood pressure is 122/82 mm Hg, pulse rate is 110/min, and respiration rate is 24/min. The patient responds to deep stimulation with a grimace. No rash is present.

Cerebrospinal fluid (CSF) studies:

Erythrocyte count	3/μL (3×10^6/L)
Leukocyte count	11/μL (11×10^6/L)
Glucose	66 mg/dL (3.7 mmol/L)
Protein	76 mg/dL (760 mg/L)
Gram stain	No organisms

MRI of the brain is shown (top of next page).

Empiric treatment with intravenous dexamethasone, vancomycin, ceftriaxone, ampicillin, and acyclovir is begun. The next day, herpes simplex virus polymerase chain reaction assay of the CSF returns a negative result.

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Which of the following is the most likely diagnosis?

(A) Enteroviral meningoencephalitis
(B) Herpes simplex encephalitis
(C) Pneumococcal meningitis
(D) West Nile neuroinvasive disease

Item 62

A 25-year-old woman is admitted to the hospital for a 3-day history of severe headache localizing to the back of the head. She recently had an episode of sinusitis and has a history of sinus infections. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, temperature is 38.9 °C (102.0 °F), blood pressure is 134/82 mm Hg, pulse rate is 95/min, and respiration rate is 13/min. The general medical examination is unremarkable except for mild, bilateral maxillary sinus tenderness. On neurologic examination, she is awake and alert but reports photophobia. There are no focal findings.

Lumbar puncture is performed.

Cerebrospinal fluid (CSF) profile:

Leukocyte count	1200/μL (1200 × 10^6/L) with 60% neutrophils and 40% lymphocytes
Glucose	30 mg/dL (1.7 mmol/L)
Pressure (opening)	2200 mm H_2O
Protein	350 mg/dL (3500 mg/L)

Gram stain of a CSF specimen shows gram-positive cocci in chains.

In addition to appropriate empiric antibiotics, which of the following additional interventions is most likely to improve outcomes?

(A) Dexamethasone
(B) Diuresis
(C) Maintaining head of the bed at greater than 30 degrees
(D) Mannitol

Item 63

A 23-year-old woman is evaluated in the ICU. She was in a motor vehicle accident 7 days ago and has required mechanical ventilation since admission. She now has fever, an increased oxygen requirement, and increased respiratory secretions requiring suctioning every hour. Three other patients in the ICU are colonized or infected with extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae*. Medical history is unremarkable.

On physical examination, temperature is 39.0 °C (102.2 °F), blood pressure is 105/70 mm Hg, pulse rate is 110/min, and respiration rate is 16/min. Pulmonary examination reveals scattered rhonchi. On cardiac examination, the heart is hyperdynamic but otherwise normal. Her trauma sites are clean and dry.

Laboratory studies show a leukocyte count of 19,300/μL (19.3 × 10^9/L). Sputum Gram stain reveals 2+ leukocytes and 3+ gram-negative rods; sputum culture is pending. Blood cultures return no growth.

Chest radiograph shows a new right lower-lobe infiltrate.

Which of the following is the most appropriate empiric antimicrobial treatment?

(A) Cefepime
(B) Ceftazidime
(C) Meropenem
(D) Piperacillin-tazobactam

Item 64

A 26-year-old man is evaluated in follow-up after starting antiretroviral therapy 1 month ago. He reports no adverse effects of the medications. Medical history is notable for chronic active hepatitis B virus infection. His only medication is once-daily combination tenofovir-emtricitabine-cobicistat-elvitegravir initiated last month.

On physical examination, temperature is 36.6 °C (97.9 °F), blood pressure is 122/76 mm Hg, pulse rate is 68/min, and respiration rate is 12/min. The lungs are clear. No edema or rash is present.

Laboratory studies are significant for an increase in his serum creatinine from his pretreatment baseline of 1.2 mg/dL (106 μmol/L) to 1.5 mg/dL (133 μmol/L). Serum electrolytes are normal. Urinalysis is dipstick negative for blood or protein, and microscopic examination shows no cells or casts. The HIV viral load is undetectable.

Which of the following is the most appropriate management?

(A) Change antiretroviral therapy to an abacavir-lamivudine–based regimen
(B) Hold antiretroviral therapy and reassess kidney function in 4 weeks
(C) Kidney biopsy
(D) Continue current antiretroviral regimen

Item 65

A 37-year-old man is hospitalized for diabetic foot infection with sepsis of the right lower extremity. He is treated with piperacillin-tazobactam and vancomycin and symptoms improve. However, 4 days later he develops a fever and diarrhea, described as four to five liquid bowel movements

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over the last 24 hours. Medical history is significant for type 2 diabetes mellitus with a baseline creatinine of 1.0 mg/dL (88.4 µmol/L). Medications are piperacillin-tazobactam, vancomycin, and metformin.

On physical examination, temperature is 38.7 °C (101.7 °F), blood pressure is 150/72 mm Hg, pulse rate is 106/min, and respiration rate is 18/min. The patient's abdomen is soft and mildly tender with positive bowel sounds.

Laboratory studies reveal leukocyte count is 18,800/µL (18.8 × 10^9/L) and serum creatinine level is 1.6 mg/dL (141 µmol/L). Result of stool polymerase chain reaction assay is positive for *Clostridium difficile* toxin.

Which of the following is the most appropriate treatment?

(A) Oral metronidazole
(B) Oral vancomycin
(C) Oral vancomycin plus intravenous metronidazole
(D) Oral vancomycin plus intravenous vancomycin
(E) Oral vancomycin plus oral metronidazole

Item 66

A 60-year-old woman is admitted to the hospital for a 2-week history of confusion and change in personality. Her symptoms began acutely and have progressed steadily since onset. She is no longer able to maintain activities of daily living. She has had an ataxic gait for 2 days. She has no history of travel outside the United States and no known infectious exposures. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 140/70 mm Hg, pulse rate is 88/min and regular, and respiration rate is 14/min. She is oriented to person only and has difficulty finding words. The general medical examination is unremarkable. On neurologic examination, the cranial nerves are intact. She has preserved motor strength throughout, although myoclonus is present.

Laboratory studies demonstrate a normal metabolic profile, kidney and liver function, and complete blood count. On lumbar puncture, the opening pressure is normal. The cerebrospinal fluid is clear with a leukocyte count of 1/µL (1 × 10^6/L) and an erythrocyte count of 0/µL. The glucose level is normal, and the 14-3-3 protein is elevated.

MRI of the brain reveals focal cortical hyperintensity.

Which of the following is the most likely diagnosis?

(A) Alzheimer disease
(B) Kuru
(C) Neurosyphilis
(D) Sporadic Creutzfeldt-Jakob disease

Item 67

A 32-year-old man is evaluated in the emergency department for a 2-day history of fever, rash, severe headache, back pain, sore throat, and vomiting. He is employed as an international emergency aid worker and recently returned to the United States after an extended overseas assignment. The rash began a few days after the onset of fever, beginning first on the inside of the mouth and then spreading to his face, hands, and eventually both arms and legs. The initial lesions were flat and red but later became raised and blistered. Other members of his work team have also fallen ill. He does not recall his complete vaccination history but believes that he received all of his scheduled immunizations and that he was exposed as a young child to chickenpox when his sister had it. Medical history is unremarkable, and he takes no medications.

On physical examination, the patient appears very ill. Temperature is 39.3 °C (102.7 °F), blood pressure is 114/70 mm Hg, pulse rate is 110/min, and respiration rate is 16/min. BMI is 28. He has multiple clusters of pus-filled vesicles dispersed on the face, arms, and legs. Bilateral conjunctivitis is present. Pulmonary examination reveals mild bilateral lower lung field crackles. No meningeal signs are found.

Which of the following is the most likely infection in this patient?

(A) Measles
(B) Rickettsial pox
(C) Smallpox
(D) Varicella

Item 68

A 32-year-old man is evaluated in the emergency department for a severe occipital headache. He reports flulike symptoms for the past 2 to 3 weeks, with fever, malaise, fatigue, neck stiffness, generalized achiness, sore throat, and mild nausea. He also notes having "swollen glands" in his neck and neck stiffness but no vomiting, abdominal pain, diarrhea, or cough. He indicates that he had a reddish skin rash located across his chest and upper abdomen that first appeared several days after onset of his fevers and other symptoms and began to fade several days ago; the rash was present for approximately 1 week. Medical history is unremarkable, and he takes no medications. The patient thinks he had all standard childhood vaccinations. He is sexually active with both men and women, with intermittent condom use.

On physical examination, the patient appears uncomfortable. Temperature is 38.3 °C (100.9 °F), and other vital signs are normal. No abnormalities are seen on nondilated funduscopic examination. Cervical lymphadenopathy and pharyngeal erythema are noted. A faint maculopapular rash is present on the trunk. The remainder of the examination is unremarkable.

A lumbar puncture is performed.

Cerebrospinal fluid (CSF) profile:

Leukocyte count	55/µL (55 × 10^6/L), with lymphocytic predominance
Glucose	70 mg/dL (3.9 mmol/L)
Pressure (opening)	80 mm H_2O
Protein	149 mg/dL (1490 mg/L)

CSF Gram stain is negative, and culture results are pending.

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Which of the following studies is most likely to confirm the diagnosis in this patient?

CONT.

(A) CSF enterovirus polymerase chain reaction assay
(B) HIV antigen/antibody combination immunoassay
(C) Lyme serologic testing
(D) Mumps IgM serologic testing

Item 69

A 59-year-old man is evaluated in the emergency department after sustaining a puncture wound to the right foot 12 days ago. He is a construction worker. He stepped on a metallic object that punctured through his leather work boots into the plantar aspect of his foot. He reports pain on walking and notes swelling, warmth, and erythema on the top of his foot above the site of injury. He reports no fever or chills and has noted no drainage from the area of injury. Medical history is significant only for a fracture of the fourth and fifth metatarsal bones of the right foot 27 years ago treated with an internal fixation plate. His only medication is as-needed acetaminophen.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 146/76 mm Hg, pulse rate is 89/min, and respiration rate is 16/min. BMI is 31. Examination is unremarkable except for the right foot, which is edematous, warm, and erythematous on the dorsal surface with a closed puncture wound on the plantar aspect of the foot directly beneath the first metatarsal-phalangeal area. The foot is tender to palpation but displays no drainage or fluctuance. The proximal leg is unremarkable, and no lymphadenopathy is detected.

Laboratory studies reveal a leukocyte count of 12,300/μL (12.3×10^9/L) and serum creatinine level of 1.0 mg/dL (88.4 μmol/L).

Plain radiograph of the right foot shows diffuse soft tissue swelling and metallic fixation plate. No gas is detectable in the soft tissues.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT with contrast
(B) MRI with gadolinium
(C) Tagged leukocyte nuclear scanning
(D) Three-phase nuclear bone scanning

Item 70

A 29-year-old woman is evaluated for a 5-day history of nodules over her lower extremities. She reports that she regularly visits a local spa that uses whirlpool footbaths during her pedicure procedures; she always shaves her legs with a razor before these visits. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 120/70 mm Hg, pulse rate is 70/min, and respiration rate is 14/min. BMI is 22. No inguinal lymphadenopathy is apparent. Several mildly tender, erythematous nodules and papules are noted over the distal lower extremities bilaterally; several lesions appear furuncular with associated ulceration. The remainder of the examination is normal.

Punch biopsy of a lesion reveals a necrotizing granulomatous dermatitis, and tissue culture grows a mycobacterial species within 4 days.

Which of the following is the most likely cause of infection?

(A) *Mycobacterium fortuitum*
(B) *Mycobacterium gordonae*
(C) *Mycobacterium kansasii*
(D) *Mycobacterium marinum*

Item 71

A 46-year-old man is evaluated in the emergency department for fever and altered mental status. Five days ago he underwent replacement of a ventriculoperitoneal shunt used to manage congenital hydrocephalus. The procedure was unremarkable, and he did well postoperatively until the rapid onset of confusion and fever over the past several hours. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, the patient is confused and mildly agitated. Temperature is 39.7 °C (103.5 °F), blood pressure is 142/87 mm Hg, pulse rate is 110/min, and respiration rate is 16/min. The general medical examination shows healing surgical incisions on the scalp, neck, and upper abdomen that are clean and dry. Marked nuchal rigidity is noted. Neurologic examination reveals altered sensorium but is otherwise nonfocal.

Head CT shows the ventriculoperitoneal shunt in proper position and no hydrocephalus or other focal lesions.

Laboratory evaluation of the cerebrospinal fluid shows a leukocyte count of 4660/μL (4660×10^6/L) with neutrophilic predominance, glucose level of 15 mg/dL (0.8 mmol/L), and protein level of 480 mg/dL (4800 mg/L). Gram stain and culture results are pending.

Which of the following is the most appropriate empiric antibiotic treatment?

(A) Ampicillin, vancomycin, and ceftriaxone
(B) Meropenem and vancomycin
(C) Moxifloxacin
(D) Vancomycin and ceftriaxone

Item 72

A 22-year-old man is evaluated in follow-up for a recent diagnosis of HIV infection. He has sex with other men and is careful about selection of partners; because of this, he expresses disbelief at the diagnosis. He is asymptomatic and has no history of opportunistic infections. Medical history is otherwise unremarkable. He uses marijuana and cocaine recreationally but reports no injection drug use.

Oh physical examination, vital signs are normal. BMI is 22. Oral, genitourinary, and anal examinations are without lesions. No lymphadenopathy or rash is present. The remainder of the examination is normal.

Laboratory study results include an absolute CD4 cell count of 680/μL and HIV viral load of 3285 copies/mL; complete blood count is normal, as are kidney and liver function studies. HIV genotypic testing demonstrates resistance to efavirenz and nevirapine.

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Counseling on HIV transmission prevention is provided.

Which of the following is the most appropriate next step in management?

(A) Begin antiretroviral therapy today
(B) Begin trimethoprim-sulfamethoxazole
(C) Defer therapy pending further discussion of HIV treatment
(D) Initiate antiretroviral therapy when CD4 cell count is less than 350/μL

Item 73

A 36-year-old woman is evaluated in the ICU for a possible urinary tract infection. She was admitted for management of injuries sustained in a motor vehicle accident and has undergone multiple orthopedic surgical procedures. Yesterday, her temperature was elevated to 38.1 °C (100.6 °F) and a urinalysis with culture was ordered. She has no urinary symptoms. Medical history is otherwise unremarkable. Her only medication is vancomycin.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 110/70 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. BMI is 22. The general medical examination is unremarkable except for multiple contusions and surgical incision sites on the left upper extremity and bilateral lower extremities that are clean and dry. An indwelling urinary catheter is in place.

Urinalysis reveals 25 to 30 leukocytes/hpf and more than 10^5 colony-forming units of yeast identified as *Candida albicans*.

Which of the following is the most appropriate management?

(A) Amphotericin B bladder irrigation
(B) Caspofungin
(C) Fluconazole
(D) Voriconazole
(E) No antifungal therapy

Item 74

A 46-year-old man is diagnosed with methicillin-sensitive *Staphylococcus aureus* osteomyelitis of the L2 and L3 vertebrae during a recent hospitalization. He is discharged home to complete 6 weeks of nafcillin therapy. Medical history is otherwise unremarkable, and he takes no other medications.

Which of the following tests should be completed weekly in monitoring this patient?

(A) Complete blood count, liver enzyme tests, and serum potassium level
(B) Serum creatinine level and complete blood count
(C) Serum creatinine level, complete blood count, and liver enzyme tests
(D) Serum creatinine level, liver enzyme tests, and serum potassium level

Item 75

A 40-year-old man is evaluated for a 2-day history of cough and progressive dyspnea. He notes that the cough is minimally productive of a small amount of whitish sputum. He reports receiving his influenza vaccination this season. Medical history is notable only for cellulitis 2 months ago treated with a brief course of cephalexin. He does not smoke cigarettes or consume alcohol. He takes no medications.

On physical examination, temperature is 37.7 °C (99.9 °F), blood pressure is 127/78 mm Hg, heart rate is 87/min, and respiration rate is 20/min. Oxygen saturation is 99% breathing ambient air. Pulmonary examination reveals decreased breath sounds at the right lung base with no wheezes, crackles, or rhonchi auscultated. The remainder of the examination is unremarkable.

Chest radiograph shows a right lower lobe infiltrate.

Which of the following is the most appropriate empiric antibiotic therapy for this patient?

(A) Amoxicillin-clavulanate
(B) Azithromycin
(C) Doxycycline
(D) Moxifloxacin

Item 76

A 22-year-old man is evaluated in the emergency department for a 1-day history of fever and headache. One week ago, he presented to his internist with a skin eruption on his abdomen, which was diagnosed as erythema migrans. A 14-day course of amoxicillin was initiated. The skin eruption has since resolved.

On physical examination, temperature is 39.1 °C (102.4 °F), blood pressure is 122/64 mm Hg, pulse rate is 104/min, and respiration rate is 22/min. The patient is ill-appearing. No skin lesions are noted.

Laboratory studies:

Haptoglobin	125 mg/dL (1250 mg/L)
Hematocrit	45%
Leukocyte count	2300/μL (2.3×10^9/L)
Platelet count	96,000/μL (96×10^9/L)
Alanine aminotransferase	74 U/L
Aspartate aminotransferase	88 U/L
Bilirubin, total	1.0 mg/dL (17.1 μmol/L)
Lactate dehydrogenase	95 U/L

Which of the following is the most likely diagnosis?

(A) Infection with *Anaplasma phagocytophilum*
(B) Infection with *Babesia microti*
(C) Infection with Powassan virus
(D) Relapsed Lyme disease

Item 77

An 82-year-old woman is evaluated for a 1-week history of urinary incontinence with lower abdominal discomfort. She reports no dysuria, fever, or back pain. Medical history is significant for hypertension and allergic reaction to sulfa drugs, which cause a generalized rash. Her only medication is hydrochlorothiazide.

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On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 150/90 mm Hg, pulse rate is 72/min, and respiration rate is 16/min. Mild suprapubic tenderness but no costovertebral angle tenderness are noted on abdominal examination. The remainder of the examination is noncontributory.

Urine dipstick is positive for leukocyte esterase and nitrites.

Which of the following is the most appropriate management?

(A) Levofloxacin
(B) Nitrofurantoin
(C) Urine culture
(D) Clinical observation

Item 78

A 25-year-old man is admitted to the hospital for chills and fever of 3 days' duration. He reports that he injects heroin daily. Medical history is notable for multiple methicillin-resistant *Staphylococcus aureus*–associated skin and soft tissue infections and for vancomycin hypersensitivity, which causes respiratory failure and hypotension. He takes no medications.

On physical examination, temperature is 39.4 °C (102.9 °F), blood pressure is 104/65 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. A recent injection site in the antecubital fossa is noted, with erythema, tenderness to palpation, and warmth. He has no mucosal lesions or lymphadenopathy. Cardiopulmonary examination is normal. The remainder of the examination is normal.

Laboratory studies show a leukocyte count of 19,000/μL (19×10^9/L) with 95% neutrophils.

Multiple blood cultures reveal gram-positive cocci in clusters. Findings on chest imaging and electrocardiography are normal.

Which of the following is the most appropriate empiric antibiotic treatment for this patient?

(A) Ceftriaxone
(B) Daptomycin
(C) Imipenem
(D) Nafcillin

Item 79

A 19-year-old man is evaluated for a 4-day history of dysuria and pruritus in the area of the meatus. Scant urethral discharge is noted. He has recently become sexually active with a new female partner. He takes no medications and has no known allergies.

On physical examination, vital signs are normal. The remainder of the physical examination is unremarkable.

The results of a nucleic acid amplification test on first voided urine are positive for *Chlamydia trachomatis* and negative for *Neisseria gonorrhoeae*. Urine culture reveals fewer than 10,000 CFU/mL of *Escherichia coli*.

Which of the following is the most appropriate treatment?

(A) Amoxicillin
(B) Azithromycin
(C) Cefixime
(D) Ceftriaxone plus azithromycin

Item 80

A 36-year-old woman is evaluated for fever and right flank pain of 1 day's duration and dysuria of 3 days' duration. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 38.9 °C (102.0 °F), blood pressure is 100/70 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. Right costovertebral angle tenderness is noted. The remainder of the examination is noncontributory.

Urinalysis is positive for leukocyte esterase and nitrites, with a leukocyte count greater than 10/hpf and with many bacteria present. Urine culture is pending.

Which of the following is the most appropriate empiric therapy?

(A) Ampicillin and gentamicin
(B) Ciprofloxacin
(C) Ertapenem
(D) Nitrofurantoin

Item 81

A 45-year-old man is evaluated for a persistent intermittently draining wound. He sustained an open comminuted fracture of the left lower leg 4 years ago during a military deployment. Since that time, he has had a dry eschar over the original open wound that intermittently drains whitish-colored fluid. He reports no fever, chills, or fatigue and indicates only a dull ache around the injury site. He has had no previous evaluation or treatment for this condition. Medical history is significant for hypertension. His only medication is hydrochlorothiazide.

On physical examination, temperature is 37.3 °C (99.1 °F), blood pressure is 130/82 mm Hg, pulse rate is 78/min, and respiration rate is 13/min. Slight induration, hyperpigmentation, and an irregularly shaped 2.5- × 1.5-cm dry eschar are noted on the anteromedial aspect of the left lower leg. A sinus tract is noted after removal of the eschar with drainage of a scant amount of seropurulent fluid. The surrounding soft tissues are not warm, fluctuant, or crepitant.

Laboratory studies are significant for a leukocyte count of 7600/μL (7.6×10^9/L) and erythrocyte sedimentation rate of 32 mm/h.

Plain radiography of the lower extremity demonstrates a healed tibial fracture site surrounded by a bone callus and an anterior soft tissue defect.

Gram stain of sinus tract drainage shows scant leukocytes and rare gram-positive cocci in pairs and clusters. Culture shows moderate growth of *Enterococcus faecalis* and light growth of *Staphylococcus epidermidis*.

Which of the following is the most appropriate next step in management?

(A) Bone biopsy and culture
(B) Intravenous vancomycin
(C) MRI
(D) Oral linezolid

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Item 82

A 65-year-old woman is evaluated for a 3-month history of right knee pain. She reports no previous injury to the joint. She lives in a rural area and has experienced frequent tick bites over the last several years but does not recall any tick attachments in the last 6 months. She has had no fever.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 134/72 mm Hg, pulse rate is 86/min, and respiration rate is 16/min. The right knee is swollen but without warmth or erythema. Crepitus is present with passive flexion and extension. The patient has no skin lesions.

Arthrocentesis is performed, and synovial fluid analysis is compatible with inflammatory arthritis. On laboratory testing, result of Lyme antibody screen (enzyme immunoassay) is positive. Findings on subsequent Western blot IgM are positive, and Western blot IgG result is negative.

Which of the following is the most appropriate management?

(A) *Borrelia burgdorferi* polymerase chain reaction on synovial fluid
(B) Prescribe ceftriaxone
(C) Prescribe doxycycline
(D) No additional evaluation or treatment for Lyme disease

Item 83

A 74-year-old man is evaluated in the emergency department for a 1-day history of grossly bloody diarrhea, abdominal cramps, and chills. Two days ago, he attended a church picnic where he ate coleslaw, corn, and oysters. Several other attendees also developed diarrhea. Medical history is significant for cirrhosis related to chronic hepatitis C.

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 148/82 mm Hg, pulse rate is 117/min, and respiration rate is 22/min. He is diaphoretic. He has gynecomastia and spider angiomata on the chest. Abdominal examination is unremarkable.

The patient's stool is liquid with bright red blood streaks.

Which of the following is the most likely causative organism of this patient's dysentery?

(A) *Clostridium difficile*
(B) *Norovirus*
(C) *Vibrio parahaemolyticus*
(D) *Yersinia enterocolitica*

Item 84

A 20-year-old woman is evaluated in follow-up after an anaphylactic reaction associated with a blood transfusion given emergently following a motor vehicle accident; she has recovered completely from her injuries. Medical history is significant for systemic lupus erythematosus diagnosed 1 year ago and for recurrent sinus and respiratory tract infections since adolescence. Her only medication is hydroxychloroquine.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 110/50 mm Hg, pulse rate is 86/min, and respiration rate is 14/min. BMI is 21. Examination of the nasal passages and upper airway is normal, and the remainder of the physical examination is unremarkable.

Laboratory studies show an undetectable serum IgA level.

Which of the following is the most appropriate management?

(A) Meningococcal conjugate vaccine
(B) Monthly intravenous IgA
(C) Monthly intravenous immune globulin
(D) Stem cell transplantation
(E) Clinical follow-up

Item 85

A 47-year-old man is evaluated for a skin eruption. Approximately 2 weeks ago, his wife noted an erythematous macule on his back. Over the ensuing week, the site became progressively larger. He notes mild fatigue but no fevers. He recently returned from a vacation in Massachusetts, which included outdoor activities such as bike riding and walking to the beach. He reports no known tick attachment.

On physical examination, temperature is 37.2 °C (100.0 °F), blood pressure is 117/68 mm Hg, pulse rate is 52/min, and respiration rate is 18/min. The skin lesion is shown.



Which of the following is the most appropriate management?

(A) Prescribe doxycycline
(B) Prescribe levofloxacin
(C) Serologic testing for *Babesia microti*
(D) Serologic testing for *Borrelia burgdorferi*

Item 86

A 23-year-old woman is hospitalized for a 2-day history of diarrhea. In the last 24 hours, there has been blood in the

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CONT.

stools. She has had abdominal cramping but reports no fevers or chills. She eats only organically grown foods and drinks unpasteurized milk.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 115/72 mm Hg, pulse rate is 86/min, and respiration rate is 18/min. She has mild abdominal pain diffusely on palpation.

The patient's stool shows visible bright red blood streaking.

Which of the following is the most common complication associated with this patient's dysentery?

(A) Aortitis
(B) Guillain-Barré syndrome
(C) Hemolytic uremic syndrome
(D) Mesenteric adenitis
(E) Reactive arthritis

Item 87

A 45-year-old man is evaluated after notification that he received a blood transfusion from a donor who subsequently developed babesiosis. He received 2 units of packed red blood cells 2 months ago after trauma associated with a motor vehicle collision. Since hospital discharge, he has noted mild fatigue but reports no fevers, chills, weight loss, or myalgias.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 134/72 mm Hg, pulse rate is 84/min, and respiration rate is 18/min. No jaundice, hepatomegaly, or splenomegaly is present.

Laboratory studies:

Hematocrit	45%
Leukocyte count	7600/μL (7.6×10^9/L)
Platelet count	358,000/μL (358×10^9/L)
Bilirubin, total	1.4 mg/dL (23.9 μmol/L)
Reticulocyte count	1% of erythrocytes

Results of *Babesia* polymerase chain reaction of whole blood are positive.

Which of the following is the most appropriate management?

(A) Perform exchange transfusion
(B) Repeat polymerase chain reaction in 3 months
(C) Treat with atovaquone and azithromycin
(D) Treat with clindamycin and quinine

Item 88

A 21-year-old woman is hospitalized for a 4-day history of progressively worsening right-lower-quadrant abdominal pain with dyspareunia, fever, and chills. On the day of admission, the patient developed nausea with several episodes of vomiting. She takes no medications and has no known allergies.

On physical examination, temperature is 38.8 °C (101.8 °F), blood pressure is 100/60 mm Hg, pulse rate is 110/min, and respiration rate is 12/min. Abdominal examination reveals positive bowel sounds with tenderness in the right lower quadrant accompanied by localized rebound. On pelvic examination, the cervix is erythematous with a small amount of mucopurulent discharge. Cervical motion tenderness and tenderness in the right adnexal region are noted, without adnexal fullness or masses.

Result on a pregnancy test is negative, and pelvic ultrasonography shows fluid in the cul de sac with thickening of the right fallopian tube but no tubo-ovarian abscess.

Which of the following is the most appropriate treatment?

(A) Cefoxitin plus doxycycline
(B) Ceftriaxone plus azithromycin
(C) Ciprofloxacin
(D) Piperacillin-tazobactam

Item 89

A 78-year-old man is admitted to the ICU with fever, malaise, weakness, and abdominal pain of 5 days' duration. He reports no nausea, vomiting, or diarrhea. Medical history is notable only for diverticulosis, and he takes no medications.

On physical examination, temperature is 38.6 °C (101.5 °F), blood pressure is 120/60 mm Hg, pulse rate is 112/min, and respiration rate is 18/min. Oxygen saturation is 92% breathing ambient air. Abdominal distention and moderate midabdominal tenderness are noted. Bowel sounds are normal. The remainder of the examination is noncontributory.

Laboratory studies show a leukocyte count of 21,000/μL (21×10^9/L).

CT scan shows diverticulosis and a 3-cm × 4-cm enhancing fluid collection.

Percutaneous drainage and culture is pending.

Which of the following is the most appropriate antimicrobial treatment?

(A) Intravenous aztreonam and vancomycin
(B) Intravenous vancomycin and oral clindamycin
(C) Oral ampicillin and metronidazole
(D) Oral ciprofloxacin and metronidazole

Item 90

A 25-year-old man is evaluated in follow-up after HIV testing. He states he has sex with other men and usually uses condoms. He had a negative HIV test result 1 year ago. He feels well today but reports having a flulike illness last week with mild fever, headache, myalgias, and fatigue; these symptoms have resolved. Medical history is unremarkable for sexually transmitted or other infections. Other than taking over-the-counter ibuprofen last week, he takes no medications.

On physical examination, he is afebrile and has small palpable anterior and posterior cervical, axillary, and inguinal lymph nodes. The remainder of the examination is normal.

HIV-1/2 antigen/antibody combination immunoassay is reactive. Result of an HIV-1/HIV-2 antibody differentiation immunoassay is negative for HIV-1 and HIV-2. Result of an HIV-1 nucleic acid amplification testing is positive, with 51,455 copies/mL.

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Which of the following is the most appropriate next step in management?

(A) Repeat HIV-1/HIV-2 antibody differentiation immunoassay in 6 weeks
(B) Saliva rapid HIV testing
(C) T-cell subset testing
(D) Western blot HIV-1 antibody testing

Item 91

A 65-year-old woman is evaluated for a 3-day history of diarrhea and fever. She reports no abdominal pain or vomiting. She notes mucus intermixed with the stool, but no visible blood. She is also experiencing fatigue and anorexia. She works as a nurse.

On physical examination, the patient appears uncomfortable but is in no acute distress. Temperature is 38.2 °C (100.8 °F), blood pressure is 148/66 mm Hg, pulse rate is 84/min, and respiration rate is 22/min. Abdominal examination reveals hyperactive bowel sounds and mild diffuse tenderness to palpation.

Laboratory studies reveal a leukocyte count of 11,400/μL (11.4×10^9/L) and a positive result on a fecal occult blood test.

Empiric levofloxacin is started for presumed bacterial gastroenteritis, and a stool sample is sent for culture. Twenty-four hours later, the culture reveals *Campylobacter jejuni* resistant to levofloxacin. A call to the patient confirms she feels well, with resolution of diarrhea and fever.

Which of the following is the most appropriate management?

(A) Discontinue levofloxacin
(B) Perform blood culture testing
(C) Repeat stool culture
(D) Switch to azithromycin
(E) Switch to ciprofloxacin

Item 92

A 45-year-old man is evaluated for right-sided chest discomfort and cough of 2 weeks' duration. His chest discomfort is described as a vague, painful sensation on the right. The cough occasionally produces a small amount of sputum; he reports no hemoptysis or shortness of breath. He has felt feverish with mild fatigue but has had no weight loss. He is a smoker with a 20-pack-year history. He takes no medications.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 130/70 mm Hg, pulse rate is 86/min, and respiration rate is 18/min. BMI is 27. Oxygen saturation breathing ambient air is 98%. Chest examination is normal, and the remainder of the physical examination is unremarkable. No skin rash is present.

Chest radiograph shows a nodule in the right lower lung lobe, which CT of the chest confirms. CT-guided biopsy of the nodule is performed. Findings on histologic testing are positive for budding yeast, and culture indicates *Cryptococcus neoformans*.

An HIV test result is negative.

Which of the following is the most appropriate management?

(A) Caspofungin
(B) Lumbar puncture
(C) Surgical removal of the nodule
(D) Clinical observation

Item 93

A 31-year-old man is evaluated in the emergency department for a 5-day history of abdominal discomfort, vomiting, and loose stools, accompanied by progressively increasing fever. He also has a moderate headache and a rash. He arrived from Sri Lanka 6 days ago.

On physical examination, temperature is 40 °C (104 °F), blood pressure is 102/70 mm Hg, pulse rate is 64/min, and respiration rate is 20/min. BMI is 26. The patient appears sick. There are blanching erythematous macules on the lower chest and upper abdominal wall. He has scleral icterus and injected conjunctivae. The pharynx is erythematous. Abdominal examination reveals tender hepatosplenomegaly. The remainder of the examination is normal.

Laboratory studies:

Hemoglobin	12.1 g/dL (121 g/L)
Leukocyte count	4550/μL (4.55×10^9/L); 68% polymorphonuclear cells, 10% band forms, 16% lymphocytes, 6% monocytes
Platelet count	95,000/μL (95×10^9/L)
Alanine aminotransferase	250 U/L
Aspartate aminotransferase	125 U/L

Peripheral blood smear is normal. Two sets of aerobic blood cultures show gram-negative bacilli.

Which of the following is the most likely diagnosis?

(A) Brucellosis
(B) Lassa fever
(C) Leptospirosis
(D) Typhoid fever

Item 94

A 24-year-old woman is hospitalized for a 1-month history of increasing paranoia and delusions according to her husband. On the day of admission, she had a tonic-clonic seizure with incontinence. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, temperature is 37.9 °C (100.2 °F), blood pressure is 107/48 mm Hg, pulse rate is 102/min, and respiration rate is 16/min. The patient is unresponsive but withdraws her extremities to painful stimuli. The neck is supple to passive flexion. Occasionally, choreoathetoid movements of the bilateral upper extremities are observed.

Lumbar puncture is performed.

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Cerebrospinal fluid (CSF) studies: CONT.

Leukocyte count	57/μL (57×10^6/L); 97% lymphocytes, 3% neutrophils
Erythrocyte count	14/μL (14×10^6/L)
Glucose	57 mg/dL (3.2 mmol/L)
Protein	142 mg/dL (1420 mg/L)
Gram stain	No organisms

Results of herpes simplex virus polymerase chain reaction of the CSF are negative. HIV antibody serum test results are negative.

Brain MRI reveals no focal abnormality.

Which of the following tests is most likely to confirm the diagnosis?

(A) Anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies
(B) *Borrelia burgdorferi* (Lyme) antibody serology
(C) Nuchal skin biopsy
(D) VDRL test of CSF

Item 95

A 75-year-old man is evaluated in the emergency department for fever, productive cough, and shortness of breath of 5 days' duration. Medical history is significant for type 2 diabetes mellitus. He has never smoked and does not drink alcohol. His only medication is metformin.

On physical examination, temperature is 39.2 °C (102.6 °F), blood pressure is 95/65 mm Hg, heart rate is 110/min, and respiration rate is 32/min. Oxygen saturation is 83% breathing ambient air and rises to 94% with 30% oxygen by face mask. BMI is 29. Pulmonary examination reveals decreased breath sounds and crackles at the left lung base. The remainder of the examination, including mental status, is normal.

Laboratory studies show a leukocyte count of 18,000/μL (18×10^9/L). A basic metabolic panel is normal. Blood cultures are pending.

Chest radiograph shows left lower lobe consolidation.

The patient is transferred to the ICU, and empiric broad-spectrum antibiotics are ordered.

Which of the following additional studies is most appropriate in this patient?

(A) C-reactive protein level
(B) Chest CT
(C) Procalcitonin level
(D) Sputum cultures

Item 96

A 29-year-old man is hospitalized for a 3-week history of fever, malaise, night sweats, and weight loss. Medical history is significant for HIV/AIDS infection, with an episode of *Pneumocystis jirovecii* pneumonia 2 years ago. He is nonadherent with all his HIV medications.

On physical examination, temperature is 39.2 °C (102.6 °F), blood pressure is 100/60 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. BMI is 19. He appears cachectic. Abdominal palpation elicits mild pain without guarding or rebound and reveals hepatosplenomegaly. The remainder of the examination is normal.

Laboratory study results show a CD4+ cell count of 45/μL.

Blood cultures are positive for *Mycobacterium avium* complex.

Which of the following is the most appropriate treatment?

(A) Clarithromycin, ethambutol, and rifabutin
(B) Isoniazid and rifabutin
(C) Isoniazid, rifabutin, ethambutol
(D) Rifabutin, isoniazid, pyrazinamide, ethambutol

Item 97

A 64-year-old man is evaluated for a 3-day history of fever, chills, and cough productive of yellow-green, but sometimes brownish, sputum. Although his breathing is comfortable at rest, he feels short of breath with minimal activity. He reports having received a flu shot this season. Medical history is significant for COPD, type 2 diabetes mellitus, and a 50-pack-year smoking history, although he quit 5 years ago. Medications are tiotropium and as-needed albuterol metered-dose inhalers and metformin.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 130/90 mm Hg, pulse rate is 90/min, and respiration rate is 24/min. Oxygen saturation is 92% breathing ambient air. Pulmonary examination is notable for diffusely decreased breath sounds throughout and crackles at the right lung base; occasional mild expiratory wheezes are present. Cardiac and abdominal examinations are normal, and the remainder of the examination is unremarkable.

Chest radiograph shows a right lower lobe infiltrate.

Which of the following is the most appropriate management?

(A) Inpatient treatment with ampicillin-sulbactam and doxycycline
(B) Inpatient treatment with ceftriaxone and azithromycin
(C) Outpatient treatment with azithromycin
(D) Outpatient treatment with levofloxacin

Item 98

A 53-year-old man is evaluated in the hospital for fever. He underwent elective coronary artery bypass graft surgery 2 days ago. An indwelling urinary catheter was inserted in the operating room. Medical history is unremarkable, and he takes no medications.

On physical examination, temperature is 38.4 °C (101.1 °F), blood pressure is 130/84 mm Hg, pulse rate is 88/min, and respiration rate is 18/min. Lungs are clear to auscultation. The sternotomy incision site is clean and dry. He has mild suprapubic tenderness but no costovertebral angle or flank tenderness.

Urinalysis reveals 10 to 20 leukocytes/hpf. Urine culture grows 10^4 colony-forming units of gram-negative rods. Chest radiograph shows no infiltrate.

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CONT.

In addition to removing the urinary catheter, which of the following is the most appropriate management?

(A) Await antimicrobial sensitivities before beginning antimicrobial therapy
(B) Begin antimicrobial therapy now
(C) Repeat urinalysis and urine culture in 24 hours
(D) Provide no additional treatment

Item 99

A 50-year-old man is admitted to the hospital for fever with increasing pain and redness of his left foot and leg. He stepped on a fishhook 2 days ago while wading through brackish water. He reports that only the foot was involved initially, but symptoms have spread up his leg to just below the knee. Medical history is significant for cirrhosis secondary to chronic hepatitis C. He is up to date on all immunizations. Medications are propranolol and as-needed furosemide.

On physical examination, temperature is 39.3 °C (102.7 °F), blood pressure is 90/60 mm Hg, pulse rate is 70/min, and respiration rate is 22/min. The left foot and leg up to the knee are edematous, exquisitely tender, and covered with several hemorrhagic bullae. The remainder of the examination is unremarkable.

Laboratory studies show a leukocyte count of 20,000/μL (20×10^9/L), with 85% neutrophils, 10% immature band forms, and 5% lymphocytes.

Emergent surgical debridement shows necrotizing fasciitis. Gram stain of the intraoperative tissue specimen reveals curved gram-negative bacilli.

Empiric antimicrobial agents are initiated.

Which of the following is the most likely infectious agent?

(A) *Erysipelothrix rhusiopathiae*
(B) Methicillin-resistant *Staphylococcus aureus*
(C) *Mycobacterium marinum*
(D) *Vibrio vulnificus*

Item 100

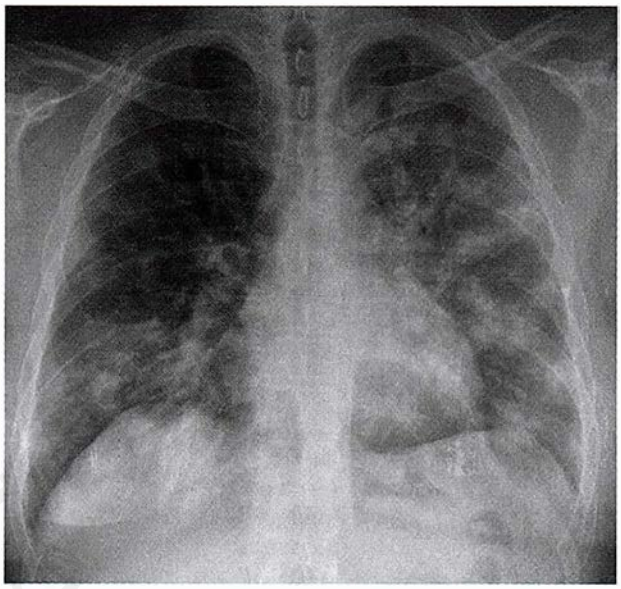
A 33-year-old man is evaluated in the emergency department in July for respiratory distress. He recently returned from an extended business trip through Guangdong Province of China, Saudi Arabia, and Liberia. Over the final 3 days of the trip, he noted feeling short of breath with exertion with dry cough, headache, nausea, and diarrhea. He is unaware of known exposure to ill contacts. Medical history is otherwise unremarkable, and he takes no medications. He has received all recommended travel-related immunizations.

On physical examination, temperature is 39.1 °C (102.4 °F), blood pressure is 110/72 mm Hg, pulse rate is 98/min, and respiration rate is 22/min. BMI is 28. Oxygen saturation is 91% breathing ambient air. No lymphadenopathy is detected. Pulmonary auscultation reveals diffuse bronchial breath sounds and rhonchi. He has no abdominal tenderness or hepatosplenomegaly, and no rash is present. The remainder of the examination is normal.

Laboratory studies:

Hemoglobin	10.9 g/dL (109 g/L)
Leukocyte count	4750/μL (4.75×10^9/L) (82% neutrophils, 10% lymphocytes, 8% monocytes)
Platelet count	97,000/μL (97×10^9/L)
Prothrombin time/INR	Normal
Alanine aminotransferase	98 U/L
Blood urea nitrogen	30 mg/dL (10.7 mmol/L)
Creatinine	1.6 mg/dL (141 μmol/L)
Lactate dehydrogenase	355 U/L

Chest radiograph is shown.



Which is the following is the most likely diagnosis?

(A) Ebola virus infection
(B) Influenza virus infection
(C) Middle East respiratory syndrome
(D) Respiratory syncytial virus infection

Item 101

A 62-year-old man is evaluated in the hospital for fever and chills of 1 day's duration. He was admitted 3 days ago for lower gastrointestinal bleeding and hypotension, and a right internal jugular venous catheter was inserted for intravenous fluid hydration and blood transfusion. Blood cultures drawn through the central catheter and peripherally during initial evaluation of the fever were positive for gram-positive cocci in clusters. The central venous catheter was removed and vancomycin started. Medical history is otherwise unremarkable, and he takes no other medications.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 118/74 mm Hg, pulse rate is 94/min, and respiration rate is 16/min. The previous intravenous catheter site is mildly tender to palpation, without erythema, drainage, or fluctuance. The remainder of the examination is unremarkable.

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CONT.

The original blood cultures grew methicillin-sensitive *Staphylococcus aureus*, and repeat blood cultures 24 hours after the start of antibiotics are positive for gram-positive cocci. Transthoracic echocardiography shows no valvular vegetations.

Which of the following is the most appropriate management?

(A) Add rifampin
(B) Change vancomycin to nafcillin
(C) Obtain a serum vancomycin peak level
(D) Perform ultrasonography on the right internal jugular vein

Item 102

A 55-year-old woman is evaluated in the emergency department for fever, cough, decreased appetite, and night sweats of 2 weeks' duration. She has experienced a 4.5-kg (10 lb) weight loss over past 2 months. She lives in China and is visiting her daughter in the United States. Medical history is otherwise unremarkable, and she takes no medications

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 120/70 mm Hg, pulse rate is 90/min, and respiration rate is 19/min. BMI is 20. Egophony is heard in the upper lobes of both lungs.

Bilateral apical infiltrates are seen on chest radiograph.

In addition to standard precautions, which of the following empiric infection control precautions should be instituted for this patient?

(A) Airborne
(B) Contact
(C) Droplet
(D) No additional precautions

Item 103

An 18-year-old young man is evaluated for a tender skin lesion on the right leg, which appeared 2 days ago. He is a wrestler at his high school. Medical history is notable for a documented hypersensitivity allergy to trimethoprim-sulfamethoxazole. He takes no medications.

On physical examination, temperature is 36.9 °C (98.4 °F), blood pressure is 120/74 mm Hg, pulse rate is 80/min, and respiration rate is 13/min. BMI is 23. No lymphangitis or right inguinal lymphadenopathy is evident. A single 3-cm by 2-cm fluctuant, tender soft tissue lesion without erythema is noted over the right distal anterior thigh.

Complete blood count is normal.

In addition to incision and drainage of the furuncle, which of the following is the most appropriate treatment?

(A) Oral dicloxacillin
(B) Oral doxycycline
(C) Oral rifampin
(D) Clinical follow-up

Item 104

A 70-year-old woman is admitted to the hospital for a 1-week history of fever, productive cough, and worsening shortness of breath. Because of poor oxygenation and hypotension, she is admitted directly to the ICU. Medical history is significant for oxygen-dependent COPD and bronchiectasis with frequent exacerbations. She has a 55-pack-year smoking history and is a current smoker. Medications are tiotropium, fluticasone-salmeterol, and as-needed albuterol metered-dose inhalers; she recently completed a 10-day prednisone taper.

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 88/60 mm Hg, pulse rate is 105/min, and respiration rate is 30/min. Oxygen saturation is 82% breathing ambient air, which increases to 92% with 50% oxygen by face mask. Lung examination shows diffuse rhonchi. The remainder of the examination is unremarkable.

Laboratory studies are significant for a leukocyte count of 16,400/μL (16.4×10^9/L), a normal metabolic profile, and normal kidney function. Sputum and blood cultures are pending.

Chest radiograph shows multilobar infiltrates.

Which of the following is the most appropriate empiric antibiotic treatment for this patient?

(A) Cefepime, levofloxacin, and gentamicin
(B) Ceftriaxone and azithromycin
(C) Levofloxacin and ceftriaxone
(D) Meropenem

Item 105

A 39-year-old man undergoes consultation about HIV prevention. He has a male sex partner with HIV infection. He reports they use condoms "most of the time." He asks about other options that can reduce his risk for acquiring HIV from his partner. He is asymptomatic. Medical history is noncontributory, although he has been vaccinated for hepatitis B. He takes no medications.

On physical examination, vital signs are normal, as is the remainder of the examination.

Results of testing for HIV are negative. Testing for hepatitis B surface antigen yields negative findings, and hepatitis B surface antibody results are positive.

Which of the following is the most appropriate management?

(A) Counsel that consistent condom use provides adequate protection
(B) Prescribe daily combination tenofovir-emtricitabine
(C) Prescribe daily combination tenofovir-emtricitabine and raltegravir
(D) Prescribe daily tenofovir

Item 106

A 45-year-old woman is seen for follow-up evaluation of daily fevers and fatigue of 1 month's duration. She reports measured temperatures as high as 38.3 °C (100.9 °F) but

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has no focal symptoms or weight loss. Medical history is unremarkable. She reports no travel or known infectious exposures. She takes no medications.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 130/60 mm Hg, pulse rate is 90/min and regular, and respiration rate is 14/min. BMI is 27. The patient appears well, and the remainder of the physical examination is normal and unchanged from a clinic visit 3 weeks ago.

Laboratory studies:

Erythrocyte sedimentation rate	<20 mm/h
Hemoglobin	14.2 g/dL (142 g/L)
Leukocyte count	6800/μL (6.8×10^9/L) with normal differential
Platelet count	223,000/μL (223×10^9/L)
Alkaline phosphatase	77 U/L
Aminotransferases	Normal
Urinalysis	0-2 leukocytes/hpf
Complete metabolic profile and kidney function	Normal

Results for antinuclear antibody are negative. Findings on HIV serologic testing, tuberculin skin test, and serum pregnancy test are negative. Three sets of blood cultures show no growth.

A chest radiograph and CT of the abdomen and pelvis with and without contrast are normal.

Which of the following is the most appropriate next step in management?

(A) Bone marrow aspirate and biopsy
(B) Empiric course of broad-spectrum antibiotics
(C) Empiric trial of systemic glucocorticoids
(D) Whole-body CT
(E) Clinical observation

Item 107

A 68-year-old woman is admitted to the hospital for a 2-day history of fever, increasing dyspnea, and worsening cough. She was diagnosed with influenza pneumonia approximately 3 weeks ago. She had stayed home from work following her diagnosis and was beginning to recover when her current symptoms began. She started with fever and began to notice increasing shortness of breath. Her cough, which had almost resolved, returned and has been productive of moderate amounts of grey-colored sputum. Medical history is significant for hypertension. Her only medication is hydrochlorothiazide.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 136/82 mm Hg, pulse rate is 89/min, and respiration rate is 28/min. Oxygen saturation is 90% breathing ambient air. Lung examination shows diffuse rhonchi. Cardiac and abdominal examinations are normal.

Chest radiograph shows bilateral cavitary infiltrates.

Which of the following is the most likely causative pathogen in this patient?

(A) *Legionella* species
(B) *Pseudomonas aeruginosa*
(C) *Staphylococcus aureus*
(D) *Streptococcus pneumoniae*

Item 108

A 26-year-old woman is evaluated for recurrent episodes of cystitis. She has had four episodes within the previous 6 months but is currently asymptomatic. She has increased her fluid intake and voids after sexual intercourse. However, she continues to have episodes of infection. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 110/60 mm Hg, pulse rate is 60/min, and respiration rate is 14/min. BMI is 19. The remainder of the examination is normal.

Which of the following is the most appropriate management?

(A) Antimicrobial prophylaxis
(B) Daily methenamine hippurate
(C) Daily vitamin C
(D) Urethroscopy

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Answers and Critiques

Item 1 Answer: B

Educational Objective: Treat a patient with tuberculous meningitis.

This patient has tuberculous meningitis and should receive glucocorticoid therapy in addition to antituberculous therapy. Dexamethasone is recommended for adults with tuberculous meningitis because limited data show some mortality benefits. The recommended dose of dexamethasone is 12 mg/d for 3 weeks, with gradual tapering during the following 3 weeks. Some experts use prednisone instead of dexamethasone, and others recommend a slightly longer duration of glucocorticoid therapy (approximately 8 weeks). The recommendations for duration of treatment of extrapulmonary tuberculosis are generally the same as for pulmonary tuberculosis (6-9 months). However, the recommended treatment duration for tuberculous meningitis is longer (9-12 months), with the exact duration determined by response to therapy and antibiotic sensitivities of the isolate.

Diuretics—such as acetazolamide and furosemide, which decrease cerebrospinal fluid (CSF) production by the choroid plexus—have been used as temporizing measures for management of hydrocephalus in patients who are not stable enough to undergo surgical decompression. However, there is no indication for their use in this patient.

Patients with tuberculous meningitis can develop hydrocephalus, usually secondary to impaired CSF resorption. Ventriculoperitoneal shunts can be used to manage hydrocephalus. This patient has no evidence of hydrocephalus, which is typically associated with increased intracranial pressures and ventriculomegaly on brain imaging. Serial lumbar punctures after initiation of glucocorticoids and antituberculous medications can be attempted initially in patients with hydrocephalus before attempting surgical drainage with a shunt.

KEY POINT

- Patients with tuberculous meningitis should receive a glucocorticoid in addition to antituberculous therapy.

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Item 2 Answer: D

Educational Objective: Diagnose central nervous system toxoplasmosis.

This patient most likely has central nervous system (CNS) *Toxoplasma gondii* infection. He has not been adherent to antiretroviral therapy, and his CD4 cell count has decreased to less than 100/μL, putting him at risk for opportunistic infection. Clinical presentation of CNS toxoplasmosis typically involves new headaches and focal neurologic deficits and may also include fever and seizures. The findings on this patient's MRI are classic for toxoplasmosis, with multiple ring-enhancing lesions. Because CNS toxoplasmosis in AIDS results from reactivation of earlier infection, patients usually have a positive result for IgG antibody but not IgM. He should be treated empirically and followed for clinical and radiographic response, which typically occurs within 1 to 2 weeks.

Primary CNS lymphoma generally requires a more severe degree of immunosuppression than most other AIDS-related complications, most commonly occurring when the CD4 cell count drops below 50/μL; the incidence has decreased with effective antiretroviral therapy. Although primary CNS lymphoma may present with more than one lesion on MRI, it most often presents with a single large lesion. Primary CNS lymphoma is strongly associated with Epstein-Barr virus infection, and polymerase chain reaction of cerebrospinal fluid to detect Epstein-Barr virus can facilitate the diagnosis. The prognosis remains poor.

Cryptococcal meningoencephalitis is another common CNS infection in AIDS but rarely results in focal mass lesions on imaging, more often presenting with mental status changes than focal deficits and seizure. The serum cryptococcal antigen and cerebrospinal fluid antigen are positive in 95% and 99% of cases, respectively; therefore, a negative antigen test result argues against this diagnosis.

Progressive multifocal leukoencephalopathy presents in AIDS with focal deficits and mental status changes. Onset usually occurs over several weeks, compared with several days for toxoplasmosis, and fever is uncommon. Furthermore, progressive multifocal leukoencephalopathy lesions on MRI are typically white-matter, noninflammatory lesions (unless accompanied by immune reconstitution inflammatory syndrome) with minimal enhancement and no mass effect.

KEY POINT

- Central nervous system toxoplasmosis in AIDS results from reactivation of earlier infection, typically involves new focal neurologic deficits and headaches, and may also include fever and seizures.

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Item 3 Answer: D

Educational Objective: Manage nonresponse to antimicrobial therapy in a patient with ventilator-associated pneumonia.

This patient should undergo thoracentesis to determine why he is not improving with treatment. Nonresponsive pneumonia is defined as an inadequate clinical response despite appropriate antimicrobial therapy. In most patients with ventilator-associated pneumonia (VAP), effective antimicrobial treatment usually results in defervescence and reduction in leukocyte count within 72 hours of beginning therapy, with improvement of oxygenation and decreased secretions, if hypoxia and excessive secretions were present. In patients who do not respond to appropriate antimicrobial treatment after 72 hours or who do not continue improving or worsen after an initial therapeutic response, it is imperative to search for another explanation for the patient's clinical findings (such as an infectious complication, another site of infection, or an alternate diagnosis). The possibility of a parapneumonic process should always be considered in the differential diagnosis of nonresponsive pneumonia. A new, or increasing, pleural effusion could represent a parapneumonic effusion, empyema, or a lung abscess. Thoracentesis and pleural fluid examination should be performed because the results could significantly alter management.

Suprainfections can occur, including suprainfection with gram-negative organisms, but the finding of only gram-positive cocci on Gram stain does not support this as a cause of nonresponse. Thus, broadening antimicrobial therapy to cover gram-negative organisms is not warranted.

With a new fever and no change in respiratory symptoms or oxygenation requirements, drug fever resulting from nafcillin therapy might be considered, especially if the chest radiograph was unchanged or showed improvement. Antimicrobial agents, particularly β-lactam agents, can cause drug fever but usually do not cause the level of leukocytosis seen in this patient. Because treatment for methicillin-sensitive *Staphylococcus aureus* VAP should continue for at least 7 days, the antibiotic should be changed to a different class if drug fever is suspected but not stopped altogether.

Evaluation of infectious complications or extrapulmonary sources of infection should occur before considering a bronchoscopy and bronchoalveolar lavage (BAL). BAL may be considered when there is a suspicion of antibiotic-resistant organisms not isolated from sputum culture.

KEY POINT

- Patients with ventilator-associated pneumonia who do not improve within 72 hours of initiation of appropriate antimicrobial therapy should be evaluated for infectious complications, an alternate diagnosis, or another site of infection to explain the clinical picture.

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Item 4 Answer: D

Educational Objective: Treat vancomycin-intermediate, methicillin-resistant *Staphylococcus aureus* bacteremia.

This patient's vancomycin therapy should be discontinued, and treatment with an alternative agent, such as daptomycin, should be initiated. Although vancomycin is a reasonable choice for empiric therapy in patients suspected of having methicillin-resistant *Staphylococcus aureus* (MRSA) skin or soft tissue infection, it is only slowly bactericidal and generally less effective than agents more potently bactericidal against MRSA for treatment of bacteremia or infective endocarditis. The minimum inhibitory concentration (MIC) to vancomycin of the infecting organism is typically used to guide therapy. For isolates with a vancomycin MIC of 2 μg/mL or less, the patient's clinical response should determine whether to continue vancomycin or change to an alternative agent independent of the MIC. However, vancomycin is not recommended for bacteremia if the MIC to vancomycin is greater than 2 μg/mL. Therefore, continuing the current vancomycin dose in this patient would not be appropriate, and switching therapy to an alternative agent is indicated. If daptomycin is used, the MIC of the organism to daptomycin should also be verified to ensure susceptibility.

In patients in whom treatment with vancomycin for MRSA bacteremia is appropriate (vancomycin MIC of 2 μg/mL or less), the goal serum vancomycin trough level is 15 to 20 μg/mL. When the vancomycin trough level is within this range, as in this patient, increasing the vancomycin dose creates the risk of the trough level being higher than 20 μg/mL, which would increase the risks for adverse effects without providing additional clinical benefit. However, because the MIC of this organism to vancomycin is greater than 2 μg/mL, continuing dose-adjusted vancomycin would not be appropriate.

Adding rifampin to vancomycin has not been shown to improve clinical outcomes.

KEY POINT

- Daptomycin is a better therapeutic option than vancomycin for treating methicillin-resistant *Staphylococcus aureus* with a vancomycin minimum inhibitory concentration greater than 2 μg/mL.

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Item 5 Answer: D

Educational Objective: Manage a patient receiving ethambutol for treatment of tuberculosis.

This patient has strongly suspected pulmonary tuberculosis and will begin four-drug therapy with isoniazid, rifampin, pyrazinamide, and ethambutol. All patients starting antituberculous therapy should have baseline measurements of aminotransferases, bilirubin, alkaline phosphatase, serum creatinine, and a platelet count. Specific adverse effects of ethambutol include a retrobulbar neuritis manifesting as decreased green-red color discrimination or decreased visual acuity. Therefore, baseline testing of color discrimination and visual acuity with monthly questioning regarding any visual abnormalities is recommended for patients taking ethambutol, with monthly testing for patients taking the drug for more than 2 months, patients with kidney disease, and patients receiving more than 15 to 25 mg/kg of ethambutol. Rash and peripheral neuritis are also reported with ethambutol use. Adverse effects of isoniazid use include peripheral neuropathy, hepatitis, rash, and a lupus-like syndrome. Pyrazinamide can cause hepatitis, rash, gastrointestinal upset, and hyperuricemia. Rifampin can cause hepatitis, gastrointestinal upset, rash, and orange coloring of body fluids. All patients should be evaluated at least monthly for adherence to these medications as well as possible adverse reactions.

Baseline audiogram and vestibular testing (including Romberg testing) is recommended for patients receiving streptomycin, an aminoglycoside with adverse effects, including ototoxicity (hearing and vestibular disturbances), neurotoxicity, and nephrotoxicity. Monthly questioning regarding vestibular/auditory symptoms and monthly assessments of kidney function are recommended.

Patients with HIV who become infected with tuberculosis should have a CD4 cell count performed as part of baseline monitoring.

KEY POINT

- Before starting ethambutol, patients should be evaluated for color discrimination and visual acuity because an adverse effect of the drug is a retrobulbar neuritis manifesting as decreased green-red color discrimination or decreased visual acuity.

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Item 6 Answer: D

Educational Objective: Diagnose Rocky Mountain spotted fever.

The most likely diagnosis for this patient, who presents with fever, lymphocytic meningitis, and petechial rash following tick exposure, is Rocky Mountain spotted fever (RMSF). Headache is common in RMSF, and meningoencephalitis is seen in as many as 20% of cases. A rash is present in 85% to 90% of cases of RMSF, although the onset of skin findings may be delayed several days after the initial fever. Early on, the rash is often macular and localized to the wrists and ankles. Over time, this evolves to a diffuse petechial eruption, usually sparing the face. Involvement of palms and soles is characteristic of RMSF, although it is not universal. The low platelet counts and elevated liver enzyme levels also suggest RMSF. Finally, the rapid clinical response to doxycycline is characteristic of RMSF and would make viral entities less likely. The negativity for RMSF antibodies should not discount this diagnosis. During the acute presentation, antibodies to *Rickettsia rickettsii* are often undetectable because of insufficient time to mount a serologic response to the infection. Testing a convalescent serum specimen obtained more than 14 days after symptom onset allows for retrospective confirmation of RMSF infection. Skin biopsy frequently reveals evidence of vasculitis, and the diagnosis may be confirmed by immunohistochemistry; however, this test is not widely available. A clinically compelling presentation for RMSF should prompt initiation of doxycycline treatment, and this should be continued despite the absence of detectable antibodies.

Rash caused by enterovirus is distinguishable from RMSF because it appears morbilliform rather than petechial. Hematologic abnormalities are uncommon with enterovirus infection.

Heartland virus is a newly identified phlebovirus transmitted by the same tick that causes ehrlichiosis. Although this infection is associated with thrombocytopenia and elevated liver enzyme levels, it can be distinguished from RMSF by lack of a rash or response to doxycycline treatment.

Lyme disease can cause neurologic manifestations, including meningitis, but is associated with erythema migrans rather than a petechial rash.

West Nile virus causes neuroinvasive disease in less than 1% of infected patients. It may be associated with a nonspecific rash; however, symptoms would not improve with doxycycline.

KEY POINT

- Following a tick bite, symptoms of fever, petechial rash, and lymphocytic meningitis suggest Rocky Mountain spotted fever and should be treated with doxycycline.

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Item 7 Answer: B

Educational Objective: Treat hospital-acquired diarrhea with an antimotility medication.

This patient, whose diarrhea began more than 3 days after hospitalization, tested negative for *Clostridium difficile*

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CONT.

infection (CDI), so she should be prescribed an antimotility agent for symptomatic relief. CDI is the most common infectious cause of diarrhea in hospitalized patients. Antibiotic administration is a major risk factor; however, infection can also be acquired through person-to-person spread or environmental contamination. Diagnostic evaluation for CDI is appropriate for all patients with hospital-acquired diarrhea, regardless of antibiotic history. Nucleic acid amplification tests, such as polymerase chain reaction (PCR) for *C. difficile* toxin genes, are highly sensitive and specific and offer the advantage of rapid results. Antiperistaltic agents should be avoided in CDI treatment because they may obscure symptoms and increase risk for toxic megacolon. In this patient, however, the negative PCR test result essentially excludes this diagnosis. For noninfectious diarrhea, antimotility agents may relieve symptoms.

Hospital-acquired bacterial gastroenteritis, other than CDI, is exceedingly rare, with one study identifying an alternative bacterial enteropathogen in less than 1% of stool cultures submitted at 3 days of hospitalization or longer. Because of the low yield, many laboratories reflexively reject stool cultures submitted on patients who develop diarrhea more than 72 hours after admission.

Patients with confirmed CDI require antimicrobial treatment. Oral metronidazole, as well as vancomycin, is effective in the treatment of mild to moderate CDI. However, it is not indicated in the setting of a negative PCR test result.

Repeat PCR testing after a negative result is rarely indicated and only increases the probability of a false-positive result. Stool enzyme immunoassay, which detects glutamate dehydrogenase, an enzyme ubiquitous in *C. difficile*, is an accepted alternative to PCR in diagnosing CDI. When the result of stool enzyme immunoassay is negative, no further testing is necessary; however, when it is positive, a second, more specific test, such as PCR, is required for diagnosis.

KEY POINT

- Patients with hospital-acquired diarrhea who test negative for *Clostridium difficile* infection should be treated with antimotility agents to suppress symptoms and not undergo additional testing or treatment for *C. difficile*.

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Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. J Antimicrob Chemother.2014 Apr;69(4):881-91. [PMID: 24324224]

Item 8 Answer: C

Educational Objective: Diagnose immune reconstitution inflammatory syndrome caused by disseminated *Mycobacterium avium* complex infection.

This patient has immune reconstitution inflammatory syndrome (IRIS) caused by disseminated *Mycobacterium avium* complex (DMAC) infection. She developed symptoms typical for DMAC (fever, chills, sweats, fatigue, weight loss) approximately 1 month after starting antiretroviral therapy (ART). The infection was likely present before therapy initiation, but her improved immune response, made possible by treating her HIV infection, resulted in development of symptoms (the so-called "unmasking" of a preexisting infection). Her lymphadenopathy, hepatosplenomegaly, anemia, leukopenia, and elevated alkaline phosphatase level are typical signs. DMAC is usually seen in patients whose CD4 cell count is, or recently was, less than 50/μL. The diagnosis can be confirmed by culture of the blood or other normally sterile site, such as bone marrow, lymph node, or liver. A macrolide-based multidrug regimen, usually clarithromycin and ethambutol, and continued ART are the recommended treatment. IRIS is most common with mycobacterial or fungal infections but also has been reported with various opportunistic infections and with non-Hodgkin lymphoma.

Cytomegalovirus occurs in patients with AIDS with low CD4 cell counts and can present with nonspecific systemic symptoms, cytopenias, and hepatitis. However, it usually presents with focal organ involvement, most often in the gastrointestinal tract as esophagitis or colitis or in the eye as retinitis.

Candidal infection usually does not disseminate in HIV infection (compared with the risk in neutropenia) but rather causes mucocutaneous disease (such as esophagitis), which is not clinically present in this patient. Candidal infection also should not cause systemic symptoms or this patient's CT findings.

Gastrointestinal adverse effects are common with ART and often improve with time. Elevated liver enzymes may occur but often involve aminotransferases, not only alkaline phosphatase. Abacavir is associated with an uncommon hypersensitivity reaction consisting of fever, rash, gastrointestinal symptoms, hepatitis, and malaise, although abacavir toxicity would not explain this patient's lymphadenopathy or cytopenias and usually occurs shortly after therapy initiation.

KEY POINT

- Treatment of HIV infection improves immune response, which can result in immune reconstitution inflammatory syndrome and symptomatic infection that may have been present at the time of antiretroviral therapy initiation.

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Item 9 Answer: B

Educational Objective: Treat a patient with *Coccidioides immitis* meningitis.

This patient should be treated with fluconazole. She has coccidioidal meningitis caused by *Coccidioides immitis*.

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Coccidioides species are endemic in desert regions of the southwestern United States and Central and South America. Primary infection is subclinical or manifests as self-limited chest pain, cough, and fever in most patients. However, disseminated coccidioidal infection may occur, and meningeal disease is the most serious form of disseminated infection, with significant associated morbidity and mortality. Patients at highest risk for coccidioidal meningitis are those with immunodeficiency (such as HIV/AIDS infection), diabetes mellitus, alcohol abuse, and pregnancy. Headache, vomiting, and change in mental status are the most common presenting findings. Cerebrospinal fluid (CSF) demonstrates a lymphocytic pleocytosis with elevated protein and low glucose. Eosinophils in the CSF are seen in up to 70% of patients with coccidioidal meningitis. Detection of complement-fixing antibodies in the CSF is more sensitive than is culture in diagnosing coccidioidal meningitis. Complement-fixing IgG is present in up to 90% of patients. Fluconazole is the treatment of choice. It offers a good response rate and a favorable safety profile; therefore, it has replaced intrathecal amphotericin B as the therapy of choice. Intrathecal amphotericin B is now used only in those who have not responded to fluconazole.

Caspofungin does not have activity against *C. immitis* and does not penetrate into CSF. Therefore, it would not be the best choice of therapy in this patient with coccidioidal meningitis.

Experience with the use of itraconazole for coccidioidal meningitis has been less than that with fluconazole; therefore, it is considered second line-therapy and should not be chosen before first-line therapy with fluconazole is provided.

KEY POINT

- Fluconazole is the treatment of choice for coccidioidal meningitis, because it offers a good response rate and a favorable safety profile.

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Item 10 Answer: A

Educational Objective: Evaluate for neurosyphilis with cerebrospinal fluid analysis.

This patient, who has serologic results consistent with syphilis of unknown duration, should undergo cerebrospinal fluid (CSF) analysis to exclude the possibility of neurosyphilis as a contributing factor to her cognitive decline. CSF should be sent for protein, glucose, cell count with differential, and VDRL testing. Neurosyphilis must be confirmed or excluded in this patient because this will determine the appropriate therapeutic approach.

A positive CSF VDRL result in the absence of visible blood contamination or any other unexplained abnormality of the spinal fluid (elevated protein, elevated leukocyte count) should prompt treatment of neurosyphilis with intravenous penicillin. If the CSF analysis yields normal results, treatment for late-latent syphilis with intramuscular benzathine penicillin is appropriate.

Both rapid plasma reagin and VDRL are nonspecific tests. The positive serum rapid plasma reagin result in this case was confirmed by a positive specific test (the fluorescent treponemal antibody absorption test). Therefore, syphilis is confirmed by serologic testing, and it would not be necessary to perform an additional nonspecific test for syphilis. Neurosyphilis must be diagnosed by CSF analysis.

KEY POINT

- Patients who have syphilis of unknown duration and an abnormal neurologic examination should undergo cerebrospinal fluid analysis to confirm or exclude the diagnosis of neurosyphilis before treatment is started.

Bibliography

Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010 [erratum in MMWR Recomm Rep. 2011 Jan 14;60(1):18]. MMWR Recomm Rep. 2010 Dec 17;59(RR-12):1-110. [PMID: 21160459]

Item 11 Answer: B

Educational Objective: Determine treatment duration for a patient with active pulmonary tuberculosis.

This patient has pulmonary tuberculosis and is completing a 2-month initial phase of treatment with the three-drug regimen of rifampin, isoniazid, and ethambutol and will require a 7-month continuation phase consisting of isoniazid and rifampin. Although most patients with active tuberculosis are treated with a four-drug regimen, usually consisting of rifampin, isoniazid, ethambutol, and pyrazinamide, pyrazinamide is contraindicated for use in patients with active gout and should be used with caution in chronic gout because it inhibits renal tubular excretion of uric acid. In most patients, a continuation phase of 4 months of isoniazid and rifampin is recommended for treatment of drug-susceptible tuberculosis. However, a 7-month continuation phase of isoniazid and rifampin is recommended in patients who do not receive pyrazinamide during the initial phase, in patients receiving once-weekly isoniazid and rifapentine whose sputum cultures are still positive at the end of the initial treatment phase, and in patients with cavitary pulmonary tuberculosis whose sputum cultures are positive at end of the initial phase of treatment. Because this patient did not receive pyrazinamide as part of his initial drug regimen, he should be treated with a 7-month continuation phase.

In the absence of drug resistance, 6 to 9 months of total treatment is sufficient. Longer courses extending beyond 9 months are reserved for multidrug-resistant tuberculosis.

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KEY POINT

- A 7-month therapy continuation phase is recommended in patients with active tuberculosis who have certain comorbidities or positive sputum cultures after completing initial therapy.

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Item 12 Answer: C

Educational Objective: Manage immunizations in a patient after transplantation.

This patient should receive a booster immunization with the tetanus-diphtheria-acellular pertussis (Tdap) vaccine because he has not received it as an adult. The childhood version of this vaccine, DTaP, is highly effective, but immunity against pertussis may wane into the adult years, increasing the risk for infection in this population. Because of this, the Advisory Committee on Immunization Practices recommends that all adults receive a single booster administration with Tdap, regardless of the timing of a previous diphtheria-tetanus booster. This recommendation does not differ for patients who have undergone transplantation; because the Tdap is not a live vaccine, administration to immunocompromised patients carries no contraindication.

This patient was immunized for *Streptococcus pneumoniae*, including receiving the pneumococcal conjugate and polysaccharide vaccines, before transplantation as appropriate for immunocompromised patients. Therefore, he does not require a booster of the pneumococcal conjugate vaccine and should receive instead a one-time booster of the pneumococcal polysaccharide vaccine, but not until 5 years after the first administration.

The varicella vaccine is a live-attenuated vaccine. As such, its administration is contraindicated after transplantation. Ideally, it should be given before transplantation, if needed. The zoster vaccine, indicated later in life, is also a live-attenuated vaccine and is contraindicated in immunosuppressed patients.

KEY POINT

- All adults, including immunocompromised patients, should receive a one-time booster immunization with the tetanus-diphtheria-acellular pertussis vaccine.

Bibliography

Rubin LG, Levin MJ, Ljungman P, et al; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host [erratum in Clin Infect Dis. 2014 Jul 1;59(1):144]. Clin Infect Dis. 2014 Feb;58(3):309-18. [PMID: 24421306]

Item 13 Answer: B

Educational Objective: Interpret tuberculin skin test results in a person with recent exposure to tuberculosis.

This patient should start receiving isoniazid therapy for latent tuberculosis infection (LTBI). He is asymptomatic and has a normal chest radiograph; however, a tuberculin skin test (TST) reaction of 5-mm or larger induration is interpreted as positive in patients who have recently been in contact with a person with active tuberculosis. A TST reaction of 10-mm or larger induration is interpreted as positive in patients who use injection drugs, are recent arrivals from countries with a high prevalence of tuberculosis, or reside in homeless shelters. Treatment for LTBI with isoniazid for 9 months is recommended. Other possible treatment regimens for LTBI include a 12-week regimen of directly observed once-weekly isoniazid and rifapentine. This regimen is not recommended for patients suspected of having infection with isoniazid- or rifampin-resistant tuberculosis strains. Four months of daily rifampin therapy is acceptable for patients with LTBI that is suspected to be resistant to isoniazid or who cannot take isoniazid.

This asymptomatic patient with a normal chest radiograph has LTBI. CT may be helpful in detecting abnormalities in the lung not seen with plain radiographs. However, this patient has no indications of active disease, so CT is not indicated.

Four-drug therapy with isoniazid, rifampin, pyrazinamide, and ethambutol would be recommended as initial therapy for a patient with active tuberculosis. This patient, who has no symptoms or evidence of active infection and a normal chest radiograph, has LTBI. Therefore, four-drug therapy would not be appropriate.

Pursuing no additional evaluation or therapy would not be appropriate for this patient. Treatment of LTBI significantly reduces the risk of progression to active disease.

KEY POINT

- Tuberculin skin test results must be accurately interpreted in patients who are asymptomatic and were recently exposed to active tuberculosis so that treatment for latent tuberculosis infection can be initiated.

Bibliography

Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep. 2000 Jun 9;49(RR-6):1-51. [PMID: 10881762]

Item 14 Answer: D

Educational Objective: Treat a patient with necrotizing fasciitis with empiric antimicrobial therapy.

This patient has necrotizing fasciitis and should receive empiric treatment with vancomycin plus piperacillin-tazobactam. Clues to a potential necrotizing skin infection include systemic toxicity (abnormal liver and kidney function, metabolic acidosis) with fever, chills, and hypotension. The patient's pain may be disproportionate to the physical examination findings. Skin changes can evolve rapidly and become ecchymotic, vesiculobullous, and gangrenous in appearance. "Woody" induration is also characteristic. Prompt surgical intervention is indicated as the primary treatment, with concurrent antibiotic therapy. The

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microbiologic cause can be monomicrobial or polymicrobial. Until the microbiology is determined, empiric therapy should be broad and consist of coverage against mixed aerobic and anaerobic gram-positive and gram-negative organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). Recommended regimens include vancomycin, linezolid, or daptomycin plus one of the following: piperacillin-tazobactam, a carbapenem (such as imipenem or meropenem), or metronidazole with either ceftriaxone or a fluoroquinolone. Polymicrobial infections are generally seen in patients with gastrointestinal and genitourinary infections, pressure ulcers, or at injection sites in patients using illicit drugs.

Ceftriaxone plus metronidazole alone provides broad-spectrum coverage against many organisms, but lacks MRSA activity. The addition of vancomycin or linezolid to this regimen would be needed until the microbiologic causes of necrotizing fasciitis are determined.

Doxycycline plus ciprofloxacin or ceftriaxone is the recommended regimen for patients with monomicrobial *Aeromonas hydrophila*-associated necrotizing skin infection. Patients who are immunocompromised, including those with liver disease and cancer, are at increased risk for serious skin infections and bacteremia/sepsis with this gram-negative bacillus. Wound infection usually occurs by inoculation through the skin. *A. hydrophila* is found in freshwater environments, but may also be present in brackish water. This regimen would not provide reliable empiric coverage against anaerobic bacteria or MRSA.

If *Streptococcus pyogenes* is confirmed by Gram stain and culture as the cause of necrotizing fasciitis, then penicillin plus clindamycin are recommended, particularly with associated toxic shock syndrome. Clindamycin is included because it inhibits toxin production and remains effective even in the presence of a high inoculum of bacteria. This regimen also would not provide adequate empiric coverage against gram-negative aerobic bacteria.

KEY POINT

- Patients with necrotizing fasciitis should receive empiric treatment with broad-spectrum antimicrobials that include coverage of aerobic and anaerobic gram-positive and gram-negative organisms, including methicillin-resistant *Staphylococcus aureus*, until microbiology is determined.

Bibliography

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Item 15 Answer: A

Educational Objective: Evaluate pyelonephritis not responding to appropriate therapy.

This patient has had a persistent, high fever after 72 hours of appropriate antibiotic therapy; therefore, ultrasonography or contrast-enhanced CT should be performed to exclude an intrarenal or perinephric abscess. Both are acceptable imaging modalities, but CT is considered the gold standard because it offers better anatomic detail. MRI could also be performed to investigate for these complications. Abscess formation is an uncommon complication of urinary tract infection (UTI). The most common predisposing factors for perinephric abscess are diabetes mellitus and the presence of urinary tract calculi. Abscess formation within the kidney usually occurs from infective disruption of the kidney parenchyma secondary to obstruction, frequently by a stone. Perinephric abscesses may result from rupture of an abscess in the corticomedullary region of the kidney through the fascia surrounding the kidney and into the perinephric space. A smaller number of abscesses associated with UTI result from hematogenous spread of bacteria from the highly vascular kidney. Most intrarenal or perinephric abscesses are caused by gram-negative enteric bacilli, whereas gram-positive cocci are generally seen when the abscess occurs secondary to bacteremia. Infection may also be polymicrobial, and fungal organisms such as *Candida* may be causative in some abscesses. Abscess drainage is usually required except for very small collections or those for which the causative factor (such as a kidney stone) may be removed to allow drainage.

This patient is receiving appropriate therapy for pyelonephritis caused by *Escherichia coli*, and the isolate is known to be susceptible to ceftriaxone. Therefore, a change in antibiotic to gentamicin, which has significant toxicity, is not indicated, and changing the antibiotic therapy might delay diagnosis of a complication from her UTI.

Repeating the urine culture is not indicated. A culture was performed on admission and has already revealed the causative organism with susceptibility testing. It is highly unlikely that another pathogen would be identified or a resistant *E. coli* strain would emerge during appropriate and adequate therapy.

Because most patients respond to antibiotic therapy with defervescence within 72 hours, continued observation without any further diagnostic interventions would be inappropriate.

KEY POINT

- Patients with pyelonephritis who remain febrile after 72 hours of appropriate antibiotic therapy should undergo kidney ultrasonography, CT, or MRI to investigate for complications, such as perinephric or intrarenal abscess.

Bibliography

Gardiner RA, Gwynne RA, Roberts SA. Perinephric abscess. BJU Int. 2011 Apr;107(Suppl 3):20-3. [PMID: 21492371]

Item 16 Answer: C

Educational Objective: Treat nonoccupational exposure to HIV.

The patient should be treated with postexposure prophylaxis with tenofovir-emtricitabine and raltegravir while awaiting

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the results of HIV testing. This management of significant HIV exposure is the same whether the exposure was occupational or nonoccupational. Baseline HIV testing is performed as soon as possible after exposure to ensure the exposed person is not already infected. Postexposure prophylaxis must begin immediately, however, without waiting for results. The preferred regimen for postexposure prophylaxis is a three-drug regimen of combination tenofovir-emtricitabine and raltegravir, which has been shown to be effective in reducing acquisition of HIV when used prophylactically.

Although higher levels of viral load are associated with an increased risk for transmission, knowing the partner's recent viral load level would not alter appropriate prophylactic treatment because even an undetectable viral load does not indicate no risk is present. Beginning prophylactic therapy should not be delayed while this information is obtained.

Combination tenofovir-emtricitabine is FDA approved for preexposure prophylaxis in those at significant risk for exposure. However, postexposure prophylaxis should involve a three-drug regimen of these two nucleoside analogues and a third agent, with raltegravir being the preferred agent.

Receptive anal intercourse qualifies as a potential significant HIV exposure and puts the exposed person at risk for infection. Although the likelihood of transmission may be reduced if the person who is the source of the exposure is receiving antiretroviral therapy, as in this patient, it is not lowered to zero. Therefore, awaiting the results of HIV testing without postexposure prophylaxis would be inappropriate.

KEY POINT

- Patients who have experienced a significant HIV exposure should immediately begin postexposure prophylaxis with a three-drug regimen of tenofovir-emtricitabine and raltegravir.

Bibliography

Kuhar DT, Henderson DK, Struble KA, et al; US Public Health Service Working Group. Updated US Public Health Service guidelines for the management of occupational exposures to human immunodeficiency virus and recommendations for postexposure prophylaxis [erratum in Infect Control Hosp Epidemiol. 2013 Nov;34(11):1238]. Infect Control Hosp Epidemiol. 2013 Sep;34(9):875-92. [PMID: 23917901]

Item 17 Answer: C

Educational Objective: Manage encephalitis.

This patient has symptoms consistent with encephalitis (obtundation, fever, elevated cerebrospinal fluid [CSF] leukocyte count) and should undergo electroencephalography (EEG). Recent consensus guidelines promote standardized evaluation for encephalitis, which includes lumbar puncture, brain MRI, and EEG. EEG is indicated to confirm the diagnosis of encephalitis, provide information that may help identify a causative organism, and assess the need for antiepileptic therapy. Nonconvulsive seizures, defined as the presence of seizure activity on EEG in the absence of myoclonic movements or other clinical evidence of seizures, could contribute to alterations in consciousness. Nonconvulsive status epilepticus may be focal or generalized and has been reported with viral and autoimmune encephalitides. Nonconvulsive status epilepticus in patients with encephalitis is associated with a delay in initiating antiepileptic therapy and an increased risk for death.

Cerebral edema is a poor prognostic factor in encephalitis, and patients with evidence of increased intracranial pressure based on neuroimaging or increased opening pressure are best managed in an intensive care setting. The opening CSF pressure for this patient is within normal limits, indicating the absence of cerebral edema or increased intracranial swelling. Therefore, intracranial pressure monitoring or initiating mannitol, which is used to decrease intracranial edema, is not necessary.

Transcranial Doppler ultrasonography is useful for monitoring patients at risk for vasospasm after subarachnoid hemorrhage. It has not been found to be beneficial in the management of patients with encephalitis and would not be indicated in this patient.

KEY POINT

- Standardized evaluation for encephalitis includes lumbar puncture, brain MRI, and electroencephalography.

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Item 18 Answer: C

Educational Objective: Diagnose late complement component deficiency.

This patient most likely has a late complement component deficiency. He has a history of meningococcal meningitis, and the current episode suggests recurrent meningococcal meningitis with bacteremia. Patients with late (terminal) complement component deficiencies (C5, C6, C7, C8, C9) may present with recurrent, invasive meningococcal or gonococcal infections. Complement deficiency can be acquired or inherited. The likelihood of complement deficiency is increased to greater than 30% among persons who have had more than one episode of meningococcal infection or who have a family history of meningococcal infection; for those with inherited late complement component deficiencies, the mode of inheritance is autosomal codominant. C5 deficiency confers impaired chemotaxis and absent serum bactericidal activity. C6, C7, and C8 deficiencies result in absent serum bactericidal activity, and C9 deficiency results in impaired serum bactericidal activity. The susceptibility to systemic neisserial infections, especially meningococcal disease, is greatest for those deficient in C5,

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C6, C7, or C8 compared with those deficient of C9. Meningococcal disease is the most common infection in those with complement deficiency. Up to 60% of those with a deficiency of a late complement component or of the circulating complement-potentiating protein properdin will experience at least one episode of infection during their lifetime. Meningococcal disease in patients with complement deficiencies also tends to be caused by uncommon serogroups, especially groups Y, W-135, and X relative to nondeficient patients with meningococcal meningitis. Recurrent meningococcal disease occurs in approximately 45% of those deficient in C5, C6, C7, or C8.

Common variable immunodeficiency (CVID) involves B- and T-cell abnormalities, and the usual manifestation is hypogammaglobulinemia. Bacterial infections, often of the sinus tract and lungs, are common, and the immune dysregulation seen in CVID is associated with autoimmunity and malignant disease. However, CVID is not associated with recurrent meningococcal infection.

Selective IgA deficiency is a common B-cell immunodeficiency. Most patients are asymptomatic or have sinopulmonary infections or gastrointestinal involvement with inflammatory bowel disease, sprue-like illness, or celiac disease. Giardiasis may also be seen. It is not associated with recurrent meningococcal infection.

Classical complement pathway (C1, C4, C2) deficiencies are often associated with a rheumatologic disorder, such as systemic lupus erythematosus, vasculitis, dermatomyositis, or scleroderma. Frequency of infection is relatively low in those with C1, C4, or C2 deficiency compared with deficiencies of other complement components. When they do occur, common infections are caused by encapsulated bacteria, especially *Streptococcus pneumoniae*.

KEY POINT

- Patients with late complement component deficiencies may present with recurrent, invasive meningococcal or gonococcal infections.

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Tichaczek-Goska D. Deficiencies and excessive human complement system activation in disorders of multifarious etiology. Adv Clin Exp Med. 2012 Jan-Feb;21(1):105-14. [PMID: 23214307]

Item 19 Answer: B

Educational Objective: Treat a patient with a brain abscess resulting from dental sepsis with intravenous penicillin and metronidazole.

This patient should begin empiric antibiotic treatment with intravenous penicillin and metronidazole. She has severe, unremitting headache and focal neurologic findings, both indicating a presumed brain abscess with an odontogenic source. Abscesses resulting from dental sepsis are usually caused by mixed *Fusobacterium*, *Prevotella*, and *Bacteroides* species and by streptococci. Penicillin covers most mouth flora, including both aerobic and anaerobic streptococci, and metronidazole provides additional anaerobic coverage with excellent tissue penetration.

Meropenem would be an appropriate antibiotic choice if there was concern about *Pseudomonas aeruginosa* infection, which would be more common in a brain abscess involving neurosurgical procedures. However, *P. aeruginosa* is not a typical source of brain abscess resulting from an odontogenic focus.

Trimethoprim-sulfamethoxazole and vancomycin would provide inadequate coverage against the pathogens typically found in brain abscesses with an odontogenic source. Intravenous vancomycin and a third-generation cephalosporin would be most appropriate for management of brain abscess related to neurosurgery or trauma. This patient's brain abscess is from an odontogenic source, so treatment with penicillin and metronidazole is most appropriate.

KEY POINT

- Patients suspected of having brain abscess from a likely odontogenic source should begin empiric antibiotic therapy with intravenous penicillin and metronidazole.

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Helweg-Larsen J, Astradsson A, Richhall H, Erdal J, Laursen A, Brennum J. Pyogenic brain abscess, a 15 year survey. BMC Infect Dis. 2012 Nov 30;12:332. [PMID: 23193986]

Item 20 Answer: B

Educational Objective: Manage potential bioterrorism-related anthrax exposure.

This patient likely has been exposed to anthrax and should be treated with ciprofloxacin. Although this woman's cutaneous lesion may be a methicillin-resistant *Staphylococcus aureus* furuncle resulting from contact with her infected husband, the distinctive "coal-like" black eschar, together with similar lesions on two coworkers, requires that anthrax be considered in the differential diagnosis. Oral monotherapy with ciprofloxacin, levofloxacin, moxifloxacin, or doxycycline is recommended as treatment of uncomplicated cutaneous anthrax. Uncomplicated cutaneous anthrax is defined as the absence of systemic symptoms and involvement of the head or neck in the absence of extensive swelling. Moreover, suspicion of any bioterrorism event must immediately be reported to local health authorities.

The addition of one or two preferably bactericidal antibiotic agents is indicated for treating anthrax when systemic disease is clinically suspected or confirmed. Because this patient does not have systemic disease, doxycycline, imipenem, and rifampin are not necessary.

Trimethoprim-sulfamethoxazole (TMP-SMX) is an appropriate antibiotic for treating most methicillin-resistant *S. aureus* soft tissue infections, but TMP-SMX is

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not adequate treatment for anthrax because it has unreliable activity.

In cases of suspected bioterrorism, deferring treatment until culture and biopsy results are available could have serious adverse consequences. Untreated cutaneous anthrax is associated with an estimated mortality rate of 10% to 20% because of secondary bacteremic spread. Treatment should be initiated as soon as the diagnosis is suspected.

KEY POINT

- Uncomplicated cutaneous anthrax should be treated with ciprofloxacin, levofloxacin, moxifloxacin, or doxycycline and should be reported to local health authorities.

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Item 21 Answer: A

Educational Objective: Treat asymptomatic bacteriuria in a pregnant woman.

This patient is pregnant and has asymptomatic bacteriuria caused by *Escherichia coli* susceptible to multiple antibiotics, so she should begin a course of amoxicillin. Asymptomatic bacteriuria during pregnancy increases the risk of pyelonephritis and has been associated with preterm birth and low-birthweight infants. Therefore, pregnancy is one of the few indications for screening for bacteriuria in asymptomatic patients and should occur in the first and third trimesters. Bacteriuria is defined as bacterial counts of 10^5 or greater colony-forming units/mL on urine culture; the prevalence of asymptomatic bacteriuria in pregnancy is approximately 4% to 7%. Risk factors for bacteriuria during pregnancy include lower socioeconomic status, increased parity, older age, increased sexual activity, diabetes mellitus, sickle cell trait, and history of urinary tract infection. In patients with untreated bacteriuria early in pregnancy, approximately 20% to 40% will develop acute symptomatic pyelonephritis later in pregnancy. Antibiotic therapy should be culture guided using an antibiotic with a known safety profile in pregnancy, such as amoxicillin. Amoxicillin-clavulanate and cephalexin are also effective and safe for many cases of asymptomatic bacteriuria. Urine cultures should be obtained 1 to 2 weeks after completing therapy and monthly for the remainder of the pregnancy.

Nitrofurantoin is an effective agent for uncomplicated cystitis but is contraindicated in the third trimester of pregnancy.

Trimethoprim-sulfamethoxazole is also an effective agent for uncomplicated cystitis when the rate of resistance of *E. coli* in the community is less than 20%. However, trimethoprim-sulfamethoxazole should not be used in pregnant patients near term because it may cause hyperbilirubinemia and kernicterus in the newborn.

No treatment is necessary for asymptomatic bacteriuria except during pregnancy or if a patient is scheduled to undergo an invasive urologic procedure, which is the only other indication for screening asymptomatic persons. Because this patient is pregnant, treatment for identified bacteruria is indicated.

KEY POINT

- Asymptomatic bacteriuria should be treated in patients who are pregnant, and amoxicillin is safe to use in the third trimester of pregnancy.

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Nicolle LE. Asymptomatic bacteriuria. Curr Opin Infect Dis. 2014 Feb;27(1). [PMID: 24275697]

Item 22 Answer: D

Educational Objective: Manage a false-positive HIV test result.

No further testing is needed for this patient, who does not have HIV infection. The fourth-generation antigen/antibody combination assay, which evaluates for the presence of HIV antibodies and the p24 viral nucleic acid protein, is recommended for initial HIV testing. This patient's initial testing was reactive, so further testing was indicated. The preferred follow-up testing for a positive result on an antigen/antibody combination assay includes an HIV-1/HIV-2 antibody differentiation assay and HIV nucleic acid amplification testing (NAAT) if the antibody differentiation assay finding is indeterminate or negative. HIV-1/HIV-2 antibody differentiation assay can identify the presence of HIV-1 or HIV-2 antibodies in the serum; HIV NAAT can detect viral RNA and is used to rule out the antibody-negative "window period" of acute HIV infection. Despite her initial positive test results, both follow-up test results were negative, and the appropriate interpretation is that her initial positive result on the screening test was a false positive. Although the recommended initial screening test has a reported specificity of 99.6%, in persons at low risk with very low pretest probability, the rate of false-positive results may still be significant. If the patient is at low risk and has no symptoms to suggest acute HIV infection, she should be reassured that the initial test result was a false positive (on the basis of her negative follow-up testing) and she does not have HIV.

T-cell subsets should never be used in diagnostic testing for HIV infection because a reduced CD4 cell count is neither sensitive nor specific for HIV infection.

Western blot testing for HIV antibody is no longer recommended for confirmatory testing of immunoassay results because of a higher risk for false-negative or indeterminate results early in the course of HIV infection.

Repeating HIV screening testing is unnecessary because the antibody differentiation immunoassay and NAAT have

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already clarified that the result of the initial combination assay was falsely positive. Repeating this study is therefore not indicated.

KEY POINT

- A reactive HIV-1/2 antigen/antibody combination immunoassay followed by negative result on confirmatory testing indicates that the initial combination assay result was a false positive.

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Item 23 Answer: C

Educational Objective: Treat a nonimmune immunocompromised adult exposed to varicella infection.

This patient should be given varicella-zoster immune globulin. Varicella-zoster is transmitted through infected respiratory secretions and, much less frequently, after direct contact with virus-containing cutaneous vesicular fluids. Persons with active varicella infection can shed virus beginning a few days before developing the typical rash. Susceptible household contacts are at greatest risk for contracting disease, which is estimated to occur at a rate of 90%. Historically, varicella is a childhood exanthem illness with limited morbidity and mortality providing life-long immunity thereafter, but infection in adults, pregnant women, and immunocompromised persons can result in more severe disease, at times resulting in death.

Following a known exposure to a person with varicella, the recommended postexposure prophylaxis to prevent varicella infection in nonimmune patients should be based on the type of exposure, susceptibility assessment, and risk factors for development of serious disease. When clinically warranted, postexposure preventive measures include active immunization or passive immunoprophylaxis. When administered within 3 to 5 days of exposure, the varicella vaccine has proved beneficial in preventing infection and diminishing disease severity in susceptible persons when infection occurs. However, this is a live-attenuated vaccine and is contraindicated in patients who are immunocompromised or taking immunosuppressive therapies, as well as in pregnant women. Under such circumstances, passive immunoprophylaxis using a purified human varicella-zoster immune globulin containing high levels of varicella-specific IgG antibodies is recommended and has been found to be most effective when administered within 4 days of exposure.

The efficacy of antiviral agents, such as acyclovir, to prevent postexposure development of varicella has not been proved and is not recommended.

Observation without providing postexposure prophylaxis may result in serious consequences in specific patient populations, including this patient, who is taking an immunosuppressive medication.

KEY POINT

- In patients with contraindication to vaccination, passive immunoprophylaxis with varicella-zoster immune globulin is the postexposure prevention of choice for varicella infection.

Bibliography

Gershon AA, Gershon MD. Pathogenesis and current approaches to control of varicella-zoster virus infections. Clin Microbiol Rev. 2013;26(4):728-43. [PMID: 24092852]

Item 24 Answer: B

Educational Objective: Diagnose a superficial incisional surgical site infection.

This patient should undergo Gram stain and culture of the fluid drainage from the incision site. Most surgical site infections (SSIs) occur within 30 days of the surgical procedure, except in procedures involving an implant, which may present up to a year after the operation. SSIs are categorized as superficial incisional, deep incisional, and organ/deep space infections. They are differentiated on the basis of presenting clinical signs and symptoms as well as the implicated organism (for example, some organisms cause minimal to no drainage). A superficial incisional infection involves only the skin and subcutaneous tissues, whereas a deep incisional infection involves the underlying soft tissue. Signs and symptoms of a superficial incisional infection include inflammatory changes at the incision site, with or without purulent drainage, and generally without systemic signs of infection such as fever, as seen in this patient. In such situations, the infection is usually managed with antibiotics alone and does not require debridement. Although the organisms obtained from a drainage culture may only reflect skin flora, the culture and Gram stain are helpful for identifying possible antibiotic-resistant organisms not covered by empiric therapy. Deep incisional SSIs generally present with more systemic signs of infection (fever, leukocytosis), and management requires debridement and antibiotic therapy guided by results of deep tissue cultures.

A patient with a superficial incisional SSI would not be expected to be bacteremic, so a blood culture would not be helpful in guiding management. Obtaining blood cultures should be guided by the clinical presentation and may be useful in some patients with organ/deep space SSIs.

Surgical site imaging with ultrasonography or CT may be helpful in patients with suspected organ/deep space SSIs to localize the site of infection, identify any fluid collections, and help to plan a drainage procedure. However, imaging would not be helpful in this patient who has a superficial SSI.

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KEY POINT

- Patients with superficial incisional surgical site infection typically have inflammatory changes at the incision site, with or without purulent drainage, and generally without systemic signs of infection such as fever.

Bibliography

Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America [erratum in Clin Infect Dis 2014; 59:147-59]. Clin Infect Dis. 2014;59:e10-52. [PMID: 24973422]

Item 25 Answer: A

Educational Objective: Treat a patient with bacterial meningitis with the appropriate empiric antimicrobial regimen.

This patient should begin treatment with intravenous ampicillin, ceftriaxone, and vancomycin. She has bacterial meningitis, and although the definitive cause has not been determined, empiric treatment should be initiated to cover the most likely infecting organisms. The most common causes of bacterial meningitis are *Streptococcus pneumoniae* and *Neisseria meningitides*, which account for more than 80% of cases. Therefore, primary empiric antibiotic therapy must adequately cover these two organisms. Common empiric regimens include the third-generation cephalosporins ceftriaxone or cefotaxime, which are bactericidal β-lactams that penetrate the central nervous system (CNS) well with excellent coverage of these organisms. One of these agents is combined with vancomycin, which also penetrates the CNS adequately when it is inflamed and provides coverage of possible penicillin-resistant organisms until specific identification and sensitivities are known. Additional antibiotic coverage is needed in patients with risk factors for specific infections. Although *Listeria monocytogenes* makes up only a small percentage (<5%) of meningitis cases in immunocompetent persons, the incidence increases significantly with age. Therefore, in patients older than 50 years, such as this patient, or persons with impaired cell-mediated immunity, ampicillin is added to empiric therapy because *Listeria* is not adequately covered by the usual components of empiric antibiotic regimens. Therefore, in this patient, the combination of ampicillin, ceftriaxone, and vancomycin provides the most appropriate empiric coverage of the suspected pathogens while culture results are pending.

Ceftazidime and vancomycin without ampicillin would be inadequate for this patient because it lacks coverage for *Listeria*.

Meropenem is used primarily in patients with impaired cell-mediated immunity or nosocomial or neurosurgery-related meningitis in which more extensive coverage of gram-negative organisms, including *Pseudomonas aeruginosa*, is indicated.

Fluoroquinolones, such as moxifloxacin, have not been well studied for treatment of bacterial meningitis, and their use is typically limited to patients who cannot tolerate typical empiric therapies, such as those with a severe allergic response to β-lactam antibiotics.

KEY POINT

- Empiric antibiotic therapy for bacterial meningitis in the older adult should include ampicillin, ceftriaxone, and vancomycin.

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van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in treatment of bacterial meningitis. Lancet. 2012 Nov 10;380(9854):1693-702. [PMID: 23141618]

Item 26 Answer: B

Educational Objective: Treat cervicitis with ceftriaxone and azithromycin.

This patient most likely has cervicitis and should be treated with ceftriaxone and azithromycin. It is important to differentiate cervicitis from vaginitis because the treatments differ. Cervicitis, characterized by an inflamed and friable cervix, is typically caused by gonorrhea and chlamydia. Vaginitis refers to inflammation of the vagina and is caused by infections such as candidiasis and trichomoniasis or by noninfectious conditions such as atrophic vaginitis or vaginal irritation. Bacterial vaginosis is a syndrome that appears noninflammatory, is characterized by alterations in the microbial composition of the vaginal flora, and may cause vaginal discharge and odor. In this patient with cervicitis, it is appropriate to give empiric therapy to cover *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. The regimen of choice is a single intramuscular dose of ceftriaxone, 250 mg, and a single oral dose of azithromycin, 250 mg. Oral cefixime can be used but only if ceftriaxone is unavailable; cefixime is associated with increasing minimum inhibitory concentrations of *N. gonorrhoeae*.

Cefotetan plus doxycycline is preferred for the treatment of patients with pelvic inflammatory disease who require hospitalization. The absence of cervical motion, uterine, or adnexal tenderness makes ascending genital tract infection unlikely in this patient.

Fluconazole is used to treat *Candida* vaginitis, a disease that would not result in clinical findings of cervicitis. Additionally, fungal organism would be visualized on the potassium hydroxide preparation.

Metronidazole is used to treat bacterial vaginosis and trichomonas. The pH of vaginal secretions would be elevated, clue cells would be visible on the wet mount (rather than numerous leukocytes), and the whiff test would have a positive result in bacterial vaginosis. Trichomonas would result in numerous leukocytes on the wet mount, but motile organisms would also be visible; the clinical findings should include vulvar and vaginal mucosal erythema.

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KEY POINT

- Cervicitis is characterized by an inflamed, friable cervix and should be treated with ceftriaxone and azithromycin.

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Wilson JF. In the clinic. Vaginitis and cervicitis. Ann Intern Med. 2009 Sep 1;151(5):ITC3-1-ITC3-15. [PMID: 19721016]

Item 27 Answer: D

Educational Objective: Diagnose West Nile neuroinvasive disease.

This patient, who has a fever and acute flaccid paralysis of a lower extremity after outdoor activity, should be screened for the West Nile virus (WNV) antibody. Transmission is most often from an infected mosquito, and infections often occur during the summer and fall when mosquito populations are largest. Focal motor weakness is a common finding in West Nile neuroinvasive disease (WNND), either combined with meningoencephalitis or as an isolated myelitis. In its most severe form, infection of the anterior horn cells can cause a symmetric or asymmetric flaccid paralysis, analogous to that seen with polio in the prevaccination era. Respiratory failure may occur when diaphragmatic nerves are involved. The diagnosis of WNND can be confirmed through identification of the IgM antibody in the cerebrospinal fluid (CSF). Positivity for serum antibodies suggests infection but is less specific because WNV IgM remains detectable more than 1 year after acute infection. Furthermore, cross-reactivity occurs with other flaviviruses (such as Saint Louis encephalitis virus or Japanese encephalitis virus), which may produce a false-positive antibody result after natural infection or vaccination. WNV polymerase chain reaction of the CSF is of limited diagnostic utility in most patients because when symptoms become apparent, the virus has cleared the bloodstream and spinal fluid.

Eastern equine encephalitis virus infection is also caused by transmission from an infected mosquito. However, it predominantly occurs along the Atlantic and Gulf states, and encephalitic illness is characterized by fever, headache, vomiting, diarrhea, and convulsions.

La Crosse encephalitis virus infection is also transmitted by mosquito but typically occurs in the Eastern and central United States. Motor weakness is not associated with this infection, and symptoms are generally mild.

Powassan virus is spread by ticks rather than mosquitos, and infections are limited to the northeastern and north central United States. Symptoms include fever, headache, weakness, and other neurologic complications.

KEY POINT

- Fever, headache, and focal limb weakness following outdoor activities suggest West Nile neuroinvasive disease, and the most appropriate diagnostic test is for West Nile virus antibodies within cerebrospinal fluid.

Bibliography

Hart J Jr, Tillman G, Kraut MA, et al; NIAID Collaborative Antiviral Study Group West Nile Virus 210 Protocol Team. West Nile virus neuroinvasive disease: neurological manifestations and prospective longitudinal outcomes. BMC Infect Dis. 2014 May 9;14:248. [PMID: 24884681]

Item 28 Answer: C

Educational Objective: Prevent catheter-associated urinary tract infection.

This patient's indwelling urinary catheter should be removed now. The prevention of catheter-associated urinary tract infection (CAUTI) relies on using urinary catheters only if they are essential to the patient's care and only for as brief a period of time as possible. The risk for a CAUTI increases by 3% to 7% each day a urinary catheter is in place. This translates to a risk for CAUTI of up to 70% when a urinary catheter has been in place for 10 days. Although urinary catheters are useful in select patients when fluid balance must be managed carefully, they should not be used routinely in hospitalized patients, in patients not requiring detailed information about urine output, or for convenience of the patient or staff. Appropriate indications for a urinary catheter include perioperative use for selected surgeries (should be removed before the end of the second postoperative day), need for accurate measurement of urine output in critically ill patients in the ICU, management of acute urinary retention or bladder outlet obstruction, assistance in open sacral or perineal wound healing for patients who are incontinent, and, as an exception, end-of-life patient comfort if needed. Urinary catheters should be inserted by trained personnel following aseptic technique and maintained in a manner that minimizes the chance of contamination or introduction of organisms into the bladder (that is, using a closed drainage system, gravity drainage, and keeping the drainage bag off the floor).

Changing a urinary catheter, whether at the time of hospital admission from the emergency department or routinely (such as every 3 or 5 days), does not decrease the risk for a CAUTI and should not be done for that purpose.

In this patient with chronic kidney disease and decompensated heart failure, monitoring diuretic effect with standard urine collection procedures should be adequate to guide therapeutic decision making. Kidney function remaining above baseline is not an indication for continuing the indwelling urinary catheter. Therefore, continued use of an indwelling catheter has no clear indication.

KEY POINT

- Preventing catheter-associated urinary tract infection relies on using urinary catheters only if they are essential to the patient's care and only for as short a period of time as possible.

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Item 29 Answer: D

Educational Objective: Manage a central line-associated fungal bloodstream infection.

Removal of the peripherally inserted central venous catheter and initiation of antifungal therapy is the most appropriate management in this patient. When candidemia is likely to be the result of an intravenous catheter, the catheter must be removed promptly because it serves as a nidus for ongoing candidemia. The duration is shorter and mortality rate is lower for candidemia related to intravenous catheters when the catheter is removed than when it remains in place. Additionally, catheter salvage is extremely difficult with fungal colonization, almost always requiring removal of the catheter. Although removal of long-term catheters may be a management challenge in patients being treated with a prolonged course of antibiotics, such as this patient, alternative short-term access is indicated to continue treatment and allow antifungal therapy to be given.

Empiric antifungal therapy should be based on the most likely organism (such as *Candida albicans*) because candidemia can be prolonged and may lead to metastatic complications (endophthalmitis, endocarditis, osteomyelitis) if not already present at the time of diagnosis. Other considerations in choosing empiric therapy include a history of recent azole exposure, prevalence of different species and susceptibility data in a particular institution, the severity of illness, comorbidities (such as neutropenia), and evidence of disseminated involvement (such as the central nervous system or eyes). Some experts recommend an echinocandin as the preferred agent for all patients with candidemia and not just for those who may have recently received an azole or are moderately to severely ill. Blood cultures should always be repeated until candidemia clearance is documented. Treatment should be given for 2 weeks after symptoms resolve and blood cultures are negative for candidemia or longer if metastatic complications are present.

KEY POINT

- In patients with candidemia associated with an intravenous catheter, the catheter should be removed and empiric antifungal therapy initiated.

Bibliography

Pappas PG, Kauffman CA, Andes D, et al; Infectious Diseases Society of America. Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503-535. [PMID: 19191635]

Item 30 Answer: B

Educational Objective: Treat secondary syphilis with benzathine penicillin.

This man presents with a rash consistent with secondary syphilis and should be treated with benzathine penicillin. The most common clinical manifestation of secondary syphilis is a generalized rash that is typically nonpruritic and often involves the palms and soles. Lesions may be macular, papular, or pustular. Silvery gray erosions with an erythematous border may be visualized on mucosal surfaces (mucus patches). Patients with secondary syphilis frequently have generalized lymphadenopathy and systemic symptoms. A single dose of 2.4 million units given intramuscularly is the treatment of choice, preferably at the time of presentation if follow-up cannot be guaranteed. Syphilis among men who have sex with men, particularly in urban areas, has increased significantly in the past several years, so recognition of the characteristic clinical presentation is essential. Diagnostic testing with syphilis serologic assessment should still be obtained to confirm the diagnosis and provide a baseline titer that can be followed to assess the adequacy of therapy. In addition, the patient should be screened for other sexually transmitted infections including HIV, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* infections; specimens for *N. gonorrhoeae* and *C. trachomatis* should be obtained from all potentially exposed anatomic sites (throat, urethra, and anus) on the basis of the sexual history obtained.

A single 2-g dose of azithromycin is effective for the management of early syphilis; however, resistance associated with treatment failure has been reported recently. Azithromycin should be used only when treatment with penicillin or doxycycline (the recommended alternative in the setting of penicillin allergy) is not possible.

Ceftriaxone may be used to treat neurosyphilis as an alternative in a patient allergic to penicillin whose reaction is not life threatening, but it is not recommended in any other setting.

Although an allergic reaction may be in the differential diagnosis of a rash, involvement of the palms and soles is uncommon. Empiric treatment with methylprednisolone in a person with a high-risk sexual history is inappropriate.

KEY POINT

- A high-risk sexual history and erythematous macules and papules on the palms and soles indicate secondary syphilis, which should be treated with benzathine penicillin.

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Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010 [erratum in MMWR Recomm Rep. 2011 Jan 14;60(1):18]. MMWR Recomm Rep. 2010 Dec 17;59(RR-12):1-110. [PMID: 21160459]

Item 31 Answer: C

Educational Objective: Diagnose cytomegalovirus infection after transplantation.

This patient likely has colitis resulting from cytomegalovirus (CMV) infection. CMV infection is a common complication of transplantation, especially in the first few months after transplantation when immunosuppression is typically highest. Unless donor and recipient are CMV seronegative and the risk is low, prophylaxis with valganciclovir is often used during this time period. This patient recently finished the

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prophylaxis period and is at risk for CMV reactivation. She has symptoms typical for colitis; the colon and esophagus are common sites for CMV disease after transplantation. Hepatitis, gastritis, and small bowel enteritis may also occur, although less often. Quantitative polymerase chain reaction testing in serum for CMV can be suggestive, but colonoscopy with biopsy for characteristic histopathology and viral tissue culture provide a definitive diagnosis.

Candidal infection does not cause colitis, even in immunocompromised patients. *Candida* species are part of the normal bowel flora, with positive stool cultures commonly occurring in the absence of systemic disease. This patient has no evidence of invasive candidal infection, which makes this an unlikely cause of her presenting symptoms.

Although she is at risk for *Clostridium difficile* colitis, her negative results on nucleic acid testing makes this a less likely cause of her clinical findings than CMV disease.

Although mycophenolate can cause diarrhea as an adverse effect, this patient is at significant risk for opportunistic infections, which must be considered more likely, especially in the presence of fever.

Polyoma BK virus is a DNA virus present in approximately 5% of kidney transplant recipients. Its activity is usually related to the degree of immunosuppression and can occur at this stage or later after transplantation. However, it primarily causes tubulointerstitial nephropathy, not colitis.

KEY POINT

- Cytomegalovirus is a common complication of transplantation, especially in the first few months after transplantation when immunosuppression is typically highest, and patients who have just finished prophylaxis against cytomegalovirus are at risk for reactivation.

Bibliography

Lemonovich TL, Watkins RR. Update on cytomegalovirus infections of the gastrointestinal system in solid organ transplant recipients. Curr Infect Dis Rep. 2012 Feb;14(1):33-40. [PMID: 22125047]

Item 32 Answer: C

Educational Objective: Manage osteomyelitis of the foot in a patient with type 2 diabetes mellitus.

This patient with type 2 diabetes mellitus most likely has osteomyelitis of the foot and should be treated with vancomycin and piperacillin-tazobactam. Surgical debridement is also important to ensure removal of all nonviable and purulent tissue and allows for collecting more representative tissue specimens for microbiologic studies. Infections in the feet of patients with diabetes may come on suddenly, present with sepsis, and rapidly become limb-threatening. Most often these infections result from ulcerations created by prior surgical procedures, trauma, or local pressure. Diminished sensation, decreased blood flow, and poor glycemic control are frequent contributing factors. Empiric broad-spectrum antimicrobial therapy aimed at gram-positive cocci (β-hemolytic streptococci and staphylococci) along with aerobic and anaerobic gram-negative bacilli should be initiated as soon as possible in patients with suspected osteomyelitis and systemic findings. Methicillin-resistant strains of *Staphylococcus aureus* should be considered potential pathogens in these clinical situations and included in the antimicrobial coverage until proven absent. Vancomycin and a broad-spectrum β-lactam/β-lactamase inhibitor, such as piperacillin-tazobactam, would be an appropriate empiric regimen; it is appropriate to narrow the antibiotic spectrum once bone culture results are known. Surgical debridement is essential in the treatment of this patient's obviously gangrenous foot.

Antimicrobial therapy with the combination of cefazolin and metronidazole has too narrow a spectrum under these clinical circumstances. Coverage against a greater variety of aerobic, gram-negative bacilli is required.

Clindamycin has activity against most of the gram-positive cocci and anaerobic gram-negative bacilli associated with diabetic foot infections. However, gentamicin to provide coverage against aerobic gram-negative bacilli in complex diabetic foot infections is not recommended because of its narrow toxicity-to-benefit ratio.

Grossly visible bone or the ability to probe to bone is highly predictive of osteomyelitis, making the need for a bone biopsy and delay in treatment inadvisable.

KEY POINT

- Osteomyelitis of the foot in a patient with a diabetic foot infection with sepsis should be immediately treated with broad-spectrum antibiotics and surgical debridement.

Bibliography

Game FL. Osteomyelitis in the diabetic foot: diagnosis and management. Med Clin North Am. 2013 Sep;97(5):947-56. [PMID: 23992902]

Item 33 Answer: C

Educational Objective: Diagnose dengue fever.

This patient, who recently travelled to the Caribbean, has symptoms characteristic of dengue fever (DF), a flavivirus transmitted by the *Aedes* mosquito. DF is the most common arthropod-borne viral infection in humans. Endemic areas include Southeast Asia, the South Pacific, South and Central America, and the Caribbean. Most infections encountered in the United States are diagnosed in persons visiting or returning from endemic geographic areas. Recently, the incidence of infection from the Caribbean islands has increased. The hallmarks of DF are sudden high fever, frontal headache and retro-orbital pain, myalgia and arthralgia, severe lower back pain ("break-bone fever"), and a maculopapular rash that often appears as the fever abates. Mild hemorrhagic symptoms and the development of petechiae, elicited by a tourniquet test, can occur. A more severe and rare form of infection (dengue hemorrhagic fever) can be seen in patients previously infected by one of the four dengue virus serotypes who subsequently become infected with another serotype.

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Typical laboratory findings in DF include leukopenia with relative lymphocytosis, hemoconcentration, thrombocytopenia, and elevation of hepatocellular enzymes. Diagnosis confirmation generally relies on specific serologic assays.

Human granulocytic anaplasmosis is one of the forms of ehrlichiosis transmitted by ticks. This febrile illness is accompanied by laboratory abnormalities similar to those seen with DF; however, rash with human granulocytic anaplasmosis is rare. This obligate, intracellular, gram-negative organism can be seen in the cytoplasm of neutrophils in 20% to 80% of infected patients. Although ehrlichiosis can occur worldwide, the *Ixodes* tick vector is infrequently found in the Caribbean. The diagnosis usually is made using serologic assays.

Chikungunya virus is also transmitted by the bite of an *Aedes* mosquito and recently has become an epidemic in several Caribbean islands. Although it shares many clinical features with DF, an important distinction is its severe joint pain and stiffness. Other distinguishing features include high fever, which often recurs after a brief afebrile period ("saddle-back fever"); more significant polyarticular and migratory joint pains involving the small joints of the hands, wrists, and ankles; and much less thrombocytopenia.

Leptospirosis may be confused with DF but typically involves more organ systems, including the pulmonary, renal, hepatic, and central nervous systems. Characteristically, conjunctival suffusion occurs but a generalized rash is rare. Aseptic meningitis is a common feature of the immune or delayed phase of this spirochetal infection. A more severe form of infection, known as icteric leptospirosis (Weil syndrome), presents with profound jaundice, hepatic necrosis, kidney disease, and pulmonary manifestations.

KEY POINT

- Dengue fever is characterized by sudden high fever, frontal headache and retro-orbital pain, myalgias and arthralgias, severe lower back pain, and rash that appears as the fever abates.

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Item 34 Answer: B

Educational Objective: Evaluate a patient with nonresponsive community-acquired pneumonia using chest CT.

A chest CT should be obtained in this patient with nonresponsive pneumonia. He presents with severe community-acquired pneumonia (CAP) and has been treated with appropriate empiric antibiotics. Most patients with uncomplicated CAP will show improvement in clinical symptoms (fever, cough, dyspnea) within 2 to 3 days; nonresponsive pneumonia is defined as a lack of significant clinical response within 72 hours of initiating therapy. Chest CT or, possibly, high-resolution chest CT is the usual initial radiographic study used to evaluate patients with nonresponsive pneumonia. Compared with plain chest radiography, chest CT provides improved detection of parenchymal abnormalities, including foci of infection such as a lung abscess or cavitary lesions and occult empyema. These findings may help guide additional therapy, or CT may identify other causes of failure to improve that were not previously considered, particularly in a patient whose baseline plain radiograph may be difficult to interpret.

Fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy may be helpful in the diagnosis of nonresponsive pneumonia but is typically performed after chest CT, particularly if there are findings (focal areas of fluid collection or consolidation or lymphadenopathy) that help guide bronchoscopic evaluation or be amenable to bronchoscopic biopsy.

Chest ultrasonography is used primarily to diagnose pleural effusions and guide therapeutic thoracentesis and may be helpful in diagnosing pleural abnormalities such as thickening or nodules. It is less helpful for evaluating the lung parenchyma. This patient has not had evidence of pleural effusions on chest radiography, so the diagnostic yield of chest ultrasonography would be low, particularly compared with chest CT.

More invasive biopsy procedures such as thoracoscopic or open lung biopsy are typically reserved for instances when a specific disorder requiring direct tissue evaluation is needed or if other diagnostic interventions are unrevealing in a patient requiring a diagnosis. Therefore, lung biopsy would not be an appropriate next step before additional imaging.

KEY POINT

- Chest CT, which provides improved detection of parenchymal abnormalities, is the usual initial radiographic study used to evaluate patients with nonresponsive pneumonia.

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Item 35 Answer: B

Educational Objective: Manage vertebral osteomyelitis by determining microbiologic cause for appropriate treatment.

This patient has vertebral osteomyelitis and should undergo CT-guided needle biopsy and aspirate to determine a microbiologic diagnosis and the most adequate antimicrobial therapy. Single isolates of *Corynebacterium* species are generally regarded as blood culture contaminants and would be uncommon pathogens in this scenario. Furthermore, although the patient was recently treated for a central line-associated bloodstream infection caused by

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Staphylococcus aureus, it cannot be assumed the same organism is infecting the lumbar spine. Treatment of this patient should not be initiated until the infecting microbial agent has been identified. Neck or back pain that persists or increases in severity over weeks to months is the most common symptom associated with infection of the vertebral column or disc space. Bacteremia may result from infective endocarditis, intravenous drug use, intravenous catheters, or foci of infection at distant sites. The lumbar vertebrae are most frequently involved and, if left undiagnosed and untreated, may progress to an epidural abscess with subsequent neurologic deficits.

Spread of infection from the urinary tract through vertebral veins (Batson plexus) is considered unlikely; therefore, empiric antimicrobial treatment with ciprofloxacin aimed at the previous *Proteus* infection is not warranted. Likewise, initiating antimicrobial therapy with vancomycin before attempting to make a microbiologic diagnosis may adversely alter the culture result. However, it would be an appropriate choice if *S. aureus* was determined to be the causative pathogen considering the patient's allergy to penicillin. Empiric therapy is indicated in patients who are unable or unwilling to undergo an invasive diagnostic procedure.

The blood culture did not demonstrate persistent bacteremia, and no signs or symptoms were consistent with infective endocarditis. Therefore, performing echocardiography is unnecessary.

Three-phase nuclear bone scanning has a high sensitivity for diagnosing osteomyelitis but lacks the specificity provided by MRI, which this patient has already undergone. Additional imaging would add no relevant information in this patient.

KEY POINT

- When blood cultures are negative, the microbiologic cause of vertebral osteomyelitis should be determined by CT-guided needle aspiration biopsy to determine the most appropriate antimicrobial therapy.

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Item 36 Answer: D

Educational Objective: Manage immunizations in a patient with HIV infection.

This patient should receive the 13-valent pneumococcal conjugate vaccine (PCV13) now. Vaccination against *Streptococcus pneumoniae* is indicated in all persons with HIV infection because of the increased risk of invasive pneumococcal disease. Immunocompromised persons, including those with HIV, should receive PCV13 first, followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV23) at least 8 weeks later, in a "prime-boost" strategy that is used to improve the antibody response to immunization. This recommendation applies regardless of the patient's CD4 cell count.

HIV infection alone is not an indication to receive hepatitis A vaccination. Hepatitis A vaccination would be indicated if the patient had another risk factor, such as men who have sex with men or other liver disease, including chronic hepatitis B or C virus infection. She does not have hepatitis B or C virus infection, as shown by negative results on laboratory testing, so hepatitis A vaccination is unnecessary at this time.

All patients with HIV should be vaccinated for hepatitis B if not already immune or infected. However, this patient has positivity for hepatitis B surface antibody, demonstrating existing immunity. Therefore, she does not require hepatitis B immunization.

This patient is beyond the recommended age (approximately 11-26 years) for females in the general population to receive human papillomavirus vaccination. This recommendation does not change for patients with HIV infection.

This patient should receive PPSV23, but not until at least 8 weeks after PCV13, so giving it now would be inappropriate. Patients with HIV infection who have received PPSV23 in the past should receive PCV13 followed by another PPSV23 dose at least 8 weeks later.

KEY POINT

- Immunocompromised persons, including those with HIV, should receive the 13-valent pneumococcal conjugate vaccine first, followed 8 weeks later by the 23-valent pneumococcal polysaccharide vaccine.

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Item 37 Answer: B

Educational Objective: Prevent spread of infection of disseminated varicella-zoster virus.

This patient should be placed on airborne and contact precautions. Varicella-zoster virus can be transmitted from persons with zoster to susceptible hosts (that is, those who have never had chickenpox and are not vaccinated against it) who may develop chickenpox as a result of the exposure. The virus can spread through direct contact with active lesions, which is most common with localized zoster. Localized zoster is defined as rash in one or two dermatomes, most commonly along a thoracic dermatome, that does not cross the midline. Patients with localized zoster who are not immunocompromised can be managed with contact precautions alone; a person is no longer infectious after all the lesions have crusted over. Disseminated zoster is defined as a more widespread rash involving three or more dermatomes. Disseminated zoster can appear similar to varicella (chickenpox). Vesicles usually appear in various stages of development and generally form over 3 to 5 days before they start to dry and crust over. Immunocompromised persons

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(such as this patient) are at increased risk for disseminated zoster, which may involve the respiratory tract. In patients with disseminated zoster or those who are immunocompromised, the virus may be transmitted via the airborne route from infected small (≤5 µm) respiratory droplet nuclei that can remain suspended for extended periods or travel long distances on air currents. Airborne (negative-pressure room) and contact precautions are appropriate management for patients who have disseminated zoster or localized zoster and are immunocompromised. Other organisms transmitted via the airborne route include those causing tuberculosis, measles, and chickenpox.

Droplet precautions are applied for organisms that are transmitted via large (>5 µm) droplets that travel less than 3 feet on air currents (such as respiratory, pertussis, and mumps viruses).

KEY POINT

- Airborne and contact precautions are indicated to prevent spread of infection in patients with disseminated zoster infection or those who are immunocompromised with localized zoster infection.

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Item 38 Answer: D

Educational Objective: Manage mild travelers' diarrhea.

Fluid replacement with aggressive oral hydration without further treatment is the most appropriate treatment recommendation for this patient with mild travelers' diarrhea. Travelers' diarrhea is defined as the occurrence of three or more unformed stools per day with abdominal pain or cramps, nausea or vomiting, bloody stools, or fever and is the most common travel-related infection. Depending on the geographic region, the incidence of gastrointestinal infection may occur in greater than 30% of travelers. Africa, Asia, South and Central America, and Mexico are considered the regions with the greatest risk. The diarrhea is usually self-limited, lasting 1 to 4 days. Enterotoxigenic and enteroaggregative *Escherichia coli* are the most common bacterial pathogens. Less often, *Salmonella*, *Shigella*, *Campylobacter*, *Aeromonas*, *Plesiomonas*, and noncholera *Vibrio* species are involved. With the exception of rotavirus and norovirus, travelers' diarrhea caused by viral infections is uncommon; norovirus has been associated with diarrheal disease outbreaks aboard cruise ships. Protozoan pathogens are isolated in less than 10% of cases. However, no definitive microbiologic agent is identified in approximately one third of patients. The use of prophylactic antibiotics is effective in reducing the risk for travelers' diarrhea, but, to avoid potential adverse effects, is generally reserved for patients with a history of inflammatory bowel disease, immunosuppressive illnesses, or chronic diseases that could become more severe or be exacerbated by dehydration brought on with significant diarrhea.

Antibiotics lessen the duration of diarrhea by a few days, but their use is generally limited to patients with more severe disease, usually defined as more than four unformed stools per day with fever and blood, pus, or mucus in the stool. Antibiotic treatment may also be a reasonable option in patients with milder illness if it is markedly disruptive to travel plans.

Antimotility agents, such as loperamide, may relieve symptoms in patients with travelers' diarrhea. However, they do not treat the underlying infection. Concern exists that using antimotility agents alone may prolong dysenteric illnesses without treatment of the underlying infection. For this reason, antimotility agents are generally not recommended without concurrent use of antibiotics for treatment of travelers' diarrhea.

KEY POINT

- Fluid replacement with aggressive oral hydration without further treatment is the most appropriate treatment recommendation for otherwise healthy persons with mild travelers' diarrhea.

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Item 39 Answer: B

Educational Objective: Identify criteria for establishing that a patient with tuberculosis is noncontagious.

The Centers for Disease Control and Prevention has established three criteria that must be met to establish that a patient with tuberculosis is noncontagious: adequate treatment for tuberculosis for at least 2 weeks, improvement of symptoms, and three consecutive negative sputum smears (collected at 8- to 24-hour intervals, including one early morning collection). This patient has met two of these criteria but must complete at least 2 weeks of treatment with rifampin, isoniazid, pyrazinamide, and ethambutol before he is considered noncontagious.

Factors associated with the contagiousness of a patient infected with tuberculosis include presence of a lung cavity, cough, or acid fast bacilli on sputum smear; receiving inadequate treatment; pulmonary or laryngeal tuberculosis; coughing without covering the mouth; and sputum culture positivity. The absence of a cavity does decrease the contagiousness of a patient but is not a criterion for establishing that a patient is noncontagious.

A positive result on a tuberculin skin test (TST) indicates that a patient has been infected with *Mycobacterium tuberculosis*. A negative TST result makes it unlikely that the patient has been infected. However, false-negative results

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do occur. Physiologic causes of false-negative TST results include active tuberculosis infection, HIV infection, use of immunosuppressive agents (such as glucocorticoids), kidney injury, lymphoproliferative disorders, and recent vaccination with live virus. Therefore, the lack of a positive result does not correlate with contagiousness.

The leukocyte count may be normal, decreased, or increased in patients with active tuberculosis. It is not used as a criterion for determining whether a patient is contagious.

KEY POINT

- A patient with active tuberculosis must undergo adequate tuberculosis treatment for at least 2 weeks, demonstrate improvement of symptoms, and have three consecutive negative sputum smears to be considered noncontagious.

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Item 40 Answer: D

Educational Objective: Treat candidemia in a postsurgical patient.

This patient should be treated with micafungin. He most likely has candidemia. His risk factors include recent major abdominal surgery, the presence of an intravascular catheter, and exposure to antibiotics. Echinocandins (caspofungin, anidulafungin, and micafungin) are considered the therapy of choice for candidemia and most other forms of invasive candidiasis. All three agents are considered to be equally effective, are well tolerated, and have good safety profiles. Kidney disease does not necessitate dose adjustment, and the potential for drug interactions is low. Transition to fluconazole can occur after 5 to 7 days of therapy with an echinocandin if the patient is clinically stable, the isolate is susceptible to fluconazole, and repeat blood cultures are negative.

Amphotericin B deoxycholate would be an effective therapy but has an adverse effect profile that includes kidney injury and other systemic reactions that preclude it as a good treatment option, especially considering the availability of therapies that are equally effective and have better adverse effect profiles.

Although for many years fluconazole was considered the drug of choice for treating candidemia, recent studies show lesser efficacy compared with the echinocandins, even in treating *Candida albicans*. Additionally, the spectrum of fluconazole is limited compared with the echinocandins or amphotericin B–based compounds because it is inactive against *Candida krusei*, and resistance has been reported for *Candida glabrata*.

Liposomal amphotericin B has similar efficacy to the echinocandins but has a higher rate of nephrotoxicity. Because this patient already has kidney disease, liposomal amphotericin B would not be recommended.

KEY POINT

- In a patient with candidemia, echinocandins such as caspofungin, anidulafungin, and micafungin are the empiric therapy of choice.

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Item 41 Answer: D

Educational Objective: Diagnose acute progressive disseminated histoplasmosis.

This patient's clinical illness and laboratory findings are most consistent with acute progressive disseminated histoplasmosis. *Histoplasma* is the most common endemic mycosis in the United States (primarily in the Ohio and Mississippi river valleys) and is also prevalent in Central America. The causative agent, *Histoplasma capsulatum*, is typically found in soil contaminated with bird or bat droppings, which encourage spore formation. Infection is usually through inhalation of spores and, in immunocompetent patients, may be asymptomatic or cause mild, self-limited pulmonary symptoms. However, in patients who are severely immunosuppressed, especially those with AIDS or hematologic malignancies, disseminated histoplasmosis may occur. In persons with HIV infection, the risk factors for histoplasmosis are a CD4 cell count less 200/μL and a history of exposure. Clinical manifestations are nonspecific. Fever and weight loss are common. The most common findings on physical examination include hepatosplenomegaly and lymphadenopathy. Common laboratory abnormalities include anemia, thrombocytopenia and leukopenia, and elevated serum aminotransferases and alkaline phosphatase. Chest radiographs may be normal or show scattered nodular densities or a diffuse reticular pattern. Diagnosis is by detection of histoplasma antigen in body fluids, which is present in up to 90% of patients with acute progressive disseminated histoplasmosis, or by isolation of *H. capsulatum* from bodily fluids or tissues. Bone marrow and blood cultures may also be useful in establishing the diagnosis (blood smear shown top of next page). Therapy is typically with liposomal amphotericin B with long-term suppressive therapy following short-term treatment.

Disseminated blastomycosis most commonly manifests as skin lesions, which this patient does not have. Other sites of disseminated disease include bones, joints, and the male genitourinary tract. Blastomycosis has been reported as a late complication in patients with AIDS, in whom central nervous system complications of blastomycosis are common

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and manifest as abscess or meningitis. The yeast forms of *Blastomyces dermatitidis* have a distinct appearance with broad-based budding.

Although mucosal candidiasis is common in advanced HIV infection, candidemia and disseminated candidiasis are rare.

Disseminated coccidioidomycosis most commonly presents with skin lesions, which this patient does not have. Other common sites of dissemination include bones, joints, and the meninges. Spherules (large, round, thick-walled structures containing endospores), noted by cytologic or histopathologic evaluation, are the classic finding.

KEY POINT

- Acute progressive disseminated histoplasmosis is most often seen in patients who are severely immunosuppressed, especially those with AIDS or hematologic malignancies, and common signs and symptoms include fever, weight loss, and hepatosplenomegaly.

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Item 42 Answer: C

Educational Objective: Manage conversion from an intravenous to an oral antimicrobial agent.

Sequential antimicrobial therapy, also known as intravenous to oral antimicrobial switching, should be considered in patients who have an intact and functioning gastrointestinal tract and whose clinical status is improving. This patient meets criteria for changing from intravenous ceftriaxone to an oral antimicrobial agent to complete the course of treatment for *Escherichia coli* pyelonephritis. When making a parenteral-to-oral antimicrobial switch, the bioavailability of the oral antimicrobial option is important and depends on the infection being treated. In patients with bacteremia, an agent with excellent bioavailability should be used (quinolones, trimethoprim-sulfamethoxazole, metronidazole, clindamycin, linezolid). Trimethoprim-sulfamethoxazole has excellent bioavailability, so it is the oral antimicrobial agent of choice.

Oral ciprofloxacin would be an option for this patient rather than intravenous. However, ciprofloxacin has a broader spectrum of activity than trimethoprim-sulfamethoxazole, so it would not be preferred. The most focused, narrowest-spectrum agent possible is preferred when an antimicrobial agent is prescribed.

Nitrofurantoin is used for acute, uncomplicated urinary tract infections. It is not adequate treatment for pyelonephritis, with or without bacteremia, because active levels are achieved only in the urine and not in the kidney parenchyma.

KEY POINT

- In patients taking intravenous antimicrobial therapy, a switch to oral therapy should be considered in all patients with an intact and functioning gastrointestinal tract and whose clinical status is improving.

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Item 43 Answer: A

Educational Objective: Manage a reactive tuberculin skin test in an immunosuppressed patient.

This patient should undergo chest radiography to exclude active tuberculosis infection. The patient is asymptomatic and is taking infliximab, a tumor necrosis factor α inhibitor, for management of her psoriasis. A tuberculin skin test (TST) reaction of 5-mm or larger induration is interpreted as positive in patients who are immunosuppressed, including those who are taking tumor necrosis factor α inhibitors or the equivalent of at least 15 mg/d of prednisone for 1 month or longer. Other patients for whom 5-mm or larger induration is considered positive include patients with HIV infection, organ transplants, and fibrotic changes on chest radiograph consistent with old tuberculosis, and recent contacts of a person with active tuberculosis. If the chest radiograph is negative, treatment for latent tuberculosis infection, usually consisting of daily isoniazid with pyridoxine (vitamin B_6) for 9 months, is recommended to decrease the risk for progression to active disease.

Testing with both the TST and interferon-γ release assay is not routinely recommended. According to the Centers for Disease Control and Prevention, using both tests may be helpful when the result of the initial test is positive and additional validation of infection is required before recommended treatment is initiated, such as in health care professionals who previously received the bacillus Calmette-Guérin vaccine or patients at low risk for infection and progression to active disease. Conversely, both tests may be helpful when the result of the initial test is

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negative and the risk for infection, active disease, and a poor outcome is increased, such as in patients infected with HIV or children younger than 5 years who have been exposed to a patient with active tuberculosis. Using both tests also may be helpful when the result of the initial test is negative but symptoms, signs, or imaging results are suspicious for TB and evidence of infection with *M. tuberculosis* is being sought. Because this patient does not fit into one of these categories, interferon-γ release assay would not be indicated.

Rifampin, isoniazid, pyrazinamide, and ethambutol would be recommended as initial therapy for a patient with active tuberculosis. This patient has no symptoms of active infection. Unless the chest radiograph suggests active tuberculosis, beginning four-drug antituberculous therapy is not indicated and would not be appropriate before further evaluation.

No additional intervention, including evaluation or therapy, would be inappropriate for this patient. Although she is asymptomatic, she is at risk for active tuberculosis if untreated for latent tuberculosis infection.

KEY POINT

- Patients who have a positive reaction to tuberculin skin testing should be further evaluated by chest radiography to rule out active tuberculosis infection.

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Item 44 Answer: B

Educational Objective: Diagnose a primary genital herpes simplex virus infection.

A polymerase chain reaction (PCR) test of a lesion specimen should be performed for genital herpes simplex virus (HSV) infection. The patient has genital lesions characteristic of HSV infection (shallow ulcers on an erythematous base), and primary infection is likely because of the presence of multiple lesions, regional lymphadenopathy, and systemic symptoms. It is important that all first presentations of genital HSV infection be microbiologically confirmed. PCR is the most sensitive of the available testing modalities and can also distinguish between HSV-1 and HSV-2, which can help inform discussions with the patient regarding risk of recurrent genital ulcer disease. HSV-1 is the most common and is less likely to cause recurrent infection or asymptomatic shedding. If the diagnosis is confirmed, the patient should be offered screening for other sexually transmitted infections and counseled regarding the need to inform prospective sexual partners and her obstetrician should she become pregnant.

Direct florescent antibody testing of a genital lesion is a specific study for HSV infection and is also able to identify the type of virus present. However, it is less sensitive than PCR testing and is no longer recommended for the diagnosis of genital HSV.

Type-specific serum antibodies to HSV develop within weeks of primary infection and persist indefinitely. However, their presence does not confirm that the genital ulcers are caused by HSV; therefore, this study would not be appropriate for this patient.

Tzanck smear is an older test that assesses the presence of multinucleate giant cells in a lesion specimen that demonstrates the cytopathic effects of the virus. However, the sensitivity and specificity of this test are low, and the test does not differentiate among serotypes of HSV; it is therefore no longer used frequently.

KEY POINT

- Polymerase chain reaction testing of genital lesions is the most sensitive diagnostic modality available for herpes simplex virus infection.

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Item 45 Answer: B

Educational Objective: Diagnose giardiasis.

The most appropriate diagnostic test for this patient with subacute diarrheal illness is the stool *Giardia* antigen test. The constellation of steatorrhea, abdominal distention, and weight loss in the absence of fever suggests a parasitic gastrointestinal illness, most likely *Giardia* infection. *Giardia* is ubiquitous in the environment and can cause human infection through ingestion of contaminated food or water. Less commonly, transmission can occur through fecal-oral routes. Giardiasis is a common gastrointestinal infection in outdoor enthusiasts and international travelers, who may become infected after drinking contaminated water. Boiling or filtering water is protective, but chlorination does not prevent infection.

Amebiasis is an uncommon cause of dysentery in developed countries and would be unlikely in the absence of a history of travel, as is the case in this patient. Therefore, a stool *Entamoeba* antigen test would be inappropriate.

Stool microscopy is no longer the preferred diagnostic test for giardiasis, as *Giardia* antigen testing has a sensitivity greater than 80%. Identification of cysts or trophozoites by microscopy in stool samples is hindered by intermittent shedding of the parasite, and multiple stool samples are therefore required to exclude the diagnosis.

Several enteric parasites are not well visualized using traditional microscopy and require modified acid-fast stains for optimal diagnosis. These include *Cyclospora* and *Cystoisospora* species, both of which are uncommon causes of diarrhea in the absence of travel or HIV/AIDS. *Cyclospora* infections in the United States have been associated with outbreaks traced to imported fruits and vegetables, but this

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patient's history of backcountry camping makes giardiasis a much more likely diagnosis.

KEY POINT

- Steatorrhea, abdominal distention, and weight loss suggest giardiasis, most common in travelers and outdoor enthusiasts, who may become infected from drinking contaminated water.

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Item 46 Answer: C

Educational Objective: Identify preferred screening for *Mycobacterium tuberculosis* infection in a patient who is unlikely to return for follow-up.

This patient uses injection drugs, so she is at higher risk for exposure to or infection with *Mycobacterium tuberculosis* and should be screened for the pathogen, preferably with an interferon-γ release assay (IGRA). An IGRA or a tuberculin skin test (TST) can be used to diagnose tuberculosis, although neither differentiates between active disease and latent tuberculosis infection (LTBI). An IGRA can be used instead of a TST in all cases in which TST is recommended; however, an IGRA is preferred for persons from groups who are at high risk for not returning for interpretation of their TST result (such as injection drug users or homeless persons) and those who have received bacillus Calmette-Guérin as a vaccine or for cancer treatment. Although IGRA tends to be more expensive than TST, the resultant increase in rates of test completion are likely more cost-effective in persons at high risk for noncompletion of TST testing and also allows for improved public health efforts in the management of infected persons at significant risk for infection.

If the IGRA result is positive, then an evaluation for active disease includes review of symptoms (fever, night sweats, weight loss, cough, fatigue, chest pain), chest radiography, and possibly microbiologic assessment of sputum (or other involved fluid). LTBI can be diagnosed when active disease is ruled out. However, chest radiography or induced sputum examination is not used for screening for LTBI.

KEY POINT

- Interferon-γ release assay is preferred for tuberculosis screening in groups at high risk for not returning for interpretation of skin test results and those who have received bacillus Calmette-Guérin as a vaccine or for cancer treatment.

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Item 47 Answer: A

Educational Objective: Treat a patient with HIV infection with opportunistic infection prophylaxis.

This patient should begin azithromycin. Because his CD4 cell count is less than 50/μL, he is at significant risk for disseminated *Mycobacterium avium* complex infection and should begin prophylaxis immediately with azithromycin. He has HIV infection and meets the definition for AIDS based on a CD4 cell count less than 200/μL. Although he has not yet had an opportunistic infection, he should also receive prophylaxis against *Pneumocystis jirovecii*, for which daily trimethoprim-sulfamethoxazole is the drug of choice.

Although this patient is at risk for candidal infections, such as oroesophageal disease, or infection by other fungi, including *Cryptococcus neoformans*, primary antifungal prophylaxis is not recommended in HIV infection. Therefore, fluconazole is not indicated in this patient.

The risk for tuberculosis (TB) infection increases in patients following HIV seroconversion and increases as loss of CD4 cells and immunosuppression progress. Therefore, all patients with HIV infection should be screened for latent TB, and close follow-up for primary TB infection should be maintained. However, this patient has no evidence of latent or active TB infection. The interferon-γ release assay result is indeterminate because of his very low CD4 count and consequent inability to react to the positive control used in the testing. He has no clinical symptoms or signs of TB and has not had any exposure. Therefore, treatment with isoniazid and vitamin B_6 is not indicated.

Pyrimethamine is an agent with activity against *Toxoplasma gondii*, which this patient is at risk for based on his positive serologic results and CD4 cell count less than 100/μL. Leucovorin is given concomitantly to lessen the risk for cytopenias, which are a common adverse effect associated with pyrimethamine therapy. However, the trimethoprim-sulfamethoxazole already being used for *Pneumocystis* prophylaxis will also protect against toxoplasmosis, so additional medication is unnecessary.

Although the patient is at risk for reactivation disease due to cytomegalovirus, primary prophylaxis is not recommended because of the hematologic toxicity of valganciclovir.

KEY POINT

- Patients with HIV/AIDS with CD4 cell counts less than 50/μL and less than 200/μL should undergo prophylaxis against *Mycobacterium avium* complex and *Pneumocystis jirovecii*, respectively.

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Item 48 Answer: C

Educational Objective: Manage opportunistic infection prophylaxis in a patient who has undergone solid organ transplantation.

This patient's level of immunosuppression must be increased for this episode of acute rejection, and therefore prophylaxis for *Pneumocystis jirovecii* infection should be reinitiated. Because of defects in cell-mediated immunity resulting from antirejection drugs, patients who have undergone transplantation are at high risk for *P. jirovecii* infection and are usually treated with prophylaxis for *Pneumocystis* infection, especially for the first 6 to 12 months when immunosuppression is given at higher levels. Long-term prophylaxis is not typically required when immunosuppression for the transplant can be minimized. However, these patients are also at increased risk beyond the first year if episodes of rejection require increases in immunosuppression, such as in this patient. It is thus important to reinstitute prophylaxis for *Pneumocystis* infection under these circumstances, even if increased immunosuppression is temporary. Trimethoprim-sulfamethoxazole is the preferred prophylactic agent in most patients without a contraindication.

Pulmonary aspergillosis is more likely to occur in the neutropenic period after hematopoietic stem cell transplantation or after lung transplantation; it would be uncommon in a patient after other solid organ transplantation, and prophylaxis is not indicated.

Both recipient and donor in this case were seronegative for cytomegalovirus before transplantation and thus cytomegalovirus disease is unlikely, even with increased immunosuppression, and prophylaxis is not necessary.

In contrast to the high risk in patients with advanced AIDS, *Mycobacterium avium* complex infection is unusual after transplantation, and prophylaxis against this is not indicated.

KEY POINT

- Patients who have undergone transplantation are at high risk for *Pneumocystis jirovecii* infection, especially during the first 6 to 12 months and after episodes of rejection requiring increased immunosuppression.

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Item 49 Answer: B

Educational Objective: Prevent hepatitis A in a traveler to South Asia.

This patient should receive hepatitis A virus (HAV) vaccine and a dose of intramuscular immune globulin now. Travel-related risk for acquiring HAV depends on the person's immune status to HAV and level of endemicity of this hepatotropic pathogen in the geographic area being visited. The adoption of routine childhood HAV vaccination programs in recent years has greatly decreased the incidence of infection. However, only approximately 40% of adults are immune to HAV and, therefore, are at risk for infection, particularly when traveling to developing parts of South Asia, Africa, and South and Central America. Transmission occurs by the fecal-oral route from close contact with an infected person or ingestion of contaminated water or food. Therefore, active immunization using either of the two available inactivated vaccines is effective for preventing infection and is strongly recommended when traveling to areas of high disease prevalence, such as Cambodia.

One dose of vaccine administered any time before departure generally provides protection to most persons 40 years or younger, although a second dose given 6 to 12 months after the initial dose is required for long-term protection. However, persons older than 40 years, those with chronic medical conditions, immunocompromised persons, or those with chronic liver disease who plan to depart within 2 weeks to an endemic area should be treated with hepatitis A vaccination and intramuscular immune globulin given at a distant injection site to provide optimal protection. The use of immunosuppressive medications (as in this patient), including tumor necrosis factor α inhibitors, is not a contraindication to immunization with killed or inactivated vaccines.

Hepatitis A vaccine is the primary method for triggering immunity to the virus, with immune globulin providing additional protection in patients at high risk. The use of immune globulin alone without hepatitis A vaccination is not indicated or recommended.

Administering hepatitis A vaccine or immune globulin following exposure to hepatitis A in nonimmunized patients (postexposure prophylaxis) is effective in reducing attack rates of infection. However, preexposure prophylaxis is not contraindicated in this patient, and postexposure prophylaxis should not be necessary.

KEY POINT

- Hepatitis A virus vaccine, with a dose of intramuscular immune globulin to provide optimal protection to persons traveling within 2 weeks, should be given to any person planning travel to developing parts of South Asia, Africa, and South and Central America.

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Item 50 Answer: E

Educational Objective: Treat a patient with a second recurrence of *Clostridium difficile* infection.

This patient with a second recurrence of mild to moderate *Clostridium difficile* infection (CDI) should be treated with

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oral vancomycin for 6 weeks. Approximately 20% of patients with CDI will experience a relapse. In 2010, an expert panel outlined evidence-based recommendations for treatment of CDI. A recent study found that adherence to these guidelines resulted in significantly improved outcomes and fewer recurrences of CDI.

The initial treatment regimen is based on the severity of illness, with a 10- to 14-day course of oral metronidazole recommended for mild to moderate illness and a 10- to 14-day course of oral vancomycin for severe illness. For the first recurrence, guidelines specify that treatment decisions should be based on the severity of illness, similar to the determination of appropriate treatment with the initial presentation. However, for subsequent relapses, the probability of sustained response is significantly decreased, and it is therefore recommend that all patients receive a prolonged course of vancomycin, typically given at tapered doses over 6 to 8 weeks.

Metronidazole is not recommended for use in multiple recurrences of CDI because prolonged administration is associated with a risk for neurotoxicity, and luminal concentrations of the antibiotic decrease to subtherapeutic levels after resolution of colitis.

Small studies have suggested that rifaximin may be useful in multiple recurrences of CDI when given at the end of the vancomycin taper, but this agent is not recommended as a stand-alone therapy.

KEY POINT

- Patients who have more than one recurrence of *Clostridium difficile* infection should be treated with oral vancomycin given at tapered doses over 6 to 8 weeks.

Bibliography

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Item 51 Answer: B

Educational Objective: Treat a patient with community-acquired pneumonia who has reached clinical stability by switching to oral antibiotic therapy.

This patient should be switched to an oral antibiotic agent, and he should be discharged when otherwise clinically ready. Empiric intravenous antibiotic therapy is usually started in patients requiring hospital admission for community-acquired pneumonia (CAP), as was done with this patient, to cover the most likely infecting organisms. He has had an appropriate response to therapy as indicated by improvement in his clinical symptoms (fever, cough, dyspnea) within the 3 days of treatment. Patients treated with intravenous antibiotics for CAP with an appropriate clinical response can be switched to an oral agent, generally of the same antimicrobial class and with similar spectrum of activity, when clinical stability has been attained. Parameters suggesting clinical stability include 1) temperature of 37.8 °C (100.0 °F) or less, 2) heart rate of 100/min or less, 3) respiration rate of 24/min or less, 4) systolic blood pressure of 90 mm Hg or greater, 5) arterial oxygen saturation of 90% or more or Po_2 of 60 mm Hg (8.0 kPa) or greater breathing ambient air (or requiring a similar amount of supplemental oxygen as before admission if the patient receives chronic oxygen therapy), 6) ability to maintain oral intake, and 7) normal mental status.

Extended intravenous antibiotic therapy in stable patients without another indication for prolonging this treatment has not been shown to be more beneficial than oral therapy. Similarly, overlapping intravenous and oral antibiotic therapy, or hospital monitoring of stable patients following the transition from parenteral to oral therapy, has not been shown to improve outcomes.

KEY POINT

- Patients treated with intravenous antibiotics for community-acquired pneumonia with an appropriate clinical response can be switched to an oral agent, generally of the same antimicrobial class and with similar spectrum of activity, when clinical stability has been attained.

Bibliography

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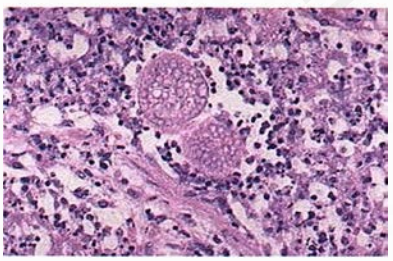
Item 52 Answer: B

Educational Objective: Diagnose a traveler with coccidioidomycosis.

The patient has coccidioidomycosis, most likely acquired during her recent trip to Arizona. *Coccidioides immitis*, a dimorphic fungus, is regularly found in the soil in the southwestern United States, along with parts of Mexico and Central and South America. Even limited exposure in endemic areas can result in inhalation of airborne spores of this pathogen. In most patients, the primary lung infection of coccidiomycosis is asymptomatic; patients who develop clinical disease often report influenza-like illness. Chest imaging studies are nonspecific; findings may be normal in asymptomatic patients or include diffuse infiltrates, nodules, and cavities, sometimes in combination. The endospore-containing spherule detected in the bronchoalveolar lavage specimen shown is characteristic of *C. immitis*.



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CONT.

Unilateral hilar lymphadenopathy and pleural effusions are observed in approximately one fifth of symptomatic patients. Constitutional and pulmonary symptoms predominate, often beginning weeks after returning from travel. The presence of erythema nodosum lesions on the anterior lower extremities is also fairly common. Severe pulmonary disease and hematogenous dissemination of the organism to skin, bone, joints, peritoneum, and central nervous system occur infrequently, but patients with impaired T-cell–mediated immunity, such as this patient, are at significantly higher risk for more severe disease. Confirmation relies on isolation of the organism from clinical specimens, histologic identification, serologic assays, and DNA probes. *Coccidioides* infections generally resolve without antifungal therapy, but immunocompromised patients with severe or disseminated infection warrant antifungal therapy. An amphotericin B deoxycholate formulation is recommended in severely ill patients. In all others, fluconazole or itraconazole can be used.

Blastomycosis and histoplasmosis are dimorphic fungi that share clinical features with coccidioidomycosis but are mostly concentrated in the central river valleys and south-central and southeastern United States. Morphologically, the organisms are easily distinguishable from *Coccidioides* species on clinical specimens.

Mycoplasma pneumoniae is less common in adults and rarely presents as severe pneumonia. A single reactive IgM antibody assay may not be reliable in confirming the diagnosis because both the sensitivity and specificity of this test are suboptimal. Diagnosis is best confirmed by showing a four-fold increase or decrease in paired sera titers or by detecting *M. pneumoniae*–specific antigens in respiratory secretions using newer immunoassays.

KEY POINT

- Coccidioidomycosis should be considered in any patient with a respiratory illness who lives or has spent time in an endemic area, which includes the southwestern United States, Mexico, and South and Central America.

Bibliography

Galgiani JN, Ampel NM, Blair JE, et al; Infectious Diseases Society of America. Coccidioidomycosis. Clin Infect Dis. 2005;41(9):1217-23. [PMID: 16206093]

Item 53 Answer: A

Educational Objective: Manage *Enterococcus faecalis* bacteremia.

This patient should receive ampicillin in place of meropenem. Distinguishing between bacteremia caused by *E. faecalis* versus *Enterococcus faecium* is necessary because *E. faecium* is relatively more resistant than *E. faecalis* and more likely to be vancomycin resistant, depending on local epidemiology. Intravenous ampicillin is the most appropriate treatment option for sensitive *E. faecalis* because it is the most narrow-spectrum agent and antibiotic of choice for this organism. Antibiotic stewardship requires that empiric antimicrobial therapy be modified or de-escalated as soon as culture results are available, even when a patient is improving with the empiric antimicrobial regimen. Doing so helps preserve the effectiveness of broad-spectrum agents used to initially treat patients requiring aggressive therapy. Meropenem is highly effective against a wide range of organisms, and this breadth of coverage is unnecessary after the primary infecting organism has been identified. Additionally, it is less active against *E. faecalis* than ampicillin or vancomycin and should therefore be discontinued.

Adding gentamicin to ampicillin or vancomycin is not necessary in nonendocarditis *E. faecalis* infections, including bacteremia. In this patient, *E. faecalis* bacteremia occurred secondary to urinary tract infection; he has no evidence of endocarditis by history, examination, or clinical course. In patients with enterococcal endocarditis, adding gentamicin (if high-level aminoglycoside resistance is not present) to ampicillin or vancomycin for a limited period early in the treatment course improves clinical outcomes.

Vancomycin is used in patients who are allergic to penicillin or in ampicillin-resistant *E. faecalis* but is not the initial agent of choice for use against *E. faecalis*.

KEY POINT

- Empiric antimicrobial therapy should be modified or de-escalated as soon as culture results become available to provide the narrowest-spectrum agent available.

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Item 54 Answer: A

Educational Objective: Diagnose invasive *Aspergillus* infection.

This patient most likely has acute *Aspergillus* rhinosinusitis. Invasive fungal infections, such as sinusitis, are uncommon except in immunocompromised persons with prolonged neutropenia, such as this patient who has an underlying hematologic malignancy and is undergoing chemotherapy. His clinical symptoms (sinus pain), examination and radiographic findings (sinusitis and exophthalmos), and laboratory studies (positive result on galactomannan antigen immunoassay and characteristic histopathologic findings) support the diagnosis of *Aspergillus* rhinosinusitis. Direct invasion into the palate can occur from infection of the maxillary sinus. Infection of the ethmoid sinus may extend into the cavernous sinuses and cause cranial nerve deficits and internal carotid artery thrombosis. Central nervous system (CNS) involvement may also occur as a complication. Additionally, periorbital infection with subsequent loss of vision may occur. The mortality rate of *Aspergillus* rhinosinusitis is high. Definitive diagnosis requires a tissue biopsy demonstrating hyphae and a positive culture for *Aspergillus*.

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CONT.

The appearance of septate hyphae with acute angle branching on histopathologic testing can be diagnostic. The galactomannan assay is an important non culture-based tool for the diagnosis of invasive aspergillosis. Detection of galactomannan in serum has a high sensitivity and specificity in patients at high risk; galactomannan can also be detected in cerebrospinal fluid specimens from patients with CNS aspergillosis and in bronchoalveolar lavage fluid from those with invasive pulmonary aspergillosis. It is useful in early detection and in therapeutic monitoring. Voriconazole is the therapy of choice for most patients with invasive aspergillosis because of its potent fungicidal activity against *Aspergillus* species. Culture confirmation is important to distinguish *Aspergillus* from other filamentous fungal infections.

Candida and *Cryptococcus* are yeasts that are unlikely causes of rhinosinusitis and do not result in a positive finding on galactomannan assay or have the characteristic morphologic features of *Aspergillus*.

Although rare in otherwise healthy patients, *Pseudomonas* rhinosinusitis is encountered most frequently in immunocompromised or severely traumatized patients. *Pseudomonas* is a gram-negative, bacillary bacterium that also does not cause a positive galactomannan test result.

KEY POINT

- Definitive diagnosis of *Aspergillus* sinusitis requires a tissue biopsy demonstrating hyphae and a positive culture for *Aspergillus*, and use of the galactomannan antigen immunoassay to detect galactomannan in serum has a high sensitivity and specificity in patients at high risk.

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Item 55 Answer: C

Educational Objective: Diagnose posttransplant lymphoproliferative disease.

This patient most likely has posttransplant lymphoproliferative disease (PTLD). She is at increased risk for PTLD because she was seronegative for Epstein-Barr virus (EBV) and the organ donor was seropositive. PTLD is related to B-cell proliferation induced by infection with EBV in the setting of chronic immunosuppression and resulting decreased T-cell immune surveillance. She presents within a typical timeframe (first few months to 1 year after transplantation) with lymphadenopathy found on CT scan and systemic symptoms consistent with PTLD. In addition to PTLD, EBV after transplantation can cause a mononucleosis syndrome, leukopenia and thrombocytopenia, and hepatitis or pneumonitis. Quantitative serum polymerase chain reaction for EBV can suggest a diagnosis of PTLD, which is confirmed by biopsy and histopathologic evaluation of the swollen lymph nodes or extranodal mass. Management consists of reduction in immunosuppression, if possible, and may require chemotherapy, which often includes rituximab.

Cytomegalovirus infection is common after transplantation, especially in seronegative recipients with seropositive donors, and can manifest as a nonspecific febrile syndrome. However, cytomegalovirus would be unlikely to cause a single, significantly enlarged lymph node; this presentation makes PTLD more likely.

Although this patient has whitish plaques in her oropharynx consistent with oral thrush, and disseminated fungal infections may cause systemic symptoms such as this patient is experiencing, an invasive *Candida* infection would not cause her isolated lymphadenopathy and is not supported by her negative fungal blood cultures.

Tuberculosis reactivation increases in incidence after solid organ transplantation and is more likely to have extrapulmonary findings. It could present with lymphadenopathy and fever but clear lungs, as in this patient. However, she had a negative result on a test for latent tuberculosis before transplantation, which makes reactivation of tuberculosis unlikely.

KEY POINT

- Patients are at high risk for posttransplant lymphoproliferative disease if they received an organ from a donor seropositive for Epstein-Barr virus when they are seronegative.

Bibliography

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Item 56 Answer: A

Educational Objective: Treat a patient with a dog bite.

This patient has experienced a dog bite and should receive treatment with amoxicillin-clavulanate. A 3- to 5-day course of prophylaxis (early preemptive therapy) with amoxicillin-clavulanate is recommended for patients who are immunosuppressed (including those with asplenia or significant liver disease); have moderate to severe wounds (particularly on the face or hand); have wounds near a joint or bone; or have wounds associated with significant crush injury or edema. Amoxicillin-clavulanate, an oral β-lactam/β-lactamase inhibitor, is a good choice because it has a broad spectrum of activity against the aerobic and anaerobic bacteria that constitute a dog's oral flora. Prompt wound irrigation and debridement, if appropriate, are also indicated. Each patient should also be evaluated for the need for tetanus and rabies prophylaxis.

Metronidazole provides anaerobic bacterial coverage but lacks coverage against aerobic bacteria in dogs' mouth flora. If used, it should be combined with a fluoroquinolone (such as ciprofloxacin or levofloxacin) or trimethoprim-sulfamethoxazole.

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Patients with bite wounds should be vaccinated with tetanus toxoid if they have not received a tetanus immunization within the past 5 years because this type of wound is considered a "dirty" wound. Other wounds that are considered "dirty" include those contaminated with soil, saliva, dirt, or feces; avulsions; puncture wounds; and wounds resulting from burns, frostbite, crushing, or missiles. This patient has been immunized within this time period, so she does not require tetanus immunization. For a clean and minor wound, a booster dose of tetanus toxoid would be given to prevent tetanus if more than 10 years have elapsed since immunization.

Pursuing no additional therapy or evaluation would not be appropriate for this patient, who is receiving a tumor necrosis factor α inhibitor, which is an immunosuppressant. Although the patient has no signs or symptoms of infection, antibiotic prophylaxis is recommended as soon as possible after a bite to decrease the risk for infection.

KEY POINT

- A 3- to 5-day course of antibiotic prophylaxis with a broad-spectrum agent, such as amoxicillin-clavulanate, is recommended for patients who have received an animal bite and are immunosuppressed.

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Item 57 Answer: C

Educational Objective: Diagnose recurrent herpes simplex virus type 2 genital infection.

Recurrent herpes simplex virus 2 (HSV-2) infection is the most likely cause of this patient's rash. HSV-2 is the leading cause of genital ulcerative disease in the world. Although herpes simplex virus 1 (HSV-1) is rapidly gaining prevalence as a cause of this form of herpetic infection in younger white populations, it tends to be milder, with significantly fewer recurrences; however, it is clinically indistinguishable from HSV-2. Therefore, the diagnosis of suspected HSV infection should be confirmed with viral culture, polymerase chain reaction assay, or type-specific serologic tests.

Primary infection follows introduction of the virus onto a mucosal surface or through damaged skin. The findings with primary infection are highly variable, ranging from no symptoms to severe, painful genital ulcers; fever; tender inguinal lymphadenopathy; and headache. However, this patient has had several episodes of a similar rash over the past year, suggesting recurrent disease from a primary infection that may have occurred in the distant past. Although HSV-2 lesions characteristically appear in the genital region, they may also present at locations not classically thought of as the genitalia, such as the gluteal and presacral surfaces. Sacral HSV infection may be accompanied by episodes of aseptic meningitis. The pattern of recurrence may be influenced by diverse factors, including systemic infection, hormonal fluctuations associated with menstrual cycles, stress, and immune dysfunction. Long-term valacyclovir treatment taken on a daily basis decreases the frequency of recurrences and significantly diminishes asymptomatic viral shedding (which may occur without active skin lesions), which helps decrease transmission.

Dermatitis herpetiformis is an autoimmune disease associated with a gluten-sensitive enteropathy leading to skin deposition of IgA antibodies to gluten-tissue transglutaminase found in the gut. The lesions take the form of erythematous papules or plaques with clustered herpetiform vesicles and are usually located on the extensor surfaces of knees and elbows, but they may also be present on the shoulders and buttocks. Once present, the disease is chronic with periods of exacerbation and remission.

Fixed drug eruptions are cutaneous disorders associated with systemic exposure to various medications. The mechanism of disease is postulated to be a cell-mediated response to the offending drug acting as a hapten when it binds to specific cells in the skin. Outbreaks may occur on any cutaneous surface but seem to be more common on the lip and genitalia, where they appear as erythematous patches (often with blisters), postinflammatory necrosis, and hyperpigmentation. NSAIDs are included among the dozens of medications associated with this condition.

Sacral dermatomal distribution of HSV lesions is often confused with herpes zoster. However, multiple recurrences of zoster in a relatively young, immunocompetent woman would be very unusual.

KEY POINT

- Herpes simplex virus 2 is the most common cause of genital ulcer disease worldwide, although herpes simplex virus 1 as a cause of genital ulcer disease is increasing.

Bibliography

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Item 58 Answer: E

Educational Objective: Treat mild nontyphoidal *Salmonella* gastroenteritis.

This patient has acute diarrhea consistent with mild *Salmonella* gastroenteritis, which requires no therapy at this time. Nontyphoidal *Salmonella* infections typically cause an inflammatory diarrhea, sometimes associated with fever and abdominal pain. In young, healthy persons, such as this patient, the illness is usually self-limited and resolves without antibiotic therapy. In this population, antibiotic therapy is associated with prolonged asymptomatic fecal shedding with no decrease in duration of diarrhea. In contrast, *Salmonella* gastrointestinal infection in older patients, immunocompromised patients, or patients with sickle cell

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disease is associated with an increased risk for bacteremia and endovascular infection. In these populations, as well as in patients with severe salmonellosis or those requiring hospitalization, antibiotic therapy is warranted.

Azithromycin is the preferred empiric treatment option for *Campylobacter* gastroenteritis, considering increasing rates of quinolone resistance for this bacterium.

Ciprofloxacin is effective for most bacterial agents causing gastroenteritis but should be reserved for febrile patients with moderate to severe inflammatory diarrhea when the suspicion for *Salmonella* or Shiga toxin–producing *Escherichia coli* is low.

Loperamide and other antimotility agents are not recommended for inflammatory diarrhea because of the potential for delaying bacterial clearance and prolonging the illness.

Most studies of probiotics for infectious diarrhea have been performed in children. In that population, probiotics have been associated with an average decrease in the duration of symptoms by 1 day; however, the benefit for adults is less certain.

KEY POINT

- Therapy for mild nontyphoidal *Salmonella* gastroenteritis should be withheld in otherwise healthy patients because treatment may increase duration of bacterial shedding.

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Onwuezobe IA, Oshun PO, Odigwe CC. Antimicrobials for treating symptomatic non-typhoidal Salmonella infection. Cochrane Database Syst Rev. 2012 Nov 14;11:CD001167. [PMID: 23152205]

Item 59 Answer: C

Educational Objective: Treat a patient with acute, uncomplicated prostatitis.

This patient with likely acute bacterial prostatitis should begin empiric treatment with a fluoroquinolone, such as ciprofloxacin. Acute prostatitis most commonly results from an ascending urethral infection, although bacterial cystitis or epididymo-orchitis may be an underlying source of infection. Patients most often present with fever, chills, malaise, nausea and vomiting, dysuria, urgency, frequency, and pain in the lower abdomen, perineum, and rectum. The onset of symptoms is typically rapid. On physical examination, the prostate is tender and tense or boggy. Excessive palpation of the prostate should be avoided because it may contribute to bacteremia. As was done with this patient, blood and urine cultures should be obtained, and empiric broad-spectrum antibiotics should be started. Gram-negative bacillary organisms, including *Escherichia coli, Serratia* species, and *Klebsiella* species, are the most common causative agents in patients with uncomplicated acute bacterial prostatitis who are at low risk for sexually transmitted infections (STIs). The course of therapy with a fluoroquinolone is at least 14 days and up to 4 weeks. Trimethoprim-sulfamethoxazole is also an appropriate first-line choice if the isolate is known to be susceptible or if the rate of *E. coli* resistance in the community is less than 20%.

Ampicillin, which had been an alternative therapeutic option for prostatitis, can no longer be recommended as empiric therapy because of the high rate of resistance among community-acquired microorganisms.

A single dose of ceftriaxone, 250 mg intramuscularly, is indicated for uncomplicated acute bacterial prostatitis in patients at risk for STIs with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Generally, men younger than 35 years are at risk for infection with these organisms. Doxycycline, 100 mg twice daily for 10 days, is also indicated in these patients. This patient is not sexually active and therefore does not require coverage for possible STIs.

Treatment with a carbapenem, such as meropenem, should be reserved for systemically ill patients who require hospitalization or when a fluoroquinolone-resistant organism is a concern. The incidence of fluoroquinolone-resistant *E. coli* is very high (up to 90%) following prostate biopsy.

KEY POINT

- Patients with uncomplicated acute bacterial prostatitis, most commonly caused by *Escherichia coli, Serratia* species, and *Klebsiella* species, who are at low risk for sexually transmitted infections should be treated empirically with ciprofloxacin.

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Item 60 Answer: C

Educational Objective: Manage potential influenza exposure in a person who has not had an annual influenza vaccination.

This patient should be given postexposure prophylaxis with the inactivated influenza vaccine and oseltamivir chemoprophylaxis. Outbreaks of seasonal influenza virus infection generally occur during autumn and winter but may last into the spring. Most severe outbreaks are related to influenza A viruses, but they may also occur with type B influenza virus. Yearly preexposure immunization is recommended for all persons age 6 months or older, assuming no contraindications. In patients who have not been immunized, chemoprophylaxis with the neuraminidase inhibitors oseltamivir or zanamivir is recommended for persons who have been exposed to someone known or suspected of having active influenza, but only if the antivirals can be started within 48 hours of the most recent exposure. Both medications have activity against influenza A and B viruses, with resistance occurring in less than 1% of strains. However, zanamivir, which is administered by oral inhalation, is contraindicated in persons with chronic respiratory conditions, including those with asthma, such as this patient. Because chemoprophylaxis lowers but

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does not eliminate the risk for influenza, immunization with an influenza vaccine preparation should also be provided. Despite this patient's concern, the relative and attributable risks of neurologic sequelae such as Guillain-Barré syndrome after seasonal influenza vaccination are lower than those that occur in association with influenza infection.

The adamantine medication amantadine does not have activity against influenza B, and increasing drug resistance among influenza A strains make it an inappropriate medication for chemoprophylaxis.

The live-attenuated influenza vaccine given by nasal mist is approved only for persons age 2 to 49 years and would therefore not be appropriate in this patient.

KEY POINT

- Chemoprophylaxis with oseltamivir or zanamivir lowers but does not eliminate the risk for influenza, so immunization with an influenza vaccine preparation should also be provided to persons who may have been exposed to active influenza virus infection.

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Item 61 Answer: B

Educational Objective: Diagnose herpes simplex encephalitis.

Despite the negative result on a herpes simplex virus (HSV) polymerase chain reaction (PCR) test, herpes simplex encephalitis remains the most likely cause of this patient's illness. HSV type 1 infection of the central nervous system causes a necrotizing infection of the temporal lobes, although atypical presentations may occur. Localization of inflammation to one or both temporal lobes on neuroimaging strongly suggests herpes simplex encephalitis and should prompt diagnostic testing and empiric therapy for this life-threatening infection. The sensitivity and specificity of cerebrospinal fluid (CSF) PCR for the diagnosis of herpes simplex encephalitis are greater than 95%, and PCR has replaced brain biopsy as the gold standard for laboratory confirmation of that condition. However, early in the course of infection, the PCR result may be falsely negative. Therefore, when clinical suspicion for herpes simplex encephalitis is high on the basis of the clinical presentation, acyclovir should be continued with repeat CSF PCR 3 to 7 days later. Delay in initiation of acyclovir therapy or premature cessation of treatment for herpes simplex encephalitis is associated with a significantly worse prognosis.

Enteroviruses are a common cause of lymphocytic meningitis but rarely cause meningoencephalitis in adults. In the case of enterovirus, no anatomic localization would be seen on imaging.

Pneumococcal meningitis is a life-threatening infection most commonly affecting the very old or very young; however, the absence of a neutrophilic pleocytosis (typically a CSF leukocyte count >1000/μL [1000 × 10^6/L]) and the focal involvement of brain parenchyma would essentially exclude this diagnosis.

West Nile virus may cause meningoencephalitis that is more common and severe in older adults, but neuroimaging findings are typically normal or show abnormalities of the thalami, basal ganglia, or spinal cord.

KEY POINT

- Initial cerebrospinal fluid polymerase chain reaction assay may be falsely negative early in herpes simplex encephalitis and should be repeated 3 to 7 days later (in addition to empiric acyclovir) in patients with high clinical suspicion for herpes simplex encephalitis.

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Item 62 Answer: A

Educational Objective: Treat a patient with bacterial meningitis caused by *Streptococcus pneumoniae*.

Treatment with adjunctive dexamethasone is the most likely intervention to improve neurologic outcomes in this patient with a presumptive diagnosis of bacterial meningitis due to *Streptococcus pneumoniae*. Meningitis leads to severe central nervous system (CNS) inflammatory changes that may cause acute neurologic changes and result in permanent, long-term neurologic damage. Neurologic sequelae associated with pneumococcal meningitis include seizures, hearing loss, cranial nerve deficits, and paralysis. The glucocorticoid dexamethasone decreases inflammation in the CNS and leads to lower mortality, fewer short-term neurologic sequelae, and decreased hearing loss in pneumococcal meningitis when used as adjunctive therapy in developed countries. Because of these potential benefits, guidelines recommend early dexamethasone treatment of possible or suspected pneumococcal meningitis; it should be given approximately 15 minutes before administration of antimicrobial agents and should be continued for the duration of antibiotic therapy.

Of interest, several recent studies have investigated therapeutic hyperthermia as a possible treatment of severe bacterial meningitis, but results have been conflicting and data not definitive enough to recommend this therapy.

Although excess intravascular volume has been associated with poorer outcomes in patients with severe bacterial meningitis, no evidence supports the benefit of fluid restriction or diuresis in euvolemic patients early in the management of bacterial meningitis compared with maintaining normal intravascular volume.

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CONT.

Patients with meningitis frequently have increased intracranial pressure (ICP), and several interventions may lower the ICP, including maintaining the head of the bed at greater than 30 degrees, administering a hyperosmolar agent (such as glycerol), and placing a ventricular drain. However, monitoring and treating increased ICP are beneficial primarily in patients with bacterial meningitis who are stuporous or comatose, unlike this patient. The effect of interventions to lower ICP in patients without significant neurologic findings associated with meningitis is unclear.

Experimental animal models of pneumococcal meningitis have shown that infusions of mannitol modulate and reduce ICP. The mechanism for this effect on ICP may be related to reduction of hydroxyl radicals, which are implicated in CNS injury from ischemia and neuronal damage. The use of mannitol in this patient who has no clinical evidence of ICP is not appropriate.

KEY POINT

- Adjunctive dexamethasone will improve outcomes in patients with a presumptive diagnosis of bacterial meningitis due to *Streptococcus pneumoniae*.

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Item 63 Answer: C

Educational Objective: Treat a patient with multidrug-resistant ventilator-associated pneumonia with empiric antibiotic therapy.

This patient should be treated empirically with a carbapenem, such as meropenem, for a possible infection with a multidrug-resistant organism (MDRO). She is at high risk for ventilator-associated pneumonia (VAP) with multidrug-resistant *Klebsiella pneumoniae* as suggested by gram-negative rods on sputum Gram stain and the presence of other patients in the same ward with extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* infection. ESBLs are enzymes that confer resistance to most β-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam; they occur only in gram-negative organisms, primarily *K. pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*. Carbapenems are less susceptible to ESBLs and provide adequate empiric coverage against this organism, as well as coverage for other possible gram-negative organisms such as *Pseudomonas* species, which is the second most common cause of VAP following *Staphylococcus aureus*. With any empiric regimen, antibiotic de-escalation should occur when culture results are available. Meropenem should be changed to ertapenem, a carbapenem without antipseudomonal activity, if an ESBL-producing organism is isolated without *Pseudomonas*. MDROs are more commonly associated with late-onset (>4 days) VAP. ESBL-producing *K. pneumoniae* are transmitted by health care personnel using improper hand hygiene or not following contact precautions. Contaminated shared patient care equipment that is not appropriately disinfected between patient uses is another possible route of transmission.

Because extended-spectrum penicillins and cephalosporins share susceptibility to ESBL, cefepime, ceftazidime, and piperacillin-tazobactam would not be optimal empiric therapy in this patient.

KEY POINT

- Carbapenems, such as meropenem, are the appropriate choice for empiric therapy in patients with ventilator-associated pneumonia likely caused by extended-spectrum β-lactamase-producing *Enterobacteriaceae* species.

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Item 64 Answer: D

Educational Objective: Manage HIV infection accompanied by serum creatinine elevation.

This patient should continue his current antiretroviral regimen. Antiretroviral therapy for HIV usually comprises a "backbone" of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus a third agent, which may be a boosted protease inhibitor, a nonnucleoside reverse transcriptase inhibitor, or an integrase inhibitor. This patient's initial regimen contains the backbone of tenofovir and emtricitabine, primarily because these agents also have activity against hepatitis B. The third agent is elvitegravir, which is an integrase inhibitor; cobicistat is a cytochrome P-450 inhibitor used to boost the level of elvitegravir, which is metabolized through this pathway. This particular combination is available as a once-daily formulation, which is convenient for patients and encourages medication adherence. However, cobicistat also inhibits tubular secretion of creatinine, leading to increased levels of serum creatinine that do not reflect an actual change in the glomerular filtration rate (GFR). The creatinine level increases by an average of 0.14 mg/dL (12.4 μmol/L) with cobicistat. Because this does not actually affect the GFR, it is an expected occurrence and is not a reason to change the antiretroviral regimen, which is successful in this patient as demonstrated by the reduction in his viral load to undetectable levels. Investigation for true kidney dysfunction is recommended if the increase in creatinine level in patients taking cobicistat is 0.4 mg/dL (35.4 μmol/L) or more.

Changing the patient's antiretroviral regimen to an alternative NRTI backbone, such as abacavir-lamivudine or zidovudine-lamivudine, plus a third agent would be reasonable if a change in medications from his currently effective regimen were indicated, but this is not the case. Additionally, changing regimens from tenofovir and emtricitabine would lose the dual treatment effect of these agents for the patient's hepatitis B.

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Even a brief discontinuation of antiretroviral therapy would be inappropriate because the patient is tolerating therapy well and it has been effective. Moreover, in this patient with chronic active hepatitis B, discontinuing agents with hepatitis B activity (tenofovir and emtricitabine) can lead to an acute flare in activity of the hepatitis, which can be severe.

Although this patient is at risk for several potential kidney diseases, including HIV-associated nephropathy, hepatitis B–associated kidney disease, and tenofovir renal toxicity, the likely artifactual increase in his serum creatinine level in combination with his negative urinalysis result and bland urine sediment does not suggest active kidney disease requiring further evaluation, such as by kidney biopsy.

KEY POINT

- Cobicistat can inhibit tubular secretion of creatinine but does not actually affect glomerular filtration rate, so an increase in the creatinine level is expected when this agent is used.

Bibliography

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Item 65 Answer: B

Educational Objective: Treat a severe case of *Clostridium difficile* infection.

This patient has severe *Clostridium difficile* infection (CDI) and should be treated with oral vancomycin. Consensus guidelines for the treatment of CDI indicate that the specific antibiotic and route of administration should be guided by the severity of disease. Severe CDI is defined by the Infectious Diseases Society of America as a leukocyte count of 15,000/μL (15×10^9/L) or greater and a serum creatinine level greater than 1.5 times the baseline level. Although more recent guidelines (see citation) use slightly different measures for defining severity, infectious disease and gastroenterology specialties concur that the preferred treatment for severe CDI is oral vancomycin. This is based on lower cure rates with oral metronidazole compared with vancomycin for patients with severe disease.

Oral metronidazole is the recommended initial therapy for patients with mild to moderate CDI (leukocyte count <15,000/μL [15×10^9/L] and serum creatinine level <1.5 times baseline) based on cure rates similar to those of vancomycin and lower cost. A newer antimicrobial agent, fidaxomicin, showed noninferiority to vancomycin in the treatment of patients with mild to moderate CDI and, in a subset of patients, was associated with fewer relapses. However, the cost difference is substantial. A 10-day course of fidaxomicin approaches $3000, whereas metronidazole costs less than $30 and oral vancomycin costs less than $700. The indications for fidaxomicin will likely evolve, but as of publication it is not recommended as initial therapy for mild to moderate CDI.

Complicated CDI is defined as severe disease with the additional findings of hypotension, ileus, or megacolon. Patients with ileus may have limited transit of oral antibiotics to distal sites of infection in the colon. Therefore, in this critically ill group, the recommendation is to give vancomycin orally or through a rectal tube in addition to intravenous metronidazole. Parenteral metronidazole has variable penetration but provides some delivery to the distal colon in the setting of ileus. In contrast, intravenous vancomycin does not achieve appreciable levels intraluminally, and this route of administration is not indicated for treatment of CDI.

No treatment benefit results from combination therapy with oral metronidazole and oral vancomycin for CDI regardless of severity of infection.

KEY POINT

- Severe *Clostridium difficile* infection should be treated with oral vancomycin.

Bibliography

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Item 66 Answer: D

Educational Objective: Diagnose sporadic Creutzfeldt-Jakob disease.

This patient most likely has sporadic Creutzfeldt-Jakob disease (CJD). She has a compatible clinical presentation, with acute onset of rapidly progressive dementia, ataxic gait, and myoclonus. In addition, the cerebrospinal fluid (CSF) demonstrates elevated 14-3-3 protein. Brain biopsy would be required for definitive diagnosis. Sporadic CJD is the most common form of human prion disease, with onset usually in the seventh decade of life. Myoclonus is seen in 90% of patients. In the appropriate clinical setting, the CSF test for the 14-3-3 protein is relatively specific and sensitive for this diagnosis. Other disorders that increase CSF 14-3-3 protein, such as acute stroke or multiple sclerosis, are rarely confused with CJD clinically.

Patients with Alzheimer disease have a more insidious and chronic presentation of dementia and other neurologic findings than seen in this patient.

Kuru was the first prion disease recognized to be transmissible and was linked to cannibalism among tribes of Papua, New Guinea. Common initial manifestations of kuru include headaches and joint pain. Subsequent symptoms include ataxia, dysarthria, and tremors. Myoclonus and dementia are generally seen only late in the illness. The incidence of kuru has decreased with the cessation of the practice of cannibalism.

Neurosyphilis may be asymptomatic or may manifest as syphilitic meningitis, meningovascular syphilis, tabes dorsalis (demyelination of the posterior columns of the spinal

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CONT.

cord), or general paresis. General paresis is a chronic meningoencephalitis that results in gradual, progressive loss of cortical function. The CSF is nearly always abnormal, with a lymphocytic pleocytosis and increased protein.

KEY POINT

- Patients with sporadic Creutzfeldt-Jakob disease usually present in the seventh decade of life and have disordered cognition, ataxia or spasticity, myoclonus, and elevated 14-3-3 protein in the cerebrospinal fluid.

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Lee J, Hyeon JW, Kim SY, Hwang KJ, Ju YR, Ryou C. Review: Laboratory diagnosis and surveillance of Creutzfeldt-Jakob disease. J Med Virol. 2015 Jan;87(1):175-86. [PMID: 24978677]

Item 67 Answer: C

Educational Objective: Diagnose a patient with smallpox.

Smallpox (variola) infection is the most likely diagnosis in this patient. Smallpox was once a significant worldwide cause of morbidity and mortality but was declared eradicated by the World Health Organization in 1980. Routine active vaccination against this viral illness ended more than 35 years ago. However, owing to its highly contagious nature, ability to cause illness and death, and a population largely nonimmune to infection, smallpox has gained a position on the category A list of potential bioterrorism agents. Because natural infection no longer occurs and most physicians are unfamiliar with the clinical presentation of smallpox, a high level of suspicion must be maintained for the possibility of infection in persons at potential risk, such as this patient with recent travel to an area where bioterrorism agents might be used. An incubation period of 10 to 14 days precedes clinical infection; patients are not contagious during that time. Most infected persons present with a prodromal phase characterized by fever, back pain, headache, vomiting, and pharyngitis. The rash begins as small red dots on the pharyngeal and buccal mucosa, at which time patients become contagious. The lesions then spread in centrifugal fashion to the hands and face, followed by the arms, legs, and feet. Classically, the rash of smallpox progresses in synchronous fashion, from macules to papules to vesicles and pustules before crusting over. Patients remain contagious until all crusts are shed.

Measles, or rubeola, is characterized by fever, malaise, and prominent upper respiratory infection manifestations consisting of the classic triad of conjunctivitis, cough, and coryza. Generally, the exanthem begins 2 to 4 days later, often with small, whitish spots on the buccal mucosa (Koplik spots), followed by a morbilliform rash on the face and neck, which eventually spreads to the extremities. Unlike the rash of smallpox, these lesions typically blanch and do not become vesicular. Additionally, universal measles vaccination has resulted in almost complete elimination of this childhood disease; therefore, if this patient had been immunized, it would make measles infection much less likely.

Rickettsial pox, caused by *Rickettsia akari*, occurs following the bite of a mite found on a reservoir mouse. A papular lesion initially forms at the site of inoculation, later becoming vesicular before eventually forming an eschar and then healing. Occasionally, the rash may become more generalized but can be differentiated from that seen with smallpox by its asynchronous mode of development. Fever and muscle aches accompany the skin lesion.

Chickenpox (varicella) is the viral infection most resembling smallpox, but clearly differs by fact that the rash is mostly localized to the trunk and spreads centripetally to the periphery of the body. Additionally, varicella lesions can be found in various stages on the same body area at any one time and rarely involve the palms and soles.

KEY POINT

- The rash of smallpox begins as small red dots on the pharyngeal and buccal mucosa with centrifugal spreading to the hands and face, followed by the arms, legs, and feet; the rash progresses in synchronous fashion, from macules to papules to vesicles and pustules before crusting over.

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Christian MD. Biowarfare and bioterrorism. Crit Care Clin. 2013 Jul;29(3):717-56. [PMID: 23830660]

Item 68 Answer: B

Educational Objective: Identify acute HIV infection as a cause of aseptic meningitis.

An HIV antigen/antibody combination immunoassay would be most likely to confirm the diagnosis of meningitis due to acute HIV infection in this patient. Acute HIV infection, clinically known as acute retroviral syndrome, is frequently associated with the clinical findings seen in this patient, including fever, lymphadenopathy, pharyngitis, myalgias and arthralgias, and a generalized maculopapular rash. Neurologic findings are also common, with headache occurring in one third of patients and meningitis in a smaller percentage.

Polymerase chain reaction of the cerebrospinal fluid (CSF) is used to test for enterovirus infection. Although enterovirus infections can produce aseptic meningitis, the presence of other findings, such as rash and pharyngitis and the lack of gastrointestinal symptoms characteristic of enterovirus infections, makes this diagnosis less likely than acute HIV infection.

This patient does not have a clear exposure history suggesting Lyme disease, and his clinical presentation, including the lack of the characteristic erythema migrans rash associated with *Borrelia burgdorferi* infection, makes this a less likely diagnosis.

This patient does not have parotitis or orchitis or other findings consistent with acute mumps infection. Also, given

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CONT. his age and the likelihood that he received a primary immunization series against mumps infection as a child, it would be unlikely for him to develop acute mumps infection causing aseptic meningitis in adulthood. Aseptic meningitis can be seen with mumps infection, although the CSF profile typically has a low glucose level.

KEY POINT

- Because acute HIV infection can cause aseptic meningitis, patients with meningitis and clinical signs and symptoms of HIV infection—such as pharyngitis, rash, and lymphadenopathy—should undergo testing by nucleic acid amplification.

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Item 69 Answer: A

Educational Objective: Diagnose acute osteomyelitis with imaging studies.

This patient has focal signs and symptoms of an acute bacterial skin and skin-structure infection or osteomyelitis and should undergo contrast-enhanced CT. Physical findings and laboratory data often cannot distinguish soft tissue from bone infection in the acute setting; therefore, imaging studies are heavily relied on in making the diagnosis. Plain radiographs are often not sufficiently sensitive to detect any bony abnormality early on in cases of acute osteomyelitis. MRI would be the imaging modality of choice for evaluating acute or chronic osteomyelitis. However, this patient is unable to undergo MRI because of his metallic implant. CT is helpful in evaluating bone anatomy and delineating the adjacent soft tissues and is the next best choice when MRI with contrast is contraindicated.

Tagged leukocyte nuclear scanning has a relatively high sensitivity for detecting bone infection but is limited by diminished specificity in clinical situations when alternative reasons for accumulation of the radionuclide tracer at the suspected site exist, such as trauma, recent surgery, malignancy, and degenerative bone or joint disease. This is particularly true in assessment of small bones, such as in the feet.

Three-phase nuclear bone scanning carries similar specificity limitations as tagged leukocyte nuclear scanning. However, a negative test result is very good evidence of no bone infection.

KEY POINT

- Contrast-enhanced CT is the next best choice when MRI with contrast, the study of choice in evaluating for acute or chronic osteomyelitis, is contraindicated.

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Lindbloom BJ, James ER, McGarvey WC. Osteomyelitis of the foot and ankle: diagnosis, epidemiology, and treatment. Foot Ankle Clin. 2014 Sep;19(3):569-88. [PMID: 25129362]

Item 70 Answer: A

Educational Objective: Diagnose *Mycobacterium fortuitum* skin infection.

This patient has *Mycobacterium fortuitum*–associated skin infection. Nontuberculous mycobacteria can colonize salon water, and *M. fortuitum* furunculosis has been well described in patients who obtain pedicures at nail salons that use contaminated whirlpool footbaths. Recent leg shaving with a razor increases the risk for these infections, likely owing to resultant skin nicking. The distal lower-extremity skin lesions, which usually arise 3 to 4 weeks after inoculation of the organism, appear in areas that have been exposed to spa water. Initially papular, these progress to a boil before ulcerating. The fast growth of the organism in culture (<7 days) is consistent with rapidly growing mycobacteria, such as *M. fortuitum*, *Mycobacterium chelonae*, or *Mycobacterium abscessus*.

Mycobacterium gordonae, *Mycobacterium kansasii*, and *Mycobacterium marinum* are slowly growing bacteria (that is, growth on solid media requires more than 7 days and usually 2 to 4 weeks). *M. gordonae* is a ubiquitous organism that rarely causes infection in immunocompetent hosts. Isolation of the organism in patients who are not immunosuppressed usually reflects colonization or contamination.

An environmental pathogen, *M. kansasii* typically causes a lung infection that mimics tuberculosis. Risk factors include COPD, HIV, alcohol abuse, exogenous immunosuppression, and cancer. Skin infection is uncommon and usually occurs in immunosuppressed patients with disseminated disease.

M. marinum can cause trauma-associated skin infection after exposure to fresh or salt water, including fish tanks and swimming pools. Initially papular before ulcerating, skin lesions are sometimes referred to as "fish tank granuloma." The rapid growth of the culture from this patient's lesions (<7 days) makes *M. marinum* unlikely.

KEY POINT

- *Mycobacterium fortuitum* furunculosis is a well-described skin infection in patients who obtain pedicures at nail salons that use contaminated whirlpool footbaths.

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Item 71 Answer: B

Educational Objective: Provide empiric antimicrobial therapy with meropenem and vancomycin for a patient with nosocomial bacterial meningitis.

This patient should begin empiric antimicrobial therapy with intravenous meropenem and vancomycin. He developed

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fever, nuchal rigidity, and altered mental status after a neurosurgical intervention, and analysis of the cerebrospinal fluid is consistent with bacterial meningitis following an invasive central nervous system (CNS) surgical procedure. In the setting of nosocomial meningitis, empiric antimicrobial therapy must cover a broad spectrum of pathogens, including gram-negative organisms (including *Pseudomonas aeruginosa*, *Acinetobacter* species, and Enterobacteriaceae) and *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]). Meropenem, a monobactam, is a broad-spectrum, bactericidal β-lactam with excellent coverage of gram-positive and gram-negative organisms that effectively penetrates the CNS, making it an excellent agent for empiric treatment of nosocomial meningitis. Vancomycin is necessary to provide coverage for possible β-lactam gram-positive organisms, including MRSA. Therefore, the combination of meropenem and vancomycin is the most appropriate antibiotic regimen to cover the potential causative pathogens in this patient.

Because the combination of vancomycin and ceftriaxone, with or without ampicillin, would not provide adequate coverage for *P. aeruginosa*, this regimen would not be the most appropriate treatment choice in this patient.

Moxifloxacin may cover appropriate gram-negative and gram-positive organisms; however, fluoroquinolones have not been well studied for use in bacterial meningitis and are generally reserved for patients with an allergy to β-lactam antibiotics. Fluoroquinolones also do not provide empiric coverage for MRSA.

KEY POINT

- Empiric antimicrobial therapy for nosocomial meningitis must cover a broad spectrum of pathogens, including gram-negative organisms and *Staphylococcus aureus*, particularly methicillin-resistant *S. aureus*.

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van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. N Engl J Med. 2010 Jan 14;362(2):146-54. [PMID: 20071704]

Item 72 Answer: C

Educational Objective: Manage initiation of treatment for a patient with newly diagnosed HIV infection.

The most appropriate next step in management is to defer initiation of antiretroviral therapy (ART) or other HIV-associated treatment pending further discussion of this patient's diagnosis and its management. Although ART initiation is recommended in all patients regardless of CD4 cell count and there are public health benefits to early treatment to reduce transmission of infection, this patient raises several concerns for possible poor adherence to therapy and the likelihood of suboptimal treatment. Adherence to HIV treatment may be influenced by numerous factors, including behavioral (denial, nondisclosure of HIV status, fear of stigma), psychosocial (mental illness or low levels of social support), and structural (poverty, homelessness, inconsistent access to medications) barriers; low health literacy; active substance use; and age (young adults have increased difficulty with adherence). It is important for patients with any of these risk factors to discuss their disease and the goals of therapy to optimize the chance for adequate adherence to treatment. Therefore, the most prudent strategy is to take additional time for counseling and education to prepare this patient for success in adhering to ART and other HIV treatments. Because his CD4 cell count is still high and viral load is low, his risk for rapid progression of disease is low, allowing additional time to accomplish this.

The patient's CD4 cell count is not less than 200/μL and is unlikely to decrease that low in the near future considering his high CD4 cell count now and low level of viral activity. Therefore, providing *Pneumocystis jirovecii* prophylaxis with trimethoprim-sulfamethoxazole before initiating ART is unnecessary.

Because of the concerns for adherence with this patient, initiation of any ART is best delayed until the chances for medication adherence are improved. Once that is accomplished, however, it would be inappropriate to wait for an arbitrary CD4 count to begin therapy. There are benefits to initiating ART early, in terms of both improving the patient's health and reducing potential transmission to others.

KEY POINT

- For patients with high CD4 cell counts and low viral loads, it is safe to defer antiretroviral therapy until chances for medication adherence are improved.

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Item 73 Answer: E

Educational Objective: Manage asymptomatic candiduria.

This patient has asymptomatic candiduria, which requires no antifungal therapy. Candiduria is a common finding in patients in the ICU. *Candida albicans* is the most common colonizing and infecting species, and most strains are fluconazole susceptible. The presence of candiduria may represent a contaminated urine sample, colonization of the bladder or catheter, upper or lower urinary tract infection (UTI), or a manifestation of candidemia rather than true UTI. In patients who have candiduria and an indwelling urinary catheter, the catheter should be removed, if possible, and a urine sample obtained several days later to assess whether the candiduria has resolved. If the catheter cannot be removed, it should be replaced and a urine sample collected through the new catheter. Most patients with candiduria are asymptomatic, and asymptomatic candiduria rarely results

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in candidemia. Asymptomatic candiduria should not be treated with antifungal agents except in certain populations at risk for candidemia, including patients who are neutropenic or who are undergoing urinary tract procedures. Patients who have symptoms of UTI should be treated. If treatment becomes necessary, oral fluconazole is the drug of choice.

Amphotericin B and flucytosine are less desirable alternatives to fluconazole. Local instillation of amphotericin B into the bladder is effective in eliminating the organism, but the effect is short lived and guidelines on the management of urinary tract candidiasis do not recommend it except for a few situations, including as adjunctive treatment for *Candida glabrata* or *Candida krusei* cystitis.

The echinocandins (micafungin, anidulafungin, and caspofungin), voriconazole, and posaconazole are not recommended for treatment of *Candida* UTI because very little active drug is found in the urine.

KEY POINT

- Patients with asymptomatic candiduria require no antifungal therapy, except in certain populations at risk for candidemia; however, if an indwelling catheter is present, it should be removed if possible.

Bibliography

Revankar SG, Hasan MS, Revankar VS, Sobel JD. Long-term follow-up of patients with candiduria. Eur J Clin Microbiol Infect Dis. 2011 Feb;30(2):137-40. [PMID: 20857164]

Item 74 Answer: C

Educational Objective: Monitor a patient receiving outpatient parenteral nafcillin therapy.

Serum creatinine level, complete blood count, and liver enzyme tests should be monitored weekly in this patient. Outpatient parenteral antimicrobial therapy (OPAT) is becoming more common, with some patients receiving therapy for extended periods (≥6 weeks for osteomyelitis). Outpatient monitoring for adverse drug effects and other potential complications resulting from intravenous administration (such as intravenous catheter infection) are part of an OPAT management plan. The plan should be confirmed with all physicians involved in the care of the patient. The monitoring schedule for adverse drug effects depends on the agent being used; the most common antibiotics used for OPAT require weekly laboratory monitoring. For nafcillin, this includes monitoring for bone marrow suppression with a complete blood count (CBC) and liver enzyme tests. Kidney function testing with a serum creatinine level should also be performed weekly, because the dosage of nafcillin may require adjustment if significant deterioration of kidney function occurs or if the patient already has kidney injury and it improves while receiving therapy. Nafcillin does not affect potassium levels, so no monitoring is needed. Monitoring of oxacillin and carbapenems is similar to that of nafcillin, and monitoring of other β-lactam antibiotics is similar to that of nafcillin except that liver enzyme testing is not necessary; antipseudomonal penicillins necessitate checking the serum potassium level weekly.

KEY POINT

- Patients undergoing outpatient parenteral antimicrobial therapy must undergo weekly monitoring for adverse drug effects.

Bibliography

Tice AD, Relm SJ, Dalovision JR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy. Clin Infect Dis. 2004;38:1651-1672. [PMID: 15227610]

Item 75 Answer: D

Educational Objective: Treat a patient with potential drug-resistant *Streptococcus pneumoniae* community-acquired pneumonia with appropriate antibiotic therapy.

This patient should begin empiric antibiotic therapy with moxifloxacin. He has community-acquired pneumonia (CAP) confirmed by chest radiograph. Because he is lacking other risk factors or associated comorbid conditions that would make other pathogens more likely, his CAP infection is probably caused by *Streptococcus pneumoniae*. The possibility of drug-resistant *S. pneumoniae* (DRSP) should be assessed because it will determine which agents are appropriate for empiric treatment. Factors that increase the risk for DRSP include age greater than 65 years, alcoholism, immunosuppression, certain medical comorbidities (COPD, chronic liver or kidney disease, cancer, diabetes, functional or anatomic asplenia, chronic heart disease), and recent (within the past 3-6 months) antimicrobial therapy with a β-lactam, macrolide, or fluoroquinolone antibiotic. Recent β-lactam use is associated with an increased risk for β-lactam resistance, while recent use of macrolides or fluoroquinolones is associated with pneumococcal resistance to the same class of antibiotic. Because this patient received treatment with a β-lactam within the past 3 months, he is at increased risk for DRSP. Recommended empiric therapy for patients with possible DRSP includes a respiratory fluoroquinolone (such as moxifloxacin) or a β-lactam plus a macrolide or doxycycline; however, because he was recently treated with a β-lactam antibiotic, treatment with a respiratory fluoroquinolone would be preferable.

Combination therapy with a β-lactam plus a macrolide or doxycycline is recommended, rather than monotherapy with a β-lactam, to provide coverage for atypical pathogens (such as *Mycoplasma* species), which are common causes of CAP. However, this therapy is not optimal for this patient with recent β-lactam use.

Patients with CAP who are otherwise healthy and without risk factors for DRSP are eligible for monotherapy with a macrolide (such as azithromycin) or doxycycline. However, this patient's recent use of antibiotics and subsequent increased risk for DRSP make either of these agents an inappropriate therapeutic choice.

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KEY POINT

- Patients with uncomplicated community-acquired pneumonia who are suspected of having infection with drug-resistant *Streptococcus pneumoniae* should be treated empirically with a respiratory fluoroquinolone or a β-lactam plus a macrolide or doxycycline.

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Item 76 Answer: A

Educational Objective: Diagnose a tick-borne coinfection.

This patient most likely has coinfection with *Anaplasma phagocytophilum*, a bacterium spread by the *Ixodes* tick (the same vector associated with Lyme disease). The constellation of fever, leukopenia, thrombocytopenia, and mild elevation in liver enzymes in a patient with recent Lyme disease is highly suggestive of anaplasmosis. Among patients with erythema migrans, up to 10% are coinfected with anaplasmosis. Although amoxicillin is active against Lyme disease, it is not effective therapy for *A. phagocytophila*. Doxycycline would have offered the advantage of treating the Lyme disease and an incubating asymptomatic infection with *Anaplasma*. Recrudescent symptoms of Lyme disease would not be expected in a patient receiving treatment, and patients with erythema migrans rarely develop later-stage disease after completing therapy.

Babesia microti is a parasite also transmitted by the *Ixodes* tick. Patients with symptomatic babesiosis often present with fever and signs of hemolysis, including jaundice, scleral icterus, and splenomegaly. This patient has leukopenia, thrombocytopenia, and a normal hematocrit and haptoglobin level, making babesiosis unlikely.

Powassan virus is also spread by *Ixodes* ticks but causes meningoencephalitis. No human coinfection has been documented with both Lyme disease and Powassan virus infection.

Serial episodes of erythema migrans can occur, and, until recently, it has been debated whether a second episode of erythema migrans represents relapse of inadequately treated disease. Genotyping of sequential erythema migrans lesions has shown that these cases are caused by a genetically distinct strain of *Borrelia* and represent reinfection rather than latent infection.

KEY POINT

- Fever, leukopenia, and thrombocytopenia in a patient undergoing treatment for Lyme disease suggest coinfection with *Anaplasma phagocytophilum*.

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Item 77 Answer: B

Educational Objective: Manage cystitis in an older woman.

This older adult patient most likely has cystitis and should begin nitrofurantoin therapy. Although the most common symptoms of cystitis in premenopausal women are dysuria, frequency, urgency, and suprapubic discomfort, postmenopausal women with cystitis may experience incontinence. Fever is unusual. The urine dipstick reveals pyuria and bacteriuria with positivity for leukocyte esterase and nitrites, respectively. With her symptoms and positive results on urine dipstick, cystitis is highly likely. Urinary tract infection (UTI) is one of the most commonly diagnosed infections in older adults, and *Escherichia coli* is the most frequently isolated organism. In one study, *E. coli* accounted for more than 80% of UTIs in this population. The treatment of cystitis in older adults who do not have significant concurrent medical illnesses is the same as that used in younger patients. This patient should begin nitrofurantoin, 100 mg twice daily for 5 days. Nitrofurantoin should not be used in patients whose creatinine clearance is less than 50 mL/min. Trimethoprim-sulfamethoxazole, one double-strength tablet twice daily for 3 days, is first-line therapy in the absence of a sulfa allergy and if local *E. coli* resistance to trimethoprim-sulfamethoxazole is less than 20%. Most women with lower UTI have only a superficial mucosal infection and can be cured with short courses of therapy. The advantages of short-course therapy include better adherence, lower cost, fewer adverse effects, and less selective pressure for the emergence of resistant organisms. Three days of therapy is considered superior to single-dose therapy. Nitrofurantoin for 5 days demonstrates better efficacy than a 3-day course of this medication. Treatment is indicated because this patient is symptomatic. If she were asymptomatic, treatment would not be indicated.

Fluoroquinolones, such as levofloxacin and ciprofloxacin, are considered second-line therapy because of their higher cost and the concern for emergence of resistance with widespread use.

A urine culture is indicated if pyelonephritis, complicated UTI, recurrent UTI, multiple antibiotic allergies, or a resistant organism is suspected; in pregnant women with asymptomatic bacteriuria; and for patients undergoing urologic procedures. Urine cultures are not generally indicated to diagnose cystitis.

KEY POINT

- Treatment is indicated in all patients with symptomatic cystitis, and nitrofurantoin for 5 days is the regimen of choice in patients allergic to sulfa drugs.

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Item 78 Answer: B

Educational Objective: Treat suspected methicillin-resistant *Staphylococcus aureus* cellulitis and bacteremia in a patient who is intolerant of vancomycin.

The most appropriate treatment for this patient is daptomycin. He has a history of methicillin-resistant *Staphylococcus aureus* (MRSA) skin infections and now presents with injection drug use–associated cellulitis and bacteremia with gram-positive cocci in clusters, presumably MRSA. Because of his history of vancomycin intolerance, daptomycin, an alternative to vancomycin for the empiric treatment of MRSA-associated bacteremia and infective endocarditis, should be given. Daptomycin is a lipopeptide-type antibiotic and is bactericidal against MRSA. He will require echocardiography and repeat blood cultures after intravenous antibiotics have been initiated. Additionally, patients receiving daptomycin should be assessed regularly for clinical or laboratory signs of muscle weakness or pain, particularly in those receiving statin-based lipid-lowering agents or with kidney disease. Intravenous antibiotics must be administered for at least 2 weeks for *S. aureus* bacteremia.

Ceftriaxone could be used to treat nonpurulent cellulitis because β-hemolytic streptococci are the likely cause. However, it does not provide effective coverage against MRSA.

Imipenem, a broad-spectrum β-lactam antibiotic with activity against many aerobic and anaerobic bacteria, does not provide effective coverage against MRSA.

Additionally, *S. aureus* that may be resistant to methicillin also may be resistant to oxacillin, nafcillin, and other β-lactam agents, including ceftriaxone and imipenem. Nafcillin or oxacillin would be appropriate choices if the infection were found to be caused by methicillin-susceptible *S. aureus*. Until that time, however, empiric therapy should reliably target MRSA. The only β-lactam with reliable activity against MRSA is ceftaroline, a fifth-generation cephalosporin approved by the FDA for treatment of skin infections and community-acquired bacterial pneumonia.

KEY POINT

- Daptomycin is an effective alternative to vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* cellulitis and bacteremia in patients unable to take vancomycin.

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Item 79 Answer: B

Educational Objective: Treat urethritis due to *Chlamydia trachomatis* with azithromycin.

This patient has urethritis due to *Chlamydia trachomatis* and should be treated with azithromycin. Azithromycin, a macrolide antibiotic, is the preferred treatment of urethritis and cervicitis due to *C. trachomatis* because it can be given as single-dose therapy. The patient should be screened for other sexually transmitted infections and encouraged to refer his sexual partner for evaluation and treatment. Doxycycline is also effective against chlamydia; however, a 7-day regimen is required. The single-dose therapy of azithromycin is preferred to enhance adherence.

Penicillins have activity against *C. trachomatis* but have far lower cure rates than do azithromycin, doxycycline, or the fluoroquinolones ofloxacin or levofloxacin. Because of the lower cure rate, a test of cure is indicated when these agents are used.

Cefixime, an oral third-generation cephalosporin, has no activity against *C. trachomatis*, although it is an alternative for the treatment of *Neisseria gonorrhoeae* infections if ceftriaxone is unavailable. It would provide adequate antimicrobial coverage for treatment of urinary tract infection; however, this patient's colony count of *Escherichia coli* in the urine culture is insignificant and does not warrant therapy.

Dual treatment with ceftriaxone plus azithromycin for *N. gonorrhoeae* and *C. trachomatis* would be appropriate if empiric therapy were given before availability of the nucleic acid amplification test results. If only *N. gonorrhoeae* is diagnosed, dual therapy with ceftriaxone and azithromycin is recommended because of the high incidence of concomitant infection with *C. trachomatis*. Dual therapy also offers potential increased efficacy for treating gonorrhea in men, considering increasing minimum inhibitor concentrations for cephalosporins among gonorrhea isolates.

KEY POINT

- The preferred therapy for urethritis due to *Chlamydia trachomatis* is single-dose azithromycin for optimum adherence; alternative treatments include longer courses of doxycycline or the fluoroquinolones ofloxacin or levofloxacin.

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Item 80 Answer: B

Educational Objective: Treat a patient with acute, uncomplicated pyelonephritis.

This patient should begin treatment with ciprofloxacin. She has signs and symptoms most consistent with acute pyelonephritis. Cystitis is infection of the bladder and lower

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urinary tract and commonly presents with dysuria, frequency, and urgency. However, the presence of fever or other systemic symptoms (chills, nausea, vomiting) and back or flank pain are more consistent with pyelonephritis, or kidney infection. Lower urinary tract symptoms may antedate fever and upper urinary tract symptoms by approximately 2 days. Most cases of pyelonephritis may be managed in the ambulatory setting; indications for hospitalization include hemodynamic instability, inability to tolerate oral medications, host factors such as pregnancy or presence of kidney stones or other obstructions, presence of comorbidities, and an unstable social situation that may compromise adherence or follow-up. A urine culture and susceptibility testing should always be performed in patients with suspected pyelonephritis to confirm the diagnosis and guide therapy. However, empiric treatment should be provided pending culture results, with initial therapy modified appropriately when the infecting organism is identified and susceptibilities are known. A fluoroquinolone is the preferred agent for empiric therapy when resistance in the community does not exceed 10%. If fluoroquinolone resistance exceeds 10%, an initial, one-time intravenous dose of a long-acting agent such as ceftriaxone or a 24-hour dose of an aminoglycoside should be administered. A 7-day course of a fluoroquinolone is as effective as a 14-day course in women. If high-dose levofloxacin (750 mg) is administered, the duration is 5 days. If once-daily oral ciprofloxacin (1000 mg extended release) is administered, it should be given for 7 days.

Ampicillin with gentamicin is an appropriate regimen for treating acute pyelonephritis in patients requiring hospitalization. Other choices for hospitalized patients include therapy with a fluoroquinolone, an extended-spectrum cephalosporin, an extended-spectrum penicillin, or a carbapenem such as ertapenem. However, despite this patient's systemic findings, she is clinically stable and can undergo outpatient therapy. Therefore, intravenous, broad-spectrum antibiotic therapy with either ampicillin with gentamicin or ertapenem is not indicated.

Nitrofurantoin or fosfomycin are indicated for treatment of uncomplicated cystitis and are not effective for pyelonephritis because they do not achieve adequate tissue levels in the kidney parenchyma. Therefore, they are not appropriate for patients with pyelonephritis.

KEY POINT

- Patients with acute pyelonephritis who do not require hospitalization should begin empiric treatment with an oral fluoroquinolone, such as ciprofloxacin.

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Item 81 Answer: A

Educational Objective: Diagnose chronic osteomyelitis with histopathologic and microbiologic studies.

The most appropriate management for this patient is bone biopsy and culture. He has classic signs of long-bone osteomyelitis related to his previous fracture. The presence of chronic or intermittent drainage from a demonstrable sinus tract overlying an area of previous trauma, along with consistent clinical findings and radiographic evidence of a bone sequestra (dead bone) or involucrum (new bone formation), are hallmarks of chronic osteomyelitis. Other than local signs of ongoing infection, patients with chronic osteomyelitis rarely manifest systemic symptoms. Laboratory studies are generally not diagnostically helpful because leukocyte counts are almost always normal and inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), although supportive of chronic infection when elevated, are very nonspecific for focal infection. Bone biopsy for histopathologic assessment and full microbiologic studies is important for diagnosing osteomyelitis, excluding other entities (such as neoplasm), and isolating the causative pathogen(s).

With the exception of *Staphylococcus aureus*, microorganisms from the surface of wounds or draining sinus tracts rarely correlate with cultures obtained from bone specimens and should not be acted upon. However, when *S. aureus* is isolated, it may be considered the causative pathogen, and therapy may be initiated without bone biopsy when the clinical picture is consistent with osteomyelitis. This patient's bone infection likely resulted from the introduction of bacteria at the time of his military injury. Although osteomyelitis resulting from hematogenous entrance of bacteria most often involves a single organism (such as *S. aureus*), infection that arises from a contiguous focus of infection or open trauma may comprise a multitude of potential pathogens alone or in combination.

Initiating empiric antimicrobial therapy without an attempt at confirming a histologic and microbiologic diagnosis is strongly discouraged and best delayed until more information is available to best select specific antimicrobial agent(s), route of administration, and duration of therapy.

MRI is the most sensitive and specific imaging modality for diagnosing osteomyelitis but is unnecessary in the presence of a chronic draining sinus. The demonstration of microorganisms coupled with characteristic features of osteomyelitis eliminates the need for MRI confirmation of the diagnosis.

KEY POINT

- Histopathology and full microbiologic studies are important for diagnosing osteomyelitis and isolating the causative pathogen in order to direct appropriate treatment.

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Item 82 Answer: D

Educational Objective: Interpret results of serologic testing for Lyme disease.

This patient has inflammatory arthritis and tests negative for *Borrelia burgdorferi*, so she requires no additional evaluation or treatment for Lyme disease. Arthritis is a late manifestation of Lyme disease, typically occurring months to years after infection. This typically presents as inflammatory arthritis, involving a single or limited number of large joints, with the knee most commonly affected. Even without treatment, symptoms wax and wane, with spontaneous remission of inflammation often followed several months later by involvement of the same or a different joint. Because the clinical presentation of Lyme arthritis is nonspecific, laboratory confirmation of infection is required using a two-tiered serologic testing strategy. The initial test, an enzyme immunoassay (EIA), is exquisitely sensitive but not specific. If the result of this test is negative, no further evaluation is necessary. When the EIA finding is positive or equivocal, a more specific Western blot test is recommended for confirmation. A negative Western blot result is interpreted as a negative serologic result. A positive result must be further interpreted with respect to acuity of symptoms. When symptoms are present for less than 1 month, an isolated positive IgM Western blot result may be diagnostic of acute infection. However, symptoms present for more than 1 month provide ample time for IgG seroconversion. Many laboratories perform the IgM and IgG Western blots reflexively on any sample with a positive EIA finding. When this is the case, a positive Western blot IgM result without associated positive IgG result in a patient with more than 30 days of symptoms should be interpreted as a false-positive result. Therefore, results of Lyme serologic testing for this patient would be interpreted as negative, and the diagnosis of Lyme arthritis excluded. Further evaluation or treatment for Lyme disease is not necessary at this time, and other causes for this patient's inflammatory arthritis should be evaluated.

Detection of *Borrelia* bacteria in synovial fluid or tissue is not necessary to diagnose Lyme arthritis and would be indicated only in selected scenarios, such as new-onset arthritis in a patient previously known to be seropositive for Lyme disease.

If the Western blot IgG had returned positive, the recommended treatment would be a 28-day course of doxycycline or amoxicillin. Parenteral therapy with ceftriaxone would be indicated for patients with Lyme arthritis who do not experience a clinical response to oral antibiotics.

KEY POINT

- Lyme arthritis is excluded if symptoms have been present for longer than 1 month and Western blot IgG result is negative; there is no need for further evaluation or treatment for Lyme disease in these patients.

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Item 83 Answer: C

Educational Objective: Diagnose *Vibrio* gastroenteritis.

This patient's dysentery is most likely caused by *Vibrio parahaemolyticus* gastrointestinal infection. Bloody stools, fever, and vomiting commonly occur with *Vibrio* infection. The fact that other diners developed a gastrointestinal illness suggests a common source associated with the shared meal. *Vibrio* species are widespread in salt or brackish water, and human infections are associated with ingestion of contaminated seafood, particularly shellfish. In a large case series of *V. parahaemolyticus* infections reported to the U.S. Centers for Disease Control and Prevention, bloody diarrhea was noted in 29% of cases. Chronic liver disease is a risk factor for severe infection with this organism, and sepsis is a common and often fatal complication in this population. *Vibrio* species do not grow well on traditional stool culture media, so when this diagnosis is being considered, the laboratory should be notified to allow plating onto saline-enriched agar.

Clostridium difficile colitis has a similar presentation with diarrhea, fever, and abdominal pain and cramping, but gross blood in the stool is uncommon. *C. difficile* infection is not a foodborne illness, and therefore a clustering of cases following a shared meal would not be expected.

Norovirus is the leading cause of foodborne outbreaks in the United States, with spread through fecal-oral contamination. This virus causes a watery stool, often with associated vomiting; however, fever is uncommon and grossly bloody stools would exclude this diagnosis.

Yersiniosis typically occurs following ingestion of contaminated food or water. Outbreaks of *Yersinia enterocolitica* have been traced to consumption of chitterlings (pork intestines). *Yersinia* gastroenteritis is clinically indistinguishable from other forms of inflammatory diarrhea and is most commonly identified in young children. It does not cause grossly bloody stools. In some cases, diarrhea may be absent with bacteria localizing to lymphoid tissue in Peyer patches and associated mesenteric lymph nodes. This presentation may mimic appendicitis clinically.

KEY POINT

- Gastrointestinal infections caused by *Vibrio* species are associated with ingestion of contaminated seafood, particularly shellfish, and can be severe in patients with liver dysfunction.

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Item 84 Answer: E

Educational Objective: Manage selective IgA deficiency.

Clinical follow-up without directed treatment is indicated for this patient. She has selective IgA deficiency, which has no specific therapy except for antibiotic treatment as needed for those with recurrent sinopulmonary infections. Selective IgA deficiency is the most common of the congenital immune defects, with an incidence of about 1:500. The disease is usually sporadic, but autosomal dominant and autosomal recessive inheritance is found. Most people with IgA deficiency are asymptomatic, although the most common clinical manifestation is sinopulmonary infection, which is often the reason quantitative serum immunoglobulin levels are obtained. IgA deficiency is defined as a serum IgA level less than 7 mg/dL (0.07 g/L). A less common but potentially severe finding in selective IgA deficiency is anaphylaxis with blood product transfusion. IgA deficiency is also frequently associated with autoimmune illnesses, including systemic lupus erythematosus, rheumatoid arthritis, hemolytic anemia, and immune thrombocytopenic purpura. Additional manifestations include atopic eczema, asthma, urticaria, and a variety of other allergic disorders. Gastrointestinal disorders, including infection with *Giardia lamblia*, may also occur. Despite these multiple potential clinical consequences associated with IgA deficiency, the indicated treatment approach is primarily preventive and supportive.

Patients with terminal complement deficiencies are at higher risk for meningococcal disease, but those with immunoglobulin deficiency are not. Therefore, the meningococcal conjugate vaccine is not indicated specifically for IgA deficiency.

Secreted IgA is produced and generally acts locally. Therefore, administration of intravenous concentrates of IgA would not achieve adequate levels in mucosal secretions, so it would not be helpful in this patient.

IgA deficiency is selective, occurring without deficits in other immunoglobulins in these patients. Therefore, administration of intravenous immune globulin would not be indicated in this patient. Intravenous immune globulin is used in patients with severe deficiencies in most immunoglobulins, as is seen in X-linked agammaglobulinemia and common variable immunodeficiency.

Stem cell or bone marrow transplantation is appropriate treatment for severe combined immune deficiency syndrome, but not selective IgA deficiency. Selective IgA deficiency is usually asymptomatic or has mild symptoms that are easily treated or managed; therefore, the potential risks and long-term immunosuppression associated with stem or bone marrow transplantation are greater than the potential benefits of this treatment for selective IgA deficiency.

KEY POINT

- Patients with selective IgA deficiency require no specific therapy except for preventive measures against known potential complications and as-needed antibiotic therapy for those with recurrent sinopulmonary infections.

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Item 85 Answer: A

Educational Objective: Treat a patient with early localized Lyme disease.

This patient has an enlarging erythematous skin lesion with central clearing suggestive of erythema migrans and should be prescribed doxycycline. Erythema migrans is the most common presentation of Lyme disease, seen in up to 80% of patients, although an initial heterogenous patch of erythroderma is more common than the classic target-like appearance. Erythema migrans is often the only manifestation of early localized Lyme disease because fevers or constitutional symptoms are uncommon at this stage. Treatment of early stage Lyme disease with doxycycline prevents progression to later-stage cardiac, neurologic, or rheumatologic complications in more than 90% of patients. Amoxicillin or cefuroxime axetil could be alternative options for the treatment of Lyme disease; however, these agents have not been evaluated for the treatment of southern tick-associated rash illness (STARI). STARI also presents as erythema migrans and can be identical to Lyme disease. Therefore, in a patient presenting with erythema migrans, treatment with an oral antibiotic active against localized Lyme disease and STARI, such as doxycycline, would be most appropriate.

Babesiosis is a parasitic disease that is spread by the same tick as Lyme disease but does not cause erythema migrans. Although coinfection with *Borrelia burgdorferi* can occur, serologic testing is not recommended in the absence of signs or symptoms, which include fever, jaundice, and scleral icterus. Lyme disease and human granulocytic anaplasmosis coinfection has also been reported; however, doxycycline is active against the bacterium causing this infection as well.

Laboratory testing for Lyme disease is insensitive at the early stage of infection, with less than 50% of patients having detectable titers to *B. burgdorferi*. In addition, laboratory confirmation is not necessary when erythema migrans is present.

KEY POINT

- Early localized Lyme disease and southern tick-associated rash illness present with erythema migrans and are clinically indistinguishable; therefore, patients with erythema migrans should be treated with doxycycline, which is effective in both conditions.

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Item 86 Answer: C

Educational Objective: Identify the most common complication of *Escherichia coli* O157:H7 dysentery.

This patient with dysentery most likely has *Escherichia coli* infection and is at risk for hemolytic uremic syndrome (HUS). *E. coli* O157:H7, a Shiga toxin–producing *E. coli* (STEC) serotype, is the most common cause of acute bloody diarrhea in the United States. It differs from other causes of dysentery in that fever is distinctly uncommon. STEC organisms are widespread in the gastrointestinal tract of domesticated animals, particularly cattle, and cause disease through ingestion of contaminated food or, as in this case, unpasteurized milk. One of the most serious complications of STEC infection is the development of HUS, which occurs in 5% to 10% of cases, most frequently in children. HUS is a form of thrombotic microangiopathy characterized by fever, hemolytic anemia, consumptive thrombocytopenia, neurologic findings, and kidney failure. Antibiotic and antimotility therapies are both associated with increased risk for HUS and should not be prescribed when there is clinical concern for STEC gastrointestinal disease.

The other choices are complications associated with bacterial causes of dysentery, but unlike STEC infections, these are usually associated with fevers. Aortitis is an inflammation of the aortic wall and can potentially be caused by *Salmonella* infection, which has a propensity for causing endovascular infection, particularly when there is significant atherosclerosis or graft material. Guillain-Barré syndrome is a rare complication of *Campylobacter* infection, occurring in less than 1% of cases; however, up to 40% of cases of Guillain-Barré are triggered by an antecedent *Campylobacter* infection. Several strains of *Yersinia* cause infection of the mesenteric lymph nodes and can mimic acute appendicitis. Grossly bloody stools are uncommon with *Yersinia* infection. Reactive arthritis can occur following *Campylobacter*, *Shigella*, *Salmonella*, or *Yersinia* infections in patients who are positive for the HLA-B27 gene.

KEY POINT

- One of the most serious complications of *Escherichia coli* O157:H7 infection is hemolytic uremic syndrome, with this risk increased if antibiotics or antimotility therapy is administered.

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Item 87 Answer: B

Educational Objective: Manage an asymptomatic patient who has babesiosis.

This patient has asymptomatic babesiosis and should undergo repeat polymerase chain reaction (PCR) assay in 3 months. No treatment is indicated at this time, but the patient should be followed closely for clearance of the parasite. Babesiosis is a protozoal infection that is primarily spread through *Ixodes* ticks and is most commonly found among residents or travelers to the coastal northeastern United States. Following infection, the parasite lives inside erythrocytes. More than 150 cases of transmission have been documented through transfusion of blood products from asymptomatically infected donors. This probably significantly underestimates the true frequency of this route of transmission because up to 1% of donors from highly endemic regions are seropositive for *Babesia microti*. Microscopy using Giemsa or Wright staining on a thin blood smear will show trophozoites, appearing as ring forms inside erythrocytes. PCR is the most sensitive method for diagnosing infection, particularly when there is relatively low-level parasitemia, as is the case for asymptomatic infections. Although many *Babesia* infections resolve spontaneously, an asymptomatic infection that has persisted for more than 3 months after the initial diagnosis is an indication for treatment.

Patients with severe anemia and greater than 10% parasitemia may benefit from exchange transfusion, in which the patient's blood is removed by catheter and replaced with healthy donor blood, but would not be indicated in this patient with asymptomatic disease.

Symptomatic infection is an indication for treatment. Atovaquone combined with azithromycin is the recommended treatment for mild babesiosis. This regimen is equally effective as quinine plus clindamycin, with significantly fewer adverse effects. Severe disease is characterized by significant hemolysis and requires hospitalization for supportive care and monitoring. Quinine plus clindamycin is the preferred therapy for severe disease.

KEY POINT

- Patients diagnosed with babesiosis who are asymptomatic should undergo a repeat polymerase chain reaction assay in 3 months to detect parasite clearance but do not need treatment.

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Item 88 Answer: A

Educational Objective: Treat a hospitalized patient with pelvic inflammatory disease with antibiotics.

This patient has clinical evidence of pelvic inflammatory disease (PID) and should be treated with cefoxitin plus

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CONT.

doxycycline. Although the ultrasonographic findings excluded a tubo-ovarian abscess, nausea and vomiting and inability to tolerate an oral treatment regimen are indications for hospital admission and initial parenteral therapy. PID occurs primarily in sexually active women, with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* implicated in approximately two thirds of patients. However, PID is considered a polymicrobial infection that may also involve vaginal organisms, including anaerobes, enteric gram-negative rods, and streptococci. Additionally, organisms associated with bacterial vaginosis, such as *Gardnerella vaginalis*, may play a role. Therefore, antibiotic therapy with coverage directed to *C. trachomatis* and *N. gonorrhoeae* is essential, with broader-spectrum coverage to treat other potentially causative organisms. The antibiotic regimen of choice for patients who are hospitalized with PID is cefoxitin or cefotetan (second-generation cephalosporins) plus intravenous doxycycline.

Ceftriaxone plus azithromycin can be used in single-dose regimens for uncomplicated cervicitis, but this regimen is not recommended for treatment of PID. Ceftriaxone as a single-dose intramuscular injection plus a 14-day course of oral doxycycline (with or without metronidazole) can be used to treat PID in patients who do not have an indication for hospitalization. In this patient, symptoms of nausea and vomiting raise concern for the ability to tolerate oral therapy and are an indication for hospitalization. Ciprofloxacin is no longer recommended for an infection requiring coverage for *N. gonorrhoeae* because fluoroquinolone resistance is common with this organism.

Piperacillin-tazobactam does not provide coverage for *C. trachomatis* and would not be appropriate monotherapy in this patient. Additionally, although PID is considered a polymicrobial infection, and piperacillin-tazobactam would provide coverage for Enterobacteriaceae and anaerobes, it is also an antipseudomonal agent and is unnecessarily broad spectrum for this patient.

KEY POINT

- Parenteral therapy for pelvic inflammatory disease in a hospitalized patient consists of cefoxitin or cefotetan plus doxycycline.

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Item 89 Answer: D

Educational Objective: Treat critically ill patients with oral antimicrobial agents.

The most appropriate treatment regimen for this patient is oral therapy with ciprofloxacin and metronidazole. Aerobic gram-negative and anaerobic organisms should be considered for empiric coverage in this patient with a community-acquired intra-abdominal abscess pending drainage and fluid Gram stain and culture results. Admission to an ICU or step-down unit does not require that the patient receive intravenous antimicrobial therapy. Oral antimicrobials can be used in critically ill patients who have an intact and functioning gastrointestinal tract (no vomiting, no ileus), if the type of infection being treated does not require intravenous antibiotics (infection involving the central nervous system, *Staphylococcus aureus* bacteremia, endocarditis, osteomyelitis), and if the oral agent(s) with the appropriate spectrum of activity and acceptable bioavailability for the infection being treated is available. This patient has an intact and functioning gastrointestinal tract and is a candidate for oral antimicrobial therapy. Ciprofloxacin and metronidazole have excellent bioavailability and tissue penetration (including abscesses) and provide the necessary spectrum of antimicrobial coverage for aerobic gram-negative and anaerobic bacteria.

Aztreonam provides aerobic gram-negative coverage, and vancomycin adds gram-positive coverage, but the combination does not provide the anaerobic coverage for this patient's empiric therapy.

The combination of vancomycin and clindamycin provides gram-positive and anaerobic coverage but no aerobic gram-negative coverage. Clindamycin has excellent bioavailability and should be considered for oral administration when it is the indicated antibiotic.

Although ampicillin and metronidazole are offered as an oral regimen, they do not provide adequate aerobic gram-negative coverage, including commonly resistant *Escherichia coli*.

KEY POINT

- Oral antimicrobial agents can be used in critically ill patients who have an intact and functioning gastrointestinal tract and infection with an organism that does not require intravenous therapy.

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Item 90 Answer: C

Educational Objective: Diagnose acute HIV-1 infection.

This patient should be informed that he has acute HIV-1 infection, and further baseline evaluation of new HIV infection with T-cell subset testing and other appropriate laboratory studies should be pursued. The antigen/antibody combination immunoassay is reactive, indicating the presence of HIV-1 or HIV-2 antibody or HIV p24 antigen. The result on a differentiation immunoassay for HIV-1 and HIV-2 antibodies is negative, suggesting that the initial immunoassay was detecting the presence of viral p24 protein. This is confirmed by the nucleic acid amplification test, which had strongly positive results for HIV RNA, indicating the presence of

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virus even though the patient did not yet have detectable antibodies. These results are most consistent with acute HIV infection presenting in the "window period" before development of a serologic response. His nonspecific febrile illness the previous week may have represented symptoms of acute HIV infection.

The rapid tests for HIV infection, such as a saliva assay, are convenient for patients but are based on detecting HIV antibodies. They would therefore be expected to yield negative or indeterminate results in this patient because he is presenting in the "window period" of acute infection before antibody development.

The Western blot test is no longer recommended for confirmatory HIV testing. Because this patient has early HIV infection, results of Western blot testing for HIV antibody would likely be negative or indeterminate anyway.

Repeating the HIV 1/HIV-2 antibody differentiation immunoassay at a later time is not necessary because acute HIV infection has been diagnosed on the basis of the high level of viral RNA. Antibody testing results will become positive within a few weeks to a few months, but it would not be appropriate to delay further management for HIV until that time.

KEY POINT

- Positive antigen/antibody immunoassay, negative antibody differentiation assay, and positive nucleic acid amplification test results are consistent results for patients presenting in the "window period" of acute HIV infection before development of a serologic response.

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Item 91 Answer: A

Educational Objective: Manage *Campylobacter* gastroenteritis.

This patient, who has spontaneous symptom resolution of *Campylobacter jejuni* infection, requires no further evaluation or treatment. Treatment of bacterial dysentery is controversial; most cases resolve spontaneously, but, in the case of *Salmonella* gastroenteritis, antibiotics may actually prolong bacterial shedding. However, when patients are at risk for extraintestinal complications because of advanced age or immunocompromise, or when symptoms are particularly severe, the benefits of empiric treatment outweigh the risks. For most causes of dysentery, fluoroquinolones, such as levofloxacin, are considered first-line therapy based on limited resistance to most bacterial agents. The exception is *Campylobacter*, which a recent study documented 14% fluoroquinolone resistance in domestically acquired infections and greater than 50% link to international travel. Consumption of undercooked poultry may raise suspicion for *Campylobacter* infection, but symptoms substantially overlap among the various agents causing dysentery; culture is required to identify the causative agent. Despite treatment with an antibiotic to which the organism was resistant, symptoms completely resolved by the time the culture results were finalized. This underscores the fact that in most cases of bacterial gastroenteritis, infection resolves spontaneously without therapy, and further evaluation or treatment is unnecessary.

Blood cultures are appropriate if symptoms worsen and the patient is at risk for sepsis and extraintestinal infections. However, because this patient's symptoms have resolved, blood cultures would be inappropriate.

Asymptomatic excretion of *Campylobacter* can persist for several weeks following resolution of symptoms; however, person-to-person transmission is uncommon, and surveillance stool cultures are not recommended to document clearance. Considering the patient's occupation, strict attention to hand hygiene would be important to minimize risk for secondary spread.

Macrolides are the preferred treatment for *Campylobacter* infection. This would be an appropriate choice if symptoms had persisted.

Ciprofloxacin would not be a viable option after resistance to levofloxacin is confirmed. *Campylobacter* bacteria resistant to levofloxacin are likely to be resistant to other fluoroquinolones as well.

KEY POINT

- In most cases of bacterial gastroenteritis, infection resolves spontaneously without therapy, and further evaluation or treatment is unnecessary.

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Ricotta EE, Palmer A, Wymore K, et al. Epidemiology and antimicrobial resistance of international travel-associated Campylobacter infections in the United States, 2005-2011. Am J Public Health. 2014 Jul;104(7):e108-14. [PMID: 24832415]

Item 92 Answer: B

Educational Objective: Manage cryptococcal infection in an otherwise healthy patient.

This patient has pulmonary cryptococcosis and should undergo lumbar puncture. Whenever *Cryptococcus* is found at a site outside of the central nervous system (CNS), a lumbar puncture should be performed to determine whether CNS infection is also present, even in the absence of CNS symptoms. Patients who are immunocompromised or become immunocompromised following primary infection are at risk for more progressive infection or disseminated infection.

The echinocandins, such as caspofungin, have no activity against *Cryptococcus* and, therefore, play no role in therapy for pulmonary cryptococcosis.

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Removal of the pulmonary nodule is not indicated at this time. If radiologic abnormalities and symptoms persist despite antifungal therapy, then surgery should be considered. Because of this patient's smoking history, further histologic investigation might be appropriate if his lung findings do not improve following therapy.

In immunocompetent patients, infection may resolve spontaneously, remain stable for a prolonged duration, or become progressive. Although most immunocompetent patients with primary pulmonary cryptococcosis may be asymptomatic and their infection may resolve without treatment, treatment is indicated to prevent progressive or disseminated disease and usually consists of daily fluconazole for 6 to 12 months. Therefore, providing no additional treatment would not be appropriate.

KEY POINT

- In patients with pulmonary cryptococcosis, lumbar puncture should be performed to determine if central nervous system (CNS) infection is also present, even in the absence of CNS symptoms.

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Brizendine KD, Baddley JW, Pappas PG. Pulmonary cryptococcosis. Semin Respir Crit Care Med. 2011 Dec;32(6):727-34. [PMID: 22167400]

Item 93 Answer: D

Educational Objective: Diagnose typhoid fever.

This patient's most likely diagnosis is typhoid fever, also known as enteric fever. It is commonly caused by ingestion of the bacterium *Salmonella enterica* serotype Typhi. Infection is usually acquired via the fecal-oral route either from food or water handled by asymptomatic carriers or by introduction of the organism into sewage-contaminated water systems. Typhoid fever occurs throughout the world but is endemic in the underdeveloped areas of Africa, Asia, and Latin America. In the United States, infection is usually diagnosed in travelers who have come from the Indian subcontinent. The typical clinical presentation of typhoid fever is a progressively rising fever, accompanied by abdominal pain, initial constipation followed by diarrhea, and relative bradycardia. One third of patients develop salmon-colored blanching maculopapular lesions on the trunk or abdominal wall. Tender hepatosplenomegaly is a common finding. Abnormal laboratory results often include anemia, leukopenia with a relative lymphopenia, thrombocytopenia, and elevated liver enzymes and bilirubin levels. The diagnosis may be supported by serologic assays. However, isolation of the organism from blood, stool, urine, and/or bone marrow is required for confirmation.

Brucellosis, another zoonotic infection mostly caused by one of four species named for a specific animal reservoir, occurs through direct contact with infected animals, ingestion of infected animal products, or inhalation. Fever occurs and is often intermittent or undulant. Arthralgia and arthritis, neurologic and psychiatric symptoms, and genitourinary involvement are also common. Gastrointestinal symptoms are infrequent and nonspecific.

Lassa fever is caused by an arenavirus endemic to Western Africa. Infection can be acquired after direct or indirect contact with infected rodent excreta. High fever, abdominal pain, and headache may progress to hemorrhagic manifestations and death.

Leptospirosis is a common zoonotic infection caused by spirochetes found throughout the world. Human infection often follows occupational (farmers, abattoir workers, veterinarians) exposure of damaged skin or mucous membranes to body fluids or environmental sources that have been contaminated with urine from an actively infected animal. However, acquisition of infection related to travel and recreational activities is becoming more common. Disease manifestations include acute fever, muscle pain (typically lumbar and calf regions), redness of the conjunctiva, and, occasionally, aseptic meningitis. Gastrointestinal symptoms are infrequent. Progression to a more severe disease phase of consisting of multisystem damage is rare.

KEY POINT

- The typical clinical presentation of typhoid fever is a progressively rising fever accompanied by abdominal pain, initial constipation followed by diarrhea, and relative bradycardia; tender hepatosplenomegaly is common.

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Waddington CS, Darton TC, Pollard AJ. The challenge of enteric fever. J Infect. 2014 Jan;68 Suppl 1:S38-50. [PMID: 24119827]

Item 94 Answer: A

Educational Objective: Recognize the clinical presentation of anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.

Testing this patient's anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies will confirm her diagnosis. This young woman presents with a subacute alteration in mental status over several weeks, characterized by psychiatric symptoms, seizure activity, and involuntary movements. These features, although individually nonspecific, suggest NMDAR encephalitis when combined. A recently described entity, it is one of the most common autoimmune encephalitides, especially in children and young adults, although it is infrequently diagnosed in older adults. Patients with anti-NMDAR encephalitis classically present with psychiatric symptoms, which can vary from agitation to frank psychosis. Other common signs include autonomic instability, choreoathetoid movements, and seizures or status epilepticus. This syndrome was initially recognized in young women with teratomas but has subsequently been diagnosed in patients without an obvious antigenic trigger, such as tumor or infection. Laboratory confirmation requires detection of anti-NMDAR antibodies in serum or cerebrospinal fluid (CSF).

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Borrelia burgdorferi is the bacterium that causes Lyme disease. The most common neurologic presentations include cranial neuropathy, meningitis, radiculopathy, and encephalomyelitis, which are inconsistent with this patient's presentation.

Nuchal skin biopsy for immunohistochemistry or polymerase chain reaction may be used to diagnose rabies. Rabies often presents with localized paresthesias at the site of inoculation, with inexorable progression to coma and death over days to weeks. Autonomic instability, muscle spasm, and hydrophobia are commonly present.

VDRL testing of CSF is an indirect test for neurosyphilis. This spirochetal illness causes neurologic symptoms similar to Lyme disease. Early in the disease course, meningitis and cranial neuropathies predominate; however, in late neurosyphilis, dementia or tabes dorsalis may be seen. These symptoms are inconsistent with those distinguishing anti-NMDAR encephalitis.

KEY POINT

- Anti–*N*-methyl-D-aspartate receptor encephalitis should be considered in the differential diagnosis of patients with psychiatric symptoms, seizures, autonomic instability, and choreoathetoid movements.

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Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013 Feb;12(2):157-65. [PMID: 23290630]

Item 95 Answer: D

Educational Objective: Evaluate severe community-acquired pneumonia with sputum cultures.

Sputum cultures are the most appropriate additional study in this patient. He presents with severe community-acquired pneumonia (CAP) and meets criteria to warrant hospital admission with an age great than 65 years and respiration rate greater than 30/min, which give him a CRB-65 score of 2. Because of his hemodynamic parameters, including hypotension and tachycardia, ICU management is appropriate. In addition to blood cultures, patients with severe CAP should have sputum cultures ordered. The diagnostic yield of sputum cultures varies widely, and culture data for ambulatory patients with uncomplicated CAP do not positively influence outcomes relative to empiric antibiotic therapy. Therefore, sputum cultures are not recommended for these patients. However, in patients being hospitalized and particularly for those with severe disease requiring ICU admission, possible complications of CAP, or multiple underlying comorbidities, sputum cultures may yield diagnostic information useful in guiding treatment. This patient has severe CAP requiring ICU admission; therefore, blood and sputum cultures are indicated.

Although chest CT has higher sensitivity than chest radiography for diagnosing CAP, no evidence shows that CT for initial diagnosis improves clinical outcomes. However, CT is particularly effective for detecting pleural effusion and empyema, cavitary lung lesions, and hilar lymphadenopathy and might be an appropriate diagnostic study if clinical suspicion for one of these complications develops.

C-reactive protein (CRP) is an inflammatory marker that tends to be increased to greater levels in bacterial pneumonia than viral pneumonia and may be helpful in differentiating the cause of pneumonia in patients in whom the diagnosis is unclear. Additional studies regarding use of CRP for this purpose are needed, and it would not be helpful in this patient with a clinical picture consistent with bacterial pneumonia.

Procalcitonin is a circulating molecule produced by cells as a response to bacterial toxins. Therefore, serum procalcitonin levels tend to be elevated in bacterial infections, and this test can be used as an adjunctive test along with other factors to help differentiate viral from bacterial infection. However, this patient has clear evidence of a bacterial cause of his pneumonia, so this study would not yield significant clinical information.

KEY POINT

- Patients with severe community-acquired pneumonia should have sputum and blood cultures performed as part of further diagnostic testing.

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Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America, American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44(Suppl 2):S27-72. [PMID: 17278083]

Item 96 Answer: A

Educational Objective: Treat a patient with HIV/AIDS and disseminated *Mycobacterium avium* complex infection.

The combination of clarithromycin, ethambutol, and rifabutin is the most appropriate treatment for this patient who has AIDS and a disseminated *Mycobacterium avium* complex (MAC) infection. Disseminated MAC infection usually occurs in patients with CD4 cell counts less than 50/μL. Symptoms include fever, night sweats, weight loss, diarrhea, fatigue, and abdominal pain. Laboratory abnormalities often include evidence of bone marrow suppression and an elevated alkaline phosphatase level. The diagnosis is typically made by blood cultures (or cultures from other involved organs). Guidelines for the treatment of MAC in adults with HIV infection recommend clarithromycin as the preferred first agent and ethambutol as the second agent. On the basis of some evidence indicating improved survival and decreased emergence of drug resistance, some experts recommend the addition of rifabutin as a third agent. Primary prophylaxis for MAC prevention with azithromycin or clarithromycin is recommended for patients with HIV whose CD4 cell count is less than 50/μL.

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Isoniazid, rifampin, and ethambutol are typically used to treat *Mycobacterium kansasii*, which most commonly causes a lung infection that mimics tuberculosis with cough, fever, weight loss, and cavitary lung disease.

Isoniazid and rifabutin are part of the 4- to 7-month continuation phase of treatment for active tuberculosis, which follows the initial 8-week treatment phase with rifabutin, isoniazid, pyrazinamide, and ethambutol. This patient does not have active tuberculosis.

KEY POINT

- Treatment with clarithromycin, ethambutol, and rifabutin is recommended for disseminated *Mycobacterium avium* complex infection in patients with HIV/AIDS whose CD4 cell counts are less than 50/μL.

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Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Updated April 16, 2015. Accessed July 21, 2015.

Item 97 Answer: D

Educational Objective: Manage community-acquired pneumonia with empiric antibiotic therapy.

This patient should begin outpatient treatment with a respiratory fluoroquinolone, such as levofloxacin; a reasonable alternative would be an oral β-lactam antibiotic in combination with a macrolide or doxycycline. Initial assessment of patients with community-acquired pneumonia (CAP) begins with establishing an appropriate venue of care. Clinical decision tools, such as the modified CRB-65, which omits the blood urea nitrogen (BUN) component of the original CURB-65 (confusion, BUN [>20 mg/dL (7.14 mmol/L)], respiration rate [≥30/min], blood pressure [systolic <90 mm Hg, diastolic <60 mm Hg], and age ≥65 years), can be used in office-based settings to expedite determining the need for hospitalization. This patient has no confusion, is not hypotensive, and does not have significant tachypnea (respiration rate is <30/min), so his CRB-65 score is 0 and he does not require hospitalization. Empiric antibiotic therapy is focused toward the most likely organisms, modified by specific risk factors in a particular patient. Patients with no risk factors for resistant *Streptococcus pneumoniae* are candidates for treatment with either a macrolide or doxycycline. However, in patients with increased risk for resistance (age >65 years, recent [within the past 3-6 months] antimicrobial therapy [with a β-lactam, macrolide, or fluoroquinolone antibiotic], alcoholism, immunosuppression, and certain medical comorbidities [COPD, chronic liver or kidney disease, cancer, diabetes, functional or anatomic asplenia, chronic heart disease]), therapy with a respiratory fluoroquinolone or a β-lactam with a macrolide or doxycycline is appropriate. Because this patient has COPD, his risk for resistant *S. pneumoniae* is increased, and expanded antibiotic coverage is indicated instead of macrolide monotherapy (such as azithromycin).

For patients requiring hospital ward admission for treatment, an empiric regimen of an intravenous β-lactam with a macrolide or doxycycline (such as ampicillin-sulbactam and doxycycline) or a respiratory fluoroquinolone is recommended. However, this patient does not have a clear indication for hospital admission for treatment.

For patients with CAP requiring ICU admission, treatment with an intravenous β-lactam plus either azithromycin or a fluoroquinolone (such as ceftriaxone and azithromycin) is indicated. Because this patient does not require hospitalization or intensive care, this would not be an appropriate empiric treatment regimen.

KEY POINT

- In patients with increased risk for resistant *Streptococcus pneumoniae*, empiric antibiotic therapy with a respiratory fluoroquinolone, such as levofloxacin, or a β-lactam with a macrolide or doxycycline is most appropriate.

Bibliography

Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America, American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44(Suppl 2):S27-72. [PMID: 17278083]

Item 98 Answer: B

Educational Objective: Treat a patient with catheter-associated urinary tract infection.

This patient likely has a catheter-associated urinary tract infection (CAUTI), and his catheter should be removed and treatment provided for the infection. Fever with no other identifiable cause, suprapubic tenderness, and a urine culture growing 10^3 or more colony-forming units in a patient with an indwelling urinary catheter are compatible with the diagnosis of CAUTI. Other signs and symptoms that may suggest CAUTI include acute hematuria, costovertebral angle tenderness, pelvic discomfort, malaise, rigors, or confusion. It is not possible to assess for dysuria or urgency while the catheter is in place, but these symptoms may be present if the catheter is removed. Age older than 50 years and diabetes mellitus are two risk factors for CAUTI, as is prolonged catheterization. Catheters inserted in the operating room should be removed within 2 days after surgery to prevent CAUTI, unless the patient has undergone urologic surgery or other surgery on contiguous structures of the genitourinary tract, in which case it may be acceptable to keep the catheter in place longer. Treatment of CAUTI includes removing the urinary catheter if possible because bacteria may be embedded in biofilm and may not be reached by antimicrobial agents. Catheters in place for more than 2 weeks should be removed or changed before a urinalysis and culture are performed;

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otherwise, inaccurate results may be obtained, representing organisms present in biofilm and not necessarily causing UTI.

Although antimicrobial stewardship includes narrowing antibiotic coverage to a specific organism involved, awaiting sensitivity results to guide antimicrobial selection would not be appropriate in this patient with evidence of CAUTI. Empiric antimicrobial coverage based on likely infecting organisms and local resistance patterns with subsequent focused therapy when sensitivities are determined would be indicated in this patient.

The patient's symptoms and urine culture indicate he has a CAUTI; therefore, repeating a urinalysis and culture in 24 hours without treatment would not be appropriate.

No treatment is necessary for patients with asymptomatic bacteriuria, defined as bacteriuria of 10^3 colony-forming units or greater without signs or symptoms of UTI. However, this patient has evidence of active infection, so treatment is indicated.

KEY POINT

- Patients with probable catheter-associated urinary tract infection should have the catheter removed and appropriate antimicrobial treatment provided for the infection, based on results of a urine culture.

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Item 99 Answer: D

Educational Objective: Diagnose *Vibrio vulnificus*-associated necrotizing fasciitis.

This patient has necrotizing fasciitis caused by *Vibrio vulnificus*. Patients who are immunocompromised, particularly those with liver disease, are at increased risk for infection with this gram-negative bacillus. Infection usually occurs after consumption of raw shellfish (such as oysters) or skin trauma incurred in contaminated warm (>20 °C [68.0 °F]) sea water or brackish water where the organism thrives. Hemorrhagic bullae are the classic cutaneous manifestation. Guideline recommendations for the management of these infections include antibiotic therapy with doxycycline plus ceftazidime in addition to surgery.

Erysipelothrix rhusiopathiae is a gram-positive bacillus that can infect animals, including swine and poultry, and is a saprophyte associated with fish, crustaceans, and molluscs. Exposures to these types of animals or their secretions can be occupationally acquired (fisherman, fish and shellfish handlers, veterinarians, and butchers). Classically, a painful localized violaceous cutaneous infection of the hand or fingers (known as erysipeloid) develops at the site of trauma or a preexisting wound. Fever is not often present. More diffuse skin infections and systemic infections including bacteremia and endocarditis are well-described but are much less common.

Methicillin-resistant *S. aureus* can cause a monomicrobial necrotizing fasciitis and should be empirically covered by the initial antibiotic regimen while awaiting microbiologic confirmation. However, the intraoperative tissue specimen from this patient reveals gram-negative bacilli and not gram-positive cocci in clusters that would herald a MRSA infection.

Mycobacterium marinum skin infections typically develop at sites of skin injury that have been exposed to salt or fresh water, such as in fish tanks (fish tank granuloma). The upper extremity is often involved and lesions are usually papular before becoming ulcerative. Systemic toxicity is not usually seen in skin infections caused by this nontuberculous acid-fast bacillus. The Gram stain of infected tissue would be negative.

KEY POINT

- Patients who are immunocompromised, particularly those with liver disease, are at increased risk for infection with *Vibrio vulnificus*.

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Item 100 Answer: C

Educational Objective: Diagnose Middle East respiratory syndrome.

This patient has Middle East respiratory syndrome (MERS), which was first reported in Saudi Arabia in 2012 and is caused by a novel β-coronavirus (MERS-CoV). This virus is similar to but distinct from the severe acute respiratory syndrome-coronavirus (SARS-CoV) outbreak originally identified in China in 2002. Close contact with a patient infected with MERS appears to be necessary for transmission. All cases of MERS have been directly or indirectly linked to travel or residence in countries of the Arabian Peninsula but have also been imported to areas of Europe and the United States by travelers; therefore, clinical suspicion for this diagnosis must be maintained in patients with respiratory illness who have traveled in these areas. Severe disease with MERS occurs primarily in older persons with comorbidities such as diabetes mellitus, end-stage kidney disease, and obesity and has an overall mortality rate of more than 40%.

After an average incubation period of 5 days, patients report a typical viral-like syndrome. In severe illness, the patient often progresses to pneumonia and significant respiratory distress, often necessitating mechanical ventilation. Gastrointestinal manifestations and acute kidney injury may also occur. Treatment consists of supportive care. Standard care precautions using personal protective equipment and contact and airborne isolation are crucial infection control measures when MERS is suspected or diagnosed.

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Although this patient traveled to Liberia, where Ebola is endemic, Ebola is not a primary respiratory infection. Additionally, no coagulopathy, which is usually seen with Ebola infection, is evident in this patient.

Influenza infection as a cause of this patient's clinical presentation would not be likely during the summer months, and primary pneumonia is a less common presentation of influenza infection.

Respiratory syncytial virus is associated with seasonal outbreaks and may affect children and adults. It may also cause upper and lower respiratory tract illness. However, except in patients who are immunocompromised, the clinical manifestations of this infection are usually milder than those seen in this patient.

KEY POINT

- Middle East respiratory syndrome should be suspected in any person presenting with respiratory illness following travel in or around the Arabian Peninsula.

Bibliography

Sampathkumar P. Middle East respiratory syndrome: what clinicians need to know. Mayo Clin Proc. 2014;89(8):1153-8. [PMID: 25034307]

Item 101 Answer: B

Educational Objective: Manage central line-associated *Staphylococcus aureus* bloodstream infection.

Vancomycin should be changed to a penicillinase-resistant semisynthetic penicillin antibiotic (oxacillin or nafcillin). The patient's blood cultures indicate infection with a methicillin-sensitive *Staphylococcus aureus* (MSSA) isolate. The β-lactam antibiotics are more rapidly bactericidal than vancomycin and are therefore the preferred class of antibiotics for treating serious *S. aureus* infections. Because this patient is not allergic to penicillin, oxacillin or nafcillin are the best choices. Vancomycin is associated with worse outcomes when used to treat MSSA infections. Empiric therapy with vancomycin is appropriate for patients in whom infection with methicillin-resistant *S. aureus* is a consideration. However, therapy should be modified as appropriate as soon as culture and antimicrobial susceptibility results are available.

Combination antimicrobial therapy (such as vancomycin and rifampin) for the treatment of *S. aureus* bacteremia does not improve clinical outcomes. Therefore, it would not be the most appropriate management choice for this patient.

Vancomycin therapy is monitored by serum trough levels, not serum peak levels. When vancomycin is used in the appropriate setting, the usual goal for the serum trough level is 15 to 20 μg/mL.

Definite or probable thrombosis occurs in approximately 70% of patients who have central venous catheter-associated *S. aureus* bacteremia. Imaging of the previous intravenous site is not necessary unless suspicion exists for suppurative thrombophlebitis (pain, swelling, palpable cord) or a fluid collection that would require drainage.

KEY POINT

- Methicillin-susceptible *Staphylococcus aureus* should be treated with a penicillinase-resistant semisynthetic penicillin.

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Item 102 Answer: A

Educational Objective: Manage infection control practices for a patient suspected of having tuberculosis.

This patient comes from a country with a high prevalence of tuberculosis and is at increased risk for infection with *Mycobacterium tuberculosis*. Her symptoms of fever, cough, decreased appetite, night sweats, and weight loss, as well as the location of chest infiltrates in the apical area of the upper lobes, are characteristic of pulmonary tuberculosis. *M. tuberculosis* spreads by airborne particles known as droplet nuclei, which are 5 μm or smaller in size. These airborne particles are expelled when an infected patient sneezes or coughs. Transmission of infection can occur when these airborne particles are inhaled into the lung alveoli. Consequently, this patient should be placed in empiric negative-pressure airborne isolation while further evaluation is pursued. Negative-pressure isolation prevents airborne droplets from escaping the room, and at least 6 to 12 air changes of the room air are provided per hour. Doors to isolation rooms must remain closed, and all persons entering must wear a respirator that has a filtering capacity of 95% and a tight seal over the nose and mouth. Patients in airborne isolation who require transport outside of their isolation room for medical procedures should wear surgical masks that cover their nose and mouth during transport.

Contact isolation is instituted for patients who have a suspected or known illness transmitted by direct contact (such as *Clostridium difficile*, vancomycin-resistant enterococci, *Shigella* species, hepatitis A virus).

Droplet isolation is instituted for patients who have a suspected or known illness transmitted by large-particle droplets (>5 μm in size) (for example, *Neisseria meningitidis*, influenza virus, adenovirus, *Bordetella pertussis*, *Mycoplasma pneumoniae*). Droplet precautions involve a face mask without high-level respirator masks or special air handling.

Standard precautions, which include hand hygiene, respiratory hygiene, injection safety measures, use of personal protective equipment (gloves, gowns, face masks/shields, respirators), and appropriate environmental and

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disinfection measures, are instituted for all patients in a health care setting regardless of illness.

KEY POINT

- Patients with pulmonary tuberculosis, or infections with other organisms transmitted by small droplet nuclei, should be placed in airborne isolation to prevent the spread of infection.

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Siegel JD, Rhinehart E, Jackson M, Chiarello L; Health Care Infection Control Practices Advisory Committee. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings. Am J Infect Control. 2007 Dec;35(10 Suppl 2):S65-164. [PMID: 18068815]

Item 103 Answer: D

Educational Objective: Treat a patient with a furuncle without antibiotic therapy.

Clinical follow-up with no additional treatment is indicated at this time for this patient who has undergone incision and drainage of a furuncle (boil). Usually, incision and drainage alone is the primary treatment recommended for a patient with a simple furuncle. Antibiotics generally are recommended only when the response to incision and drainage is inadequate, when involved areas are challenging to drain (such as the genitalia, hands, or face); when disease is extensive or rapidly progressive with associated cellulitis; in immunodeficiency and other comorbidities; for very young or very old patients; those with clinical signs of systemic illness; and in the presence of associated septic phlebitis. Furuncles are typically due to community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Empiric use of adjunctive antibiotics with CA-MRSA activity after incision and drainage of a furuncle is generally reserved for patients who are immunosuppressed, who do not respond adequately to incision and drainage or antibiotics without MRSA activity, or who have systemic signs of infection.

Oral dicloxacillin has activity against methicillin-sensitive *S. aureus* (MSSA), but not MRSA. It would be recommended for adjunctive use when culture of purulent material from a furuncle demonstrates MSSA.

Because of the high likelihood that MRSA may be the causative agent, when antibiotics are used, empiric treatment with agents with activity against MRSA is recommended. Doxycycline has activity against MRSA and would be a reasonable choice, but it is not indicated for this patient who has undergone incision and drainage of his furuncle. Trimethoprim-sulfamethoxazole is another reasonable option for empiric MRSA therapy if antibiotic therapy is needed, although this agent would be contraindicated in this patient with a known allergy to this medication.

Although it is bactericidal against some strains of MRSA, rifampin monotherapy is not recommended because of the development of resistance.

KEY POINT

- No antibiotic treatment is needed after incision and drainage of a simple furuncle, except in patients who are immunosuppressed, who do not respond adequately to incision and drainage or antibiotics without MRSA activity, or who have systemic signs of infection.

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Item 104 Answer: A

Educational Objective: Treat a patient with appropriate antibiotic therapy who is admitted to the hospital with community-acquired pneumonia with suspected *Pseudomonas aeruginosa* infection.

Empiric antibiotic therapy with cefepime, levofloxacin, and gentamicin is the most appropriate regimen for this patient. She presents with severe community-acquired pneumonia (CAP) requiring ICU treatment and, therefore, requires appropriate antibiotics for this setting (typically, a β-lactam plus either azithromycin or a fluoroquinolone, such as cefepime, levofloxacin, or ciprofloxacin). Patients at increased risk for *Pseudomonas aeruginosa* infection include those with structural lung disease (such as bronchiectasis) and recent or frequent glucocorticoid and antibiotic use. Because this patient has bronchiectasis and recent glucocorticoid use, she is at increased risk for *Pseudomonas* infection and should be treated with a β-lactam with antipseudomonal activity (such as cefepime) as part of her regimen with the addition of another antipseudomonal agent, such as gentamicin.

A β-lactam in combination with a macrolide or doxycycline, such as ceftriaxone and azithromycin, is an appropriate empiric regimen for patients requiring inpatient treatment in a medical ward setting. However, it does not provide adequate coverage for *P. aeruginosa* infection and thus would not be an appropriate regimen for this patient. A respiratory fluoroquinolone plus aztreonam is an alternative regimen to empiric treatment with a β-lactam plus either azithromycin or a fluoroquinolone in patients requiring treatment in the ICU for CAP, particularly for patients who are allergic to penicillin. However, this regimen does not provide adequately robust coverage against *P. aeruginosa*.

The combination of ceftriaxone and levofloxacin provides some coverage against *P. aeruginosa* but would not be the best choice for an antibiotic regimen targeting suspected *P. aeruginosa* CAP because of ceftriaxone's inadequate coverage against *P. aeruginosa*.

Meropenem, a broad-spectrum carbapenem β-lactam antibiotic, would be an appropriate component of an empiric regimen for treatment of possible *Pseudomonas*

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infection only if given in combination with a respiratory fluoroquinolone or another agent providing pseudomonal coverage. Meropenem monotherapy would not provide adequate coverage against *Pseudomonas* infection and thus would not be an appropriate empiric treatment regimen for this patient.

KEY POINT

- Patients admitted to the hospital with community-acquired pneumonia thought be caused by *Pseudomonas aeruginosa* require broad coverage empiric antibiotic therapy that includes an antipseudomonal β-lactam, an aminoglycoside, and a respiratory fluoroquinolone, which offer coverage of gram-negative organisms.

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Item 105 Answer: B

Educational Objective: Provide preexposure prophylaxis for HIV to a person at ongoing risk.

This patient is at risk for HIV infection because of regular sexual activity with an infected person and should be considered for preexposure prophylaxis (PrEP). Daily combination tenofovir-emtricitabine therapy is FDA approved for prevention of HIV infection in persons considered at ongoing risk for infection. Studies have shown efficacy in men who have sex with men, heterosexual couples, and injection drug users. Rates of effectiveness in prevention depend on adherence to the medication, and prophylaxis should always be accompanied by safer-sex counseling. Testing for HIV and other sexually transmitted diseases, pregnancy, and kidney function should be performed before initiation of prophylaxis and every 2 to 3 months during preventive therapy.

Reduction in viral load with antiretroviral therapy does reduce transmission of HIV, although transmission may still occur even with undetectable blood levels. Although consistent condom use can reduce the risk for HIV transmission, the addition of PrEP can further reduce rates of acquisition of HIV and should be considered in those at high risk. Such preventive therapy should be taken daily, however, and not episodically only with exposure.

Studies on which FDA approval was based used a two-drug combination of tenofovir-emtricitabine alone without additional medication. Therefore, no clear indication exists for exposing the patient to the additional cost and risk of a third drug. The three-drug regimen of combination tenofovir-emtricitabine and raltegravir is the preferred regimen for postexposure prophylaxis. Whereas tenofovir alone has shown some benefit in reducing acquisition of HIV because of concerns about resistance, combination tenofovir-emtricitabine is preferred for PrEP.

KEY POINT

- Combination tenofovir-emtricitabine should be considered as preexposure prophylaxis to prevent HIV infection in all persons considered at ongoing risk of infection.

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Item 106 Answer: E

Educational Objective: Manage a patient with prolonged fever of unknown origin.

This patient has classic fever of unknown origin (FUO), defined as a temperature greater than 38.3 °C (100.9 °F) for at least 3 weeks that remains undiagnosed after two visits in the ambulatory setting or 3 days of in-hospital assessment. She has undergone a reasonable evaluation for the most common causes of FUO, which include infection (endocarditis, tuberculosis, abscesses, complicated urinary tract infection), neoplasm, and connective tissue disease; therefore, she should be observed carefully, and further diagnostic or therapeutic interventions should be based on changes in history or physical examination. Histopathologic examination of tissue obtained by aspiration or biopsy can provide a definitive diagnosis in some cases of FUO if the clinical evaluation suggests disease in a particular organ. An exception to performing blind biopsies is biopsy of the temporal artery, which may be indicated in older adult patients with FUO and an elevated erythrocyte sedimentation rate even if localizing signs are absent.

A bone marrow aspirate and biopsy would be indicated if hematologic abnormalities were seen and are helpful in diagnosing disseminated granulomatoses, such as tuberculosis and histoplasmosis, or malignancies, such as leukemia and lymphoma. Because the patient's blood counts are normal and she has no other clinical findings suggesting a process with bone marrow involvement, performing a bone marrow aspirate and biopsy is not indicated.

Therapeutic trials of antibiotics, glucocorticoids, or NSAIDs are rarely indicated in patients with FUO. They may be successful in eliminating fever, or fever may remit spontaneously, and the correct diagnosis may be delayed. Empiric therapy should be reserved for patients who are seriously ill or when a specific diagnosis is reasonably likely. In general, this occurs most often when disseminated tuberculosis is suspected and an empiric therapeutic trial of antibiotics is indicated.

In the absence of any new localizing signs or symptoms, repeat or more extensive imaging is likely to be low-yield and not cost-effective. The longer the duration of FUO, the less likely it is to have an infectious cause.

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KEY POINT

- When a patient has been reasonably evaluated (laboratory studies, repeat blood cultures, imaging studies) for ongoing fever, a diagnosis of fever of unknown origin should be reached and the patient should be observed in case further interventions would be appropriate later.

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Item 107 Answer: C

Educational Objective: Diagnose postinfluenza community-acquired pneumonia caused by *Staphylococcus aureus*.

This patient mostly likely has postinfluenza pneumonia caused by *Staphylococcus aureus*. She presents with recurrent cough and dyspnea after recently being diagnosed with influenza pneumonia, and her chest radiograph shows cavitary lesions, which are most consistent with S. *aureus*. Secondary bacterial pneumonia following influenza is a significant cause of morbidity and mortality, particularly in patients aged 65 years or older. Influenza virus affects the tracheobronchial epithelium, impairing normal mucociliary clearance mechanisms and predisposing to bacterial infection. The most common clinical presentation in patients with secondary bacterial pneumonia is the exacerbation of respiratory symptoms and fever after a period of initial improvement of acute influenza symptoms. Patients with secondary bacterial pneumonia typically develop higher fevers than were present with influenza and a cough productive of purulent sputum. Chest radiography will show pulmonary infiltrates.

Legionella species are an uncommon cause of secondary pneumonia associated with influenza infection compared with *Streptococcus pneumoniae* and *S. aureus*. Additionally, this patient has no additional risk factors predisposing her to developing CAP from *Legionella*, such as exposure to a community outbreak or contaminated water source.

Pneumonia due to *Pseudomonas aeruginosa* is an uncommon cause of CAP, and generally occurs in patients with chronic lung disease. It would, therefore, be an unlikely cause of secondary pneumonia in this patient.

Although *S. pneumoniae* is more common than S. *aureus* in postinfluenza pneumonia, it does not typically produce the radiographic picture of cavitary lesions, so it is unlikely to be the causative pathogen in this patient.

KEY POINT

- A patient with recently diagnosed influenza pneumonia and cavitary lesions on chest radiograph most likely has *Staphylococcus aureus* postinfluenza community-acquired pneumonia.

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Item 108 Answer: A

Educational Objective: Manage recurrent urinary tract infection with low-dose antimicrobial prophylaxis.

This patient should begin low-dose antimicrobial prophylaxis. She has recurrent urinary tract infection (UTI), which is defined as three UTIs in the previous 12 months or two UTIs in the previous 6 months. Recurrent UTI affects 20% to 30% of women. She has already tried a modifiable behavioral practice by voiding after sexual intercourse. Scientific evidence is lacking for most behavioral strategies, but they are low risk and worth attempting. Low-dose antimicrobial prophylaxis is an effective intervention to manage frequent, recurrent, acute, uncomplicated UTI. It may be administered daily or every other day, generally at bedtime, or as postcoital prophylaxis. The initial duration of prophylaxis is generally 6 months; however, 50% of women experience recurrence by 3 months after discontinuation of prophylaxis. If this occurs, prophylaxis should be reinstated for 1 or 2 years with reassessment after that time. Because continuous prophylaxis may result in unnecessary antimicrobial use, an alternative strategy is patient self-diagnosis and self-treatment at the start of symptoms.

Methenamine salts produce formaldehyde, which acts as a bacteriostatic agent without affecting microbial susceptibility to antibiotic agents. They are well tolerated and effective. However, carcinogenic potential is a concern if they are used at high doses for a prolonged duration. They can be used for up to 1 week to prevent UTI in patients without urinary tract abnormalities, but not long term.

Vitamin C (ascorbic acid) has not been shown to be effective and is therefore not recommended for the prevention of UTI based on current evidence.

Anatomic or functional abnormalities of the urinary tract should be excluded as a cause of recurrent UTI in men and postmenopausal women. In premenopausal women, however, the yield for this indication is low. Therefore, urethroscopic assessment of this patient would not be indicated.

KEY POINT

- Low-dose antimicrobial prophylaxis is an effective intervention to manage frequent, recurrent, acute, uncomplicated urinary tract infection.

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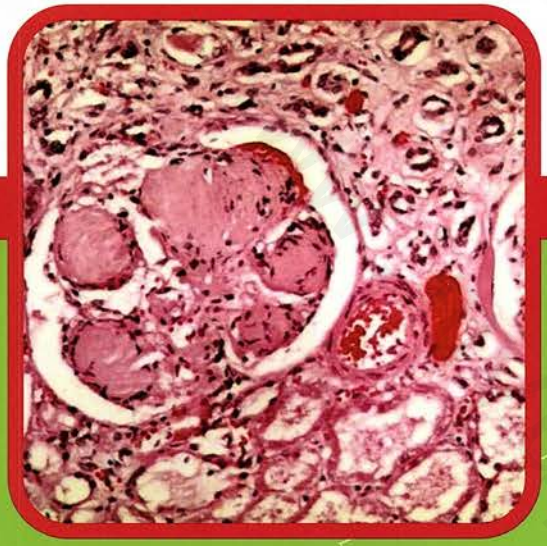

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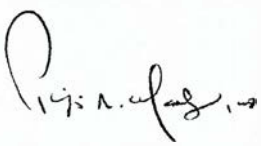

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Learning Objectives

The learning objectives of MKSAP 17 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence
- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internists and primary care physicians
- Subspecialists who need to remain up-to-date in internal medicine and in areas outside of their own subspecialty area
- Residents preparing for the certification examination in internal medicine
- Physicians preparing for maintenance of certification in internal medicine (recertification)

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For the convenience of subscribers who provide care in hospital settings, content that is specific to the hospital setting has been highlighted in blue. Hospital icons (H) highlight where the hospital-based content begins, continues over more than one page, and ends.

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Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon (HVC).

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Errata

Errata for MKSAP 17 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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Nephrology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 17 in several important ways. MKSAP 17 now includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Nephrology section of MKSAP 17.

- The presence of both leukocyte esterase and nitrites on urine dipstick is highly suggestive of a urinary tract infection (UTI), and uncomplicated patients with these findings may be treated empirically with antibiotics; the absence of both has a high negative predictive value for a UTI, and most patients will not need antibiotics.
- Urinalysis should not be used to screen for bladder cancer in asymptomatic patients.
- Ultrasonography is typically the first imaging test in the evaluation of the kidneys and upper urinary tract because of its safety, cost effectiveness, and general utility.
- The initial treatment of asymptomatic patients with the syndrome of inappropriate antidiuretic hormone secretion includes management of the underlying cause if possible and fluid restriction without limiting sodium intake (see Item 63).
- Echocardiography is not routinely indicated in the assessment of hypertension except in patients with known heart disease, the presence of left bundle branch block on electrocardiogram, or suspected white coat hypertension.
- Identification of prescription and nonprescription medications that may be contributing to blood pressure elevation is necessary in patients with elevated blood pressure not yet defined as hypertension (see Item 79).
- Prehypertension is managed with lifestyle modifications and annual follow-up visits to monitor blood pressure (see Item 1).
- In patients with white coat hypertension, close observation for the emergence of sustained hypertension or end-organ damage is recommended; drug therapy is not usually required (see Item 42).
- Lifestyle modifications are indicated for all patients with hypertension, which can produce reductions in blood pressure that are equivalent to antihypertensive agents (see Item 11).
- A combination of two hypertensive agents at moderate dose is often more successful at achieving blood pressure goals than one agent at maximal dose, which can help minimize the side effects more commonly noted at higher doses.
- For patients with chronic kidney disease, the eighth report from the Joint National Committee recommends a blood pressure target goal of <140/90 mm Hg using a medication regimen that includes an ACE inhibitor or angiotensin receptor blocker (see Item 13 and Item 68).
- The eighth report of the Joint National Committee recommends a treatment goal of <150/90 mm Hg for patients with hypertension who are ≥60 years (see Item 38).
- The risk of complications, morbidity, and mortality related to lower blood pressure in frail individuals may supersede the potential benefit of lower blood pressure goals (see Item 64).
- Adequate blood pressure control and use of an ACE inhibitor or angiotensin receptor blocker has been shown to slow the progression of diabetic nephropathy (see Item 45).
- Medical management is the primary therapeutic intervention in most patients with renal artery stenosis.
- Ultrasonography is increasingly being used as an initial diagnostic study for nephrolithiasis due to availability, lack of radiation exposure, and low cost; it is also the preferred modality during pregnancy.
- Ultrasonography is an appropriate imaging modality for patients with chronic kidney disease to avoid adverse events such as contrast-induced nephropathy or nephrogenic systemic fibrosis (see Item 2).

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- For patients with kidney stones ≤10 mm in diameter, conservative management, including analgesia, hydration, and expulsive therapy, may be attempted.
- Very elderly patients who have end-stage kidney disease with a high burden of comorbid conditions and poor functional status may live as long or longer with non-dialytic therapy that is focused on alleviating symptoms and maximizing quality of life (see Item 18).
- The incidence of dialysis initiation is increasing most rapidly among patients over the age of 75 years; decisions regarding initiation of renal replacement therapy in an older patient with impending end-stage kidney disease must take into account comorbid medical conditions, functional status, expected outcomes, and patient preferences regarding goals of care.
- Management of infection-related glomerulonephritis typically only consists of treatment of the underlying infection (see Item 12).
- Trimethoprim is known to interfere with creatinine secretion without affecting the glomerular filtration rate and can cause increases in serum creatinine of up to 0.5 mg/dL (44.2 µmol/L); this rise therefore does not reflect a drop in actual kidney function and does not require an extensive work-up (see Item 34).
- Patients with isolated hematuria with a family history of hematuria may require serial measurements of kidney function and urine protein because kidney failure may occur later in life (see Item 14).
- Proton pump inhibitors are a potentially treatable cause of chronic tubulointerstitial disease and should be discontinued to see if kidney function improves (see Item 50).
- For patients with autosomal dominant polycystic kidney disease, screening for intracranial cerebral aneurysms using MR angiography is only recommended for those with a family history of aneurysm or subarachnoid hemorrhage, those with a previous rupture, or those with high-risk occupations in which a rupture would affect the lives of others and should not be done routinely (see Item 62).
- Observation with serial blood pressure measurements, urine studies, and serum creatinine levels is appropriate for patients with IgA nephropathy with low-risk features for progression (see Item 85).
- In obese patients with likely secondary focal segmental glomerulosclerosis, weight loss is sometimes associated with a drop in proteinuria, as is the use of ACE inhibitors or angiotensin receptor blockers, and is the preferred initial therapy (see Item 87).
- An extensive evaluation for cancer is not indicated in patients with membranous glomerulopathy beyond age-appropriate cancer screening except for those with symptoms suggestive of a cancer diagnosis or significant risk factors for specific malignancies (see Item 106).

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Clinical Evaluation of Kidney Function

Assessment of Kidney Function

Glomerular filtration rate (GFR) is the net sum of the filtration rates of thousands of nephrons, providing a quantitative measure of the flow rate of filtered fluid through the kidney per minute. Normal GFR is influenced by gender and body size, with a steady decline with aging. Assessment of GFR in patients with kidney disease provides an index of the severity of kidney functional impairment. There is not an exact correlation between the loss of functioning nephrons and GFR due to compensatory hypertrophy and increased flow in residual nephrons. Consequently, patients may have significant structural kidney disease with a normal GFR and/or progression of structural kidney disease without a significant change in measured GFR.

Biochemical Markers of Kidney Function

Serum creatinine is generated from the metabolism of creatine in muscle and from dietary meat. It is freely filtered by the glomerulus without metabolism or reabsorption by renal tubules. Although some creatinine is secreted by organic cation transport mechanisms in the proximal tubule, it is useful as an endogenous marker of GFR.

Measurement of serum creatinine concentration has been used for almost a century as an indicator of kidney function. Although it is the most commonly used marker of GFR, it is an imperfect measure. The relationship between GFR and serum creatinine is not linear, but inversely proportional (**Figure 1**). In patients who become functionally anephric, the serum creatinine typically increases 1.0 to 1.5 mg/dL (88.4-133 µmol/L) per day.

Reduction of muscle mass, as seen in amputees and those with malnutrition or muscle wasting, can result in a lower serum creatinine concentration without a change in GFR. Because of decreased muscle mass, serum creatinine overestimates kidney function in elderly persons, especially women. Young persons, men, and black persons often have higher muscle mass and higher serum creatinine concentration at a given GFR compared with older persons. Patients with advanced liver disease produce lower amounts of creatine (the precursor of creatinine) and have muscle wasting, resulting in a correspondingly lower serum creatinine at a given GFR. Certain medications (such as cimetidine and trimethoprim) inhibit organic cation transporters and block tubular secretion of creatinine, resulting in a higher serum creatinine without a change in GFR. Conversely, in patients who have chronic kidney disease (CKD) with intact tubular function, creatinine secretion increases, thus leading to a progressive overestimation of GFR.

Creatinine clearance is a measure of the volume of plasma that is cleared of creatinine by the kidney per unit of time and can be directly measured from a 24-hour urine collection to approximate the GFR (**Table 1**). The "adequacy" or "completeness" of the collection is estimated by the total excreted creatinine per 24 hours. For a 20- to 50-year-old man, creatinine excretion should be 18.5-25.0 mg/kg body weight and 16.5-22.4 mg/kg body weight for a woman of the same age. Because of the secretion of creatinine in the proximal tubule, the direct measurement of creatinine clearance tends to overestimate GFR. Nonetheless, the 24-hour urine collection with an adequate collection judged by the creatinine excreted is used to estimate GFR as well as excretion of other electrolytes and metabolic products such as calcium, phosphate, and urate.

Blood urea nitrogen (BUN) is derived from the metabolism of proteins. BUN concentration is a poor marker of kidney function because it is not produced at a constant rate and is reabsorbed along the tubules; furthermore, alterations in renal blood flow markedly influence tubular reabsorption and excretion. Urea clearances significantly underestimate GFR but may be useful in estimating GFR <15 mL/min/1.73 m^2.

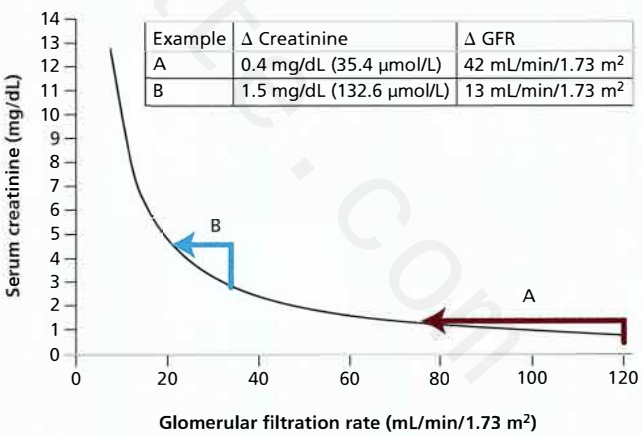

FIGURE 1. The relationship between serum creatinine and glomerular filtration rate (GFR). Example A illustrates that a small increase in the serum creatinine level in the reference range (in this case, 0.8 to 1.2 mg/dL [70.7-106 µmol/L]) reflects a relatively large change in GFR (120 to 78 mL/min/1.73 m^2). Example B illustrates that a relatively greater increase in the serum creatinine level (in the high range of 3.0 to 4.5 mg/dL [265-398 µmol/L]) reflects a proportionately smaller change in GFR (35 to 22 mL/min/1.73 m^2).

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TABLE 1. Methods for Estimating Kidney Function

Method	Considerations	Application
Creatinine Clearance		
U_{Cr} (mg/dL) × 24-hour urine volume (mL/24 h)/S_{Cr} (mg/dL) × 1440 (min/24 h)	Overestimates GFR 10%-20% Incomplete or excessive 24-hour urine collections limit accuracy	Useful in pregnancy, extremes of age and weight, amputees, and patients with cirrhosis
Serum Cystatin C		
	Levels are affected by thyroid status, diabetic status, inflammation, and glucocorticoid use	More accurate in elderly population and patients with cirrhosis
Modification of Diet in Renal Disease (MDRD) Study Equation[a]		
$GFR = 175 \times (S_{Cr})^{-1.154} \times (age)^{-0.203} \times 0.742$ (if female) or × 1.212 (if black)	Most accurate when eGFR is 15-60 mL/min/1.73 m^2 Underestimates GFR when GFR >60 mL/min/1.73 m^2 Less accurate in populations with normal or near normal eGFR, extremes of age and weight, amputees, in pregnancy, and in patients with cirrhosis	Chronic kidney disease when eGFR is 15-60 mL/min/1.73 m^2
Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration Equation[a]		
$GFR = 141 \times \min(S_{Cr}/\kappa,1)^{\alpha} \times \max(S_{Cr}/\kappa,1)^{-1.209} \times 0.993^{age} \times 1.018$ (if female) × 1.159 (if black)[b]	Superior to CGE and MDRD equations in patients with eGFR >60 mL/min/1.73 m^2	More accurate than MDRD equation in elderly population
Cockcroft-Gault Equation (CGE)		
$CrCl = \frac{(140 - age) \times (weight\ in\ kg)}{(72 \times S_{Cr})} \times (0.85\ if\ female)$	Most accurate when eGFR is 15-60 mL/min/1.73 m^2 Underestimates GFR in obesity Overestimates GFR when BMI <25 Takes into account lean body weight, age, and gender	Improved accuracy when age is <65 years
Radionuclide Kidney Clearance Scanning		
Iothalamate GFR scan Diethylenetriamine pentaacetic acid (DTPA) GFR scan	Most precise method; expensive	Kidney donor evaluation if eGFR is borderline for donation; research; prediction of eGFR following nephrectomy

CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; S_{Cr} = serum creatinine (mg/dL); U_{Cr} = urine creatinine (mg/dL).

[a]Mathematical equations recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative for estimation of GFR.

[b]κ is 0.7 for women and 0.9 for men; α is -0.329 for women and -0.411 for men; min = the minimum of S_{Cr}/κ or 1; max = the maximum of S_{Cr}/κ or 1.

Serum cystatin C is an alternative marker of GFR less influenced than serum creatinine by age, gender, muscle mass, and body weight. Cystatin C is produced by all nucleated cells, completely filtered by glomeruli, and then metabolized by renal tubules; serum levels thus provide an index of GFR, without the need to measure urine excretion. Serum cystatin C is more sensitive in identifying milder decrements in kidney function than serum creatinine.

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Estimation of Glomerular Filtration Rate

Isotopic markers that are filtered and not secreted (for example, iothalamate) provide very accurate estimates of GFR but are expensive and not available in routine clinical practice. However, the correlation of these forms of measurement with serum creatinine, age, race, and gender has led to the development of equations that provide a more accurate estimation of GFR than creatinine clearance (see Table 1).

Three estimation equations are commonly used: the Cockcroft-Gault equation (CGE), the Modification of Diet in Renal Disease (MDRD) study equation, and the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation. Each equation was developed in different study populations and uses different variables to provide an estimation of the GFR. Because of this, these equations tend to be more accurate when used in specific clinical circumstances. For example, the MDRD study equation has been validated in multiple populations with CKD but frequently underestimates GFR when it is >60 mL/min/1.73 m^2. The CKD-EPI equation performs better at higher (normal) values of GFR. Despite its long history and widespread use, the CGE equation is slightly less accurate than these newer equations for estimating GFR. Accurate estimation of GFR is important for appropriate adjustment of drug dosing in the elderly population and in patients with kidney disease. Historically, drug-dosing guidelines have been developed based on the estimated creatinine clearance derived from the CGE equation. For the purposes of drug dosing, the CGE equation correlates adequately with GFR as estimated by the MDRD study equation.

Most clinical laboratories employ the MDRD study equation to estimate GFR, with higher levels of GFR reported as ">60 mL/min/1.73 m^2." Physicians may therefore ignore other signs or symptoms of CKD (such as proteinuria) after erroneously assuming that a level reported as normal means an absence of structural kidney disease. Conversely, the appropriateness of labeling a patient who has a stable GFR around 55 mL/min/1.73 m^2 (apart from guiding appropriate drug dosing) as having stage 3 CKD, with no other signs of kidney disease, remains unclear.

KEY POINT

- The Modification of Diet in Renal Disease study equation has been validated in multiple populations with chronic kidney disease but frequently underestimates the glomerular filtration rate (GFR) when it is >60 mL/min/1.73 m^2, whereas the Chronic Kidney Disease Epidemiology Collaboration equation performs better at higher (normal) values of GFR; the Cockcroft-Gault equation is slightly less accurate than these newer equations for estimating GFR but is the basis for drug dosing guidelines.

Interpretation of the Urinalysis

Dipstick analysis and microscopic examination of the urine are indicated in the clinical evaluation of kidney function for both acute and chronic kidney disease (**Table 2**). The sample is best collected without contamination, which requires a "clean catch" midstream collection or a bladder catheterization, and should be examined within 1 hour to minimize the breakdown of formed elements.

Urine Dipstick or Automated Urinalysis

Specific Gravity

Specific gravity is the ratio of the weight of urine to an equal quantity of the weight of water. Normal specific gravity of urine is approximately 1.010, and the typical range of 1.005 to 1.030 varies depending on hydration status and the capacity of the kidneys to maximally dilute and concentrate the urine. Specific gravity is used to estimate the urine osmolality, with a specific gravity of 1.010 approximating a urine osmolality of 300 mOsm/kg H_2O, indicating isosmolar urine; higher or lower values reflect concentrated and dilute urine, respectively.

pH

A typical high-protein American diet results in the need to excrete a high acid load, primarily via the kidneys. The urine in this case is relatively more acidic, ranging from 5.0 to 6.0. An alkaline pH of ≥7.0 can occur in strict vegetarians, postprandially, in type 1 (distal) renal tubular acidosis, or with infections caused by urease-splitting organisms such as *Proteus* and *Pseudomonas* species.

Albumin

Albumin is the predominant protein detected on urine dipstick, which detects albumin excretion graded as trace (5-30 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), and 4+ (>1000 mg/dL). Highly alkaline urine specimens can produce false-positive results on dipstick testing for protein. The sulfosalicylic acid (SSA) test can be used to detect the presence of not only albumin but also other proteins that are not detected with the urine dipstick, such as urine light chains or immunoglobulins. The possibility of cast nephropathy should be raised in patients with acute kidney injury (AKI) when the urine dipstick reads negative or trace for protein, but the urine shows increased positivity for protein by the SSA test. This should be confirmed by immunoelectrophoresis, which can detect urine light chains or Bence-Jones proteins.

Glucose

Glycosuria typically occurs when the plasma glucose concentration is >180 to 200 mg/dL (10.0-11.1 mmol/L). Generalized proximal tubular dysfunction (termed *Fanconi syndrome*) may result in glycosuria in the absence of hyperglycemia or in pregnancy with a change in threshold for glucose.

Ketones

Ketones in the urine are associated with diabetic ketoacidosis, salicylate toxicity, isopropyl alcohol poisoning, and states of starvation such as alcoholic ketoacidosis. Because the urine dipstick detects acetoacetate but not β-hydroxybutyrate, patients who are ketotic with β-hydroxybutyrate as the only ketone body do not display a positive urine dipstick for

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TABLE 2. Findings on Urinalysis

	Reference Range	Comments
Dipstick		
Specific gravity	1.005-1.030	Low with dilute urine; high with concentrated urine or hypertonic product excretion such as with glycosuria and contrast dye
pH	5.0-6.5	Elevated with low acid ingestion, alkaline tide postprandial, inability to excrete acid load (renal tubular acidosis), urease-splitting organisms
Blood	None	False positives with myoglobin or intravascular hemolysis
Albumin	None to trace	Most dipsticks detect primarily albumin but not other proteins; trace positive can be normal in a concentrated specimen; specialized dipsticks designed to detect small amounts of albumin for detection of moderately increased albuminuria (microalbuminuria) are available
Glucose	None	Positive when plasma glucose level exceeds 180 mg/dL (10.0 mmol/L) with lower threshold in pregnancy or Fanconi syndrome
Ketones	None	Positive for acetoacetic acid, not acetone or β-hydroxybutyrate
Nitrites	None	Detects nitrite converted from dietary nitrate by bacteria; normally, no nitrites are present in urine
Leukocyte esterase	None	Detects the presence of leukocytes in the urine; positive test requires at least 3 leukocytes/hpf
Microscopy		
Erythrocytes	0-3/hpf	Urine microscopy should be performed to evaluate erythrocyte morphology
Leukocytes	0-3/hpf	The presence of any leukocytes may be abnormal depending on clinical circumstances
Casts	None or hyaline	Hyaline casts are indicative of poor kidney perfusion but can be benign or reversible; other casts are indicative of intrinsic injury
Crystals	None	Most common include calcium oxalate, calcium phosphate, uric acid, and struvite; occur when urine is supersaturated with a specific substance

ketones; this scenario may occur in patients with alcoholic ketoacidosis. Drugs such as captopril have sulfhydryl groups that can result in a false-positive urine dipstick for ketones.

Blood

The urine dipstick detects both free hemoglobin and intact erythrocytes via measurement of peroxidase activity. One to three erythrocytes/hpf are usually required for a positive result. Other substances with peroxidase activity can cause false-positive reactions, including myoglobin, bacteria expressing peroxidase activity, hypochlorite, rifampin, chloroquine, and certain forms of iodine. Ascorbic acid can cause a false-negative result. A positive urine dipstick for blood but without evidence of erythrocytes on microscopic urinalysis should raise suspicion for hemolysis or rhabdomyolysis; urine myoglobin levels can be measured to confirm rhabdomyolysis.

Leukocyte Esterase and Nitrites

Leukocyte esterase is an enzyme present in leukocytes. The urine dipstick is usually positive for leukocyte esterase when approximately 3 leukocytes/hpf are present. Nitrites result from the conversion of nitrates to nitrites, which occur in urinary tract infections (UTIs) caused by gram-negative organisms, including *Escherichia coli, Klebsiella pneumoniae*, and the *Proteus* and *Pseudomonas* species. False-negative results for nitrites can occur in the setting of a UTI caused by gram-positive organisms such as *Enterococcus* species. The presence of both leukocyte esterase and nitrites on urine dipstick is highly suggestive of a UTI; the absence of both has a high negative predictive value for a UTI.

Bilirubin

Conjugated bilirubin is not usually present in the urine of patients with normal serum bilirubin levels. The presence of conjugated bilirubin is suggestive of severe liver disease or obstructive jaundice. False-positive results occur with chlorpromazine, and false-negative results occur with ascorbic acid.

Urobilinogen

Urobilinogen is produced in the gut from the metabolism of bilirubin and is then reabsorbed and excreted in the urine. A positive urine dipstick for urobilinogen usually results from hemolytic anemia or hepatic necrosis but not from obstructive causes.

KEY POINTS

- Albumin is the predominant protein detected on urine dipstick.
- The presence of both leukocyte esterase and nitrites on urine dipstick is highly suggestive of a urinary tract infection (UTI); the absence of both has a high negative predictive value for a UTI.

HVC

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Urine Microscopy

Microscopic assessment of urine sediment is indicated for patients with abnormalities on urine dipstick or automated urinalysis, AKI, suspicion for glomerulonephritis, or newly diagnosed CKD. Cells, casts, and crystals are possible findings in patients with kidney disease.

Erythrocytes

Erythrocytes in the urine can originate at any location along the genitourinary tract, from the glomerulus to the urethra. Assessment of erythrocyte morphology is a key component in the evaluation of hematuria (see Clinical Evaluation of Hematuria). Isomorphic erythrocytes are of the same size and shape and usually arise from a urologic process causing bleeding into the genitourinary tract such as a tumor, stone, or infection. Dysmorphic erythrocytes have varying sizes and shapes. Acanthocytes, a specific form of dysmorphic erythrocytes, are characterized by vesicle-shaped protrusions (**Figure 2**) and suggest a glomerular source of bleeding. Acanthocytes and erythrocyte casts are highly specific for glomerulonephritis and should prompt evaluation.

Leukocytes

Pyuria refers to excess leukocytes in the urine and is defined as ≥4 leukocytes/hpf. The most common cause of pyuria is a UTI. Sterile pyuria refers to the presence of leukocytes in the urine in the setting of a negative bacterial culture. *Mycobacterium tuberculosis* is an important infectious cause of sterile pyuria. Acute interstitial nephritis is associated with sterile pyuria and low-grade proteinuria; it is often caused by antibiotics, NSAIDs, or proton pump inhibitors. Kidney stones and kidney transplant rejection can also cause sterile pyuria.



FIGURE 2. Urine microscopy demonstrating acanthocytes, indicated in the red circles. Acanthocytes, one form of dysmorphic erythrocytes, are characterized by vesicle-shaped protrusions.

Courtesy of J. Charles Jennette, MD.

Eosinophils

Urine eosinophils are visualized via Wright or Hansel stains. The presence of eosinophils in the urine can be indicative of an allergic reaction, atheroembolic disease, rapidly progressive glomerulonephritis, small-vessel vasculitis, UTI, prostatic disease, or parasitic infections. Poor sensitivity and specificity limit the utility of assays for urine eosinophils in the diagnosis of interstitial nephritis.

Epithelial Cells

Renal tubular epithelial cells have large, central nuclei and are 1.5 to 3 times larger than leukocytes; these can be seen, along with pigmented casts, in the setting of acute tubular necrosis (ATN). Transitional epithelial cells originate anywhere from the renal pelvis to the proximal urethra and are slightly larger than renal tubular epithelial cells. Squamous epithelial cells are large and irregular in shape with small central nuclei and are derived from the distal urethra or external genitalia; their presence denotes urine contaminated by genital secretions.

Casts

Urine casts consist of a matrix comprised of Tamm-Horsfall mucoprotein (also known as uromodulin), which may contain cells, cellular debris, or lipoprotein droplets. Casts are formed within the tubular lumen and are therefore cylindrical. Documentation of particular types of casts is instrumental in the diagnostic evaluation of AKI. ATN may lead to deposition of pigmented epithelial tubular debris in the proteinaceous matrix of the cast, with the formation of pigmented granular (muddy brown) casts (**Figure 3**). An abundance of these casts and renal tubular epithelial cells correlates with the severity of AKI. Erythrocyte casts are highly specific, but not particularly sensitive, for glomerulonephritis. Tubulointerstitial inflammation of the kidney, including pyelonephritis, can lead to the formation of leukocyte casts.



FIGURE 3. Tubular injury (for example, acute tubular necrosis) may lead to deposition of pigmented epithelial tubular debris in the proteinaceous matrix of the cast, with the formation of pigmented granular (muddy brown) casts.

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Crystals

Table 3 highlights the crystals commonly observed in the urine, along with morphology and associated conditions. Certain medications, including sulfadiazine, intravenous acyclovir, methotrexate, and indinavir, can result in crystals in the urine.

TABLE 3. Urine Crystals

Type	Morphology/ Shape	Associated Conditions
Calcium oxalate	Envelope; dumbbell; needle	Hypercalciuria; hyperoxaluria; calcium oxalate stones; ethylene glycol poisoning
Calcium phosphate	Prism; needle; star-like clumps	Distal renal tubular acidosis; urine pH >6.5; tumor lysis syndrome; acute phosphate nephropathy
Uric acid	Rhomboid; needle; rosette	Diabetes mellitus; obesity; gout; hyperuricemia; tumor lysis syndrome; urine pH <6.0
Magnesium ammonium phosphate (struvite)	Coffin-lid	Chronic urinary tract infection with urease-producing organisms
Cystine	Hexagonal	Cystinuria

KEY POINTS

- Isomorphic erythrocytes usually arise from a urologic process such as a tumor, stone, or infection.
- Erythrocyte casts are highly specific, but not particularly sensitive, for glomerulonephritis.

Measurement of Albumin and Protein Excretion

Proteinuria is most commonly comprised of albumin, but other proteins, including kidney-derived low-molecular-weight proteins, monoclonal immunoglobulins and light chains, myoglobin, and hemoglobin, may be present. Low-molecular-weight proteinuria is more common in tubulointerstitial disease or in generalized proximal tubular dysfunction (termed *Fanconi syndrome*), whereas a predominance of albuminuria favors a glomerular process.

Protein detected by urine dipstick should always be quantified. Quantification of proteinuria has traditionally been performed with a 24-hour urine collection, which measures all proteins present in the urine. Due to challenges in feasibility, accuracy, and patient adherence, measurement of proteinuria is now typically performed by determining the ratio of protein or albumin to creatinine on random urine samples. These ratios are easily obtained and correlate well with timed collections. See **Table 4** for the definitions of proteinuria and albuminuria.

The urine protein-creatinine ratio measures all proteins present in the urine, and a value of ≤150 mg/g is considered

TABLE 4. Definitions of Proteinuria and Albuminuria

Total Urine Protein			
Urine Collection Method	**Normal**	**Clinical Proteinuria**	
24-Hour Excretion	<150 mg/24 h	≥150 mg/24 h	
Spot Urine Protein-Creatinine Ratio[a]	≤150 mg/g ≈ ≤150 mg/24 h	>150 mg/g ≈ >150 mg/24 h	
Urine Albumin			
Urine Collection Method	**Normal**	**Moderately Increased Albuminuria (Microalbuminuria)**	**Severely Increased Albuminuria (Macroalbuminuria)**
24-Hour Excretion	<30 mg/24 h	30-300 mg/24 h	>300 mg/24 h
Conventional Spot Urine Dipstick[b]	Negative	Negative	Positive
Albumin-Specific Spot Urine Dipstick[c]	<3.0 mg/dL Negative	≥3.0 mg/dL Positive	Positive
Spot Urine Albumin-Creatinine Ratio[a]	<30 mg/g ≈ <30 mg/24 h	30-300 mg/g ≈ 30-300 mg/24 h	>300 mg/g ≈ >300 mg/24 h

[a]Because of the difficulty of obtaining a 24-hour urine collection, urine protein-creatinine ratio or urine albumin-creatinine ratio on random (spot) urine samples are used to estimate 24-hour excretion. Measurement of either urine protein or albumin concentration in a sample is divided by the creatinine concentration of the same sample to derive a unitless value. These ratios correlate well with the 24-hour excretion of protein or albumin. Although these calculations are technically dimensionless, they may be expressed by different laboratories with their units of calculation, such as mg/g (mg protein or albumin/g creatinine) or with units to reflect the proportional 24-hour excretion amount (mg or g protein or albumin/g creatinine).

[b]Conventional urine dipsticks are more sensitive for detection of albumin than non-albumin proteins; the detection limit is approximately 30 mg/dL, although they are not highly accurate for determining the degree of albuminuria if present.

[c]Urine dipsticks designed specifically to detect small amounts of albuminuria. Similar to conventional urine dipsticks, these dipsticks detect albumin above a concentration threshold but are sensitive to the presence of albumin at lower levels and can be used to indicate the presence of moderately increased albuminuria (microalbuminuria).

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normal. Levels of proteinuria may be diagnostically helpful. Urine protein-creatinine ratios >150 mg/g but <200 mg/g may indicate either tubulointerstitial disease or glomerular disease, whereas nephrotic-range proteinuria, defined as a urine protein-creatinine ratio >3500 mg/g, usually indicates a glomerular process. In patients with evidence of proteinuria, at least two samples on different days should be collected to confirm the diagnosis. It is important to characterize the proteinuria (such as in suspected cast nephropathy) with urine electrophoresis with immunofixation of monoclonal immunoglobulins when indicated.

The urine albumin-creatinine ratio measures only albumin in the urine and is helpful in evaluating for diabetic kidney disease. Because albuminuria is one of the earliest indicators of diabetic kidney disease, the American Diabetes Association (ADA) recommends annual assessment of urine albumin excretion by measuring the urine albumin-creatinine ratio in patients with type 1 diabetes mellitus of 5 years' duration and in all patients with type 2 diabetes starting at the time of diagnosis. Normal albumin excretion by this method is considered <30 mg/g. Although screening for albuminuria is commonly performed in patients with diabetes, the American College of Physicians (ACP) found the current evidence insufficient to evaluate the benefits and harms of screening for CKD in asymptomatic adults with CKD risk factors, including diabetes, hypertension, and cardiovascular disease.

The terminology for describing abnormal albumin excretion has changed. A urine albumin-creatinine ratio of 30 to 300 mg/g, previously termed *microalbuminuria*, is now referred to as *moderately increased albuminuria*, and levels >300 mg/g, previously known as *macroalbuminuria* or *overt proteinuria*, are now termed *severely increased albuminuria*. The diagnosis of moderately increased albuminuria in patients with diabetes is made when two or three random samples obtained over 6 months show a urine albumin-creatinine ratio of 30 to 300 mg/g; the use of ACE inhibitors or angiotensin receptor blockers in these patients has been shown to delay progression of CKD, underscoring the importance of early detection. Once a diagnosis of moderately increased albuminuria has been established and treatment initiated, the ACP recommends against further screening for albuminuria because it will not significantly influence management decisions.

In other patients at increased risk for kidney disease, the urine protein-creatinine ratio is appropriate to evaluate for suspected proteinuria. Transient proteinuria is common and is associated with febrile illnesses or rigorous exercise; it requires no further evaluation. Orthostatic proteinuria occurs when proteinuria increases when the patient is in an upright position and decreases when the patient is recumbent; this benign condition, more common in adolescents, can be assessed with a split urine collection. This test should be obtained in patients younger than 30 years of age who appear to have persistent proteinuria.

KEY POINT

- Measurement of proteinuria is typically performed by determining the ratio of protein or albumin to creatinine on randomly obtained urine samples; these ratios correlate with daily excretion determined by timed collections.

Clinical Evaluation of Hematuria

Hematuria is defined as >3 erythrocytes/hpf and may be either macroscopic (grossly visible) or microscopic (detectable only on urine testing). Hematuria has many potential causes and a wide range of clinical significance. False hematuria or hematuria mimics may be caused by contamination from menstrual bleeding or from substances that produce red-colored urine not due to erythrocytes or hemoglobinuria, including medications (rifampin, phenytoin), food (rhubarb, beets), acute porphyrias, and myoglobinuria. Hemoglobinuria results from the release of free hemoglobin intravascularly in conditions such as hemolysis from perivalvular leak and delayed transfusion reaction. Benign causes of hematuria include infections such as UTIs, nephrolithiasis, trauma, and exercise. Potentially life-threatening and often clinically urgent causes of hematuria include rapidly progressive glomerulonephritis and urinary tract malignancy. Glomerular causes of hematuria also include more benign or indolent diseases such as thin glomerular basement membrane disease, IgA nephropathy, and other forms of chronic glomerulonephritis.

Glomerular hematuria typically features brown- or tea-colored urine with dysmorphic erythrocytes (or acanthocytes) and/or erythrocyte casts on urine sediment examination. Urologic hematuria may include passage of blood clots or pure blood and nondysmorphic erythrocytes. Examination of the urine is not definitive in determining glomerular versus urologic sources of hematuria, especially in patients at risk for genitourinary tract malignancies. Patients with a bleeding diathesis or on anticoagulation merit a complete evaluation; hematuria should not be attributed to the coagulopathy or anticoagulation until other causes have been excluded.

Evaluation of the patient with hematuria begins with a careful history, especially for more benign causes (**Figure 4**). False hematuria should be excluded. Historical and/or laboratory clues may point to a glomerular etiology and the need for nephrology consultation. In patients with suspected glomerular hematuria, extrarenal manifestations of a systemic disease such as vasculitis should be sought.

The American Urological Association (AUA) guidelines for the evaluation of asymptomatic microhematuria recommend CT urography as the imaging modality of choice (**Table 5**, on page 9). The AUA guidelines also recommend cystoscopy for all patients over 35 years of age or those with risk factors for urologic malignancy. The AUA guidelines do not recommend urine cytology for routine evaluation of asymptomatic microhematuria. The U.S. Preventive Services Task Force recommends against using

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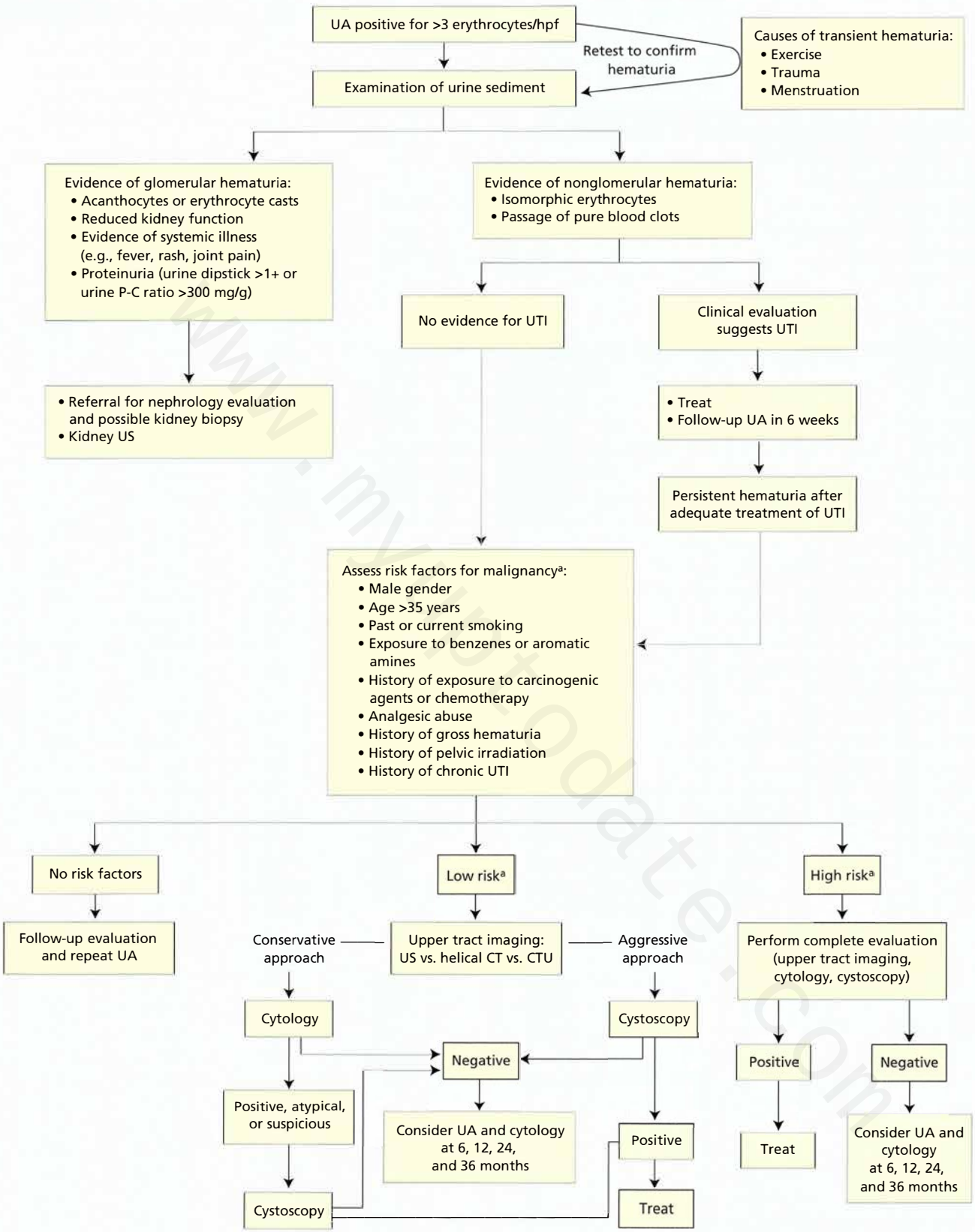

FIGURE 4. The clinical evaluation of hematuria. CTU = computed tomography urography; P-C = protein-creatinine; UA = urinalysis; US = ultrasonography; UTI = urinary tract infection.

[a]Modified from Urology. Grossfeld GD, Litwin MS, Wolf JS, et al. Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy–part II: patient evaluation, cytology, voided markers, imaging, cystoscopy, nephrology evaluation, and follow-up. 2001 Apr;57(4):604-10. [PMID: 11306357] Copyright 2001, modified with permission from Elsevier.

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TABLE 5. Imaging Used in the Evaluation of Hematuria

Study	Advantages	Disadvantages
CT urography (CTU)	High sensitivity (100%) and specificity (97%); image modality of choice	High radiation dose; Risk of CIN; contraindicated in pregnancy
MR urography	Useful in eGFR range of 30-60 mL/min/1.73 m^2 or when CTU is contraindicated	Contraindicated when eGFR <30 mL/min/1.73 m^2 (risk of gadolinium-induced nephrogenic systemic fibrosis); less sensitive than CTU for smaller cancers and stones
Ultrasonography	No contrast or radiation exposure; useful in pregnancy; lower cost	Limited sensitivity, especially for lesions <2 cm and ureteral lesions

CIN = contrast-induced nephropathy; eGFR = estimated glomerular filtration rate.

urinalysis for bladder cancer screening in asymptomatic patients, even those with risk factors.

KEY POINTS

- Potentially life-threatening and often clinically urgent causes of hematuria include rapidly progressive glomerulonephritis and urinary tract malignancy.
- Evaluation of asymptomatic microhematuria should include CT urography except in patients with chronic kidney disease, pregnant patients, or patients allergic to contrast; cystoscopy should be performed in patients over 35 years of age or those with risk factors for urologic malignancy.
- HVC Urinalysis should not be used to screen for bladder cancer in asymptomatic patients.

Imaging Studies

The four main modalities of kidney imaging (ultrasonography, CT, MRI, and radionuclide studies) provide information about structure and function of the urinary tract. Ultrasonography (US) is safe, noninvasive, relatively inexpensive, and easy to obtain. Often the first imaging test in the evaluation of kidney disease, US can assess kidney size and cortical thickness, detect renal cysts and tumors, and diagnose obstruction and hydronephrosis. US is useful for assessment of the bladder, postvoid residual, and the prostate in bladder outlet obstruction but is less helpful in evaluating diseases affecting the mid and distal ureter. Increased echogenicity of the kidney is nonspecific but implies parenchymal disease. Experienced centers have used Doppler US for detection of clinically relevant renal artery stenosis.

US is being increasingly used as an initial diagnostic study for uncomplicated nephrolithiasis. Although less sensitive than CT, particularly for detecting small stones and ureteral stones, it does not expose patients to radiation, is often more readily available, and is usually more cost-effective when compared with CT; it is also the indicated modality during pregnancy. A positive ultrasound may be adequate for initial diagnosis, with CT imaging for those with a nondiagnostic ultrasound or a more complicated clinical presentation.

Noncontrast abdominal helical CT has traditionally been the most commonly used imaging technique for suspected nephrolithiasis because it detects most stones, provides anatomic information, and visualizes the entire urinary tract; it may also suggest stone composition and potentially provide alternative diagnoses if nephrolithiasis is not detected. Contrast abdominal CT characterizes renal tumors and cysts, whereas CT urography is the preferred test for patients with unexplained urologic/nonglomerular hematuria. Intravascular iodinated contrast for CT and angiography may be complicated by contrast-induced nephropathy, especially in patients with CKD. The decision to use contrast depends on the clinical scenario, the patient's risk factors for contrast-induced nephropathy, and the availability and utility of alternative imaging modalities.

Kidney MRI can also identify renal masses, cysts, and renal vein thrombosis. MR angiography with gadolinium contrast can detect renal artery stenosis in the evaluation of possible renovascular hypertension, replacing standard angiography as the preferred modality. However, gadolinium can cause nephrogenic systemic fibrosis (NSF), a systemic fibrosing disorder that occurs predominantly in patients with CKD (typically stage 4 or 5), and gadolinium contrast must be avoided in patients with an estimated GFR <30 mL/min/1.73 m^2. See MKSAP 17 Dermatology for more information on NSF.

Often used for clinical research studies, radionuclide kidney imaging is the gold standard for measuring GFR and renal plasma flow and can be used in the evaluation of a kidney transplant donor candidate with borderline kidney function. In clinical practice, radionuclide scans are most useful for determining relative function of the kidneys, such as a hydronephrotic, atrophic, or cancerous kidney prior to nephrectomy.

KEY POINTS

- HVC Ultrasonography is typically the first imaging test in the evaluation of the kidneys and upper urinary tract because of its safety, cost effectiveness, and general utility.
- Contrast abdominal CT characterizes renal tumors and cysts, whereas CT urography is the preferred test for patients with unexplained urologic/nonglomerular hematuria.

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Kidney Biopsy

Kidney biopsy provides pathologic diagnostic information that can be useful for treatment, disease surveillance, and, potentially, prognosis. Kidney biopsy should be considered in patients with glomerular hematuria, severely increased albuminuria, acute or chronic kidney disease of unclear etiology, and kidney transplant dysfunction or monitoring. Some kidney diseases such as acute interstitial nephritis or atheroembolic disease may be occult and difficult to diagnose without biopsy. Direct visualization by ultrasound or CT is the standard for percutaneous kidney biopsy. Nonpercutaneous approaches for kidney biopsy include open, laparoscopic, or transjugular.

Contraindications to kidney biopsy include bleeding diatheses, severe anemia (especially with patient refusal of blood transfusions), UTI, hydronephrosis, uncontrolled hypertension, anatomic abnormalities, renal tumor, atrophic kidneys, and an uncooperative patient. Solitary native kidney and pregnancy are not absolute contraindications, but careful consideration of the risks and benefits is necessary. Significant complications include pain, macroscopic hematuria, hemorrhage (potentially requiring transfusions, angiography with embolization, and surgery such as nephrectomy), loss of kidney function, and death.

KEY POINT

- Kidney biopsy should be considered in patients with glomerular hematuria, severely increased albuminuria, acute or chronic kidney disease of unclear etiology, and kidney transplant dysfunction or monitoring.

Fluids and Electrolytes

Osmolality and Tonicity

Plasma osmolality is determined by the concentration of sodium and its accompanying anions, plasma glucose, and blood urea nitrogen (BUN). Total osmolality can be directly measured with an osmometer or may be calculated:

$$\text{Plasma Osmolality (mOsm/kg } H_2O) = 2 \times \text{Serum Sodium (mEq/L)} + \text{Plasma Glucose (mg/dL)}/18 + \text{BUN (mg/dL)}/2.8$$

Although both methods indicate the overall osmolality of plasma, urea is freely diffusible across most cell membranes and does not exert a significant osmotic effect. Therefore, the *effective* osmolality (tonicity) is determined by subtracting the measured concentration of urea (divided by 2.8, if in mg/dL) from the measured osmolality. Under normal conditions, the effective osmolality is maintained in the range of 275 to 295 mOsm/kg H_2O.

Disorders of osmolality are usually caused by abnormalities in the relative ratio of sodium to body water. Two key effectors in maintaining normal plasma osmolality are thirst and the level of circulating antidiuretic hormone (ADH; also known as arginine vasopressin), which promotes water reabsorption in the distal tubule and collecting duct of the kidney and has a peripheral vasoconstricting effect. Thirst and ADH release are stimulated by increases in plasma osmolality through central osmoreceptors in the hypothalamus. ADH release is also influenced by volume status; hypovolemia is associated with higher circulating ADH levels at each level of plasma osmolality.

Disorders of Serum Sodium

Hyponatremia

Hyponatremia, defined as a serum sodium concentration <136 mEq/L (136 mmol/L), most often results from an increase in circulating ADH in response to a true or sensed reduction in effective arterial blood volume with resulting fluid retention. Hyponatremia may also be caused by elevated ADH levels associated with the syndrome of inappropriate antidiuretic hormone secretion. Hyponatremia occurring with normal or suppressed ADH levels may be seen in the setting of very low solute intake (such as the "tea and toast" syndrome and "beer potomania"), in which inadequate amounts of solute are available to excrete an increased volume of ingested free water.

Evaluation

The initial evaluation of patients with hyponatremia includes measurement of plasma and urine osmolality and urine sodium as well as a careful assessment of the volume status.

Measurement of plasma osmolality is needed to exclude hyperosmolar hyponatremia and pseudohyponatremia (in which plasma osmolality is normal). Hyperosmolar hyponatremia results from elevated plasma glucose or from exogenously administered solutes such as mannitol or sucrose. Hyperglycemia causes the osmotic translocation of water from the intracellular to the extracellular fluid compartment, which results in a decrease in the serum sodium level by approximately 1.6 mEq/L (1.6 mmol/L) for every 100 mg/dL (5.6 mmol/L) increase in the plasma glucose above 100 mg/dL (5.6 mmol/L).

Pseudohyponatremia is the result of a laboratory error in the measurement of serum sodium. Clinical laboratories measure the amount of sodium present in a dilute serum sample. The serum sodium concentration is then calculated based on the assumption that plasma is 93% water. However, in patients with extreme hyperlipidemia and/or hyperproteinemia, this assumption may not be correct because lipids or protein make up a greater percentage of overall plasma volume. This may result in the reporting of a falsely low serum sodium concentration.

In patients with hypotonic hyponatremia, further evaluation is based on urine osmolality (**Figure 5**). Urine osmolality <100 mOsm/kg H_2O is consistent with appropriately suppressed ADH release as seen in primary polydipsia or inadequate solute intake. Urine osmolality >100 mOsm/kg H_2O indicates that ADH excess is playing a dominant role. Hypotonic

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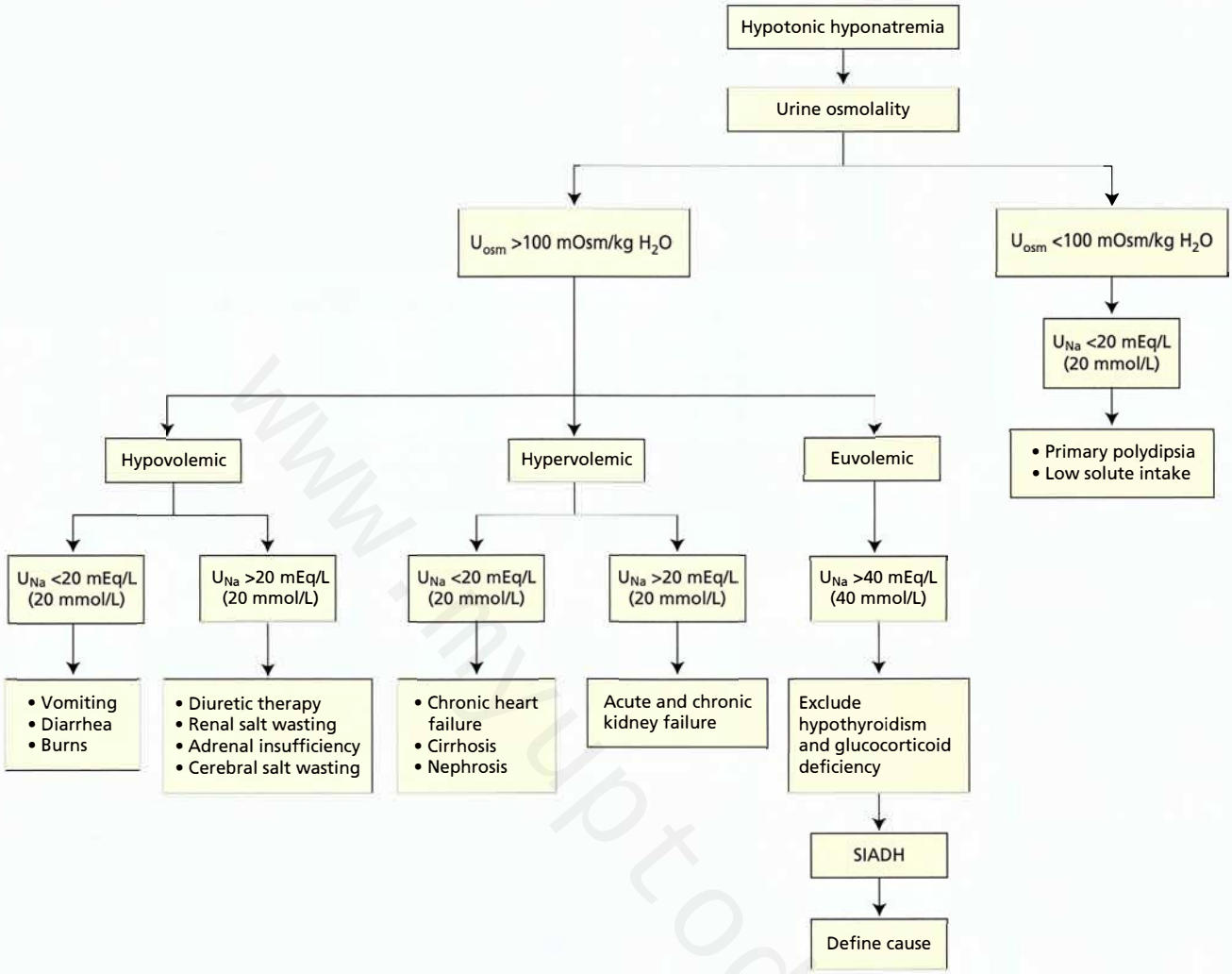

FIGURE 5. Evaluation of hypotonic hyponatremia. SIADH = syndrome of inappropriate antidiuretic hormone secretion; U_{Na} = urine sodium concentration; U_{osm} = urine osmolality.

CONT.

hyponatremia with a urine osmolality >100 mOsm/kg H_2O is classified into three groups based on the clinical volume status: hypovolemic, hypervolemic, and euvolemic.

Hypovolemic Hyponatremia

Hypovolemia causes stimulation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone (RAA) axis, and release of ADH. These adaptive responses allow volume maintenance at the expense of a low serum sodium with excessive water intake.

Extrarenal causes of hypovolemia are common and include loss of sodium from the gastrointestinal tract (vomiting or diarrhea) and insensible loss of sodium chloride (sweating, burns, respiratory tract); in these conditions, the urine sodium concentration is typically <20 mEq/L (20 mmol/L). Renal causes of hypovolemic hyponatremia result in excessive loss of salt and water in the urine with volume depletion; the urine sodium concentration is typically >20 mEq/L (20 mmol/L). Diuretic therapy is the most common cause. Less common are adrenal insufficiency and salt-wasting nephropathies with impaired renal tubular function; typical causes include reflux nephropathy, interstitial nephropathies, post-obstructive uropathy, cystic kidney diseases, and the recovery phase of acute tubular necrosis. The syndrome of cerebral salt wasting is a rare cause due to inappropriate natriuresis from intracranial disease such as subarachnoid hemorrhage, traumatic brain injury, craniotomy, encephalitis, and meningitis.

Hypervolemic Hyponatremia

Patients with hypervolemic hyponatremia have increased total body sodium and water, with the latter dominating and leading to a reduced serum sodium concentration. The pathophysiology of hyponatremia in sodium-avid edematous disorders (heart failure, cirrhosis, and the nephrotic syndrome) is similar to that in hypovolemic hyponatremia, with the kidney sensing a decreased arterial blood volume despite excess total body sodium and water. The urine sodium concentration is typically <20 mEq/L (20 mmol/L) in the absence of diuretic therapy.

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(CONT.) However, in patients with hypervolemic hyponatremia due to acute or chronic kidney failure, there is an inability to effectively manage both sodium and water, leading to an excess of water relative to sodium. In acute or chronic kidney failure, the urine sodium concentration is typically >20 mEq/L (20 mmol/L).

Euvolemic Hyponatremia

Euvolemic hyponatremia results from abnormalities in maintaining sodium and water balance in the setting of normal total volume or to a reset osmostat. Because the effective arterial blood volume is normal, the urine sodium concentration is usually >20 mEq/L (20 mmol/L). The most common cause of euvolemic hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (**Table 6**). It is important to exclude hypothyroidism and glucocorticoid insufficiency in patients with euvolemic hyponatremia and suspected SIADH because thyroid hormone and endogenous glucocorticoid are necessary for normal free water excretion by the kidney.

Reset osmostat refers to a downward setting of the level at which sensors of plasma osmolality trigger the release of antidiuretic hormone and is associated with quadriplegia, tuberculosis, advanced age, pregnancy, psychiatric disorders, and chronic malnutrition. This lowered setpoint leads to mild hypo-osmolar euvolemic hyponatremia.

Clinical Presentation

Patients with acute symptomatic hyponatremia (occurring in <48 hours) often present with symptoms and signs ranging from headache, nausea, and/or vomiting, to altered mental status, seizures, obtundation, central herniation, or death. Acute symptomatic hyponatremia can occur in several clinical settings and is a medical emergency because a sudden drop in serum sodium concentration can overwhelm the capacity of the brain to regulate cell volume, leading to massive cerebral edema.

Due to cerebral adaptation, patients with chronic hyponatremia (developing over >48 hours) are less likely to exhibit severe symptoms and may be completely asymptomatic.

TABLE 6. Causes of the Syndrome of Inappropriate Antidiuretic Hormone Secretion

Central nervous system disorders: Guillain-Barré syndrome; hemorrhage[a]; infections; inflammatory disorders; mass lesions[a]; multiple sclerosis
Drugs: 3,4-methylenedioxymethamphetamine (also known as ecstasy)[a]; antipsychotic medications; carbamazepine; chlorpropamide; clofibrate; cyclooxygenase-2 inhibitors[a]; cyclophosphamide; desmopressin[a]; ifosfamide; nicotine; NSAIDs[a]; opiates[a]; phenothiazines; selective serotonin reuptake inhibitors[a]; serotonin-norepinephrine reuptake inhibitors[a]; tricyclic antidepressants; vasopressin[a]; vincristine
Endurance exercise (marathon running)
Familial disorders
Infections: HIV infection; Rocky Mountain spotted fever
Postoperative setting: anesthesia[a]; nausea[a]; pain[a]
Pulmonary disorders: infections[a]; inflammatory disorders; positive pressure mechanical ventilation[a]; respiratory failure
Tumors: gastrointestinal tract tumors; genitourinary tract tumors; lymphomas; respiratory tract tumors[a]; sarcomas; small cell cancer[a]; thymomas

[a]Most common causes.

KEY POINTS

- Initial evaluation of hyponatremia includes measurement of plasma and urine osmolality and urine sodium as well as clinical assessment of volume status.
- Hypotonic hyponatremia evaluation begins with urine osmolality; urine osmolality <100 mOsm/kg H_2O suggests appropriately suppressed antidiuretic hormone (ADH), whereas urine osmolality >100 mOsm/kg H_2O suggests ADH excess.

Management

In patients with hyponatremia, the severity of symptoms determines the urgency and intensity of therapy. Additionally, when treating hyponatremia, the rate of correction of serum sodium concentration must be carefully considered to avoid the osmotic demyelination syndrome (ODS). Brain cells adapt to chronic hyponatremia by reducing intracellular concentration of organic osmolytes to cope with hypotonicity. Because of this, rapid correction (>8.0 mEq/L [8.0 mmol/L] within the first 24 hours and/or >16 mEq/L [16 mmol/L] within the first 48 hours) may cause neuronal cell damage with resulting demyelination. ODS classically affects the pons, resulting in central pontine myelinolysis; patients may present days after overcorrection of hyponatremia with para- or quadriparesis, dysphagia, dysarthria, diplopia, a "locked-in" syndrome, and/or loss of consciousness.

Acute Symptomatic Hyponatremia

Initial treatment of acute symptomatic hyponatremia includes hypertonic saline to acutely increase serum sodium concentration by 1.0 to 2.0 mEq/L (1.0-2.0 mmol/L) per hour to a total increase of 4.0 to 6.0 mEq/L (4.0-6.0 mmol/L) within the first 6 hours; this increase is typically sufficient to alleviate acute symptoms, avoiding overly rapid correction as previously discussed. The achieved serum sodium should be maintained at a constant level for the first 24 hours. Because the response to hypertonic saline can be highly unpredictable due to a rapid reduction in circulating ADH and the excretion of a dilute urine, frequent (every 1 to 2 hours) measurements of serum sodium concentration are necessary. Should the serum sodium concentration be inadvertently overcorrected, hyponatremia can be safely re-established by administration of the vasopressin agonist desmopressin and intravenous 5% dextrose in water, with monitoring of the serum sodium concentration.

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Intravenous loop diuretics increase free water excretion by interfering with the renal countercurrent multiplication system and may facilitate acute treatment. Vasopressin antagonists do not have a role in the management of acute symptomatic hyponatremia.

Chronic Hyponatremia

In patients with hypovolemic hyponatremia, diagnosis and correction of the underlying cause of hypovolemia are indicated. In patients requiring specific treatment, volume repletion with oral salt supplementation or intravenous isotonic saline suppresses circulating ADH and induces a water diuresis.

Management of hypervolemic hyponatremia includes treatment of the underlying disorder, sodium and free water restriction (in practical terms, fluid restriction), and diuretic therapy. In patients with heart failure, vasopressin antagonists (such as tolvaptan and conivaptan) are effective in normalizing hyponatremia; however, use of these agents should be limited to patients with a serum sodium concentration <120 mEq/L (120 mmol/L) despite optimal therapy with diuresis and RAA system inhibition. Neither tolvaptan nor conivaptan is currently recommended for the treatment of hyponatremia associated with cirrhosis.

The initial treatment of euvolemic hyponatremia includes management of the underlying cause if possible. Fluid restriction without limiting sodium intake is a cornerstone of therapy. Patients who do not respond to fluid restriction can be treated with loop diuretics combined with oral salt supplementation.

Oral demeclocycline, which induces nephrogenic water loss, can be utilized to treat SIADH that fails fluid restriction or furosemide plus salt. However, demeclocycline can be associated with acute kidney injury from natriuresis and/or direct renal toxicity and is contraindicated in patients with cirrhosis. Vasopressin antagonists (oral tolvaptan and intravenous conivaptan) have been shown to be effective in normalizing serum sodium concentration in SIADH. Oral tolvaptan should be reserved for the management of serum sodium concentrations <120 mEq/L (120 mmol/L) and persistent SIADH that has failed fluid restriction and/or oral furosemide and salt tablets. Liver chemistry test abnormalities have been reported with chronic tolvaptan therapy; therefore, the use of this drug should be limited to less than 1 to 2 months, with close laboratory monitoring.

KEY POINTS

- Initial treatment of acute symptomatic hyponatremia includes hypertonic saline to acutely increase serum sodium concentration by 1.0 to 2.0 mEq/L (1.0-2.0 mmol/L) per hour to a total increase of 4.0 to 6.0 mEq/L (4.0-6.0 mmol/L) within the first 6 hours; the achieved serum sodium should be maintained for the first 24 hours.

(Continued)

KEY POINTS *(continued)*

- Chronic asymptomatic hypervolemic hyponatremia management includes treatment of the underlying disorder, sodium and free water restriction, and diuretic therapy.
- First-line therapy of euvolemic hyponatremia includes treatment of the underlying cause and free water restriction, and second-line therapy includes loop diuretics combined with oral salt supplementation followed by oral demeclocycline; vasopressin antagonists should be reserved for patients with a serum sodium concentration <120 mEq/L (120 mmol/L) who are unresponsive to first- and second-line therapy.

HVC

Hypernatremia

Hypernatremia, defined as a serum sodium concentration >145 mEq/L (145 mmol/L), is often the result of a combined water and volume deficit, with losses of water in excess of sodium. Considerably less common than hyponatremia, hypernatremia is associated with mortality rates of approximately 40% to 60%. Elderly individuals with reduced thirst and/or diminished access to fluids are at the highest risk of developing hypernatremia. Patients with hypernatremia may rarely have a central defect in hypothalamic osmoreceptor function, with both decreased thirst and reduced ADH secretion.

More commonly, hypernatremia may develop following the loss of free water via renal or extrarenal routes. Insensible losses of water due to evaporation from the skin or respiratory tract may increase in the setting of fever, exercise, heat exposure, severe burns, or mechanical ventilation. Osmotic diarrhea and viral gastroenteritides typically generate hypo-osmotic stools, leading to significant free water loss and hypernatremia. Secretory diarrheas typically do not result in hypernatremia; rather, the isotonic stool loss causes hypovolemia with or without hypovolemic hyponatremia.

Common causes of renal water loss include osmotic diuresis secondary to hyperglycemia, post-obstructive diuresis, or drugs (contrast, mannitol). Water diuresis occurs in central or nephrogenic diabetes insipidus. Central diabetes insipidus results from inadequate secretion of ADH from the hypothalamus (see MKSAP 17 Endocrinology and Metabolism, Disorders of the Pituitary Gland). Nephrogenic diabetes insipidus results from resistance of the kidney to the action of ADH and has multiple causes. Gestational diabetes insipidus is a rare complication of pregnancy wherein increased activity of a placental protease with "vasopressinase" activity leads to reduced circulating ADH. See **Table 7** for more information.

Evaluation

In patients with hypernatremia, the history should focus on the presence or absence of thirst, polyuria, and/or an extrarenal source for water loss such as diarrhea. The physical examination should include a neurologic examination and assessment of volume status; accurate documentation of daily

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TABLE 7. Causes of Diabetes Insipidus

Central diabetes insipidus
Autoimmune hypophysitis (idiopathic)[a]
Malignancy (metastatic or primary)[a]
Neurosurgery[a]
Infiltration (sarcoidosis, histiocytosis X, lymphocytic hypophysitis, granulomatosis with polyangiitis [formerly known as Wegener granulomatosis], IgG4-related disease)[a]
Trauma
Following correction of supraventricular tachycardia
Hypoxic encephalopathy
Anorexia nervosa
Sheehan syndrome
Familial
Nephrogenic diabetes insipidus
Lithium[a]
Other medications (demeclocycline, cidofovir, foscarnet, didanosine, amphotericin B, ifosfamide, ofloxacin)[a]
Electrolyte disorders (hypercalcemia, hypokalemia)[a]
Urinary tract obstruction
Sickle cell nephropathy
Amyloidosis
Sjögren syndrome
Nephronophthisis
Cystinosis
Gestational diabetes insipidus (placental "vasopressinase")

[a]Most common causes.

TABLE 8. Correction of Hypernatremia

H_2O Deficit
Estimate total body water (TBW): 50%-60% body weight (kg) depending on body composition
Calculate free water deficit: $[(Na^+ - 140)/140] \times TBW$
Administer deficit over 48-72 h
Ongoing H_2O Losses
Calculate free water clearance (C_eH_2O): $V\left(1 - \frac{U_{Na} + U_K}{S_{Na}}\right)$ Where V is urine volume, U_{Na} is urine sodium, U_K is urine potassium, and S_{Na} is serum sodium
Insensible Losses
~10 mL/kg/d: less if ventilated, more if febrile
Total
Add components to determine H_2O deficit and ongoing H_2O loss; correct the water deficit over 48-72 h and replace daily H_2O loss

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CONT.

fluid intake and daily urine output is also required. Laboratory studies include measurement of plasma and urine osmolality as well as urine electrolytes. The appropriate renal response to hypernatremia and a plasma osmolality >295 mOsm/kg H_2O is the excretion of low volumes (<500 mL/24 h) of maximally concentrated urine (>800 mOsm/kg H_2O).

Most patients with hypernatremia and polyuria have a predominant water diuresis with hypotonic urine. However, those who have an osmotic diuresis as a cause of hypernatremia will demonstrate excessive excretion of sodium chloride, glucose, and/or urea, with a urine osmolality of >750 to 1000 mOsm/24 h (>15 mOsm/kg body water/24 h). In patients with hypotonic urine and suspected diabetes insipidus, differentiation between nephrogenic and central causes is made by the response of urine osmolality to desmopressin. For patients with hypernatremia due to renal loss of water, it is critical to quantify ongoing daily losses using the formula for electrolyte-free water clearance, in addition to calculation of the baseline water deficit (**Table 8**).

Management

The underlying condition leading to hypernatremia should be identified and addressed; patients diagnosed with desmopressin-sensitive nephrogenic diabetes insipidus should be started on chronic therapy. The approach to the management of hypernatremia is outlined in Table 8. The water deficit should be corrected over 48 to 72 hours to avoid neurologic compromise. Depending on the blood pressure or clinical volume status, initial treatment with hypotonic saline solutions (1/4 or 1/2 normal saline) may be appropriate; plasma glucose should be monitored in patients treated with large volumes of 5% dextrose in water. Calculation of urinary electrolyte-free water clearance is helpful to estimate daily, ongoing loss of free water in patients with nephrogenic or central diabetes insipidus.

KEY POINT

- Management of hypernatremia involves correction of the water deficit and replacement of daily water loss; the water deficit should be corrected slowly (over 48-72 hours) to avoid neurologic compromise.

Disorders of Serum Potassium

Hypokalemia

Hypokalemia is defined as a serum potassium concentration <3.5 mEq/L (3.5 mmol/L). Patients have minimal symptoms unless serum potassium levels are <3.0 mEq/L (3.0 mmol/L). Symptoms range from generalized weakness and malaise to paralysis, depending on the serum potassium level. Rhabdomyolysis can occur with serum potassium levels <2.5 mEq/L (2.5 mmol/L), and ascending paralysis with respiratory failure is seen with levels <2.0 mEq/L (2.0 mmol/L). Symptoms correlate with the

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rapidity of the decrease. In patients with heart conditions, mild to moderate hypokalemia increases the risk of cardiac arrhythmias.

Evaluation

Hypokalemia can occur from transcellular shift of potassium or from a decrease in total body potassium through decreased intake, renal loss, or extrarenal loss. The cause can be determined by a thorough history, physical examination, and measurement of serum and urine electrolytes (**Figure 6**). The history should focus on medications and history of vomiting or diarrhea. The blood pressure (including examination for orthostasis) and volume status should be assessed. Pseudohypokalemia, a laboratory artifact caused by uptake of potassium by cells in the test tube from patients with leukemia, should be ruled out.

Abrupt development of hypokalemia suggests a transient shift of potassium from the extracellular compartment into cells. Medications commonly result in intracellular shifts, including sympathomimetic agents (epinephrine, decongestants, bronchodilators), phosphodiesterase inhibitors (theophylline, caffeine), and insulin. Systemic alkalosis (respiratory, metabolic) may also be associated with acute hypokalemia. Hypokalemic periodic paralysis is a rare familial or acquired disorder characterized by flaccid generalized weakness from a sudden intracellular potassium shift precipitated by strenuous exercise or a high-carbohydrate meal. The acquired form occurs with thyrotoxicosis and is found in

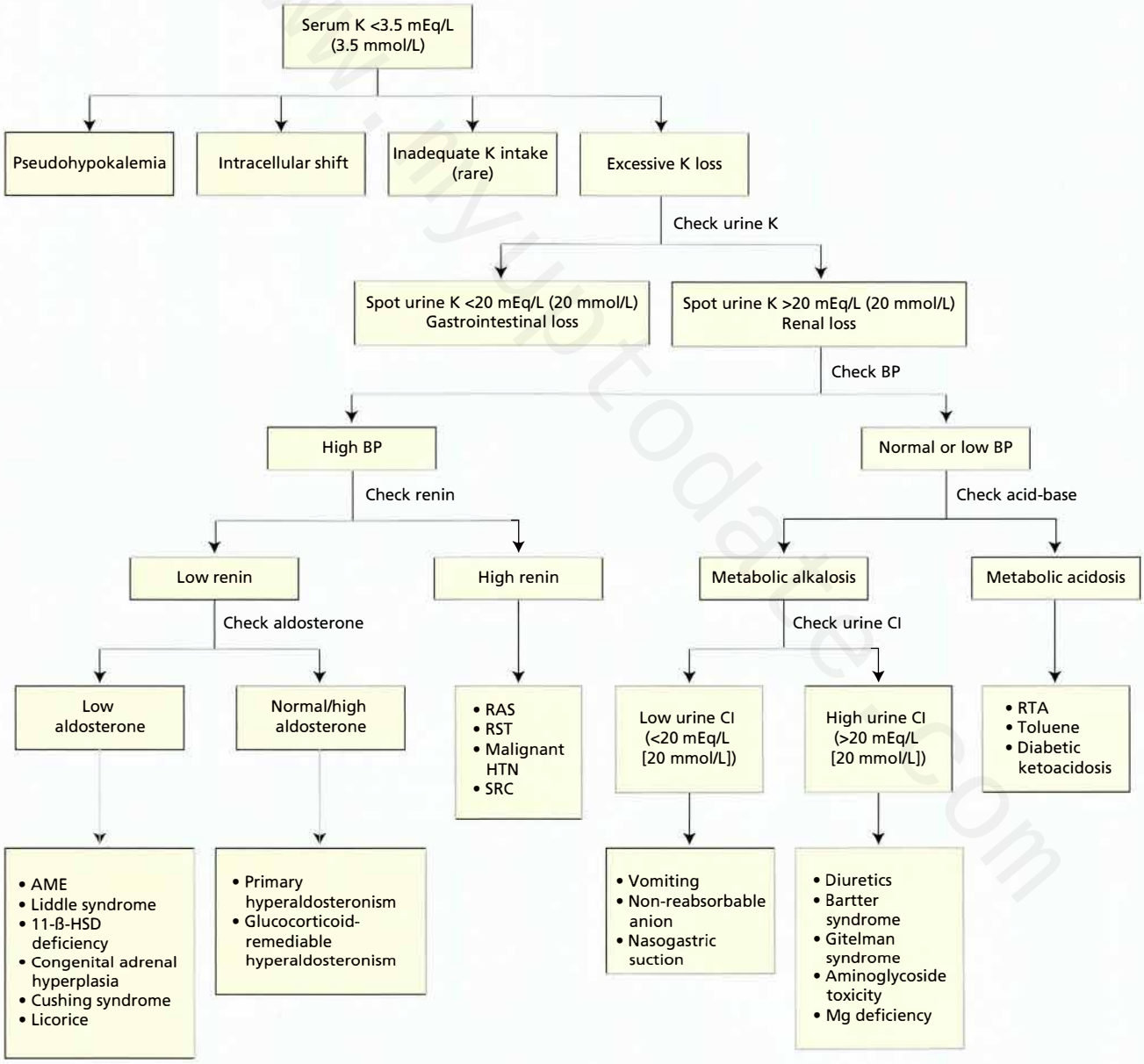

FIGURE 6. Causes of hypokalemia. AME= syndrome of apparent mineralocorticoid excess; BP = blood pressure; Cl = chloride; HSD = hydroxysteroid dehydrogenase; HTN = hypertension; K = potassium; Mg = magnesium; RAS = renal artery stenosis; RST = renin-secreting tumor; RTA = renal tubular acidosis; SRC = scleroderma renal crisis.

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men of Asian or Mexican descent. It is resolved with treatment of hyperthyroidism.

Hypokalemia from decreased total body potassium can be the result of extrarenal or renal losses. Because the kidneys can reduce urine potassium excretion to <20 mEq/24 h (20 mmol/24 h), hypokalemia from inadequate intake is uncommon. Urinary or gastrointestinal losses of potassium are most common. Assessment of urine potassium excretion is critical to establish renal potassium wasting. Urine potassium loss >20 mEq/24 h (20 mmol/24 h), a spot urine potassium >20 mEq/L (20 mmol/L), or a spot urine potassium-creatinine ratio >13 mEq/g (1.5 mEq/mmol) suggests excessive urinary losses. Conversely, urine potassium loss <20 mEq/24 h (20 mmol/24 h) suggests cellular shift, decreased intake, or extrarenal losses of potassium.

Urine potassium loss can be caused by enhanced sodium delivery and urine flow to the collecting duct and increased mineralocorticoid activity (**Table 9**). Blood pressure measurement can help define the cause; patients with increased mineralocorticoid activity have evidence of volume expansion with elevated blood pressure. The specific etiology can be further differentiated by plasma renin activity and aldosterone levels (see Figure 6). Patients with hypokalemia due to increased distal sodium delivery can have findings of volume depletion and low or normal blood pressure. The specific cause can be further determined by acid-base status and urine sodium and chloride levels (see Figure 6). Diuretics are the most common cause of increased distal sodium delivery.

TABLE 9. Causes of Renal Potassium Loss

Increased Urine Flow or Sodium Delivery to Distal Nephron
Diuretics: loop diuretics; thiazides; carbonic anhydrase inhibitors
Antibiotics: high-dose penicillin
Osmotic diuresis: diabetes mellitus; mannitol
Saline diuresis
Renal tubular acidosis
Gitelman syndrome
Bartter syndrome
Increased Mineralocorticoid Activity
Exogenous mineralocorticoid
Primary hyperaldosteronism: adrenal adenoma; bilateral adrenal hyperplasia; glucocorticoid-remediable aldosteronism
Congenital adrenal hyperplasia: 17-α-hydroxylase deficiency; 11-β-hydroxylase deficiency
Secondary hyperaldosteronism: renin-secreting tumor; renovascular disease
Liddle syndrome
11-β-hydroxysteroid dehydrogenase deficiency: congenital; acquired (licorice, carbenoxolone)
Cushing syndrome

Management

Patients with hypokalemia who have arrhythmias or symptomatic severe hypokalemia (serum potassium concentration <2.5 mEq/L [2.5 mmol/L]) should be promptly treated with intravenous potassium chloride at a rate no faster than 20 mEq/h (20 mmol/h) and a maximum concentration of 40 mEq/L (40 mmol/L). Patients with mild symptoms and serum potassium levels of 2.5 to 3.5 mEq/L (2.5-3.5 mmol/L) may only need oral potassium replacement. Potassium-sparing diuretics can be used in patients with normal kidney function who are prone to significant hypokalemia. Magnesium depletion should be corrected because it can cause and maintain renal potassium loss.

KEY POINTS

- Urine potassium loss >20 mEq/24 h (20 mmol/24 h) suggests excessive urinary losses; urine potassium loss <20 mEq/24 h (20 mmol/24 h) suggests cellular shift, decreased intake, or extrarenal losses.
- Hypokalemia due to increased mineralocorticoid activity can be associated with volume expansion and elevated blood pressure.
- Hypokalemia due to increased distal sodium delivery can be associated with volume depletion and low or normal blood pressure; diuretics are the most common cause.

Hyperkalemia

Hyperkalemia is defined as a serum potassium level >5.0 mEq/L (5.0 mmol/L). Any level >6.0 mEq/L (6.0 mmol/L) can be life-threatening. Generally, a slowly rising serum potassium level is better tolerated than an abrupt rise. Signs and symptoms are related to adverse effects of serum potassium on skeletal and cardiac muscle cell membranes, including muscle weakness and cardiac conduction and rhythm abnormalities.

Evaluation

Initial evaluation of hyperkalemia begins with the history, medication review, and physical examination. Laboratory studies should be targeted toward the diagnosis suggested by the history and physical examination. Because of the potential cardiac effects of hyperkalemia, immediate electrocardiography (ECG) is indicated. The earliest ECG changes of hyperkalemia are peaking of the T waves and shortening of the QT interval. As hyperkalemia progresses, there is prolongation of the PR interval, loss of P waves, and eventual widening of the QRS complexes with a "sine-wave" pattern that can precede asystole.

Hyperkalemia can result from increased potassium intake, decreased urine potassium excretion, or a shift of potassium from the intracellular to extracellular space (**Figure 7**). Excessive intake and extracellular shift are uncommon as the sole causes of hyperkalemia. Often, multiple etiologies are present simultaneously, such as increased potassium intake in the setting of chronic kidney disease (CKD). Disorders causing transcellular

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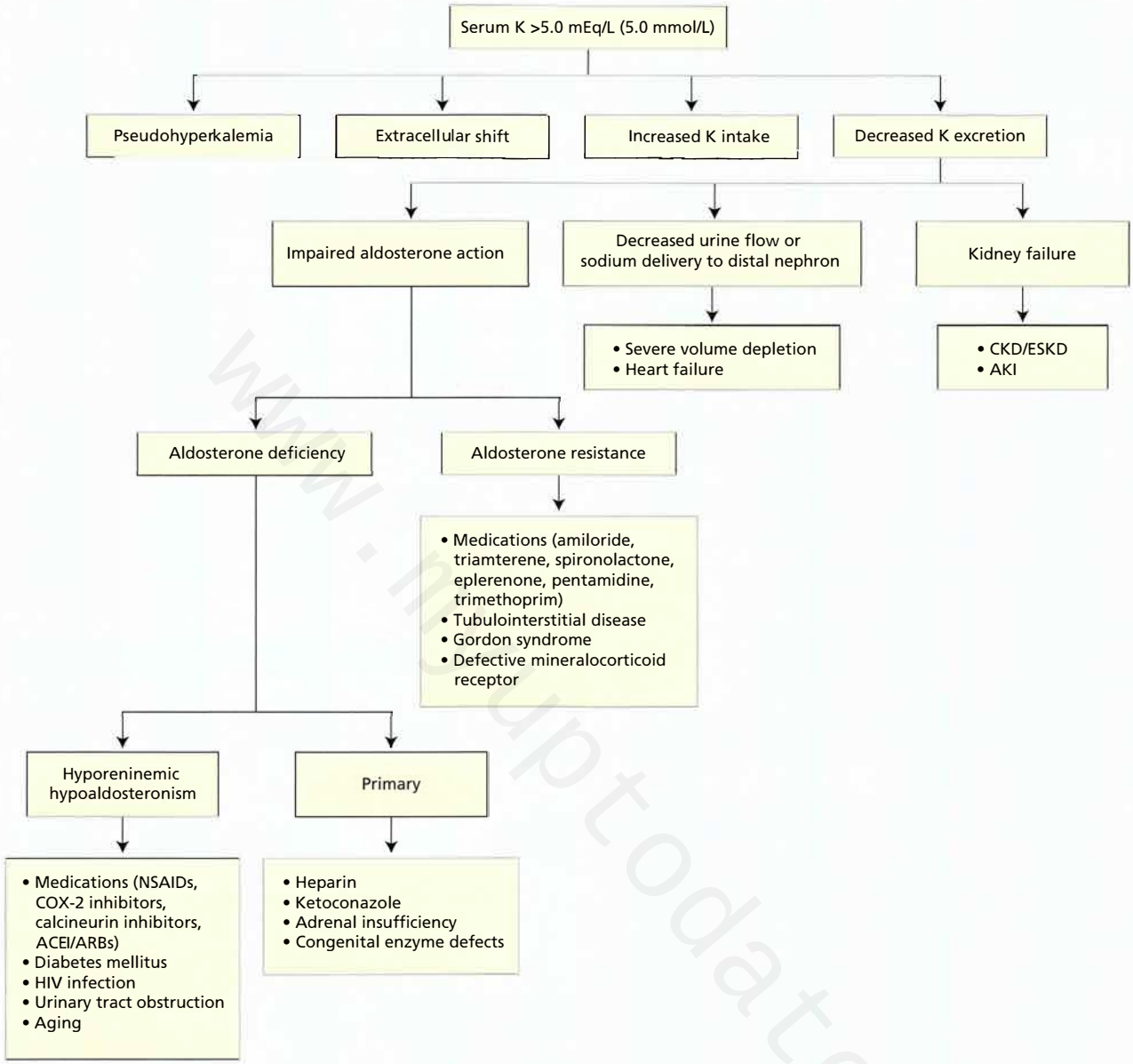

FIGURE 7. Causes of hyperkalemia. ACEI = angiotensin-converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; COX = cyclooxygenase; ESKD = end-stage kidney disease; K = potassium.

CONT.

shifts include drug-induced (digoxin toxicity, succinylcholine, β-blockers, somatostatin) and non-drug-induced (metabolic acidosis, insulin deficiency, rhabdomyolysis, tumor lysis, hemolysis, hyperosmolarity, hyperkalemic periodic paralysis) causes. Pseudohyperkalemia occurs with a false rise in potassium values from cellular release of potassium during venipuncture due to hemolysis or prolonged tourniquet use. It also occurs with significant leukocytosis or thrombocytosis. Pseudohyperkalemia can be ruled out by checking serum and plasma potassium levels simultaneously, with the plasma level being normal.

Major underlying causes of persistent hyperkalemia are disorders in which urine potassium excretion is impaired. The most common cause is CKD with a glomerular filtration rate <20 mL/min/1.73 m^2 or acute kidney injury. Other causes include decreased distal sodium delivery and impaired aldosterone action; aldosterone is the primary hormone that facilitates urine potassium excretion (see Figure 7). Medications commonly associated with hyperkalemia from impaired aldosterone activity include potassium-sparing diuretics, trimethoprim, NSAIDs, and ACE inhibitors.

A spot urine test for potassium, creatinine, and osmolality should be obtained to calculate the transtubular potassium gradient (TTKG) and assess for impaired aldosterone action. The TTKG is an assessment of renal potassium handling and is calculated as follows:

TTKG = (Urine Potassium ÷ Plasma Osmolality)/
(Serum Potassium ÷ Urine Osmolality)

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A TTKG <3 suggests decreased aldosterone effect on the collecting tubules with inadequate potassium excretion. A TTKG >8 suggests appropriate excretion by the kidneys. The TTKG is only valid if the urine osmolality exceeds plasma osmolality and if urine sodium is >20 mEq/L (20 mmol/L).

Management

Severe hyperkalemia with ECG changes requires immediate stabilization of the myocardial cell membrane, rapid shifting of potassium intracellularly, and total body potassium elimination. All sources of potassium should be removed. Intravenous calcium is used for membrane stabilization. Improvement in ECG changes occurs within minutes of calcium infusion with duration of action of 30 to 60 minutes. Repeated doses can be given while other measures are initiated. Calcium infusion is contraindicated in digoxin toxicity because it can worsen the myocardial effects. Shifting of potassium from extracellular to intracellular is done either with insulin or with high-dose inhaled β-adrenergic agonists. Insulin is given as 10 units intravenously with 50 mL of 50% dextrose; this acts in 10 to 20 minutes, and duration is 4 to 6 hours. In patients who are hyperglycemic, insulin alone may be sufficient. The onset of action of β-adrenergic agonists is 3 to 5 minutes and lasts for 1 to 4 hours. The effect of insulin and β-adrenergic agonists is additive. Sodium bicarbonate may be used to promote intracellular shift of potassium in the setting of metabolic acidosis.

Removal of total body potassium is achieved by drug therapy or dialysis. Potassium excretion can be increased with the use of loop diuretics in combination with saline infusion to ensure delivery of sodium to the distal nephron with normal kidney function. Sodium polystyrene sulfonate (SPS) binds potassium in the colon in exchange for sodium and can be given orally or as a retention enema, the latter form being faster. One of the potential adverse effects of sorbitol-containing SPS preparations is bowel necrosis. Hemodialysis is indicated for life-threatening hyperkalemia in severe CKD or unresponsiveness to standard therapy.

Long-term treatment of hyperkalemia should be directed at correcting the underlying cause in addition to initiating a low-potassium diet and discontinuing hyperkalemia-causing medications. Loop diuretics or fludrocortisone may be needed for patients who have hyporeninemic hypoaldosteronism with hyperkalemia. Chronic diuretic therapy can be used in patients with CKD and mild hyperkalemia.

KEY POINT

- Severe hyperkalemia with electrocardiogram changes requires immediate stabilization of the myocardial cell membrane with intravenous calcium; rapid shifting of potassium intracellularly with insulin or β-adrenergic agonists; total body potassium elimination with loop diuretics, sodium polystyrene sulfonate, or dialysis; and removal of all sources of potassium.

Disorders of Serum Phosphate

Hypophosphatemia

Hypophosphatemia, defined as a serum phosphate concentration <3.0 mg/dL (0.97 mmol/L), is seen in patients with chronic alcohol use, malnutrition, or critical illness. Symptoms rarely occur unless the serum phosphate concentration is <2.0 mg/dL (0.65 mmol/L); severe symptoms occur with a serum phosphate concentration <1.0 mg/dL (0.32 mmol/L). Symptoms include weakness, myalgia, rhabdomyolysis, arrhythmias, heart failure, respiratory failure, seizures, coma, and hemolysis.

Evaluation

Hypophosphatemia occurs because of inadequate intake, intracellular shift, decreased intestinal absorption, or increased urine loss (**Table 10**). Spurious hypophosphatemia can be caused by interference of paraproteins with the phosphate assay. The Fanconi syndrome is characterized by a type 2 (proximal) renal tubular acidosis with urine loss of bicarbonate as well as phosphaturia, glucosuria, and aminoaciduria.

TABLE 10. Causes of Hypophosphatemia

Inadequate Intake
Intracellular Shift
Refeeding
Treatment of diabetic ketoacidosis
Respiratory alkalosis
Drugs: insulin; glucagon; epinephrine; β_2-agonists; glucocorticoids; xanthine derivatives
Rapid cell proliferation/uptake: hungry bone syndrome; acute leukemia
Decreased Intestinal Absorption
Phosphate-binding antacids (aluminum; sucralfate)
Vitamin D deficiency
Chronic diarrhea
Steatorrhea
Increased Urine Loss
Hyperparathyroidism
Vitamin D disorders: vitamin D deficiency; hypophosphatemic rickets
Oncogenic osteomalacia
Volume expansion
Fanconi syndrome: heavy metal intoxication; Wilson disease; hereditary fructose intolerance; multiple myeloma; tenofovir; ifosfamide
Diuretics: acetazolamide; metolazone
Osmotic diuresis
Metabolic acidosis
Kidney transplantation

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CONT.

Hypophosphatemia also occurs in patients receiving continuous renal replacement therapy.

If the cause of hypophosphatemia is not evident from the history, a 24-hour urine phosphate collection or calculation of the fractional excretion of filtered phosphate (FEPO4) from a random urine sample can help differentiate renal from extrarenal causes. The FEPO4 can be calculated as follows:

$$FEPO4 = (\text{Urine PO4} \times \text{Serum Creatinine} \times 100) / (\text{Serum PO4} \times \text{Urine Creatinine})$$

Urine phosphate excretion >100 mg/d or an FEPO4 >5% indicates renal phosphate wasting.

Management

Treatment of hypophosphatemia depends on the cause, severity, and duration. Mild or moderate hypophosphatemia can be managed with oral replacement therapy. Patients with severe hypophosphatemia and clinical findings should be treated with intravenous phosphate, with serum phosphate and calcium levels monitored every 6 hours.

KEY POINTS

- Hypophosphatemia symptoms rarely occur unless the serum phosphate concentration is <2.0 mg/dL (0.65 mmol/L) and include weakness, myalgia, rhabdomyolysis, arrhythmias, heart failure, respiratory failure, seizures, coma, and hemolysis.
- Mild or moderate hypophosphatemia can be managed with oral replacement therapy; severe symptomatic hypophosphatemia should be treated with intravenous phosphate, with serum phosphate and calcium levels monitored every 6 hours.

Hyperphosphatemia

Hyperphosphatemia is defined as a serum phosphate concentration >4.5 mg/dL (1.45 mmol/L). Most patients are asymptomatic.

Evaluation

Hyperphosphatemia is caused by excessive intake, acute extracellular shift of phosphate, or decreased urine excretion (**Table 11**). Spurious hyperphosphatemia can be caused by substances that interfere with the phosphate assay, including hyperglobulinemia, hyperbilirubinemia, hyperlipidemia, and in vitro hemolysis. The cause often can be determined from the clinical history and is most commonly due to CKD or acute kidney injury.

Management

Management of hyperphosphatemia includes treating the underlying cause. Phosphate excretion can be enhanced by forced saline diuresis if kidney function is intact. Patients with symptomatic hypocalcemia and decreased kidney function may need hemodialysis. Treatment of chronic hyperphosphatemia includes dietary phosphate restriction and phosphate binders.

TABLE 11. Causes of Hyperphosphatemia

Excessive Intake
Excessive use of phosphate-containing bowel preparations
Vitamin D intoxication
Milk-alkali syndrome
Extracellular Shift
Rhabdomyolysis
Tumor lysis syndrome
Acute hemolysis
Acute acidosis
Decreased Excretion
Acute or chronic kidney failure
Hypoparathyroidism
Acromegaly
Severe hypomagnesemia
Familial tumoral calcinosis
Bisphosphonates

KEY POINT

- The most common causes of hyperphosphatemia are chronic kidney disease and acute kidney injury.

Acid-Base Disorders

Introduction

The systemic pH is controlled through renal and respiratory mechanisms, which preserve a stable internal milieu. Disturbances in acid-base balance lead to predictable responses that limit the magnitude of change of the blood pH. The cause is usually evident by reviewing results from arterial or venous blood gas studies (pH, Pco_2) and venous electrolyte measurements (serum bicarbonate and anion gap).

Primary acid-base disorders are classified by their underlying mechanism (*metabolic* or *respiratory*) and their effect on acid-base balance (*acidosis* or *alkalosis*). In primary metabolic acidosis without additional acid-base disorders, the serum bicarbonate is below the normal range. In primary metabolic alkalosis, the serum bicarbonate is above normal. In primary respiratory acidosis, the arterial Pco_2 is above the normal range. In primary respiratory alkalosis, the Pco_2 is below normal.

Analysis of acid-base disorders involves identification of the likely primary acid-base disorder, followed by assessment of the compensatory response (**Table 12**). A mixed acid-base disorder is present when measured values fall outside the range of the predicted secondary response; multiple acid-base disturbances may coexist.

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TABLE 12. Compensation in Acid-Base Disorders

Condition	Expected Compensation
Metabolic acidosis	Acute: $Pco_2 = (1.5)[Hco_3] + 8$
	Chronic: $Pco_2 = [Hco_3] + 15$
	Failure of the Pco_2 to decrease to the expected value = complicating respiratory acidosis; excessive decrease of the Pco_2 = complicating respiratory alkalosis
	Quick check: Pco_2 = value should approximate last two digits of pH
Metabolic alkalosis	For each ↑ 1.0 mEq/L (1.0 mmol/L) in $[Hco_3]$, Pco_2 ↑ 0.7 mm Hg (0.09 kPa)
Respiratory acidosis	Acute: 1.0 mEq/L (1.0 mmol/L) ↑ $[Hco_3]$ for each 10 mm Hg (1.3 kPa) ↑ in Pco_2
	Chronic: 3.5 mEq/L (3.5 mmol/L) ↑ $[Hco_3]$ for each 10 mm Hg (1.3 kPa) ↑ in Pco_2
	Failure of the $[Hco_3]$ to increase to the expected value = complicating metabolic acidosis; excessive increase in $[Hco_3]$ = complicating metabolic alkalosis
Respiratory alkalosis	Acute: 2.0 mEq/L (2.0 mmol/L) ↓ $[Hco_3]$ for each 10 mm Hg (1.3 kPa) ↓ in Pco_2
	Chronic: 4.0-5.0 mEq/L (4.0-5.0 mmol/L) ↓ $[Hco_3]$ for each 10 mm Hg (1.3 kPa) ↓ in Pco_2
	Failure of the $[Hco_3]$ to decrease to the expected value = complicating metabolic alkalosis; excessive decrease in $[Hco_3]$ = complicating metabolic acidosis

The overall effect of one or more acid-base disorders is reflected in the blood pH, which may be near normal (due to appropriate compensation), acidemic (indicated by a pH below the normal range), or alkalemic (indicated by a pH above the normal range).

Although the most accurate measurement of pH and Pco_2 is obtained from arterial blood, in many cases, venous blood gases can be used either diagnostically or to follow therapy. However, in patients in shock, there may be a significant discrepancy between arterial and venous blood gases, with lower pH and higher Pco_2 values in the latter. In other patients with critical illness, there is minimal difference between the acid-base parameters determined on venous versus arterial blood gas analysis.

Metabolic Acidosis

General Approach

A depressed serum bicarbonate level is the primary indicator of metabolic acidosis in patients without an additional acid-base disorder. Because respiratory alkalosis with renal compensation can also cause a depressed serum bicarbonate level, the diagnosis should be confirmed with measurement of the pH and Pco_2. When metabolic acidosis is present, the anion gap is useful in assessing whether the decreased serum bicarbonate is due to an unmeasured organic anion such as lactate (increased anion gap metabolic acidosis) or to a loss of bicarbonate (normal anion gap metabolic acidosis). The anion gap is calculated from the following equation:

Anion Gap = Serum Sodium (mEq/L) − [Serum Chloride (mEq/L) + Serum Bicarbonate (mEq/L)]

The normal reference range for the anion gap is approximately 8 to 10 mEq/L ± 2 mEq/L (8-10 mmol/L ± 2 mmol/L). In normal subjects, albumin is the major unmeasured anion responsible for the anion gap. Changes in the serum albumin concentration can have a significant effect on the anion gap. Unless a correction is made for the change in the albumin concentration from normal, patients with hypoalbuminemia may seem to have a decreased anion gap, and patients with hyperalbuminemia may seem to have an increased anion gap. In patients with abnormalities in albumin concentration, an albumin-corrected anion gap should be calculated as follows:

Albumin-Corrected Anion Gap = Anion Gap + 2.5 × [Normal Albumin − Measured Albumin (g/dL)]

When an increased anion gap metabolic acidosis is present, calculation of the corrected bicarbonate is helpful in assessing the possible presence of a coexisting normal anion gap metabolic acidosis and/or metabolic alkalosis:

Corrected Bicarbonate = 24 mEq/L − Δ Anion Gap (mEq/L)

(in which Δ anion gap is the increase in the albumin-corrected anion gap above normal)

A measured bicarbonate less than the corrected bicarbonate suggests a concomitant normal anion gap metabolic acidosis. A measured bicarbonate greater than the corrected bicarbonate suggests a concomitant metabolic alkalosis.

Another method is to assess the ratio of the change in the anion gap (Δ anion gap) to the change in bicarbonate level (Δ bicarbonate), or the "Δ-Δ ratio." A ratio of <1 may reflect the presence of concurrent normal anion gap metabolic acidosis, whereas a ratio of >2 may indicate the presence of metabolic alkalosis.

In patients with an increased anion gap acidosis, calculation of the plasma osmolal gap is helpful in assessing the presence of unmeasured solutes, such as ingestion of certain toxins (for example, methanol or ethylene glycol). The plasma osmolal gap is the difference between the measured and calculated plasma osmolality. Plasma osmolality can be calculated using the following formula:

Plasma Osmolality (mOsm/kg H_2O) = 2 × Serum Sodium (mEq/L) + Plasma Glucose (mg/dL)/18 + BUN (mg/dL)/2.8

When the measured osmolality exceeds the calculated osmolality by >10 mOsm/kg H_2O, the osmolal gap is considered elevated. Although an elevated osmolal gap usually reflects the presence of unmeasured solutes, an increased osmolal gap may also be seen in pseudohyponatremia, in which the plasma osmolality (and measured osmolality) is normal while the calculated osmolality is low (See Fluid and Electrolytes).

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KEY POINTS

- A depressed serum bicarbonate level is the primary indicator of metabolic acidosis in patients without an additional acid-base disorder.
- When metabolic acidosis is present, the anion gap is useful in assessing whether the decreased serum bicarbonate is due to an unmeasured organic anion (increased anion gap metabolic acidosis) or to a loss of bicarbonate (normal anion gap metabolic acidosis).

Increased Anion Gap Metabolic Acidosis

An increased albumin-corrected anion gap metabolic acidosis occurs when unmeasured anions are present. These anions may be metabolic by-products (for example, lactate or ketoacids) or associated with ingested substances (for example, ethylene glycol or methanol); the plasma osmolal gap may be used to differentiate between these causes.

Lactic acidosis is a common cause of an increased anion gap metabolic acidosis. Types and causes of lactic acidosis are described in **Table 13**.

Diabetic ketoacidosis (DKA) and alcoholic ketoacidosis (AKA) are also common causes of increased anion gap metabolic acidosis. DKA usually presents with an increased anion gap metabolic acidosis but can present with a normal anion gap in the absence of hypovolemia due to excretion of ketoacids in the urine. Symptoms include polyuria, polydipsia, dehydration, nausea, vomiting, abdominal pain, and hyperventilation. Insulin deficiency, increased catecholamines, and glucagon result in incomplete oxidation of fatty acids, which leads to the production of acetoacetate and β-hydroxybutyrate. The presence of acetoacetate or acetone can be measured using the nitroprusside assay in urine dipsticks or by directly measuring serum assays for specific ketone bodies. Because β-hydroxybutyrate is the dominant acid in DKA, the urine dipstick results can be falsely negative in the presence of severe DKA. Ketoacidosis will reverse with insulin and fluid administration; therefore, sodium bicarbonate therapy is generally reserved for patients with a pH <7.0 or metabolic instability due to acidosis (See MKSAP 17 Endocrinology and Metabolism).

AKA occurs in patients with chronic ethanol abuse. Patients present with abdominal pain and vomiting after abruptly stopping alcohol. Increased alanine and aspartate aminotransferase levels and hyperbilirubinemia are common due to concurrent alcoholic hepatitis. AKA typically responds to treatment with intravenous saline and intravenous glucose, with rapid clearance of the associated ketones due to a reduction in counter-regulatory hormones and the induction of endogenous insulin.

A number of other unmeasured anions, most often associated with medications or toxin ingestions, can also cause increases in the anion gap (**Table 14**). Although a single organic

TABLE 13. Causes of Lactic Acidosis

Condition	Cause	Clinical and Laboratory Manifestations	Treatment	Comments
Lactic acidosis		Serum lactate level >4.0 mEq/L (4.0 mmol/L)	Treat underlying cause; sodium bicarbonate when arterial pH is <7.1 to raise pH to 7.2	Most common cause of increased AG metabolic acidosis
Type A lactic acidosis	Tissue hypoperfusion	Evidence of multi-system organ dysfunction typically present	Correct cause of hypoperfusion	—
Type B lactic acidosis				
Propofol	Propofol >4 mg/kg/h for >24 h	Rhabdomyolysis; hyperlipidemia; cardiogenic shock	Discontinue propofol; HD	—
Metformin	Metformin use in patients with S_{Cr} >1.4-1.5 mg/dL (123.8-132.6 µmol/L)	—	HD	Rare complication; mortality 30%-50%
Hematologic malignancy	Thought to be due to anaerobic metabolism in cancer cells	Severe type B lactic acidosis; hypoglycemia	Treat underlying malignancy	Portends very poor prognosis; seen in high-grade B-cell lymphomas
D-Lactic acidosis	Short-bowel syndrome[a]; undigested carbohydrates in the colon are metabolized to D-lactate	Intermittent confusion; slurred speech; ataxia; increased AG metabolic acidosis with normal serum lactate level	Antibiotics (e.g., metronidazole or neomycin) directed toward bowel flora; restriction of dietary carbohydrates	Diagnosis requires measurement of D-lactate because D-isomer is not measured by specific assays

AG = anion gap; HD = hemodialysis; S_{Cr} = serum creatinine.

[a]After jejunoileal bypass or small-bowel resection.

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TABLE 14. Selected Causes of Increased Anion Gap Metabolic Acidosis

Condition	Cause	Clinical and Laboratory Manifestations	Treatment	Comments
Ethylene glycol ingestion	Glycolic acid accumulation; calcium oxalate precipitation in renal tubules and crystals in the urine	Flank pain; AKI; hypocalcemia; nephrocalcinosis; cardiovascular collapse; neurotoxicity; pulmonary edema	HD Fomepizole Sodium bicarbonate Pyridoxine and thiamine in suspected ethylene glycol toxicity	Suspect ingestion with increased AG acidosis and a serum bicarbonate level <10 mEq/L (10 mmol/L) and a plasma osmolal gap >10 mOsm/kg H_2O May be difficult to differentiate from methanol ingestion
Methanol ingestion	Formic acid accumulation	Impaired vision/ blindness mediated by formic acid; papilledema; mydriasis; afferent pupillary defect; abdominal pain; pancreatitis	Fomepizole HD Sodium bicarbonate Folic acid in suspected methanol toxicity	Suspect ingestion with increased AG acidosis and a serum bicarbonate level <10 mEq/L (10 mmol/L) and a plasma osmolal gap >10 mOsm/kg H_2O May be difficult to differentiate from ethylene glycol ingestion 80%-90% mortality rate with methanol ingestion; permanent blindness may occur
Propylene glycol toxicity	Large doses of propylene glycol (a solvent used for IV medications), most commonly lorazepam diluted in propylene glycol (80%)	AKI; AG metabolic acidosis with increased plasma osmolal gap; toxicity when propylene glycol levels >25 mg/dL or plasma osmolal gap >10 mOsm/kg H_2O	Discontinue the IV infusion HD	Monitor acid-base status and plasma osmolality when lorazepam doses >1 mg/kg/d; unlikely to develop if 24-h lorazepam dose is limited to <166 mg/d
Salicylate toxicity	Salicylate anion accumulation; ingestion of as little as 10 grams of aspirin in adults	Tinnitus; tachypnea; low-grade fever; nausea/vomiting; impaired mental status; cerebral edema and fatal brainstem herniation; acute lung injury; noncardiogenic pulmonary edema; hepatic injury; respiratory alkalosis; with severe intoxication, AG metabolic acidosis, lactic acidosis, ketoacidosis	IV glucose (100 mL of 50% dextrose) in adults when mental status changes are present, irrespective of the plasma glucose level HD for AKI, impaired mental status, cerebral edema, serum salicylate levels >80 mg/dL, severe AG metabolic acidosis, pulmonary edema Vitamin K for increased INR	Toxicity can develop from ingestion or mucocutaneous exposure to salicylate preparations such as methyl salicylate (oil of wintergreen)
Acetaminophen toxicity	Pyroglutamic acidosis; most common in critically ill patients, those with poor nutrition, liver disease, CKD, and in vegetarians	Impaired mental status; on urine testing for organic anions, high concentrations of urine pyroglutamate	Discontinue acetaminophen Sodium bicarbonate Possibly *N*-acetylcysteine to regenerate depleted glutathione stores	Female preponderance (80%); genetic factors may play a role

AG = anion gap; AKI = acute kidney injury; CKD = chronic kidney disease; HD = hemodialysis; IV = intravenous.

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CONT. anion may be primarily responsible for each condition, multiple metabolic products may also contribute to the anion gap. For example, an elevated lactate may accompany many of the disorders discussed in Table 14.

KEY POINTS

- Lactic acidosis is defined as a serum lactate level >4.0 mEq/L (4.0 mmol/L); management includes treatment of the underlying cause and sodium bicarbonate when arterial pH is <7.1.
- Ethylene glycol or methanol ingestion should be suspected in patients with an increased anion gap acidosis associated with a serum bicarbonate level <10 mEq/L (10 mmol/L) and a plasma osmolal gap >10 mOsm/kg H_2O.

Normal Anion Gap Metabolic Acidosis

The normal physiologic response to systemic acidosis is an increase in urine acid excretion. Therefore, an initial diagnostic step in normal anion gap metabolic acidosis is to determine whether the kidney is appropriately excreting acid or whether impaired kidney acid excretion is the cause of the metabolic acidosis. Increased acid excretion by the kidney is reflected as a marked increase in urine ammonium. However, urine ammonium is difficult to measure directly. Because ammonium carries a positive charge, chloride is excreted into the urine in equal amounts with ammonium to maintain electrical neutrality. Therefore, the amount of chloride in the urine reflects the amount of ammonium present, and the urine anion gap can be used as an indicator of the ability of the kidney to excrete acid:

Urine Anion Gap = Urine Sodium + Urine Potassium − Urine Chloride

If the kidney is able to appropriately excrete acid, the urine anion gap is negative, and if there is a defect in kidney acid excretion, the urine anion gap is positive. For example, in patients with normal anion gap metabolic acidosis due to extrarenal bicarbonate loss (for example, laxative abuse or diarrhea) or an acid load, the kidney should excrete increased urine ammonium (and chloride), resulting in a markedly negative (-20 to -25 mEq/L [-20 to -25 mmol/L]) urine anion gap. In contrast, in patients with impaired urine acidification due to kidney disease or a defect in the distal renal tubule, urine ammonium (and chloride) levels are low, with the urine anion gap being markedly positive (20 to 40 mEq/L [20 to 40 mmol/L]). Along with serum potassium and urine pH, determination of the urine anion gap can help differentiate between common causes of normal anion gap metabolic acidosis (**Table 15**).

Type 2 (Proximal) Renal Tubular Acidosis

Metabolic acidosis in type 2 (proximal) renal tubular acidosis (RTA) is caused by a defect in the proximal tubule resulting in a diminished ability to reabsorb filtered bicarbonate (**Table 16**). Type 2 (proximal) RTA is usually not an isolated phenomenon but rather part of Fanconi syndrome, a generalized defect in proximal tubular function. Bicarbonate will be lost in the urine until the resorptive threshold for bicarbonate is reached, causing a normal anion gap metabolic acidosis. The impaired reabsorption of bicarbonate is also associated with decreased sodium chloride reabsorption and increased sodium delivery to the distal tubule and sodium loss, causing hypovolemia and triggering secondary hyperaldosteronism; this leads to a tendency for salt wasting and hypokalemia.

Because distal urine acidification capability is preserved, the urine pH in patients with type 2 (proximal) RTA is variable. When bicarbonate intake exceeds the resorptive threshold, the proximal tubule does not reabsorb the normal amount of filtered bicarbonate and the urine pH is alkalotic. If bicarbonate intake is below the resorptive threshold, the filtered bicarbonate can be reabsorbed normally, and the intact distal tubule can acidify the urine to a pH <5.5. Treatment of type 2 (proximal) RTA consists of alkali replacement with the addition of a thiazide diuretic, which causes mild volume depletion that enhances the proximal reabsorption of sodium and bicarbonate.

Type 1 (Hypokalemic Distal) Renal Tubular Acidosis

Type 1 (hypokalemic distal) RTA results from a defect in urine acidification in the distal tubule with impaired excretion of hydrogen ions (**Table 17**). Patients with type 1 (hypokalemic distal) RTA are unable to acidify their urine below a pH of 6.0, even after an acid load. Because proximal reabsorption of

TABLE 15. Diagnostic Approach to Normal Anion Gap Metabolic Acidosis

Diagnosis	Serum Potassium	Urine AG	Urine pH
Ammonium chloride ingestion (acid load)	Normal	Negative	<5.5
Diarrhea and acidosis	Normal	Negative	<5.5
Type 2 (proximal) RTA	Decreased	Negative	Variable[a]
Type 1 (hypokalemic distal) RTA	Decreased	Positive	>5.5
Type 4 (hyperkalemic distal) RTA	Increased	Positive	<5.5

AG = anion gap; RTA = renal tubular acidosis.

[a]Patients with type 2 (proximal) RTA have normal distal renal tubular function and can acidify the urine once the serum bicarbonate drops to a point at which the filtered load of bicarbonate can be normally reabsorbed.

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TABLE 16. Causes of Type 2 (Proximal) Renal Tubular Acidosis
Isolated Type 2 (Proximal) Renal Tubular Acidosis
Primary: hereditary ($Na\text{-}HCO_3$ cotransporter); sporadic (often transient)
Hereditary carbonic anhydrase deficiency: carbonic anhydrase inhibitors
Fanconi Syndrome (associated glycosuria, phosphaturia, aminoaciduria, hypouricemia)
Primary: hereditary Fanconi syndrome
Genetic: cystinosis; Wilson disease
Acquired: Sjögren syndrome; paraproteinemias; vitamin D deficiency
Drugs/toxins: ifosfamide; tacrolimus; cyclosporine; toluene; outdated tetracycline; lead; mercury; cidofovir; tenofovir

TABLE 17. Causes of Type 1 (Hypokalemic Distal) Renal Tubular Acidosis
Primary: hereditary
Genetic: sickle cell disease; Fabry disease; Wilson disease; elliptocytosis
Medullary cystic kidney disease
Autoimmune disorders: Sjögren syndrome; systemic lupus erythematosus
Nephrocalcinosis/hypercalciuria
Dysproteinemias: amyloidosis; cryoglobulinemia; hypergammaglobulinemia
Drugs/toxins: amphotericin B; lithium; analgesic abuse
Tubulointerstitial disease: reflux nephropathy; obstructive uropathy; kidney transplant rejection

CONT. filtered citrate increases in acidosis, hypocitraturia is also present, which results in calcium phosphate kidney stones and nephrocalcinosis. Treatment consists of potassium citrate at a dose of 1 mEq/kg/d.

Type 4 (Hyperkalemic Distal) Renal Tubular Acidosis

Type 4 (hyperkalemic distal) RTA is caused by aldosterone deficiency or resistance. Primary aldosterone deficiency is seen in primary adrenal deficiency (Addison disease). Hyporeninemic hypoaldosteronism occurs in patients with various kidney diseases (including acute glomerulonephritis) and chronic nephropathies (such as diabetes mellitus, systemic lupus erythematosus, or AIDS). Patients with conditions that cause tubulointerstitial disease, including urinary obstruction, sickle cell disease, medullary cystic kidney disease, and kidney transplant rejection, may demonstrate resistance to aldosterone. Drug-induced type 4 (hyperkalemic distal) RTA can be caused by numerous drugs that reduce aldosterone production, including ACE inhibitors, cyclooxygenase inhibitors, trimethoprim, and heparin.

Initial treatment includes correction of the underlying cause if possible, with discontinuation of offending medications. In most cases, treatment of hyperkalemia with sodium bicarbonate or sodium polystyrene sulfonate results in improvement of the acidosis. Replacement of mineralocorticoids with fludrocortisone is indicated for patients with Addison disease and should be considered for those with hyporeninemic hypoaldosteronism unless hypertension or heart failure is present. Management should also include dietary potassium restriction to approximately 2000 mg/d.

Mixed Forms of Renal Tubular Acidosis

Genetic defects in carbonic anhydrase result in combined proximal and distal RTA. An acquired form can develop in patients treated with topiramate, which inhibits carbonic anhydrase in both the proximal and distal tubule. Topiramate is associated with an increased risk of calcium phosphate stones because of the high urine pH (>6.0 despite acidemia) and hypocitraturia.

Acidosis in Acute and Chronic Kidney Disease

In patients with acute and chronic kidney disease, metabolic acidosis is mediated by two mechanisms: 1) decreased urine ammonium excretion with hyperkalemia when the glomerular filtration rate (GFR) decreases to <45 mL/min/1.73 m^2, causing normal anion gap metabolic acidosis, and 2) retention of sulfates, phosphates, and organic acids when the GFR decreases to <15 mL/min/1.73 m^2, resulting in an increased anion gap metabolic acidosis. H

KEY POINTS

- Treatment of type 2 (proximal) renal tubular acidosis consists of alkali replacement with the addition of a thiazide diuretic.
- Treatment of type 1 (hypokalemic distal) renal tubular acidosis consists of potassium citrate at a dose of 1 mEq/kg/d.
- Treatment of type 4 (hyperkalemic distal) renal tubular acidosis includes correction of the underlying cause, treatment of hyperkalemia, discontinuation of offending medications, and dietary potassium restriction.

Metabolic Alkalosis H

Metabolic alkalosis is defined by the retention of excess alkali and is diagnosed by an elevation in serum bicarbonate concentration. This disorder is caused by either a loss of acid or administration or retention of bicarbonate. The organ systems responsible for the initial metabolic alkalosis include the gastrointestinal (GI) tract (in vomiting-induced acid loss), the kidney (typically a mineralocorticoid effect, either as a primary disorder or in response to other causes of intravascular volume depletion, with resulting sodium and bicarbonate retention at the expense of acid and potassium secretion),

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CONT.

and, rarely, the skin (from excessive sweating in patients with cystic fibrosis, resulting in chloride depletion and bicarbonate retention).

Metabolic alkalosis occurs in two phases: a generation phase in which the primary disorder (such as vomiting or the accumulation of alkali) occurs, and a maintenance phase in which the typical renal compensation of excreting excess bicarbonate in the distal tubule is ineffective. Conditions that contribute to the maintenance of metabolic alkalosis include volume contraction, ineffective arterial blood volume, hypokalemia, chloride depletion, and decreased glomerular filtration.

Symptoms of metabolic alkalosis are typically related to the underlying disorder itself rather than the alkalosis. The concomitant hypokalemia poses far greater risk due to the potential for cardiac arrhythmias. When severe (serum bicarbonate >50 mEq/L [50 mmol/L]), metabolic alkalosis leads to hypocalcemia, hypoventilation, and hypoxemia, with potential neurologic consequences (seizures, delirium, stupor).

The first diagnostic step is a thorough history and physical examination. The assessment of blood pressure and volume status is critical to identify the likely etiology of the metabolic alkalosis (**Figure 8**). Laboratory evaluation of metabolic alkalosis to determine volume status and etiology is based on urine chloride rather than urine sodium. The urine sodium can be artificially high during periods of appropriate compensatory urine bicarbonate excretion because sodium is the primary cation excreted together with the bicarbonate. Urine sodium may also be misleading with diuretic use. Metabolic alkalosis is considered saline-resistant when associated with increased extracellular fluid volume and hypertension. Metabolic alkalosis is considered saline-responsive when associated with true

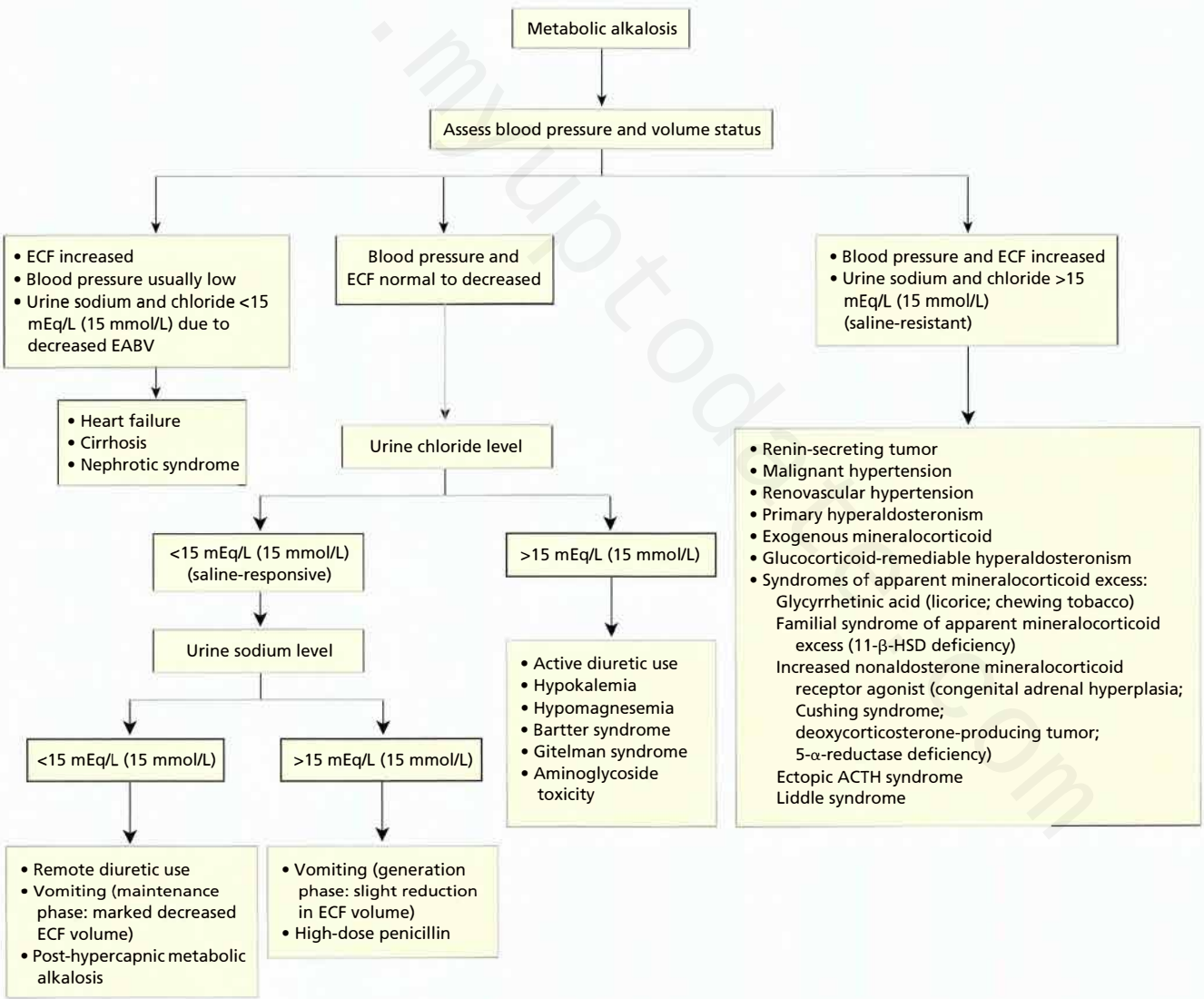

FIGURE 8. Evaluation of metabolic alkalosis. ACTH = adrenocorticotropic hormone; EABV = effective arterial blood volume; ECF = extracellular fluid; HSD = hydroxysteroid dehydrogenase.

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CONT.

hypovolemia and responds to correction of the volume deficit with isotonic saline.

The most common conditions that cause metabolic alkalosis are associated with chloride depletion (vomiting, nasogastric suction, and diuretic use). Although upper GI disorders (such as vomiting) are the most common GI source for the generation of metabolic alkalosis, rare lower GI disorders that cause chloride depletion include forms of chloride-secretory diarrhea such as villous adenoma and congenital chloridorrhea that lead to an increase in bicarbonate retention. A "contraction alkalosis" results from loss of extracellular fluid containing low amounts of bicarbonate that contract the extracellular volume around a constant amount of existing circulating bicarbonate.

In patients with low urine chloride (<15 mEq/L [15 mmol/L]), normal/low intravascular volume, and normal/low extracellular volume, treatment consists of administration of saline together with repletion of potassium (saline-responsive metabolic alkalosis) while addressing the primary cause of the alkalosis. In contrast, those with a low urine chloride (<15 mEq/L [15 mmol/L]) and normal/low intravascular volume but with an increased extravascular volume have a disorder of effective arterial blood volume such as heart failure, cirrhosis, or hypoalbuminemia from the nephrotic syndrome that results in secondary hyperaldosteronism, sodium and bicarbonate retention, and an increase in extracellular volume manifested by edema. Treatment is tailored to improving effective arterial blood volume and diuresis. For those who have a high urine chloride (>15 mEq/L [15 mmol/L]) with elevated blood pressure, hypokalemia, and do not appear to be overtly volume overloaded, a mineralocorticoid excess disorder must be considered (saline-resistant metabolic alkalosis). The lack of an overt increase in extravascular volume in the latter condition is often described as "aldosterone escape," in which sodium balance is attained through spontaneous diuresis that occurs after initial sodium retention that returns the vascular volume toward normal. This condition is treated with potassium repletion and treatment of the underlying condition.

Rarely, patients with metabolic alkalosis may appear to have clinical features consistent with saline-responsive metabolic alkalosis (normal/low extracellular fluid status, normal/low blood pressure) but have a urine chloride of >15 mEq/L (15 mmol/L). Diuretic use and inherited kidney disorders of sodium and chloride handling such as Bartter and Gitelman syndromes can mimic this presentation. These are two autosomal recessive genetic disorders of renal sodium and chloride transporters that clinically mimic loop diuretic and thiazide diuretic use, respectively. These diagnoses should be considered only after urine diuretic screening. Treatment focuses on the correction of volume and potassium depletion, and, in the case of Bartter syndrome, inhibition of prostaglandin production with indomethacin or ibuprofen to reduce sodium and chloride delivery to the distal tubule.

KEY POINTS

- The assessment of blood pressure and volume status is critical to identify the likely etiology of metabolic alkalosis.
- Treatment of metabolic alkalosis is based upon urine chloride and both extracellular and intravascular volume assessment.

Respiratory Acidosis

Respiratory acidosis is the result of inadequate CO_2 exchange from the pulmonary capillaries to the alveoli; the resultant arterial CO_2 retention (hypercapnia) is initially buffered by water, leading to formation of excess hydrogen ions and bicarbonate. Thus, the typical arterial blood gas in this setting demonstrates an elevation in P_{CO_2}, a decrease in pH, and a slight increase in bicarbonate (see Table 12).

The most common causes of respiratory acidosis are inadequate ventilation, interference with arterial-alveolar gas exchange, and airway obstruction (**Table 18**).

Clinical manifestations of respiratory acidosis are difficult to ascribe specifically to hypercapnia itself given the associated hypoxemia. Neurologic symptoms include headache, anxiety,

TABLE 18. Causes of Respiratory Acidosis

Inadequate Ventilation
Decreased respiratory drive: head trauma; cerebrovascular accident; obesity-hypoventilation syndrome; central sleep apnea; CNS tumor; edema; infection; medications (anesthetics, sedatives, opiates)
Neuromuscular dysfunction: spinal cord injury; Guillain-Barré syndrome; amyotrophic lateral sclerosis; periodic paralysis
Musculoskeletal dysfunction: kyphoscoliosis; severe obesity; polymyositis; severe hypokalemia or hypophosphatemia
Impaired Arterial-Alveolar Gas Exchange
Pneumonia
Acute lung injury/acute respiratory distress syndrome
Cardiogenic pulmonary edema
Pneumothorax
Hemothorax
Emphysema
Interstitial lung disease
Pulmonary fibrosis
Pulmonary embolism
Airway Obstruction
Upper airway: tonsillar hypertrophy; vocal cord paralysis; foreign body aspiration; laryngospasm; tracheal stenosis; angioedema
Lower airway: status asthmaticus; COPD

CNS = central nervous system.

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CONT. blurred vision, and tremor. When severe, symptoms can progress to confusion, somnolence, or seizures. Chronic respiratory acidosis may have milder neurologic effects such as memory loss, inattentiveness, or irritability. Additional symptoms of respiratory acidosis include cardiovascular effects such as vasodilation and tachycardia that may evolve to cardiac arrhythmias and decreased cardiac output. When respiratory acidosis is severe, renal vasoconstriction with enhanced sodium retention occurs, typically seen in those with severe lung disease and cor pulmonale.

Treatment entails oxygen supplementation and mechanical ventilation to decrease CO_2 if necessary while treating the underlying disease.

KEY POINT

- Respiratory acidosis is associated with hypercapnia, with an elevation in P_{CO_2}, a decrease in pH, and a slight increase in bicarbonate.

Respiratory Alkalosis

Respiratory alkalosis is the result of enhanced CO_2 exchange from the pulmonary capillaries to the alveoli and to the expired air. Without compensatory mechanisms, the fall in arterial CO_2 (hypocapnia) leads to a rapid increase in arterial pH. However, immediate diffusion of hydrogen ions from intracellular stores (from hemoglobulin, phosphate, and other protein buffers) binds with bicarbonate, causing a reduction in serum bicarbonate, thus limiting this consequence. The typical arterial blood gas in this setting demonstrates a decrease in P_{CO_2}, an increase in pH, and a slight decrease in bicarbonate (see Table 12). Other electrolyte abnormalities may result from respiratory alkalosis, including an increase in cellular lactic acid production, an increase in the anion gap in part from an increase in negatively charged albumin, and a decrease in ionized calcium from enhanced binding to negatively charged albumin. Finally, severe hypophosphatemia can occur due to a shift of phosphate from extracellular to intracellular fluid.

The most common causes of respiratory alkalosis are an enhanced respiratory drive, hypoxemia, and pulmonary disease with stimulation of thoracic stretch receptors (**Table 19**). Symptoms include tachypnea and related neurologic findings such as lightheadedness, numbness and paresthesias, cramps, confusion, and, rarely, seizures. An important consideration when evaluating a patient with respiratory alkalosis is the potential for salicylate intoxication, which in its early phases presents with mental status changes, respiratory alkalosis, and an anion gap metabolic acidosis.

Treatment of respiratory alkalosis is directed at correction of the primary disorder. For salicylate intoxication, forced diuresis, urine alkalinization, or hemodialysis should be considered. For anxiety-induced or psychogenic hyperventilation, increasing the inspired P_{CO_2} by closed bag rebreathing may increase the P_{CO_2} and improve symptoms. In rare circumstances when there is severe alkalemia (for example, pH >7.55) with hemodynamic instability, arrhythmias, or altered mental status, strategies to reduce bicarbonate via acetazolamide or controlled hypoventilation with mechanical ventilation to increase P_{CO_2} may be considered.

TABLE 19. Causes of Respiratory Alkalosis

Enhanced Respiratory Drive
Sepsis
Hepatic failure
Anxiety
Psychosis
Subarachnoid hemorrhage
Pregnancy
Nicotine
Medications: salicylates; theophylline/aminophylline
Hormones: progesterone; medroxyprogesterone; epinephrine; norepinephrine; angiotensin II
Hypoxemia
High altitude
Severe anemia
Hypotension
Chronic heart failure
Pulmonary parenchymal disease
Pulmonary Disease with Thoracic Stretch Receptor Stimulation
Pneumonia
Acute respiratory distress syndrome
Pulmonary embolism
Hemothorax
Pneumothorax
Pulmonary edema

KEY POINT

- Respiratory alkalosis is associated with hypocapnia, with a decrease in P_{CO_2}, an increase in pH, and a slight decrease in bicarbonate.

Hypertension

Epidemiology

Hypertension prevalence in the United States is increasing, albeit more slowly over the past decade, and is estimated to be 29%. Efforts to effectively treat hypertension have slightly improved over time, but only approximately 50% of patients with hypertension are controlled to a blood pressure goal of <140/90 mm Hg.

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Consequences of Sustained Hypertension

End-Organ Injury

In the brain and central nervous system, elevated blood pressure can lead to cerebral aneurysms, which may rupture (subarachnoid hemorrhage), and retinal hemorrhage. Long-standing hypertension can lead to arteriolosclerosis, resulting in arteriolar narrowing and distal ischemia. Clinical consequences include lacunar infarction and dementia.

In the heart, increased blood pressure leads to a compensatory myocardial hypertrophy that results in impaired relaxation (diastolic dysfunction) over time, which ultimately can lead to heart failure.

In the medium to large blood vessels, hypertension may cause pressure-related injury (aortic aneurysms and dissection) and contribute to the development of atherosclerosis through disruption of the vascular endothelium. When combined with elevated cholesterol, diabetes mellitus, and proinflammatory cytokines, this results in plaque formation. Plaque formation may result in thrombotic and embolic complications such as myocardial infarction, renal artery stenosis, embolic stroke, and atheroembolic peripheral arterial disease.

In the kidneys, hypertension has adverse effects on the renal vasculature, which may ultimately lead to kidney dysfunction. Chronic hypertension is associated with the development of both arteriolosclerosis and atherosclerosis. With severe hypertension, arteriolar injury with proliferation ("onion skin" lesions) and fibrinoid necrosis can occur, clinically manifesting as acute kidney injury with features of thrombotic microangiopathy and hematuria. Although debate exists as to whether hypertension as an isolated condition causes end-stage kidney disease, it clearly contributes to an accelerated progression to kidney failure in susceptible persons.

Clinical Impact

Hypertension is considered a primary cardiovascular risk factor that contributes to the development of stroke, coronary heart disease, peripheral vascular disease, and heart failure. In particular, hypertension is the strongest risk factor for hemorrhagic and ischemic stroke. Epidemiologic studies indicate that systolic blood pressures >115 mm Hg and diastolic blood pressures >75 mm Hg are associated in a linear fashion with cardiovascular events (**Figure 9**). Nearly 54% of stroke events and 47% of ischemic heart disease worldwide can be attributable

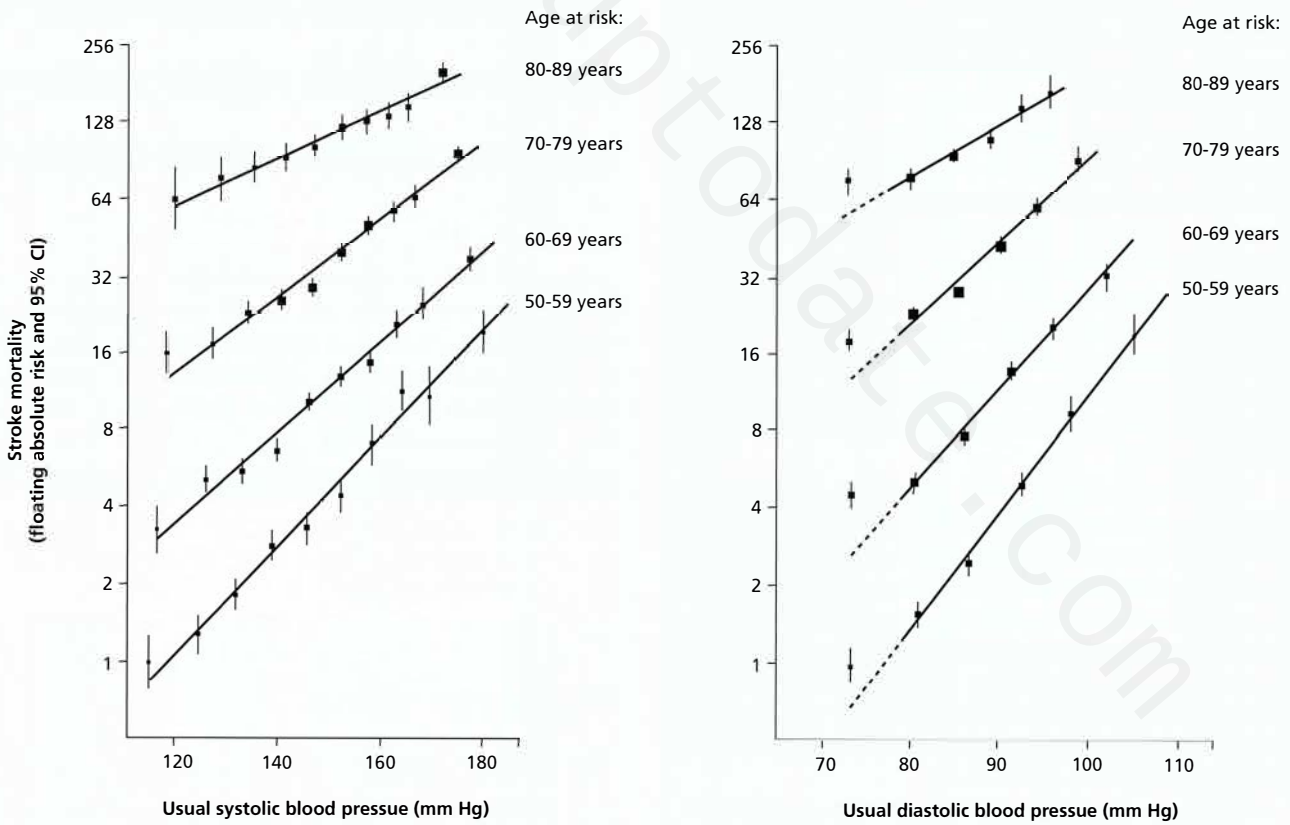

FIGURE 9. Stroke mortality rate by systolic and diastolic blood pressure, stratified by age. Meta-analysis of 61 prospective observational studies in adults with no previous vascular disease. "Usual" is defined as the long-term average blood pressure, accounting for blood pressure as a time-dependent variable in the studies included for meta-analysis.

Reprinted from The Lancet. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. 2002 Dec 14;360(9349):1903-13. [PMID: 12493255] Copyright 2002, with permission from Elsevier.

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to high blood pressure, which equates to 7.6 million premature deaths (13.5% of total) and 92 million disability-adjusted life years (6% of total). Despite these epidemiologic studies, treatment of hypertension to 115/75 mm Hg has not been demonstrated to correlate with equivalent reductions in cardiovascular risk.

KEY POINTS

- Only approximately 50% of patients with hypertension are controlled to a blood pressure goal of <140/90 mm Hg.
- Nearly 54% of stroke events and 47% of ischemic heart disease worldwide can be attributable to high blood pressure, which equates to 7.6 million premature deaths (13.5% of total) and 92 million disability-adjusted life years (6% of total).

Blood Pressure Measurement

Proper Technique

The current standard of care for blood pressure measurement employs the oscillometric method using either a properly calibrated automated device or manual measurement. This can be performed in the office or home, but the technique follows the same guidelines:

- a quiet environment with the patient in a seated position, with the back supported and feet on the floor following 5 minutes of rest
- the arm supported with the cuff at heart level; measurement should not be taken through clothes
- the cuff is placed on the upper arm, and the bladder portion should be large enough to encircle at least 80% of the arm to ensure that there is uniform compression of the brachial artery; proper cuff size is estimated by aligning the cuff parallel to the arm and wrapping the arm with the bladder; the bladder width should be large enough to encircle half the upper arm; the cuff should be inflated to a high enough pressure to exclude an auscultatory gap
- at least two measurements should be taken at least 30 seconds apart on each assessment, with repeated measurements as needed until two values are within 5 mm Hg of each other

Manual (Auscultatory) Blood Pressure Monitoring

The manual method for measuring blood pressure involves a cuff-based sphygmomanometer and stethoscope. The blood pressure is measured with the lower end of the cuff 2 to 3 cm above the antecubital fossa and the stethoscope over the brachial artery in the antecubital fossa. The cuff should be inflated at least 30 mm Hg above the estimated systolic blood pressure (indicated by disappearance of the palpated brachial pulse) to avoid error in blood pressure measurement by misinterpreting the auscultatory gap.

Electronic Blood Pressure Monitoring

Electronic blood pressure monitors are now extremely common in the office setting as well as at home due to the convenience and the relative standardization of measurement (through the elimination of user variation/error). These devices measure blood pressure through similar oscillometric methodology as manual blood pressure cuff assessment. Sensors detect the disappearance of the brachial pulse upon inflation and the increasing amplitude of the pulse upon deflation. In general, the systolic blood pressure is slightly lower and the diastolic blood pressure slightly higher than an intra-arterial measurement. Electronic devices should be properly calibrated and inspected, and patients should be encouraged to bring their devices to the office to compare readings obtained on personal versus office devices.

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) uses a continuously worn device that can be programmed to measure blood pressure every 15 to 20 minutes during the day and every 30 to 60 minutes at night. ABPM-ascertained hypertension is associated with a higher risk of cardiovascular death compared with hypertension determined in the office or at home (**Figure 10**). There is evidence supporting use of ABPM to confirm office-based blood pressure screening results to avoid misdiagnosis and overtreatment of individuals who may have elevated blood pressure readings only in the clinic. Beyond the benefits of accurate diagnosis of hypertension, there are numerous clinical circumstances under which ABPM provides valuable additional information over office-based measurements, including the evaluation of white coat hypertension, apparent resistant hypertension, masked hypertension, and suspected episodic hypertension.

Normal ranges for ABPM depend on the time frame of monitoring. Normal average daytime blood pressure by ABPM should be <140/90 mm Hg, with a normal nighttime average blood pressure of <125/75 mm Hg; the overall 24-hour average blood pressure should be <135/85 mm Hg. ABPM also can be used to determine if dipping is present, which is defined as the normal decrease in blood pressure at night by approximately 15% compared with daytime values. Failure of nighttime dipping is associated with an increased incidence of left ventricular hypertrophy. Additionally, elevated nighttime blood pressure by ABPM is strongly associated with an increased risk of cardiovascular death (see Figure 10).

Home Blood Pressure Monitoring

Patients can be instructed to perform frequent home blood pressure measurements, with readings at various times during the day totaling at least 12 measurements over 1 week. For a given systolic or diastolic blood pressure value, a home blood pressure average is associated with a risk of cardiovascular death higher than an office-based reading but lower than an ABPM average (see Figure 10). Home blood pressure monitoring

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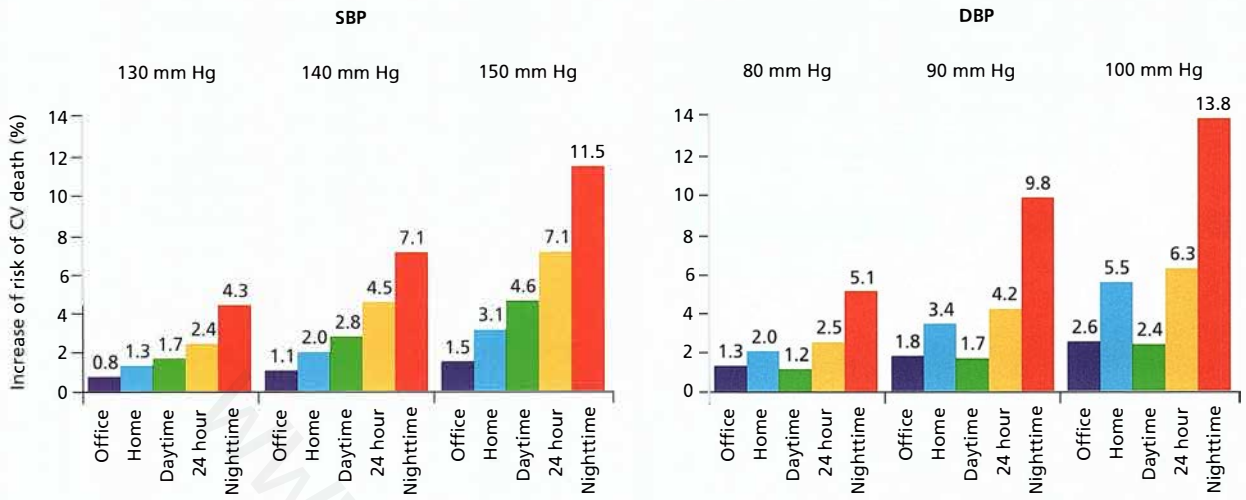

FIGURE 10. Increase in 11-year risk of cardiovascular mortality for 10 mm Hg increase in office, home, and ambulatory blood pressure at various initial blood pressure values. There were 2051 subjects. Office blood pressure at initial visit and after ambulatory blood pressure were averaged and pooled, two home blood pressure measurements (7 AM and 7 PM) concurrent with ambulatory blood pressure on the contralateral arm were averaged, and ambulatory blood pressure values were averaged over 24 hours, day (7 AM-11 PM), and night (11 PM-7 AM). CV = cardiovascular; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Reproduced with permission from Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation 2005 Apr 12;111(14):1777-83. [PMID: 15809377] Copyright 2005, Wolters Kluwer Health, Inc.

is beneficial in monitoring blood pressure response to treatment, including lifestyle modifications. Patients should be instructed on appropriate technique and counseled on the frequency and timing of measurements to avoid very frequent blood pressure monitoring and the potential for medication self-adjustment. Whenever possible, upper-arm cuffs should be used unless medical conditions (such as trauma or surgery to the upper arm) require alternative sites; in these circumstances, wrist measurements are an alternative. Systolic pressure is higher and diastolic pressure is lower in the distal arteries, and calibration is critical in interpreting these values. Finger measurements lack accuracy and validation and thus should be discouraged.

KEY POINT

- Hypertension ascertained by ambulatory blood pressure monitoring is associated with a higher risk of cardiovascular death compared with hypertension determined in the office or at home.

Evaluation of the Patient with Newly Diagnosed Hypertension

The assessment of hypertension begins with proper determination of blood pressure, followed by evaluation of the patient's history, physical examination, screening laboratory data with a focus on the identification of specific causes (secondary hypertension), additional cardiovascular risk factors, and potential end-organ targets.

For the initial diagnosis of hypertension, most guidelines define hypertension as a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg for office blood pressure readings (**Table 20**); however, exceptions exist for some subgroups, and guidelines continue to evolve. Importantly, a diagnosis should not be made in the office setting until the threshold blood pressure has been documented on at least three visits over a period of at least 1 week or longer. There is evidence that confirming clinic-based blood pressure elevations with ABPM is effective at avoiding overdiagnosis

TABLE 20. Classification of Blood Pressure for Adults

BP Category	Office-Based Readings (mm Hg)	24-Hour Ambulatory Readings (mm Hg)	Self-Recorded BP (mm Hg)
Normal	SBP <120 and DBP <80	<130/80	<135/85
Prehypertension	SBP 120-139 or DBP 80-89	—	—
Hypertension, Stage 1	SBP 140-159 or DBP 90-99	≥135/85	≥135/85
Hypertension, Stage 2	SBP ≥160 or DBP ≥100	—	—
White Coat Hypertension	≥140/90	<135/85	<135/85
Masked Hypertension	<140/90	>135/85	>135/85

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

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and overtreatment for patients in whom elevated blood pressures are detected only in the clinic.

History

The history of a patient with newly diagnosed hypertension should consider the potential for a familial pattern of hypertension as well as a family history of heart disease, kidney disease, and stroke. Questions should also focus on related symptoms, including episodic (such as headache or palpitations) and persistent (such as vision changes or foamy urine) symptoms, as well as risk factors for hypertension and cardiovascular disease (obesity, smoking, alcohol, caffeine, diet, diabetes, emotional stress, sleep apnea). A review of medications, including over-the-counter and herbal medications, is important because a number of these agents can contribute to elevated blood pressure (**Table 21**).

Physical Examination

The physical examination of a patient with newly diagnosed hypertension should focus on the following:

- accurate blood pressure measurement in both arms
- potential causes of hypertension such as the presence of an abdominal bruit suggestive of renovascular hypertension or an enlarged/palpable thyroid suggestive of hyperthyroidism
- potential end-organ targets, including an eye examination to assess for arteriovenous nicking and papilledema as well as a cardiovascular examination to assess for volume status, pulses in all extremities, bruits, and left ventricular hypertrophy (left ventricular heave, S_4 gallop)

Testing

A patient with newly diagnosed hypertension should undergo laboratory testing for kidney function, fasting plasma glucose, fasting serum lipid panel, serum potassium, and serum calcium. Electrocardiography (ECG) should be obtained to assess for the presence of left ventricular hypertrophy (LVH) or silent myocardial injury. Although echocardiography is a more sensitive test for LVH, in general, echocardiography is not indicated in the assessment of hypertension except in patients with known heart disease; the presence of left bundle branch block on ECG, given its association with sudden death; or suspected white coat hypertension.

A urinalysis should be performed to assess for albuminuria and hematuria. Standard urine dipsticks do not detect moderately increased albuminuria (formerly known as microalbuminuria), which is an increasingly recognized marker of microvascular injury and is independently associated with an increased risk of cardiovascular events in hypertensive individuals with or without diabetes. Albumin generally comprises approximately 50% of the total protein excreted in the urine, with the remainder comprised of proteins of smaller molecular weight that are secreted into the urine. Because albuminuria, and not total proteinuria, has been associated with cardiovascular events, testing should be directed in this fashion. Measurement of a first morning urine sample for albumin and creatinine can permit calculation of an albumin-creatinine ratio, which is a good estimate for moderately increased albuminuria (30-300 mg/g).

The use of plasma renin activity to risk-stratify patients with hypertension or to predict response to specific interventions is of unclear value and is not recommended for routine use.

TABLE 21. Over-the-Counter and Prescription Agents that Increase Blood Pressure

Type	Agent	Mechanism(s)
OTC	Black licorice (European)	Mineralocorticoid activity enhancement; sodium retention
OTC	Ethanol	Adrenergic stimulation
OTC	NSAIDs	Sodium retention
OTC/Rx	Sympathomimetics; appetite suppressants; decongestants; vigilance enhancers (e.g., amphetamines)	Vasoconstriction; sodium retention
Rx	Selective serotonin or serotonin-norepinephrine reuptake inhibitors	Adrenergic stimulation
Rx	Erythrocyte stimulation agents (e.g., erythropoietins)	Vasoconstriction
Rx	Antiretroviral therapies	Not clear
Rx	Vascular endothelial growth factor antagonists (e.g., bevacizumab)	Vasoconstriction (endothelial dysfunction)
Rx	Glucocorticoids (e.g., prednisone)	Sodium retention; weight gain
Rx	Oral contraceptives	Increased renin-angiotensin system activity; sodium retention
—	Caffeine	Adrenergic stimulation
—	Cocaine; 3,4-methylenedioxymethamphetamine (also known as ecstasy); recreational drugs	Adrenergic stimulation

OTC = over the counter; Rx = prescription.

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However, there are circumstances in which the plasma aldosterone-plasma renin ratio may be used to screen for primary hyperaldosteronism. The 2008 Endocrine Society recommendations include screening patients with hypokalemia and hypertension as well as patients with moderate to severe hypertension even without significant hypokalemia (>160/100 mm Hg) and those with resistant hypertension. See Hypokalemia and Hypertension for more information.

KEY POINTS

HVC
- Echocardiography is not routinely indicated in the assessment of hypertension except in patients with known heart disease; the presence of left bundle branch block on electrocardiogram, given its association with sudden death; or suspected white coat hypertension.
- Plasma aldosterone-plasma renin ratio determination is recommended for patients with hypokalemia and hypertension as well as patients with moderate to severe hypertension even without significant hypokalemia and those with resistant hypertension.

Classification of Hypertension

Overview

The eighth report of the Joint National Committee (JNC 8), along with the European Society of Hypertension and the Canadian Hypertension Education Program, all currently define hypertension for non-elderly patients without chronic kidney disease (CKD) or diabetes as ≥140/90 mm Hg.

Prehypertension

JNC 8 did not address the concept of prehypertension. However, JNC 7 defined prehypertension as a systolic blood pressure of 120-139 mm Hg or a diastolic blood pressure of 80-89 mm Hg. This definition arose from the epidemiologic associations of "high normal" blood pressure and increased cardiovascular risk (see Figure 9), and the observed progression of many to overt hypertension. It is reasonable to identify and educate persons with prehypertension regarding their risk; however, data supporting the use of pharmacologic treatment to prevent complications or progression are lacking. Thus, treatment should focus on lifestyle modification and close monitoring, described later.

Stage 1 and 2 Hypertension

Hypertension is often classified by severity to bring awareness to the strong relationship of increasing blood pressure and cardiovascular morbidity and mortality (see Figure 9). The JNC 7 defines stage 1 hypertension as a systolic blood pressure of 140-159 mm Hg or a diastolic blood pressure of 90-99 mm Hg; stage 2 hypertension is defined as a systolic blood pressure of ≥160 mm Hg or a diastolic blood pressure of ≥100 mm Hg (see Table 20). These classifications have treatment implications, as those with stage 1 with average blood pressure values just above the defined threshold may be amenable to lifestyle modification with close monitoring, whereas those with stage 2 typically require combination therapy to achieve adequate blood pressure control. See Management for more information.

KEY POINTS

- Several guidelines define hypertension for non-elderly patients without chronic kidney disease or diabetes mellitus as ≥140/90 mm Hg.
- Treatment of prehypertension should focus on lifestyle modification and close monitoring.

Primary Hypertension

Pathogenesis

Approximately 90% of patients diagnosed with hypertension have primary hypertension (formerly known as essential hypertension), in which there is no identifiable anatomic or screening laboratory finding that provides insight as to the cause of hypertension. For most patients, the pathogenesis remains unclear. A number of potential mechanisms have been proposed, with experimental data supporting all of the following theories: abnormal sodium handling by the kidney, increased sympathetic tone, and increased activity of the renin-angiotensin-aldosterone axis.

Genetic Factors

Increasingly, genetic studies have identified gene mutations or polymorphisms that may explain up to 20% to 30% of cases of primary hypertension. The best described mutations are those directly affecting sodium channels of the distal renal tubule and collecting duct as well as those that lead to excess mineralocorticoid effect upon the distal tubule. These defects lead to excess sodium reabsorption and hypertension. Other genetic polymorphisms that may predispose to hypertension involve oxidative stress mechanisms, mediators of vascular smooth muscle tone, and vasoactive mediators.

Societal Factors

The increased prevalence of hypertension is a result of worldwide changes in diet and lifestyle over time. The adoption of a Western diet and an increase in sodium intake has resulted in prevalence rates of 20% to 30% in geographic regions that previously had virtually no prior prevalence of hypertension. Age, race, obesity, insulin resistance, and hyperuricemia have all emerged as significant risk factors for hypertension.

Management

General Approach

The JNC 8 hypertension management recommendations are summarized as follows:

- Lifestyle modifications: implement in all patients with prehypertension and hypertension. Continue even if

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pharmacologic treatment becomes necessary. Modifiable risk factors should be treated.

- General adult population <60 years of age: pharmacologic treatment is recommended if the systolic blood pressure is ≥140 mm Hg or the diastolic blood pressure is ≥90 mm Hg. The goal of therapy is <140/90 mm Hg.
- Patients ≥60 years of age: pharmacologic treatment is recommended if the systolic blood pressure is ≥150 mm Hg or the diastolic blood pressure is ≥90 mm Hg. The goal of therapy is <150/90 mm Hg, although patients with a blood pressure of <140/90 mm Hg on well-tolerated therapy do not need to have their treatment changed.
- Patients ≥18 years of age with diabetes or CKD: the initiation threshold and goal for pharmacologic treatment is 140/90 mm Hg.
- General non-black population, including those with diabetes: thiazide diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) all may be considered for initial treatment.
- Black patients, including those with diabetes: initial therapy should be a thiazide diuretic or CCB. As a group, black patients have less blood pressure reduction with equivalent ACE inhibitor dosing compared with non-black patients. Furthermore, black patients initially treated with ACE inhibitors rather than CCBs have about a 50% higher rate of stroke, and combined cardiovascular outcomes are better with a thiazide diuretic than with an ACE inhibitor.
- All patients (regardless of race or the presence/absence of diabetes) >18 years of age with CKD (including those with and those without proteinuria): initial therapy should be an ACE inhibitor or ARB because these agents are renoprotective and improve renal outcomes.
- Black patients with CKD but without proteinuria: the initial agent can be a CCB, thiazide diuretic, ACE inhibitor, or ARB. If the initial choice is not an ACE inhibitor or ARB, then one of these should be the second drug added if necessary to lower the blood pressure to target (<140/90 mm Hg).

Visit http://jama.jamanetwork.com/article.aspx?articleid=1791497 for more information on the JNC 8 recommendations.

Lifestyle Modifications

A critical component of blood pressure treatment is modification of diet and activity. Lifestyle interventions should be stressed to patients not only with sustained hypertension but also to those with prehypertension to reduce future hypertension and cardiovascular disease. Examples of nonpharmacologic measures include the following: 1) a low sodium diet; 2) a diet such as DASH (Dietary Approaches to Stop Hypertension) that emphasizes vegetables, fruits, whole grains, legumes, and low-fat dairy products and limits sweets, red meat, and saturated/total fat; 3) weight loss; and 4) exercise, which can be of significant benefit for blood pressure control and management.

All interventions produce a reduction in blood pressure, even in normotensive individuals, but their effects are magnified in those who are hypertensive. In adults up to age 75 to 80 years with a blood pressure of 120-159/80-95 mm Hg, reducing sodium intake from 3300 mg/d to 1500 mg/d lowers blood pressure by an average of 7/3 mm Hg. A more modest reduction of approximately 1150 mg/d reduces blood pressure by an average of 3 to 4/1 to 2 mm Hg. Combining a reduced sodium intake with a DASH dietary pattern has an additive effect on lowering blood pressure. Weight loss of 5.0 kg (11 lb) may be expected to lead to a reduction of 4/3 mm Hg, although this effect may be higher in those who are hypertensive. Independent of weight loss or dietary intervention, aerobic exercise for 40 minutes 3 to 4 times per week lowers blood pressure by 2 to 5/1 to 4 mm Hg. Thus, implementing lifestyle interventions can produce reductions in blood pressure equivalent to antihypertensive agents and should be recommended for all patients with hypertension. Other interventions such as moderating alcohol intake and increasing potassium and calcium in the diet have more modest and less reproducible effects in lowering blood pressure. Tobacco cessation strategies should be encouraged. Although tobacco use has variable effects upon blood pressure, the strong synergistic relationship between hypertension, tobacco use, and the development of atherosclerotic disease over time should be addressed at each visit.

Pharmacologic Therapy

In patients who are unresponsive to an adequate trial of lifestyle modification, pharmacologic therapy is indicated. Timing of initiation of medications should be dictated by the severity of hypertension. For example, a non-elderly patient with a systolic blood pressure of 140-150 mm Hg may benefit from a 3- to 6-month trial of lifestyle modification alone with close monitoring, whereas an individual with stage 2 hypertension or with evidence of end-organ disease should be started on medications together with lifestyle modification. The selection of initial antihypertensive therapy has been extensively reviewed for potential individual benefits in efficacy, overall mortality, cardiovascular-related mortality, and cardiovascular and renal events. In multiple reviews and meta-analyses, the attained blood pressure is far more critical than the agent used to achieve blood pressure control and prevent cardiovascular events. For this reason, the JNC 8 recommends the use of any one of four drug classes, thiazide diuretics (thiazides), CCBs, ACE inhibitors, and ARBs, as initial therapy in the general nonblack population (elderly and non-elderly). All performed similarly in preventing cardiovascular mortality and morbidity end points with the exception of heart failure, in which a slight advantage of thiazides over CCBs and ACE inhibitors and a slight advantage of ACE inhibitors over CCBs were noted in two trials. However, these differences were not considered by JNC 8 to be compelling.

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In the general black population, initial therapy with a thiazide diuretic or CCB is recommended.

Specific non-recommended initial agents by JNC 8 include β-blockers (due to higher cardiovascular-related events and mortality compared with ARBs) and α-blockers (due to higher cardiovascular-related events and mortality compared with thiazides), although clinical conditions such as atrial fibrillation or benign prostatic hyperplasia may supersede these recommendations (**Table 22**).

See **Table 23** for a list of frequently used antihypertensive medications and their side effects.

Choice of Diuretic

Thiazide diuretics remain as a first-line option for the treatment of hypertension. Most large randomized clinical trials have been performed with either hydrochlorothiazide or chlorthalidone, medications with similar primary mechanism of action (inhibition of the Na^+Cl^- cotransporter in the distal renal tubule) but with differing potency. The maximal recommended doses are 25 mg of chlorthalidone and 50 mg of hydrochlorothiazide; side effects increase beyond these doses with little further antihypertensive effect.

Loop diuretics are short-acting agents and as such do not have a role in the management of hypertension aside from use in patients with clinically significant fluid retention. In the setting of CKD stage 4 and greater (glomerular filtration rate [GFR] <30 mL/min/1.73 m^2), thiazides lose potency, and loop diuretics may often be required.

Agents that act at the distal Na^+ channel in the renal tubule ("potassium-sparing diuretics" such as spironolactone, eplerenone, and amiloride) are weaker diuretics than thiazides and are often reserved for treatment of aldosterone-mediated hypertension or resistant hypertension. Because the mechanism of action of these agents predisposes to hyperkalemia, use of these agents in combination with other drugs that act on the renin-angiotensin system (ACE inhibitors, ARBs, and direct renin inhibitors) must be cautiously considered and closely monitored.

Choice of Calcium Channel Blocker

There are no evidence-based recommendations regarding selection of a dihydropyridine (amlodipine, felodipine, nifedipine) CCB versus a non-dihydropyridine (diltiazem, verapamil) CCB for the treatment of hypertension; therefore, the mechanisms of action and side-effect profiles typically dictate their utilization. Non-dihydropyridine CCBs act upon calcium channels in the heart and may lead to increased relaxation and decreased atrioventricular node conduction, whereas dihydropyridine CCBs act upon calcium channels of the vasculature, increasing vasodilation.

Of note, there is an FDA safety alert regarding the use of statins together with CCBs. Specifically, the use of simvastatin at doses 10 mg and above and lovastatin at doses 20 mg and above is contraindicated with verapamil or diltiazem, and simvastatin at doses 20 mg and above is contraindicated with amlodipine due to an increased risk of myopathy.

Choice of Renin-Angiotensin System Agent

ACE inhibitors and ARBs have comparable effects upon blood pressure reduction and similar efficacy in reducing proteinuria, slowing CKD progression, and preventing cardiovascular events. The direct renin inhibitor aliskiren has similar antihypertensive efficacy but has not been extensively studied in head-to-head trials compared with other renin-angiotensin system (RAS) agents. Beyond cost considerations, the primary rationale for selecting one versus another lies in side-effect profiles. ACE inhibitors are associated with a 15% to 20% incidence of dry cough not seen with ARBs. ACE inhibitors also carry a higher rate of angioedema, a rare but life-threatening side effect. Angioedema can occur with direct renin inhibitors at rates similar to ACE inhibitors, whereas the risk of angioedema with ARBs is only slightly higher than with the use of β-blockers. Individuals with a history of angioedema or who develop angioedema on an ACE inhibitor or a direct renin inhibitor may (with great caution) be tried on ARBs, with a small risk of recurrence. All RAS agents are contraindicated in pregnancy due to fetal urogenital developmental abnormalities.

TABLE 22. Potential Factors that Influence the Selection of an Initial Antihypertensive Agent

Agent	Potential Clinical Indications	Potential Clinical Contraindications
Thiazide diuretic	Isolated systolic hypertension in elderly; hypertension in black patients; heart failure	Gout; hyponatremia; glucose intolerance; concomitant lithium use
ACE inhibitor/ARB	Heart failure; post-MI; CKD; proteinuria; diabetes mellitus/metabolic syndrome	Pregnancy[a]; hyperkalemia; bilateral renal artery stenosis
CCB	Isolated systolic hypertension in elderly; hypertension in black patients	Heart failure (non-dihydropyridines)
β-Blocker	Post-MI; heart failure; tachyarrhythmia; pregnancy; angina (NOT recommended for initial use except under these conditions)	Peripheral arterial disease; COPD; glucose intolerance

ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; MI = myocardial infarction.

[a]Absolute contraindication.

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TABLE 23. Frequently Used Antihypertensive Medications

Class/Agent	Dose/Frequency	Common Side Effects
Thiazide Diuretics		**Hypokalemia; hyponatremia; hyperlipidemia; hyperuricemia; hyperglycemia**
Hydrochlorothiazide	12.5-50 mg daily	
Chlorthalidone	12.5-25 mg daily	
ACE Inhibitors		**Hyperkalemia; cough**
Captopril	25-75 mg three times daily	
Lisinopril	5-40 mg daily	
Enalapril	5-20 mg twice daily	
Benazepril	10-40 mg daily	
Angiotensin Receptor Blockers		**Hyperkalemia**
Candesartan	4-32 mg daily	
Losartan	25-100 mg daily	
Valsartan	40-320 mg daily	
Irbesartan	75-300 mg daily	
Calcium Channel Blockers		
Dihydropyridines		
Amlodipine	2.5-10 mg daily	Pedal edema
Felodipine	2.5-10 mg daily	Headache
Nifedipine (extended release)	30-180 mg daily	
Non-dihydropyridines		
Diltiazem (extended release)	120-360 mg daily	Constipation
Verapamil (extended release)	120-480 mg daily	
β-Blockers		**Fatigue; bronchospasm; sexual dysfunction; hyperglycemia**
Atenolol	25-100 mg daily	
Metoprolol tartrate	25-100 mg twice daily	
Metoprolol succinate	25-200 mg daily	
Labetalol	100-600 mg three times daily	
Potassium Channel Openers (Vasodilators)		**Edema**
Hydralazine	25-75 mg three times daily	Lupus-like syndrome
Minoxidil	2.5-10 mg twice daily	Hypertrichosis
α-Blocker		**Orthostatic hypotension; dizziness**
Prazosin	1-10 mg twice daily	
Central α-Agonists		**Fatigue; depression; rebound hypertension**
Clonidine, oral	0.1-0.4 mg twice daily	
Clonidine, patch	0.1-0.3 mg/24 h applied once every 7 days	
Potassium-Sparing Diuretics		**Hyperkalemia**
Spironolactone	25-50 mg daily	Gynecomastia
Amiloride	5 mg daily or twice daily	
Eplerenone	50 mg daily or twice daily	

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The use of dual RAS agents (ACE inhibitor, ARB, or the direct renin inhibitor aliskiren) is not recommended (see next section).

Combination Therapy

There is general agreement that a single antihypertensive agent or lifestyle modification alone is unlikely to control blood pressure in patients who are >20/10 mm Hg above target blood pressure. In this circumstance, initial therapy may include lifestyle modification with a combination of agents either separately or in a fixed-dose pill. A thiazide diuretic in combination with an ACE inhibitor or ARB is commonly employed, as is the combination of an ACE inhibitor or ARB with a CCB. These combinations have been supported by both the JNC 8 and European Society of Hypertension as reasonable approaches to management. Although no definitive recommendations exist regarding the best combination of agents to employ, there is some evidence that an ACE inhibitor/CCB combination may be more effective than an ACE inhibitor/thiazide combination. Combination of a thiazide and CCB is also an effective strategy, although there have not been large clinical trials comparing this combination to other combination therapies. Conversely, the use of dual RAS agents (ACE inhibitor, ARB, or the direct renin inhibitor aliskiren) is not recommended because of lack of benefit in renal or cardiovascular end points and increased adverse events.

Assessment of Efficacy and Medication Titration

After lifestyle modification and a pharmacologic treatment regimen have been implemented, patients should be assessed monthly until blood pressure goals have been achieved.

As antihypertensive agents are titrated or added when there is inadequate blood pressure control, it is important to recognize that there is a nonlinear and diminishing blood pressure–lowering effect when titrating from 50% maximal dose to 100% maximal dose of any agent. A general rule of thumb is that 75% of an agent's blood pressure–lowering effect may be achieved with 50% of its maximal dose. If blood pressure control requires an additional >5 mm Hg reduction, it is unlikely to be achieved by increasing the single agent from 50% to 100% maximal dose. A combination of two agents at moderate dose is often more successful at achieving blood pressure goals than one agent at maximal dose. This strategy also minimizes the side effects that are more commonly noted at higher doses.

KEY POINTS

HVC
- Modification of diet and activity can produce blood pressure reductions that are equivalent to antihypertensive agents.
- The eighth report of the Joint National Committee recommends a blood pressure goal of <140/90 mm Hg in adult patients <60 years of age and a goal of <150/90 mm Hg for those ≥60 years of age.

(Continued)

KEY POINTS *(continued)*

- The eighth report of the Joint National Committee recommends as initial therapy of hypertension in the general nonblack population the use of any one of four drug classes: thiazide diuretics, calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers.
- For patients whose blood pressure is >20/10 mm Hg above target blood pressure, initial treatment may include combination therapy.
- A combination of two hypertensive agents at moderate dose is often more successful at achieving blood pressure goals than one agent at maximal dose, which can help minimize the side effects more commonly noted at higher doses. HVC

White Coat Hypertension

The term *white coat hypertension* (also known as isolated clinic hypertension or office hypertension) is applied to patients with average blood pressure readings in the office ≥140/90 mm Hg and out-of-office readings <135/85 mm Hg as determined by home measurements or ABPM. Prevalence may be as high as 10% to 20% of patients diagnosed with hypertension. Whenever possible, ABPM should be employed to confirm the diagnosis. Although small reports suggest an increased risk of stroke in patients with white coat hypertension compared with normotensive individuals, there does not appear to be increased cardiovascular risk when studies are pooled in meta-analyses. However, white coat hypertension is associated with an increased likelihood of progressing to hypertension, therefore justifying evaluation for other risk factors, lifestyle modification, and close monitoring. In addition to the evaluation of hypertension (see Testing), screening echocardiography may be beneficial in this setting to determine early end-organ manifestations of hypertension that might guide therapy.

Masked Hypertension

Patients with masked hypertension have normal office blood pressure measurements but elevated blood pressure (>135/85 mm Hg) in the ambulatory setting. ABPM should be considered in such patients, especially in the presence of other cardiovascular risk factors or target organ damage. Although prospective trials are lacking, treatment of masked hypertension with lifestyle modification, and pharmacologic agents if necessary, should be considered to achieve ambulatory blood pressure <135/85 mm Hg.

Resistant Hypertension

Treatment-resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which is a

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diuretic. Prevalence can be as high as 10%. The approach to this condition begins with the elimination of "pseudoresistance" (inappropriate blood pressure measurement techniques, sclerotic noncompressible arteries, the presence of white coat hypertension, or poor patient medication adherence). After these factors have been eliminated, a search for identifiable causes of hypertension should be undertaken (**Table 24**). Screening for significant alcohol intake should also be performed.

The addition of a diuretic is critical before diagnosing a patient as having resistant hypertension. The combination of a calcium channel blocker, RAS agent, and diuretic is synergistic. Adding a low-dose aldosterone antagonist (such as spironolactone or eplerenone) may improve blood pressure control. Chronotherapy (moving at least one long-acting medication to nighttime) has been shown to restore dipping, which is associated with lower cardiovascular events. Although other vasodilators (such as hydralazine or minoxidil) and centrally acting agents (such as clonidine or guanfacine) have been used, side effects are common; these drugs are reserved for patients with the most resistant hypertension.

TABLE 24. Identifiable Causes of Hypertension and Associated Diagnostic Tests[a]

Diagnosis	Diagnostic Test
Chronic kidney disease	Estimated GFR
Coarctation of the aorta	CT angiography
Cushing syndrome (most commonly due to chronic exogenous glucocorticoid therapy)	Overnight dexamethasone suppression test (not necessary if the patient is on chronic glucocorticoid therapy) or 24-hour urine free cortisol; late evening salivary cortisol
Drug-induced/related	Drug screening
Pheochromocytoma	24-Hour urine metanephrines and 24-hour urine catecholamines; if preclinical suspicion is high, measure plasma free metanephrines instead
Hyperaldosteronism	Plasma aldosterone-plasma renin activity ratio, measured midmorning in an ambulatory patient who is euvolemic and normokalemic
Renovascular hypertension	Doppler flow study; MR or CT angiography
Sleep apnea	Polysomnography
Thyroid dysfunction	TSH level
Primary hyperparathyroidism	Serum calcium level

GFR = glomerular filtration rate; TSH = thyroid-stimulating hormone.

[a]Diagnostic testing for causes of secondary hypertension should be guided by history and physical examination findings consistent with the secondary cause being considered.

KEY POINT

- Resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which is a diuretic.

Secondary Hypertension

Identifiable (secondary) causes of hypertension are discovered in 2% to 10% of patients with hypertension; consequently, all patients with hypertension do not need to be screened unless a potential cause is suggested based on the history, physical examination, or the recommended initial laboratory testing for patients with newly diagnosed hypertension. Possible situations in which screening for identifiable causes should be considered include the following: young age of onset (in childhood or adolescence), especially in the absence of family history; severe or resistant hypertension; abrupt worsening of blood pressure in a previously well-controlled patient; or clinical features of an underlying disorder associated with hypertension (see Table 24).

Kidney Disease

Pathophysiology and Epidemiology

Both acute and chronic kidney disease are the most common identifiable conditions associated with hypertension. More than 80% of patients with late-stage CKD are hypertensive. The pathophysiology of hypertension in kidney disease is complex, but sodium retention is the predominant mechanism and is related to a reduction in GFR, resistance to natriuretic peptides, and increased activity of the renin-angiotensin-aldosterone system. Impaired nitric oxide availability and sympathetic overactivity are also thought to play significant roles in causing hypertension. Uncontrolled hypertension is an important correctable factor associated with CKD progression.

Clinical Manifestations

The prevalence of hypertension increases with progressive reduction in GFR. Patients may have edema, but hypervolemia may be present despite the absence of edema.

Diagnosis

Because of the strong association of hypertension with kidney disease, measurement of renal indices, including serum creatinine and urine albumin, is recommended during the initial evaluation of all patients diagnosed with hypertension. Kidney ultrasonography is recommended if kidney function is impaired, if there is suspicion for fibromuscular dysplasia, or if there is a family history of polycystic kidney disease. Additional diagnostic testing is based on urinalysis and imaging results.

Management

The JNC 8 recommends a blood pressure goal of <140/90 mm Hg for patients with CKD, with or without diabetes. The Kidney

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Disease: Improving Global Outcomes (KDIGO) guidelines suggest a lower blood pressure goal of <130/80 mm Hg in patients with proteinuria >500 mg/g.

In patients with CKD and hypertension, JNC 8 recommends use of an ACE inhibitor or ARB as initial or add-on therapy if not contraindicated, regardless of race, although special considerations may apply to black patients (see Special Populations). An increase in the serum creatinine of up to 30% is acceptable with the use of ACE inhibitors or ARBs, but if a more severe decline in kidney function occurs, overdiuresis or the presence of bilateral renal artery stenosis should be considered.

Control of sodium balance is an essential component of blood pressure management in patients with kidney disease. Dietary sodium restriction to <2000 mg/d combined with appropriate use of diuretics is advised. As the GFR declines (especially <30 mL/min/1.73 m^2), thiazide diuretics become less effective. Loop diuretics should be employed in such patients, with doses titrated to clinical response. Other drugs effective in kidney disease are CCBs. Nocturnal administration of at least one long-acting antihypertensive medication is recommended to restore the normal fall in blood pressure at night (chronotherapy), which is frequently absent in patients with CKD and hypertension. In patients with a GFR <15 mL/min/1.73 m^2, blood pressure may improve with better volume control associated with initiation of dialysis.

Renovascular Hypertension

Pathophysiology and Epidemiology

Renovascular disease is not invariably associated with renovascular hypertension. Although renovascular disease may be seen in a significant proportion of patients with hypertension, the true incidence of renovascular hypertension is unknown. The pathogenesis of hypertension in the acute stage of renal artery stenosis relates to hypoperfusion of the kidney, leading to release of renin and angiotensin and subsequent systemic vasoconstriction and hypertension. Renin and aldosterone levels are typically high at this stage. With damage to the contralateral kidney or with bilateral renal artery stenosis, the pathogenesis switches to a volume-dependent hypertension with normal or low renin levels. Correcting the stenosis at this stage may not lead to improvement in blood pressure because there may be irreversible parenchymal damage in the affected kidney from chronic ischemia or the contralateral kidney from the effects of hypertension.

Most patients with renovascular disease (>90%) have atherosclerosis. In younger patients, especially women, fibromuscular dysplasia may be seen (**Figure 11**).

Clinical Manifestations

Recurrent episodes of "flash" pulmonary edema or a marked elevation in serum creatinine with control of blood pressure, especially with the use of an ACE inhibitor or ARB, suggests renovascular disease. The presence of a renal bruit is insensitive in the diagnosis of renal artery stenosis, but hypertension and a systolic/diastolic abdominal bruit is associated with a positive likelihood ratio of 4.8.



FIGURE 11. Renal angiogram showing typical fibromuscular dysplasia. This noninflammatory, nonatherosclerotic disorder of unclear etiology most commonly affects the arterial media, causing distortion of the arterial wall ("string of beads" sign) that may result in renal artery stenosis.

Diagnosis

Duplex Doppler of the renal arteries is an effective screening test when performed in an experienced vascular laboratory. However, MR or CT angiography may be required to confirm the anatomic diagnosis. The gold standard is renal arteriography, but in view of significant side effects, this is undertaken only if an intervention to correct a discovered stenosis is planned. Peripheral renin and aldosterone profiling are generally not helpful in later stages of renovascular disease.

Management

No clinical trials have demonstrated that percutaneous intervention (angioplasty or stenting) to improve blood flow to the stenotic kidney results in improvement of hypertension or a lessening of kidney deterioration. Thus, medical management, including correction of modifiable cardiovascular risk factors, is the primary therapeutic intervention in most patients with renal artery stenosis. Percutaneous intervention may be considered in select patients such as those with a short duration of hypertension, recurrent flash pulmonary edema with bilateral renal artery stenosis, and in young women with fibromuscular dysplasia.

Hypokalemia and Hypertension

Hyperaldosteronism, usually from an aldosterone-producing adenoma or bilateral idiopathic hyperaldosteronism, may be present in up to 10% of patients with hypertension. Hypokalemia in the absence of diuretic therapy or in response to low-dose thiazide therapy is an important clue to the presence of this disorder, although not all patients with hyperaldosteronism have hypokalemia. The plasma aldosterone-plasma

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CONT.

renin activity ratio (ARR) is used to evaluate for this condition if suspected (see Table 24). Many medications can interfere with interpretation of the ARR; testing can therefore be challenging because discontinuing hypertensive medications in patients with refractory hypertension can be difficult. Spironolactone and diuretics should be stopped before testing for 4 to 6 weeks and several days, respectively. See MKSAP 17 Endocrinology and Metabolism for details on primary hyperaldosteronism.

An important differential diagnosis in patients with hypokalemia and hypertension are disorders associated with mutation of sodium channels in the distal nephron and other disorders of adrenal steroid synthesis. This group of disorders includes Liddle syndrome, syndrome of apparent mineralocorticoid excess, and familial hyperaldosteronism type 1 (also known as glucocorticoid-remediable hyperaldosteronism). In these disorders, severe early-onset hypertension associated with hypokalemia is present, but renin and aldosterone levels are suppressed because of primary sodium absorption.

Pheochromocytoma

Catecholamine-secreting tumors of chromaffin cells of the adrenal medulla (pheochromocytomas) and the sympathetic ganglia (extra-adrenal pheochromocytomas or paragangliomas) cause hypersecretion of norepinephrine and epinephrine, leading to hypertension. Patients present with symptoms of sympathetic overactivity. Screening tests for urine catecholamines and metanephrines should be performed, followed by imaging to localize the suspected tumor. Surgical removal is the only definitive treatment. See MKSAP 17 Endocrinology and Metabolism for details on pheochromocytoma.

KEY POINTS

- The eighth report of the Joint National Committee recommends a blood pressure goal of <140/90 mm Hg in patients of all ages who have chronic kidney disease with or without diabetes mellitus.
- Blood pressure management in patients with kidney disease includes the use of an ACE inhibitor or angiotensin receptor blocker as well as control of sodium balance.

HVC

- Medical management is the primary therapeutic intervention in most patients with renal artery stenosis.

Special Populations

Women

Although the prevalence of hypertension in women is lower before the age of 50 years, the eventual prevalence is similar to men. Hypertensive complications are lower in women (especially coronary artery disease). The response to hypertensive therapy is similar to men, but women derive much better cardiovascular benefit.

Oral contraceptives may be associated with overt hypertension in up to 5% of women. Stopping the drug usually leads to return of the blood pressure to baseline.

ACE inhibitors, ARBs, and aldosterone blockers should be avoided in women who are likely to become pregnant and are contraindicated in pregnant women.

Patients with Diabetes Mellitus

The JNC 8 and the American Diabetes Association both recommend a goal blood pressure of <140/90 mm Hg in patients with diabetes who are hypertensive. More aggressive lowering of the systolic blood pressure to <120 mm Hg in patients with type 2 diabetes at increased cardiovascular risk resulted in no significant cardiovascular benefit (except for a reduction in stroke) in the ACCORD study. In patients with moderately increased albuminuria or overt nephropathy (proteinuria >500 mg/g), a goal blood pressure of <130/80 mm Hg is suggested per the KDIGO guidelines.

In the absence of CKD, first-line therapy in nonblack patients with diabetes is similar to treatment of patients without diabetes: a thiazide diuretic, CCB, ACE inhibitor, or ARB. In black patients with diabetes, a thiazide diuretic or CCB is recommended for initial therapy. β-Blockers and α-blockers are not recommended as initial therapy for either group. Combination therapy of ACE inhibitors, ARBs, and direct renin inhibitors should not be used in patients with diabetes because of the increased risk of acute kidney injury and hyperkalemia without demonstrated benefit in long-term renal and cardiovascular outcomes. See Table 22 for more information.

Black Patients

Hypertension is more prevalent in black patients and associated with higher cardiovascular and renal complications than in other racial groups. The JNC 8 recommends a blood pressure goal for black patients of <140/90 mm Hg (for age ≥60 years, the target is <150/90 mm Hg, regardless of race).

A thiazide diuretic or a CCB alone or in combination is recommended as initial therapy. A potential conflict may occur with this recommendation and the guidance to use either an ACE or ARB in patients with CKD. To address this, the JNC 8 recommends that initial therapy in black patients with CKD and proteinuria be with an ACE inhibitor or ARB; in black patients without proteinuria, treatment options include a thiazide diuretic, CCB, ACE inhibitor, or ARB. See Table 22 for more information.

Older Patients

The prevalence of hypertension can be as high as 60% to 80% in patients >65 years. Frailty, sluggish baroceptor reflexes, and orthostasis are frequently seen in the elderly population. Isolated systolic hypertension (systolic >160 mm Hg and diastolic <90 mm Hg) is more common in such patients. A lower diastolic blood pressure may be associated with worse cardiovascular outcomes in epidemiologic studies, but this has not been seen in

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clinical trials; thus, there are no firm recommendations for the optimal level of diastolic blood pressure below which organ perfusion (especially coronary) is impaired. The JNC 8 treatment goal for patients ≥60 years is <150/90 mm Hg. For older patients being treated for isolated systolic hypertension, the Systolic Hypertension in the Elderly Program recommends that the diastolic blood pressure be maintained above 60 mm Hg.

The choice of antihypertensive agents is similar to the general population, but a thiazide diuretic or a long-acting CCB may be more effective. ACE inhibitors or ARBs can also be used (see Table 22). Older patients are more prone to develop hyponatremia from thiazides, and the dose of medications to control blood pressure may be lower than in younger patients. Orthostasis and subsequent falls are common in older persons, and drugs that are associated with worsening or causing orthostasis (such as α-blockers, vasodilators, and centrally acting agents) should be avoided if possible.

A recent study defining frailty as the inability to walk 6 meters in less than 8 seconds demonstrated no association with hypertension and mortality, and, in those who were unable to complete the walk test, a reduction in mortality was noted with increased blood pressure. This suggests that the risk of complications, morbidity, and mortality related to lower blood pressure in frail individuals may supersede the potential benefit of lower blood pressure goals.

KEY POINTS

- ACE inhibitors, angiotensin receptor blockers, and aldosterone blockers should be avoided in women who are likely to become pregnant and are contraindicated in women who are pregnant.
- In the absence of chronic kidney disease, first-line therapy of hypertension in nonblack patients with diabetes mellitus is similar to treatment of patients without diabetes: a thiazide diuretic, calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker.
- In black patients with hypertension, a thiazide diuretic or calcium channel blocker alone or in combination is recommended as initial therapy.
- The treatment goal for patients with hypertension who are ≥60 years is <150/90 mm Hg.

Chronic Tubulointerstitial Diseases

Pathophysiology and Epidemiology

Tubulointerstitial diseases primarily affect the tubules and/or interstitium of the kidney. Acute interstitial nephritis is an inflammatory process affecting the kidney interstitium and is associated with acute kidney injury (AKI) over the course of days to weeks, whereas chronic tubulointerstitial diseases develop over months to years and are a cause of slowly declining kidney function. Chronic tubulointerstitial diseases most commonly result from previous injury due to acute interstitial nephritis, but can also result from other glomerular, vascular, or obstructive diseases that may cause irreversible injury to the tubules and interstitium, even with treatment and resolution of the initial disease process. They are difficult to manage because of the diverse causes, an insidious presentation typically occurring over months to years, and often indeterminate findings on examination and laboratory testing; careful and meticulous evaluation is therefore essential. See **Table 25** for causes of tubulointerstitial diseases. See Acute Kidney Injury for more information on acute interstitial nephritis.

KEY POINT

- Chronic tubulointerstitial diseases most commonly result from previous injury due to acute interstitial nephritis, develop over months to years, and result in slowly declining kidney function.

Diagnosis and Evaluation

Symptoms and physical findings in patients with tubulointerstitial disease can be minimal or absent unless an active associated disease is present. Thus, the diagnosis is often triggered by abnormalities detected on laboratory testing performed for other purposes. History and physical examination should focus on conditions associated with tubulointerstitial disease and potential treatable causes. A careful review of medications is particularly important (see Table 25).

Many patients with chronic tubulointerstitial disease already have advanced kidney disease at the time of detection. Laboratory studies reflect the consequences of tubular dysfunction associated with these diseases. Urinalysis may be bland, often without the sterile pyuria and leukocyte casts associated with acute interstitial nephritis. Proteinuria may be present but is typically <2000 mg/24 h. Abnormal handling of glucose, amino acids, uric acid, phosphate, and bicarbonate (termed *Fanconi syndrome*) may be present, and renal tubular acidosis (RTA) is common. Patients often have concentrating defects and may present with nocturia and polyuria. With more advanced disease, anemia may be present due to the destruction of erythropoietin-producing cells in the kidney. Ultrasound can show atrophic kidneys consistent with chronicity. The role of kidney biopsy in diagnosing chronic tubulointerstitial disease is uncertain but may be appropriate in selected patients.

See **Table 26** for more information on the clinical manifestations of chronic tubulointerstitial disease.

KEY POINT

- Chronic tubulointerstitial disease should be considered in patients with slowly progressive or stable chronic kidney disease of unclear cause associated with bland urine sediment, proteinuria <2000 mg/24 h, and atrophic kidneys on ultrasound.

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TABLE 25. Causes of Chronic Tubulointerstitial Diseases

Autoimmune Disorders
Anti–tubular basement membrane antibody-mediated tubulointerstitial nephritis
Sarcoidosis
Sjögren syndrome
Systemic lupus erythematosus
IgG4-related disease
Tubulointerstitial nephritis with uveitis (TINU)[a]
Toxic Causes
Balkan endemic nephropathy/aristolochic acid nephropathy (with increased risk of transitional cell carcinoma)
Heavy metal nephropathy (e.g., lead, cadmium, mercury)
Hereditary Tubulointerstitial Nephritis
Medullary cystic kidney disease
Mitochondrial disorders
Nephronophthisis
Infection-Related Causes
Polyoma BK virus (most commonly post-kidney transplantation)
Brucellosis
Cytomegalovirus
Epstein-Barr virus
Fungal infections
Legionella species
Mycobacterium tuberculosis
Toxoplasmosis
Chronic pyelonephritis
Malignancy-Related Causes
Leukemia
Lymphoma
Malignancy-associated monoclonal gammopathies (e.g., multiple myeloma, plasmacytoma)
Medication-Induced Causes
Analgesic nephropathy
Phosphate nephropathy
Oxalate nephropathy
Calcineurin inhibitors
Cyclooxygenase-2 inhibitors
Lithium
NSAIDs
Prolonged exposure to any medication that can cause acute interstitial nephritis: 5-aminosalicylates (e.g., mesalamine); allopurinol; cephalosporins; fluoroquinolones; H_2 blockers; indinavir; penicillins; proton pump inhibitors; rifampin; sulfonamides
Secondary Tubulointerstitial Injury Due to Glomerular and Vascular Disorders (e.g., hypertensive nephrosclerosis)
Urinary Tract Obstruction

[a]TINU is an uncommon immune-mediated syndrome with the combination of tubulointerstitial nephritis and uveitis associated with autoimmune disorders, including hypoparathyroidism, thyroid disease, IgG4-related disease, and rheumatoid arthritis.

TABLE 26. Clinical Manifestations of Chronic Tubulointerstitial Diseases

Abnormality[a]	Cause
Decline in GFR	Obstruction of tubules; damage to microvasculature; interstitial fibrosis and sclerosis of glomeruli
Proximal tubular damage (Fanconi syndrome)	Incomplete absorption and kidney wasting of glucose, phosphate, uric acid, bicarbonate, and amino acids
Normal anion gap metabolic acidosis	Proximal and distal RTA; decreased ammonia production
Polyuria and isosthenuria	Decreased concentrating and diluting ability
Proteinuria	Decreased tubular protein reabsorption (usually <2000 mg/24 h)
Hyperkalemia	Defect in potassium secretion (type 4 [hyperkalemic] distal RTA)
Hypokalemia	Defect in potassium reabsorption (type 1 [hypokalemic] distal RTA)
Anemia	Injury to erythropoietin-producing cells in the kidney

GFR = glomerular filtration rate; RTA = renal tubular acidosis.

[a]The degree of these abnormalities depends on the extent and location of injury.

Causes

See Table 25 for a list of causes of chronic tubulointerstitial disease.

Immunologic Diseases

Various immunologic diseases are associated with tubulointerstitial disease, including Sjögren syndrome, sarcoidosis, IgG4-related disease, and systemic lupus erythematosus (SLE). The incidence and severity of kidney involvement vary with the activity of the disease and treatment of the underlying process, typically with immunosuppressive therapy.

Sjögren Syndrome

Characterized by lymphocytic and plasmacytic infiltration of the parotid, salivary, and lacrimal glands, Sjögren syndrome can produce a similar injury in other nonexocrine glands and in the kidneys. Interstitial disease is the most common kidney manifestation of Sjögren syndrome; glomerular involvement is uncommon. Diagnosis is usually made by identifying tubulointerstitial disease in the context of confirmed Sjögren syndrome, although kidney biopsy will demonstrate granuloma formation.

Sarcoidosis

The tubulointerstitial disease of sarcoidosis typically presents at the time of initial diagnosis of the disease and may be

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advanced; severe tubulointerstitial disease is uncommon in patients with long-standing disease. Because sarcoidosis can cause kidney damage through other mechanisms, including direct ureteral involvement, retroperitoneal fibrosis, and hypercalcemia, hypercalciuria, nephrolithiasis, and nephrocalcinosis via excessive production of 1,25-dihydroxy vitamin D in granulomas, tubulointerstitial disease usually requires confirmation by kidney biopsy showing the presence of noncaseating granulomas and interstitial nephritis.

IgG4-Related Disease

IgG4-related disease is a group of diseases characterized by infiltration of different organs by lymphoplasmacytic infiltrates of IgG4-positive plasma cells with resultant fibrosis and is often associated with elevated serum IgG4 levels. There is often other organ involvement and occasionally associated glomerular lesions, including membranous and membranoproliferative glomerulonephritis.

Systemic Lupus Erythematosus

The tubulointerstitial disease of SLE typically occurs with concomitant glomerulonephritis. The degree of tubulointerstitial involvement in SLE is a poor prognostic sign with an associated increased risk for hypertension, progressive kidney dysfunction, and end-stage kidney disease.

Infections

Numerous infections, including those caused by bacteria, mycobacteria, viruses, parasites, and fungi, are associated with acute interstitial nephritis and chronic tubulointerstitial nephritis (see Acute Kidney Injury). The pathophysiology of infection-related interstitial nephritis may be direct infiltration of the kidney or an inflammatory response triggered by the infecting agent.

Malignancy

Kidney infiltration by lymphoma and leukemia may occur and present with non–nephrotic-range proteinuria, sterile pyuria, and enlarged kidneys on imaging studies. Diagnosis may be confirmed by biopsy. Gammopathies associated with lymphoproliferative disorders or multiple myeloma may also cause tubulointerstitial disease (see Kidney Manifestations of Gammopathies).

Numerous antineoplastic agents have been associated with tubulointerstitial disease, including carboplatin, cisplatin, cyclophosphamide, ifosfamide, nitrosoureas (such as carmustine, lomustine, semustine, and streptozocin), and panitumumab. Clinical features may include chronic kidney disease (CKD), mild proteinuria, and evidence of tubular dysfunction manifested as Fanconi syndrome and electrolyte abnormalities.

Medications

Analgesics

Long-term use of analgesic agents, particularly combinations of potentially nephrotoxic medications, is associated with chronic tubulointerstitial disease. However, the types and doses of medications leading to CKD have not been clearly defined. NSAIDs can cause AKI and may accelerate progression of underlying CKD, but it is controversial whether NSAIDs can cause de novo chronic disease. There is some evidence that acetaminophen may increase the risk of CKD with prolonged exposure. Clinical manifestations are nonspecific and may include slowly progressive CKD, varying degrees of usually mild proteinuria, hypertension, and anemia.

Calcineurin Inhibitors

The calcineurin inhibitors cyclosporine and tacrolimus can cause reversible AKI and a usually irreversible chronic tubulointerstitial disease. Duration of exposure and cumulative dose are risk factors, and laboratory features may include kidney dysfunction, hyperkalemia, hypomagnesemia, hypophosphatemia, hyperuricemia, and type 4 (hyperkalemic distal) RTA. Kidney biopsy shows patchy tubular atrophy and interstitial fibrosis. Therapy includes calcineurin dose reduction or non-calcineurin alternatives, if possible.

Lithium

Chronic lithium therapy can cause chronic tubulointerstitial disease, CKD, and nephrogenic diabetes insipidus. Prolonged duration of therapy and the cumulative dose are risk factors, but serum lithium levels do not correlate well with the risk of nephrotoxicity (patients can develop CKD with consistently therapeutic levels). Clinical features include polyuria and nocturia due to the loss of concentrating ability in the kidney (diabetes insipidus), and type 1 (hypokalemic distal) RTA can occur.

Diagnosis is often clinical based on history of lithium exposure, inappropriately dilute urine following water restriction, and variable degrees of CKD. Therapies include stopping lithium if possible to prevent further injury or concomitant use of amiloride to prevent entry of lithium into tubular cells if stopping lithium is not possible. Following lithium discontinuation, the prognosis of CKD is variable; mild improvement, stabilization, or progressive loss of kidney function can occur.

Lead

Prolonged lead exposure over years can cause lead nephropathy. Clinical features include CKD, bland urine sediment, subnephrotic proteinuria, and hyperuricemia. Kidney biopsy reveals a nonspecific chronic interstitial nephritis. The diagnosis should be considered in patients with current or past exposure to lead, extrarenal manifestations of lead toxicity, and elevated blood lead levels (although lead levels may have normalized if exposure has been reduced or stopped).

Hyperuricemia

Hyperuricemia is associated with chronic uric acid nephropathy due to deposition of sodium urate crystals in the interstitium. The inflammatory response causes interstitial fibrosis and CKD. Clinical features include hyperuricemia, CKD, bland

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urine sediment, subnephrotic proteinuria, and unremarkable kidney imaging. Kidney biopsy is required to make the diagnosis because clinical features are nonspecific.

Obstruction

Urinary obstruction can result in AKI and CKD. Clinical features may include hypertension, CKD, and changes in urinary habits such as incontinence, nocturia, and polyuria. Flank pain and renal or ureteral colic are usually not features of chronic obstruction given its insidious course. Imaging (typically ultrasonography) may reveal hydronephrosis and renal cortical thinning. Type 4 (hyperkalemic distal) RTA may occur, consistent with the tubular atrophy and injury on pathology. Treatment includes relief of the obstruction, and prognosis depends on the duration and severity of the obstruction. Recovery is usually diminished with obstruction of longer than 6 to 12 weeks.

KEY POINT

- Causes of chronic tubulointerstitial disease include various immunologic diseases, infections, malignancy, medications, lead exposure, hyperuricemia, and obstruction.

Management

Rapid determination and treatment of underlying causes of chronic tubulointerstitial disease may result in slower progression or slight reversal of kidney dysfunction, but significant improvement is unlikely with long-standing disease and chronic tubulointerstitial fibrosis. Practical steps include discontinuation of potentially offending drugs and toxins and treatment of underlying immunologic, infectious, obstructive, malignant, or other disease. Blood pressure control, use of ACE inhibitors or angiotensin receptor blockers when significant detectable proteinuria is present, and metabolic control of calcium and phosphate should be undertaken. Immunosuppressive therapy should be considered (in consultation with a nephrologist) in selected patients with an inflammatory cause and evidence of active disease.

KEY POINT

- Chronic tubulointerstitial diseases typically have limited improvement with therapy, even with rapid assessment and treatment of underlying causes.

Glomerular Diseases

Pathophysiology and Epidemiology

The glomerulus is the basic filtering unit of the kidney (**Figure 12**). Anatomically, each glomerulus consists of a tuft of capillaries formed by the branching of the afferent arteriole supported by

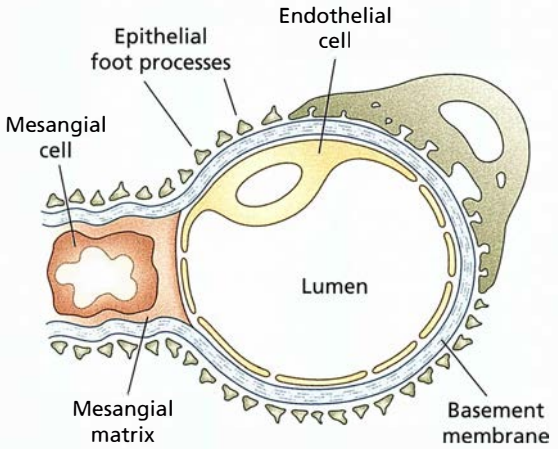

FIGURE 12. A normal glomerular capillary and surrounding structures. Each capillary consists of a layer of endothelial cells surrounded by a basement membrane on which sit specialized epithelial cells called *podocytes*. These layers constitute a barrier to plasma proteins and cells, which prevent their passage into the urine.

a structural matrix (the mesangium) produced and maintained by specialized (mesangial) cells. Each kidney has approximately 1 million glomeruli providing 2 m^2 of glomerular capillary filtering surface. The glomerular basement membrane (GBM) provides both a size- and charge-selective barrier to the passage of circulating macromolecules. On the urinary side of the GBM lies a layer of podocytes, which are specialized epithelial cells that provide another barrier to plasma proteins via a specialized intercellular junction (the slit diaphragm). The glomerular capillary tufts are surrounded by Bowman's capsule, a single layer of parietal epithelial cells that form a cup-like sac that is continuous with the renal tubule and into which the filtrate from the glomerular capillaries is collected and passed to the renal tubule.

From a histologic standpoint, glomerular disease can be *diffuse* (all glomeruli are involved) or *focal* (only some glomeruli are involved). At the level of the individual glomerulus, a process is *global* if the whole glomerular tuft is involved or *segmental* if only a part is involved. To describe the pathologic process, the terms *proliferative* (an increase in the number of cells in the glomerulus), *sclerosing* (presence of scarring), and *necrotizing* (areas of cell death) are often used (for example, focal and segmental necrotizing glomerulonephritis; diffuse global proliferative lupus nephritis). Extracapillary proliferation or *crescentic* lesions are associated with accumulations of macrophages, fibroblasts, proliferating epithelial cells, and fibrin within Bowman's space; represent rupture of the glomerular membrane; and signify severe injury to the glomerular capillary wall. Interstitial fibrosis, which accompanies uncontrolled glomerular disease, is a poor prognostic sign.

Several mechanisms lead to glomerular dysfunction. Podocyte dysfunction can occur in genetic disease affecting key basement membrane proteins such as hereditary nephritis (also known as Alport syndrome). In diseases such as

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minimal change glomerulopathy and focal segmental glomerulosclerosis (FSGS), circulating factors directly affect podocyte function and lead to proteinuria. In diabetes mellitus and amyloidosis, there is mechanical disruption of the glomerulus due to accumulation of normal or abnormal protein both in the capillary loops of the glomerulus and the mesangium. Immune mechanisms include in situ formation of immune complexes in membranous glomerulopathy or the localized effects of anti-GBM antibodies in Goodpasture syndrome; in conditions such as postinfectious glomerulonephritis and systemic lupus erythematosus, immune-mediated kidney injury is caused by deposition of circulating immune complexes.

Presently, more than 10% of the U.S. population has proteinuria or kidney dysfunction, often caused by glomerular disease. Diabetic kidney disease affects millions of people and is the major cause of end-stage kidney disease (ESKD) in the United States. Glomerular diseases associated with infections such as malaria, schistosomiasis, HIV, and hepatitis B and C are major worldwide health issues.

Clinical Manifestations of Glomerular Disease

Glomerular disease syndromes are typically classified by their characteristic features, including the pattern of abnormalities on urinalysis, any systemic features present, and the degree of kidney failure. The most common distinction is usually made between the nephrotic syndromes, in which leakage of plasma proteins is a predominant feature, and the nephritic syndromes (which reflect inflammation of the glomerulus and are also referred to as glomerulonephritis [GN]), in which there is passage of plasma proteins, erythrocytes, and leukocytes through the glomerulus into the renal tubule. These classifications, however, are not exclusive because some conditions may present with either or both patterns, and some disorders may progress from one pattern to the other. Therefore, kidney biopsy may be required to establish a diagnosis and guide appropriate therapy.

Glomerular disease may be limited primarily to the kidney but frequently occurs secondary to other systemic conditions, including infectious and autoimmune disorders. Infectious diseases linked to glomerular disease include poststreptococcal GN, HIV-associated glomerulopathy, and hepatitis C–associated cryoglobulinemic GN. Systemic lupus erythematosus is a classic example of a systemic immune complex disease associated with GN. IgA vasculitis and pauci-immune small-vessel vasculitis can also cause GN.

Glomerular disease should be suspected when proteinuria and/or hematuria are seen on urinalysis. The findings of nephrotic-range proteinuria or dysmorphic erythrocytes and erythrocyte casts in the urine sediment are also more specific for a glomerular origin. See Clinical Evaluation of Kidney Function for more details.

The Nephrotic Syndrome

The nephrotic syndrome is characterized by a urine protein excretion of >3500 mg/24 h or a urine protein-creatinine ratio of >3500 mg/g (termed *nephrotic-range proteinuria*) that may be accompanied by hypoalbuminemia, edema, and hyperlipidemia. However, many patients with high levels of proteinuria may not have the full syndrome.

The pathogenesis of the nephrotic syndrome is not completely understood. Hypoalbuminemia is thought to occur from urinary loss of albumin and increased catabolism (including uptake and catabolism of albumin by the proximal tubule). Edema results predominantly from increased sodium absorption by the distal nephron and increased capillary permeability. Elevated lipids occur from a combination of increased hepatic apolipoprotein synthesis in response to a low plasma oncotic pressure and decreased activity of key enzymes such as lipoprotein lipase and lecithin-cholesterol acyltransferase. Other complications include hypercoagulability, possibly related to loss of natural anticoagulants such as protein C and antithrombin III and upregulation of coagulation factors produced by the liver in response to a low oncotic pressure. Patients with untreated nephrotic syndrome also have a propensity for infection (possibly related to urinary loss of immunoglobulin). Urinary loss of binding proteins may be associated with deficiencies of vitamin D, thyroxine, and iron.

The nephrotic syndrome may be idiopathic (primary) or secondary to systemic diseases such as diabetes, infection, or autoimmune diseases. Although minimal change glomerulopathy is the most common cause of the nephrotic syndrome in children, membranous glomerulopathy and FSGS are the most common causes of idiopathic nephrotic syndrome in adults. Membranous glomerulopathy is the most common cause in white persons and FSGS in black persons. Diabetes is not only the most common secondary cause of the nephrotic syndrome but also the most common cause of the nephrotic syndrome in adults.

Initial evaluation begins by excluding secondary causes related to systemic disease, infection, malignancy, or medication. Screening includes testing for diabetes as well as antinuclear antibody and complement measurements for connective tissue disease. In some patients, cryoglobulins, hepatitis B and C serologies, HIV testing, serum protein and immunoelectrophoresis, and serum free light chains may be useful. Most adult patients with the nephrotic syndrome require a kidney biopsy to obtain a definitive diagnosis.

Treatment of the consequences of the nephrotic syndrome should occur simultaneously with treatment of the specific cause. Elevated lipid levels are typically treated with statin medications, with additional drugs added as needed for control of triglycerides. Anticoagulation may be needed if thrombotic complications occur. Prophylactic anticoagulation is not routinely provided to all patients with the nephrotic syndrome but is suggested in patients who have an additional risk factor for

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thrombosis. Prophylactic anticoagulation may also be considered in patients who are nephrotic with a serum albumin level ≤2.0 g/dL (20 g/L) with low bleeding risk regardless of cause. In patients with membranous glomerulopathy, the serum albumin threshold to anticoagulate in patients with low risk for bleeding has been suggested to be ≤2.8 g/dL (28 g/L). Edema is treated with a low salt diet and loop diuretics (alone or in combination with a thiazide and potassium-sparing diuretics).

The Nephritic Syndrome

The nephritic syndrome is associated with glomerular inflammation resulting in hematuria, proteinuria, and leukocytes in the urine sediment. The hallmark of hematuria in the nephritic syndrome is the presence of dysmorphic erythrocytes, with or without erythrocyte casts, that reflects a proliferative lesion in the glomeruli (which can be focal or diffuse). Proteinuria in the nephritic syndrome may be highly variable (from a few hundred milligrams to nephrotic levels). Systemic findings may include edema, hypertension, and kidney failure.

Three pathophysiologic mechanisms are associated with the nephritic syndrome: anti-GBM antibodies, pauci-immune GN (defined by necrotizing GN with few or no immune deposits), and immune complex deposition. Three different clinical syndromes may result from these mechanisms based on their time course: acute GN, rapidly progressive GN (RPGN), or chronic GN.

Serum complement levels may be useful in differentiating the underlying etiology of GN; levels are typically normal in anti-GBM antibody disease and pauci-immune GN but are low in immune complex GN (with the exception of IgA nephropathy). Additionally, crescentic lesions on pathologic examination of the kidney in a patient with the nephritic syndrome are associated with RPGN and a poor prognosis without treatment.

KEY POINTS

- The nephrotic syndrome is characterized by a urine protein excretion of >3500 mg/24 h or a urine protein-creatinine ratio of >3500 mg/g that may be accompanied by hypoalbuminemia, edema, and hyperlipidemia.
- Diabetes mellitus is the most common cause of the nephrotic syndrome in adults; membranous glomerulopathy and focal segmental glomerulosclerosis are the most common causes of idiopathic nephrotic syndrome in adults.
- The nephritic syndrome is associated with glomerular inflammation with evidence of hematuria, variable proteinuria, and sometimes leukocytes in the urine sediment; it may be associated with edema, hypertension, and kidney failure.
- Serum complement levels help differentiate the underlying etiology of glomerulonephritis (GN); levels are typically normal in anti–glomerular basement membrane antibody disease and pauci-immune GN but are low in immune-complex GN (with the exception of IgA nephropathy).

Conditions Associated With the Nephrotic Syndrome

See **Table 27** for details on nondiabetic conditions associated with the nephrotic syndrome.

Focal Segmental Glomerulosclerosis

Epidemiology and Pathophysiology

Approximately 25% of adults with idiopathic nephrotic syndrome have focal segmental glomerulosclerosis (FSGS) on biopsy. Incidence is increasing in all races, but it is especially common in black persons.

FSGS may result from genetic mutations to podocyte proteins, may be idiopathic, or may be secondary to another process. Some cases of idiopathic FSGS are thought to be related to a circulating plasma factor because a significant number of patients show recurrence after kidney transplantation. Secondary causes of FSGS include hyperfiltration injury to the glomerulus as in chronic hypertension, diabetes, and instances when kidney mass is reduced (progressive kidney disease, obesity, sickle cell disease, reflux nephropathy, congenital small kidneys, and after nephrectomy). Finally, direct podocyte injury can cause FSGS as seen in infections (HIV) and drugs (pamidronate, interferon).

Clinical Manifestations

Patients with idiopathic FSGS present with either asymptomatic proteinuria or edema. More than two thirds of patients are fully nephrotic at presentation; subnephrotic proteinuria may occur, especially with secondary FSGS from hyperfiltration injury. Hypertension, microscopic hematuria, and varying degrees of kidney failure are common. Serologic tests for systemic disease are typically negative, and complement activation is normal.

Diagnosis

The hallmark of FSGS is the presence of segmental scars in some glomeruli. Electron microscopy shows visceral epithelial cell foot process effacement but no immune deposits. There are several variants of FSGS, but the "collapsing" form is diagnosed when there is severe podocyte hyperplasia leading to collapse of the glomerular tuft. HIV infection is typically associated with collapsing FSGS.

Treatment and Prognosis

In idiopathic FSGS, only a minority of patients experience a spontaneous remission. Therefore, treatment is indicated in most patients. Therapy is usually with glucocorticoids or calcineurin inhibitors, both at the time of initial presentation and for relapsing disease. A complete or partial remission may be seen in up to 40% to 60% of patients using these treatments. Patients who enter remission (even partial) have a good prognosis compared with patients who have refractory disease. FSGS recurs in the transplanted kidney in 30% or more of cases.

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TABLE 27. Nondiabetic Conditions Associated With the Nephrotic Syndrome

Condition	Frequency as a Cause of the Nephrotic Syndrome	Comments
Focal segmental glomerulosclerosis	36%-80%	Most common cause of primary nephrotic syndrome in the United States
		Predilection for black persons
		Five subtypes: not otherwise specified; perihilar variant; tip variant; cellular variant; collapsing variant (may be associated with HIV infection, heroin use, parvovirus infection, or pamidronate exposure)
		May be associated with or secondary to:
		Genetic mutations of podocyte proteins
		Direct podocyte injury (e.g., permeability factor), viral infections (e.g., HIV), drugs (e.g., pamidronate)
		Hyperfiltration (e.g., morbid obesity) and decreased kidney mass (congenital kidney dysplasia, reflux nephropathy)
Membranous glomerulopathy	18%-41%	Primary form (most common worldwide): antiphospholipase A_2 receptor autoantibodies can be found in 75% of cases
		May be associated with or secondary to:
		Systemic lupus erythematosus
		Infections: hepatitis B and C virus infections; syphilis; malaria
		Medication exposure: penicillamine; NSAIDs; TNF-α inhibitors; tiopronin
		Mercury or gold exposure
		Malignancies: bladder, breast, colon, lung, pancreas, prostate, stomach carcinoma; carcinoid; sarcomas; lymphomas; leukemias
		Thyroid disease
		Highest predilection for renal vein thrombosis among all causes of the nephrotic syndrome
Minimal change glomerulopathy	9%-16%	Most common cause of primary nephrotic syndrome in children
		May be associated with or secondary to:
		Atopic diseases
		Mononucleosis
		Malignancies: Hodgkin lymphoma and carcinomas
		Medication exposure: NSAIDs; interferon; pamidronate; lithium; rifampin

TNF = tumor necrosis factor.

In secondary FSGS caused by infection or drugs, treatment of the infection or removal of the offending agent may halt progression of the disease and improve symptoms. In obese patients with likely secondary FSGS, weight loss is sometimes associated with a drop in proteinuria, as is the use of ACE inhibitors or angiotensin receptor blockers (ARBs), and is the preferred initial therapy.

Membranous Glomerulopathy

Epidemiology and Pathophysiology

Membranous glomerulopathy (MG) is the most common cause of idiopathic nephrotic syndrome in adult white persons. MG may also be associated with infections (hepatitis B and C, malaria, syphilis), systemic lupus erythematosus, medications (gold salts, NSAIDs), and malignancies (solid tumors, lymphomas). In most patients with idiopathic MG, circulating antibodies directed to podocyte surface antigens (phospholipase A_2 receptor [PLA_2R]) activate complement and damage the GBM.

Clinical Manifestations

Pathological changes of MG may precede clinical manifestations by months. The clinical presentation of MG is indistinguishable from other causes of the nephrotic syndrome (edema, hypertension, microhematuria), but the propensity to thromboembolic events (particularly renal vein thrombosis) is much higher. Secondary causes should be sought, particularly occult malignancy in older patients.

Diagnosis

Diagnosis of MG is made by kidney biopsy. Light microscopy shows glomerular capillary loops that often appear thickened without any proliferative lesions. Immunofluorescence and electron microscopy show subepithelial immune dense

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deposits. Where available, PLA_2R antibodies should be measured.

Treatment and Prognosis

Up to one third of patients with idiopathic MG remit spontaneously in 6 to 12 months. Conservative management is appropriate during this period. In patients with idiopathic MG who have persistent disease after 6 to 12 months or who have worsening kidney function or a thromboembolic event, regimens containing alternating glucocorticoids with cyclophosphamide or calcineurin inhibitors (cyclosporine or tacrolimus) may be employed. Other options for relapsing or refractory disease include mycophenolate mofetil, adrenocorticotropic hormone, and the anti–B-cell antibody rituximab. Renal survival is excellent if patients enter remission. In general, older patients, men, and those with heavy, persistent proteinuria and kidney dysfunction are at risk of progression.

Among the secondary causes of MG, treatment of hepatitis B virus infection with antiviral agents has been associated with improvement of proteinuria; glucocorticoids are not of benefit. Similarly, remission of proteinuria may occur with treatment of an associated malignancy or withdrawal of drugs, without needing immunosuppression. Treatment of lupus MG employs immunosuppressive regimens similar to primary MG.

Minimal Change Glomerulopathy

Epidemiology and Pathophysiology

Minimal change glomerulopathy (MCG; also known as minimal change disease) is the most common cause of idiopathic nephrotic syndrome in children and accounts for approximately 10% of cases in adults. Secondary causes of MCG include medications (such as NSAIDs, lithium, pamidronate, and the interferons) and malignancies (such as Hodgkin lymphoma and thymoma). A history of viral respiratory infection, atopy, or immunization preceding the onset of edema may be present. The pathogenesis of MCG is not fully understood but is thought to be related to production of cytokines by immune cells that lead to podocyte dysfunction.

Clinical Manifestations

Patients with MCG typically present with acute onset of edema and weight gain due to fluid retention. Urine protein levels tend to be significantly elevated (urine protein-creatinine ratio typically 5000-10,000 mg/g). Azotemia may occur, especially in older adults. The urine sediment is typically benign with few erythrocytes or erythrocyte casts. Complement levels are normal and serologic test results for systemic disease are negative.

Diagnosis

Diagnosis of MCG is confirmed with kidney biopsy, which shows normal glomeruli on both light and immunofluorescence microscopy. The tubules may show lipid accumulation. On electron microscopy, the GBM is normal with extensive effacement of visceral epithelial foot processes.

Treatment and Prognosis

Patients typically respond to glucocorticoids within 8 to 16 weeks. However, relapse is common, and in up to 40% of patients, the course of MCG is one of remission followed by relapse. For frequently relapsing or glucocorticoid-dependent disease, treatment options include cyclophosphamide, calcineurin inhibitors (tacrolimus or cyclosporine), mycophenolate mofetil, and rituximab. Although uncommon, progressive kidney failure may occur.

Diabetic Nephropathy

Epidemiology and Pathophysiology

Diabetic nephropathy (DN) is the leading cause of ESKD in the United States, accounting for approximately 40% of new patients presenting with kidney failure. Risk factors for developing DN include older age, race (American Indian, Mexican American, and black), poor glycemic control, hypertension, cigarette smoking, and a family history of kidney disease. The strongest clinical indicator for progressive kidney disease is the level of urine albumin. The pathogenesis of DN involves an early phase of hyperfiltration, which is mediated by hyperglycemia-associated elevation of angiotensin levels. This (reversible) phase is followed by a general activation of inflammatory and profibrotic pathways, resulting in laying down of extracellular matrix in all compartments of the kidney, followed by fibrosis and, eventually, ESKD.

From a pathologic standpoint, DN affects every compartment of the kidney. In the glomerulus, there is expansion of the mesangium and thickening of the basement membrane, followed by focal (nodular) sclerosis (the Kimmelstiel-Wilson lesion) then global sclerosis of the glomerulus. Interstitial fibrosis, tubular atrophy with thickened tubular basement membranes, and arteriolosclerosis are also seen.

Clinical Manifestations

Moderately increased albuminuria (formerly known as microalbuminuria), defined as a urine albumin-creatinine ratio of 30 to 300 mg/g, is typically the first abnormality seen in patients with type 1 and type 2 diabetes. It occurs in approximately 30% of patients after a mean of 5 to 15 years from diagnosis in type 1 and at less predictable intervals in type 2. Overt nephropathy (urine protein-creatinine ratio >300 mg/g) occurs around 10 to 15 years from disease onset in approximately 50% of patients with moderately increased albuminuria and progresses to ESKD in most patients.

Diagnosis

Annual testing for moderately increased albuminuria should begin at the time of diagnosis in type 2 diabetes and 5 years after diagnosis in type 1 diabetes. Kidney biopsy is not indicated unless there is a suspicion of another glomerular disease. However, the presence of findings of another systemic disease, abnormal serologies, acute onset of the nephrotic syndrome or short duration from onset of diabetes to onset of proteinuria, and rapid rate of progression of kidney

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dysfunction suggest an alternative diagnosis and are indications for kidney biopsy.

Treatment and Prognosis

Achieving targets of glycemic control (hemoglobin A_{1c} <7%) and blood pressure (<140/90 mm Hg, according to the eighth report of the Joint National Committee) has been shown to prevent or delay progression of DN. The use of tighter glycemic (hemoglobin A_{1c} <6.5%) and blood pressure (<130/80 mm Hg) targets is controversial.

In patients who have diabetes with moderately increased albuminuria or severely increased albuminuria (formerly known as macroalbuminuria or overt proteinuria), ACE inhibitors or ARBs have been shown to slow progression. However, overly aggressive inhibition of the renin-angiotensin system, particularly with a combination of direct renin inhibitors/ACE inhibitors/ARBs, has not been shown to improve kidney outcomes and may be associated with hyperkalemia and episodes of acute kidney injury. Because of this, combination therapy is not recommended.

KEY POINTS

- Treatment of idiopathic focal segmental glomerulosclerosis includes glucocorticoids or calcineurin inhibitors, both at the time of initial presentation and for relapsing disease.
- Up to one third of patients with idiopathic membranous glomerulopathy remit spontaneously in 6 to 12 months; conservative management is appropriate during this period.

(Continued)

KEY POINTS *(continued)*

- Patients with minimal change glomerulopathy typically respond to glucocorticoids; for frequently relapsing or glucocorticoid-dependent disease, treatment options include cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil, and rituximab.
- Achieving targets of glycemic control (hemoglobin A_{1c} <7%) and blood pressure (<140/90 mm Hg) has been shown to prevent or delay progression of diabetic nephropathy.
- ACE inhibitors or angiotensin receptor blockers have been shown to slow progression of diabetic nephropathy.

Conditions Associated With the Nephritic Syndrome

See **Table 28** for details on conditions associated with the nephritic syndrome.

Rapidly Progressive Glomerulonephritis

Epidemiology and Pathophysiology

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome characterized by evidence of GN with progression to kidney failure within weeks. It represents a clinical pattern of disease that may be associated with any etiology of GN or may be idiopathic. However, RPGN is particularly common with anti-GBM antibody disease (in younger patients) and pauci-immune small-vessel vasculitis (in older patients).

TABLE 28. Conditions Associated With the Nephritic Syndrome

Condition	Frequency as a Cause of the Nephritic Syndrome	Comments
Anti–glomerular basement membrane antibody disease	3%	Frequent cause of RPGN
Pauci-immune glomerulonephritis	15%-25%	Frequent cause of RPGN
Immune complex–mediated glomerulonephritis		
IgA nephropathy	25%-30%	Often asymptomatic; rarely causes RPGN
Henoch-Schönlein purpura	—	Often acute onset, occasionally with RPGN
Lupus nephritis[a]	20%	Variably associated with RPGN
Infection-related glomerulonephritis[a]	4%-8%	—
Membranoproliferative glomerulonephritis[a]	6%-10%	Rarely causes RPGN
Cryoglobulinemia[a]	—	Frequent cause of RPGN
Thin basement membrane disease	—	Asymptomatic microhematuria; good prognosis
Hereditary nephritis (also known as Alport syndrome)	—	Chronic and slowly progressive; extrarenal abnormalities involving the eye and cochlea

RPGN = rapidly progressive glomerulonephritis.

[a]Typically associated with low serum complement levels.

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CONT.

Clinical Manifestations

Patients with RPGN typically present with the nephritic syndrome and may sometimes be in advanced kidney failure at the time of presentation. Other symptoms and clinical findings related to an underlying cause may also be present, such as systemic signs of vasculitis (arthritis, epistaxis, hemoptysis) or lung hemorrhage (Goodpasture syndrome). Kidney function usually deteriorates rapidly unless treatment is instituted.

Diagnosis

The diagnostic approach to RPGN is similar to that in patients with GN. Testing may indicate the underlying condition. For example, serologic tests may show positivity to ANCA in patients with systemic vasculitis or to anti-GBM antibodies in patients with anti-GBM antibody disease. Chest imaging may show diffuse infiltrates in a patient with pulmonary hemorrhage or nodules in the presence of granulomatosis with polyangiitis (formerly known as Wegener granulomatosis). Definitive diagnosis is made with kidney biopsy, which typically shows glomerular crescents associated with inflammation of glomerular capillaries. The specific diagnosis is made with immunofluorescence microscopy (immune complexes, linear anti-GBM antibody staining, or pauci-immune GN).

Treatment and Prognosis

All patients with RPGN (except those with infection-related GN who are actively infected) should be treated with high-dose intravenous (pulse) glucocorticoids, followed by oral glucocorticoid therapy. Most patients with RPGN also receive cyclophosphamide (oral or intravenous) or rituximab in cases of pauci-immune GN. Plasmapheresis is indicated in the presence of pulmonary hemorrhage or severe kidney failure to remove circulating antibody. Rapid diagnosis is critical; a delay may result in irreversible kidney failure or death from pulmonary hemorrhage. See Anti-Glomerular Basement Membrane Antibody Disease and Pauci-Immune Glomerulonephritis for further details.

Anti-Glomerular Basement Membrane Antibody Disease

Epidemiology and Pathophysiology

Anti-GBM antibody disease is an autoimmune disease caused by antibodies directed against the noncollagenous domain of type IV collagen. These antibodies bind to the GBM, inciting an inflammatory response, damage to the GBM, and the formation of a proliferative and often crescentic glomerulonephritis. The same process can occur with the basement membrane of pulmonary capillaries, leading to pulmonary hemorrhage (known as *Goodpasture syndrome*). Anti-GBM antibody disease accounts for <15% of cases of RPGN.

Clinical Manifestations

Patients with anti-GBM antibody disease present with a nephritic picture. Kidney function may rapidly deteriorate over days to weeks. Patients with pulmonary hemorrhage may have life-threatening respiratory failure with diffuse alveolar infiltrates on chest radiograph.

Diagnosis

In anti-GBM antibody disease, all of the classic features of the nephritic syndrome are usually present at the time of diagnosis. Serologies show normal complement levels and elevated anti-GBM antibody levels. On kidney biopsy, there is a proliferative GN, often with many crescents. There is linear deposition of immunoglobulin (usually IgG) along the GBM by immunofluorescence, but electron microscopy does not show electron-dense deposits.

Treatment and Prognosis

In patients with anti-GBM antibody disease, immunosuppressive therapy with cyclophosphamide and glucocorticoids, combined with daily plasmapheresis to remove circulating anti-GBM antibodies, leads to stabilization or improvement if treated early. The renal prognosis is poor in patients who require dialysis at the time of presentation. Relapses are rare.

Pauci-Immune Glomerulonephritis

See Systemic Vasculitis in MKSAP 17 Rheumatology for more information.

Epidemiology and Pathophysiology

Pauci-immune GN is caused by microscopic vessel vasculitis affecting the kidney, resulting in necrotizing lesions in the glomeruli with few or no immune deposits. The renal lesion may occur with or without systemic vasculitis and is the most common cause of RPGN. Most patients have circulating ANCA directed against neutrophils. Three forms of systemic vasculitis are associated with pauci-immune GN: granulomatosis with polyangiitis (GPA; formerly known as Wegener granulomatosis), with granulomas associated with necrotizing vasculitis; microscopic polyangiitis (MPA), which is similar to GPA but without granulomas; and eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome).

Clinical Manifestations

Kidney manifestations of pauci-immune GN may range from minimal disease with only hematuria to RPGN. Systemic symptoms may be nonspecific, including low-grade fever, myalgia, fatigue, and arthritis. Other clinical manifestations may include leukocytoclastic vasculitis resulting in palpable purpura, as well as pulmonary disease (the spectrum can vary from a nonresolving pulmonary infiltrate to fulminant pulmonary hemorrhage.) Compared with MPA, GPA may manifest with more prominent upper and lower respiratory tract involvement with granulomatous lesions on biopsy, often associated with tissue destruction (saddle nose, tracheal stenosis, hearing loss). Patients with EGPA usually have a history of asthma, pulmonary infiltrates, and eosinophilia.

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(CONT.)

Diagnosis

More than 80% of patients with MPA or GPA are ANCA positive. GPA is closely associated with proteinase 3 (PR3)-ANCA, whereas MPA is primarily associated with myeloperoxidase (MPO)-ANCA. Up to 10% of patients with GPA and MPA are ANCA negative. Complement levels are normal. Tissue biopsy is required to make the diagnosis, but an empiric decision to begin treatment should be considered in rapidly deteriorating disease. Kidney biopsy shows absent or minimal staining with immunoglobulin (hence the term *pauci-immune*). The spectrum of abnormalities may range from mild focal and segmental GN to a diffuse necrotizing and crescentic GN. There is variable interstitial inflammation (granulomas imply a diagnosis of GPA) and vasculitis of arterioles and venules. Glomerular and interstitial fibrosis accompanies chronic disease.

Treatment and Prognosis

For induction, combination therapy with glucocorticoids and cyclophosphamide, with or without plasmapheresis, has markedly improved kidney and patient survival rates in those with ANCA vasculitis. The anti-B-cell antibody rituximab is equally effective and safer compared with cyclophosphamide in patients with mild-moderate disease. Maintenance regimens using azathioprine, mycophenolate mofetil, or methotrexate have been employed after patients have achieved remission.

Adverse prognostic signs include older age, severe pulmonary involvement, and severe kidney failure at time of presentation.

KEY POINTS

- Rapidly progressive glomerulonephritis is a clinical syndrome characterized by evidence of glomerulonephritis with progression to kidney failure within weeks.
- In patients with anti–glomerular basement membrane antibody disease, cyclophosphamide and glucocorticoids combined with daily plasmapheresis leads to stabilization or improvement if treated early.
- Kidney manifestations of pauci-immune glomerulonephritis may range from minimal disease with only hematuria to rapidly progressive glomerulonephritis; kidney biopsy shows absent or minimal staining with immunoglobulin.

Immune Complex-Mediated Glomerulonephritis

IgA Nephropathy

Epidemiology and Pathophysiology

IgA nephropathy (IgAN) is the most frequent cause of chronic GN, particularly in Asia and Northern Europe, and is rare in people of African descent. IgAN occurs more commonly in men, with a peak occurrence in the second to third decades of life. The pathogenesis of IgAN is thought to involve several sequential events beginning with genetic predisposition to the disease, the occurrence of IgA molecules that are galactose deficient at the hinge region of the immunoglobulin molecule, and the formation of autoantibodies against the abnormal IgA leading to immune complex formation. Immune complexes with associated inflammatory lesions are seen in the glomeruli in IgAN or in multiple extrarenal sites in IgA vasculitis (Henoch Schönlein purpura).

Clinical Manifestations

In adults, asymptomatic microscopic hematuria with or without proteinuria is the most common presentation of IgAN. Episodic gross hematuria following an upper respiratory tract infection (also known as *synpharyngitic nephritis*) is another classic presentation. Other features of nephritis such as hypertension, edema, and kidney failure with RPGN may occur in the acute phase or in patients with chronic disease.

Diagnosis

No serologic tests are diagnostic of IgAN. Serologic tests for systemic diseases and complement levels are usually normal. Kidney biopsy is required to make the diagnosis. On light microscopy, the most common finding is mesangial proliferation. Occasionally, endocapillary proliferation and crescents may be seen. The finding of IgA deposits as either the dominant or the codominant immunoglobulin on immunofluorescence is the diagnostic criterion for this condition.

Treatment and Prognosis

IgAN is a chronic condition, and many patients have a benign course with a 20-year kidney survival of approximately 75%. Low-risk patients are usually not actively treated and are followed with continued observation. Proteinuria >1000 mg/g, hypertension, kidney dysfunction, and mesangial and endothelial proliferation with tubulointerstitial damage are associated with a worse outcome. Patients with proteinuria and risk factors for progression may benefit from ACE inhibitors or ARBs. A 6-month course of glucocorticoids has also shown benefit in such patients.

IgA Vasculitis (Henoch-Schönlein Purpura)

Henoch-Schönlein purpura (HSP) is an IgA-associated small-vessel vasculitis seen predominantly in children but may occur in adults (see MKSAP 17 Rheumatology, Systemic Vasculitis). Kidney involvement is similar to IgAN, with the typical manifestations of the nephritic syndrome, often with acute kidney injury. Organ involvement may occur concurrently or sequentially. Recurrences, especially during the first year, are common. Diagnosis is confirmed either by finding an IgA-dominant leukocytoclastic vasculitis or by kidney biopsy, which shows lesions similar to IgAN. HSP is typically self-limiting. Some patients with severe abdominal findings are treated with short courses of high-dose glucocorticoids. Patients with severe GN are occasionally treated with immunosuppressive drugs; however, there are no reliable data to gauge efficacy.

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Lupus Nephritis

See Systemic Lupus Erythematosus in MKSAP 17 Rheumatology for more information.

Epidemiology and Pathophysiology

Kidney involvement in systemic lupus erythematosus (SLE) is common, and lupus nephritis (LN) is a major source of morbidity. SLE/LN is the archetypal immune complex disease with immune deposits in all areas of the glomerulus. This leads to distinct patterns of histology, which are classified by the International Society of Nephrology into six classes (**Table 29**).

Clinical Manifestations

Patients typically present with extrarenal symptoms of SLE at the time of diagnosis of LN, with active lupus serologies and low complement levels. Occasionally, LN may be the initial manifestation. Patients with class I or II LN may have minimal or no renal findings, and those with classes III and IV present with varying degrees of the nephritic syndrome. Patients with class V LN present predominantly with proteinuria. Class VI is the end stage of long-standing LN. A kidney biopsy is indicated when clinically manifest kidney disease is present (typically proteinuria >500 mg/g and hematuria).

TABLE 29. Classification of Lupus Nephritis

Classification	Comments
I. Minimal mesangial LN	No renal findings
II. Mesangial proliferative LN	Mild clinical kidney disease; minimally active urine sediment; mild to moderate proteinuria (never nephrotic) but may have active serology
III. Focal proliferative LN, <50% glomeruli involved (active; active and chronic; or chronic)	More active urine sediment changes; often active serology; increased proteinuria (about 25% nephrotic); hypertension may be present; some evolve into class IV pattern; active lesions require treatment, chronic lesions do not
IV. Diffuse proliferative LN (>50% glomeruli involved); all may be with segmental or global involvement (active; active and chronic; or chronic)	Most severe kidney involvement with active urine sediment, hypertension, heavy proteinuria (frequent nephrotic syndrome), and often reduced GFR; serology very active; active lesions require treatment
V. Membranous LN glomerulonephritis	Significant proteinuria (often nephrotic) with less active serology
VI. Advanced sclerosing LN	More than 90% glomerulosclerosis; no treatment prevents kidney failure

GFR = glomerular filtration rate; LN = lupus nephritis.

Diagnosis

Serologic tests for SLE, including antinuclear antibodies and anti-double-stranded DNA antibodies, are typically positive. C3 and C4 complement levels are depressed, signifying activation of the classical complement pathway. Kidney biopsy is required to make the diagnosis and classify the lesions of LN (see Table 29).The histologic class and degree of activity and chronicity on biopsy are helpful in guiding therapy.

Treatment and Prognosis

Patients with class I and II lesions require no specific therapy directed at the kidney. Most patients with class III LN and all patients with class IV LN benefit from aggressive combination immunosuppressive therapy. In class V (membranous) LN, the clinical course is generally more benign, and therapy is similar to idiopathic membranous glomerulopathy. Induction therapy for severe proliferative LN (active class III or class IV) includes glucocorticoids with either cyclophosphamide or mycophenolate mofetil. The addition of plasmapheresis has not been shown to improve outcomes. Maintenance therapy with mycophenolate mofetil or azathioprine may be used after the 6-month induction period.

See **Table 30** for more information on the treatment of the specific LN classes.

Infection-Related Glomerulonephritis

Epidemiology and Pathophysiology

In the past, streptococcal infection with nephritogenic strains followed by GN led to the term *postinfectious* or *poststreptococcal GN* (PSGN) being employed. Over the past three decades, however, there has been a shift in the epidemiology of this group of diseases, especially in developed countries. Older adults and immunocompromised patients now constitute a significant proportion of such patients. The sites of infection can be widespread (not just the upper respiratory tract and skin as in PSGN). Nonstreptococcal infection, particularly with *Staphylococcus*, is as or more common than streptococcal infection. Finally, GN can be present at the time of infection (rather than a delay of at least a week after the infection, as in PSGN). The term *infection-related glomerulonephritis* (IRGN), therefore, is more appropriate. Diabetes is a major risk factor for staphylococcal-associated GN, with methicillin-resistant strains more common in such patients. Rarely, coagulase-negative *Staphylococcus* and gram-negative organisms (*Escherichia coli* being the most common) may be associated with GN.

IRGN is an immune complex–mediated disease. The antigen in the immune complex is derived from the infectious agent. After depositing in the subepithelial area (either within preformed immune complexes or as in-situ immune complex formation), complement activation and subsequent recruitment of inflammatory cells occur, leading to a proliferative GN.

Clinical Manifestations

Patients with IRGN clinically present with acute nephritic syndrome. In PSGN, the clinical manifestations typically occur

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TABLE 30. Treatment of Lupus Nephritis

Class/Group	Treatment Recommendation
Class I	Treat as dictated by the extrarenal clinical manifestations of lupus
Class II	Proteinuria <1000 mg/24 h: as dictated by the extrarenal clinical manifestations of lupus
	Proteinuria >3000 mg/24 h with glucocorticoids or calcineurin inhibitors (CNIs)
Class III and IV	For remission induction:
	Initial therapy with glucocorticoids, combined with either cyclophosphamide or mycophenolate mofetil (MMF)
	For maintenance therapy:
	Azathioprine or MMF and low-dose oral glucocorticoids
	CNI with low-dose glucocorticoids in patients who are intolerant of MMF and azathioprine
Class V	For normal kidney function and non-nephrotic-range proteinuria: treat with antiproteinuric and antihypertensive medications, and only treat with glucocorticoids and immunosuppressives as dictated by the extrarenal manifestations of lupus
	For persistent nephrotic proteinuria, glucocorticoids plus an additional immunosuppressive agent: cyclophosphamide, or CNI, or MMF, or azathioprine
Class VI	Glucocorticoids and immunosuppressives only as dictated by the extrarenal manifestations of lupus
Pregnant patients with active disease	Hydroxychloroquine and prednisone are first-line therapy; azathioprine for more serious disease (azathioprine is inactivated by the placenta)

Recommendations from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Inter Suppl. 2012;2:139-274. Copyright, 2012. With permission from Macmillan Publishers, Ltd.

CONT. after a latent period of 1 to 6 weeks. Staphylococcal GN typically is associated with ongoing infection at the time of development of nephritis. New-onset heart failure can occur in 25% of older patients.

Diagnosis

The diagnosis of IRGN is made on clinical grounds in patients who are nephritic and have an ongoing or preceding infection. A search for infection using microbiologic cultures usually shows the inciting organism in nonstreptococcal GN.

Most patients (especially those with PSGN) show depressed complement levels (usually C3, signifying activation of the alternative complement pathway). In PSGN, antibodies to streptococcal antigens (antistreptolysin-O, anti-DNAse B) are detected in almost all cases.

Adults may need a kidney biopsy to differentiate IRGN from other causes of kidney failure, notably acute interstitial nephritis from antibiotics or toxic acute kidney injury. Kidney biopsy typically shows a diffuse endocapillary proliferative and exudative glomerulonephritis, and, rarely, crescents on light microscopy. Immunofluorescence microscopy reveals C3-dominant or C3-codominant (with IgA or IgG) glomerular staining, which shows large "humps" of immune deposits in a predominant subepithelial distribution on electron microscopy.

Treatment and Prognosis

Treatment of the underlying infection is usually all that is necessary. There are no data to show that immunosuppressive therapy has a role in the treatment of IRGN. Up to 50% of adult patients (especially those with diabetes, older patients, and those with preexisting chronic kidney disease) may have persistent kidney dysfunction or even progress to ESKD.

Membranoproliferative Glomerulonephritis

Epidemiology and Pathophysiology

Membranoproliferative glomerulonephritis (MPGN) refers to the histologic findings of mesangial and endocapillary proliferation combined with the thickening of the GBM. There are two distinct pathophysiologic mechanisms: immune complex deposition (with or without complement staining) and activation of the alternative complement pathway with complement deposition (with minimal immunoglobulin staining) of the glomeruli. Immunoglobulin-mediated MPGN is associated with immune complex disease such as SLE, infections such as hepatitis C, and monoclonal gammopathy. Complement-mediated MPGN includes dense deposit disease (DDD) and C3 glomerulonephritis (C3GN); DDD and C3GN are rare diseases associated with uncontrolled activation of the alternative complement pathway.

Clinical Manifestations

Most patients with idiopathic MPGN are children or young adults who present with proteinuria or the nephrotic syndrome; they may also present with chronic nephritis.

Diagnosis

MPGN is a descriptive diagnosis of the kidney biopsy findings. Unless obvious, a search for the underlying cause should be undertaken. The findings of immunoglobulin (with or without complement staining) on biopsy should prompt a search for infections, autoimmune disease, or monoclonal gammopathy. Serologic tests may show evidence of an underlying infection (such as hepatitis C) or autoimmune disease (such as SLE). Complement levels may be depressed in MPGN, with an intermittently low serum complement level in immunoglobulin-associated MPGN and a reduced C3 level in C3GN and DDD; MPGN with predominant complement staining on biopsy should lead to an investigation of alternative complement pathway disorders.

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Treatment and Prognosis

Treatment of the causative infection, autoimmune disease, or monoclonal gammopathy is the primary therapy in patients with MPGN. There is no specific treatment available for the C3 glomerulopathies; immunosuppressive regimens, typically involving tapering doses of glucocorticoids, have been employed with varying results. There is a significant recurrence rate of MPGN in patients with kidney transplants.

Cryoglobulinemia

Cryoglobulins are immune-related proteins that precipitate at temperatures below 37.0 °C (98.6 °F) in vitro that may be associated with a systemic inflammatory syndrome involving small- to medium-vessel vasculitis. There is wide variation in the type of kidney disease associated with cryoglobulinemia depending on the underlying etiology, including glomerulonephritis. See Kidney Manifestations of Gammopathies for more information.

Collagen Type IV-Related Nephropathies

Type IV collagen is an essential component of the GBM. Two genetic diseases affecting type IV collagen, hereditary nephritis (Alport syndrome) and thin basement membrane disease, cause glomerular disease. See Genetic Disorders and Kidney Disease for more information.

KEY POINTS

- Kidney biopsy is required for diagnosis of IgA nephropathy, with the most common finding being mesangial proliferation on light microscopy.
- Kidney biopsy is required to make the diagnosis and classify the lesions of lupus nephritis.
- Most patients with class III lupus nephritis (LN) and all patients with class IV LN benefit from aggressive combination immunosuppressive therapy.
- The diagnosis of infection-related glomerulonephritis is made on clinical grounds in nephritic patients who have an ongoing or preceding infection.
- Immunoglobulin-mediated membranoproliferative glomerulonephritis (MPGN) is associated with immune complex disease; complement-mediated MPGN includes dense deposit disease and C3 glomerulonephritis.

Kidney Manifestations of Gammopathies

Overview

Monoclonal production of protein by lymphocytes or plasma cells is associated with specific kidney disorders that may predominantly involve the glomerular or tubular compartments. There is increasing recognition of kidney diseases associated with clonal disorders that do not fulfill criteria for lymphoma or overt myeloma; these conditions are known as *monoclonal disorders of renal significance*. Kidney manifestations of monoclonal gammopathies may include variable degrees of proteinuria (sometimes the full nephrotic syndrome), tubular dysfunction, hypertension, and kidney failure.

A monoclonal gammopathy is present when serum or urine electrophoresis shows a monoclonal band or if there are abnormalities in the serum free light chain ratio. Diagnosis of kidney involvement in monoclonal gammopathy usually requires biopsy, which shows evidence of immune deposits in glomeruli, the tubulointerstitial compartment, or blood vessels. The pattern of deposition on biopsy, either organized or non-organized, may be diagnostically helpful (**Table 31**).

Management of monoclonal gammopathies with kidney involvement is focused on treatment of the underlying monoclonal disorder to prevent further kidney injury. Therapy for the associated kidney disease is primarily supportive and based on the nature and degree of kidney involvement. Management of other potentially nephrotoxic complications associated with monoclonal gammopathies, including hypercalcemia, hyperuricemia, and volume contraction in patients with multiple myeloma, is an essential component of treatment.

See Multiple Myeloma and Related Disorders in MKSAP 17 Hematology and Oncology for more information.

Amyloidosis

Amyloid consists of randomly oriented fibrils composed of various proteins that form organized β-pleated sheets within the tissues; amyloid resulting from monoclonal lambda or kappa light chains is termed *AL amyloid* (*AA amyloid* results from AA protein, an acute phase reactant seen in chronic inflammatory diseases). In amyloidosis involving the kidney, glomerular lesions tend to be prominent and present with proteinuria, often in the nephrotic range. However, amyloid deposits may also be found in tubular basement membranes, interstitial space, and blood vessels. Findings on biopsy show deposits that stain apple green on Congo red staining under a polarizing microscope; these deposits are also visible on electron microscopy. Primary treatment depends on the type of

TABLE 31. Causes and Patterns of Immune Deposition in Monoclonal Gammopathy

Organized Deposits
AL amyloid
Immunotactoid glomerulonephritis
Fibrillary glomerulonephritis
Cryoglobulinemic glomerulonephritis
Non-Organized Deposits
Monoclonal deposition disease (light chain/heavy chain/both)

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amyloidosis, with elimination of the monoclonal protein in AL amyloidosis and treatment of chronic inflammation in AA amyloidosis.

Monoclonal Immunoglobulin Deposition Disease

Monoclonal immunoglobulin deposition disease (MIDD) includes either light chain (kappa in 80% of cases) deposition, heavy chain deposition, or, rarely, both. MIDD is similar to AL amyloidosis as both entities are related to the overproduction and extracellular deposition of monoclonal immunoglobulins. However, the deposits in MIDD are not organized into β-pleated sheets, are Congo red negative, and are granular rather than fibrillar on microscopy.

In the kidney, light or heavy chains may be deposited in the glomerulus, tubule, or both, with the clinical presentation dependent on the sites of involvement. Albuminuria, sometimes with the full nephrotic syndrome, may be accompanied by hypertension and kidney failure.

Multiple Myeloma

Multiple myeloma may present with a variety of kidney manifestations depending on the nature of the monoclonal protein. Most commonly, nephrotoxic light chains are filtered and accumulate in the renal tubule, causing tubular injury and forming casts within the tubules (known as *cast nephropathy* or *myeloma nephropathy*). The risk of tubular injury and cast formation is increased with volume contraction and dehydration.

In some patients, particularly those with "smoldering" myeloma, light chains may be absorbed and crystallize in proximal tubular cells, leading to tubular dysfunction and a secondary Fanconi syndrome. Patients present with chronic kidney disease or acute kidney injury and are found to have renal glycosuria, proximal renal tubular acidosis, and phosphate wasting. Kidney biopsy shows monoclonal proteins in the proximal tubules with a crystalline structure.

Patients with multiple myeloma may also present with AL amyloidosis, which typically presents with significant proteinuria and often normal tubular function. However, other patients may also manifest MIDD with significant proteinuria but also tubular dysfunction and kidney failure.

Cryoglobulinemia

Cryoglobulins are proteins that contain immunoglobulins that precipitate in vitro at temperatures below 37.0 °C (98.6 °F). There are three types: type I (only monoclonal Ig, typically IgM), associated with Waldenström macroglobulinemia or myeloma; type II (usually polyclonal IgG associated with monoclonal IgM), associated with hepatitis C virus infection; and type III (polyclonal IgG and IgM), associated with connective tissue disease and infections, including hepatitis C. Kidney involvement typically occurs more often with type II cryoglobulins, which form immune complexes leading to a systemic vasculitic syndrome, associated with glomerulonephritis typically with membranoproliferative features.

Patients with cryoglobulinemia may manifest a spectrum of kidney abnormalities, including mild proteinuria and hematuria, the nephrotic syndrome, and rapidly progressive glomerulonephritis with rapid deterioration of kidney function. C4 (and sometimes C3) complement levels are typically low, and rheumatoid factor is positive.

See Systemic Vasculitis in MKSAP 17 Rheumatology for more information.

Fibrillary and Immunotactoid Glomerulonephritis

Fibrillary glomerulonephritis (FGN) and immunotactoid glomerulopathy (ITG) are rare kidney-limited disorders associated with deposition of nonamyloid fibrils in the glomerulus. FGN and ITG may be associated with malignancies, and ITG is more typically associated with a B-cell neoplasm. Treatment of these disorders has not been well investigated due to their rarity.

KEY POINTS

- In amyloidosis involving the kidney, glomerular lesions tend to be prominent and present with proteinuria, often in the nephrotic range.
- Cast nephropathy occurs when nephrotoxic light chains are filtered and accumulate in the renal tubule, causing tubular injury and forming casts within the tubules.
- Patients with cryoglobulinemia may manifest a spectrum of kidney abnormalities, including mild proteinuria and hematuria, the nephrotic syndrome, and rapidly progressive glomerulonephritis with rapid deterioration of kidney function.

Genetic Disorders and Kidney Disease

Cystic Kidney Disorders

Table 32 provides details on cystic kidney disorders, including autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease, tuberous sclerosis complex, and nephronophthisis.

Autosomal Dominant Polycystic Kidney Disease

The hallmark of autosomal dominant polycystic kidney disease (ADPKD) is large kidneys with multiple kidney cysts, with most cysts originating in the renal collecting duct (**Figure 13**). Genetic mutations in *PKD1* and *PKD2* account for approximately 85% and 15% of cases, respectively. These genes code for proteins that regulate differentiation and proliferation of renal

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TABLE 32. Cystic Kidney Disorders

Disorder	Inheritance	Gene(s)	Features/Comments
ADPKD	AD	*PKD1* *PKD2*	Most common inherited kidney disorder (5% of ESKD cases); intracranial cerebral aneurysm; mitral valve prolapse; hepatic cysts; diverticulosis
ARPKD	AR	*PKHD1*	Pediatric; ESKD; hepatic fibrosis; portal hypertension; homozygous mutations cause complete loss of function: severe cystic kidney disease, oligohydramnios, pulmonary hypoplasia, Potter syndrome; no specific therapies
Tuberous sclerosis complex	AD	*TSC1* *TSC2*	Characterized by benign hamartomas (kidney, brain, skin, other organs); epilepsy, brain tumors, developmental delay, autism, and lung disease may also occur; renal angiomyolipomas are common; kidney cysts may develop
Nephronophthisis	AR	Multiple (13)	Most common genetic cause of ESKD in childhood/adolescence; interstitial fibrosis; renal medullary cysts; a renal concentrating defect and/or salt wasting; retinitis pigmentosa; no specific therapies

AD = autosomal dominant; ADPKD = autosomal dominant polycystic kidney disease; AR = autosomal recessive; ARPKD = autosomal recessive polycystic kidney disease; ESKD = end-stage kidney disease.

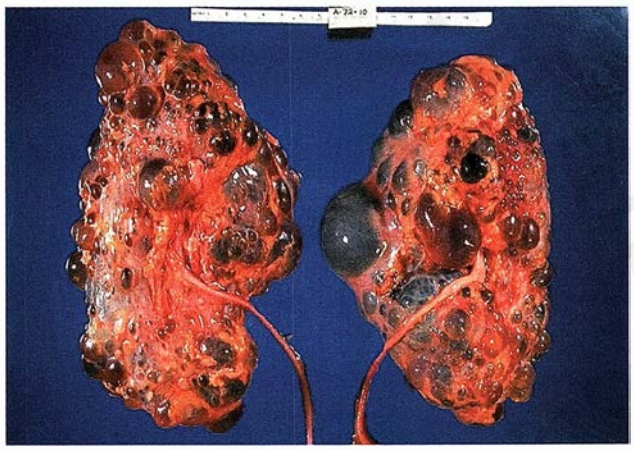

FIGURE 13. Autosomal dominant polycystic kidney disease with multiple bilateral cysts with replacement of the normal smooth architecture of the kidneys.

Image from the CDC Public Health Image Library.

tubular epithelial cells. More than 90% of the inheritance is as an autosomal dominant trait, with spontaneous germline mutations in the remaining cases.

Screening and Diagnosis

Screening for and diagnosis of ADPKD is usually performed by kidney ultrasonography with age-specific criteria. In 15- to 29-year-old at-risk individuals with a family history of ADPKD, the presence of at least two kidney cysts (unilateral or bilateral) is sufficient for diagnosis. Acquired kidney cysts are a common ultrasound finding in older patients without ADPKD, particularly those with chronic kidney disease (CKD). Therefore, in at-risk individuals 30 to 59 years of age, the presence of at least two cysts in each kidney is required for diagnosis; this increases to four cysts in each kidney for those older than 60 years. Conversely, the absence of at least two cysts in each kidney excludes the diagnosis of ADPKD in at-risk individuals between the ages of 30 and 59 years.

Direct mutational analysis of the *PKD1* and *PKD2* genes is reserved for equivocal cases and/or cases in which a definitive diagnosis is required, such as in living related donors for an affected family member.

Clinical Manifestations

Clinical manifestations of ADPKD include gradual kidney enlargement, which may cause persistent abdominal pain and/or early satiety. ESKD occurs on average at age 54 years in patients with *PKD1* mutations and at age 74 years in those with *PKD2* mutations. The total kidney volume as measured by MRI and the rate of increase in total kidney volume on serial MRI scans predict the development of ESKD.

Hypertension is common in patients with ADPKD, often preceding CKD. Kidney cyst enlargement leads to stimulation of the intrarenal and circulating renin-angiotensin-aldosterone system (RAAS).

More than 50% of patients with ADPKD develop recurrent flank or back pain; causes include kidney stones, cyst rupture or hemorrhage, or infection. Nephrolithiasis occurs in approximately 20% of patients. Hematuria usually indicates cyst rupture into the collecting system and is commonly self-limited. Hemorrhage into a cyst typically presents with pain rather than hematuria. Cyst infections can present with either positive or negative blood and urine cultures. Cardiovascular disease is the most common cause of death in patients with ADPKD.

Extrarenal manifestations include diverticulosis, hernias, valvular abnormalities (including mitral valve prolapse and aortic regurgitation), pancreatic cysts, and seminal vesicle cysts. Hepatic cysts can be detected by MRI in approximately 80% of patients but have rare clinical sequelae.

A ruptured intracranial cerebral aneurysm (ICA), resulting in a subarachnoid or intracerebral hemorrhage, is the most serious extrarenal complication of ADPKD. ICAs can be detected in 10% to 12% of patients with ADPKD. The

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prevalence is higher in ADPKD patients with a family history of hemorrhagic stroke or ICA; these patients should undergo screening MR angiography of the cerebral arteries if kidney function is normal, with follow-up scans at regular intervals.

Management

There are no specific therapies for ADPKD. The vasopressin antagonist tolvaptan has been shown to reduce the rate of increase in total kidney size and the rate of glomerular filtration rate loss in ADPKD, likely from blockade of intracellular adenosine monophosphate, which is overproduced in cysts; however, poor tolerance, hepatotoxicity, and expense are barriers to use. A generous fluid intake (>3 L/d) may reduce circulating antidiuretic hormone and thus forestall progression, in addition to reducing the risk of nephrolithiasis.

Patients with hypertension respond well to an ACE inhibitor or angiotensin receptor blocker (ARB), although dual therapy with an ACE inhibitor and ARB has not been shown to be beneficial compared to treatment with an ACE inhibitor alone. Clinical guidelines recommend treatment of patients with hypertension and CKD to a blood pressure <140/90 mm Hg, although some experts recommend <130/80 mm Hg. There is evidence that a lower blood pressure target may result in a slower increase in kidney volume and decreased albumin excretion, but without a definitive improvement of the rate of decline of the glomerular filtration rate. Therefore, the optimal blood pressure target in patients with ADPKD is unclear. Treatment of cyst infection and pyelonephritis requires antibiotics capable of penetrating the cysts, which include fluoroquinolones and trimethoprim-sulfamethoxazole. Finally, all cardiovascular risk factors should be treated.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) results from mutations in the *TSC1* or *TSC2* genes. The *TSC* genes code for proteins that have a tumor suppressing effect, and disruption of these gene products allows for abnormal cell proliferation in different tissues. Although TSC is most frequently diagnosed in the pediatric patient population, it may be detected first in adulthood when disease is mild.

Renal angiomyolipomas (AMLs) occur in 75% of patients and are detected by CT (**Figure 14**), ultrasonography, or MRI. Renal cell carcinoma is much less common, occurring in 1% to 2% of adults with TSC. Patients with TSC can also develop single or multiple kidney cysts.

Therapy is rarely required for the kidney complications of TSC. Surgery or related interventions (radiofrequency ablation, selective arterial embolization) may be required for large AMLs or hemorrhagic AMLs. The mammalian target of rapamycin (mTOR) inhibitor everolimus is approved for the nonsurgical management of TSC-associated brain tumors and AMLs; however, the role of this and other mTOR inhibitors in the prospective therapy of renal AMLs is unclear.

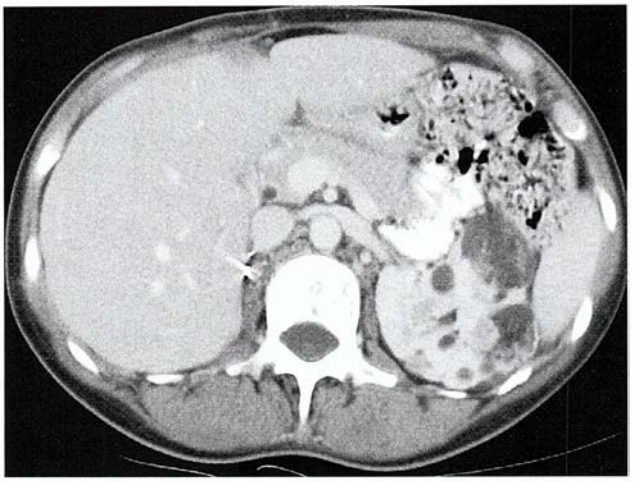

FIGURE 14. CT scan of multiple renal angiomyolipomas. In this CT scan, the kidney has multiple lesions with fat, vascular, and smooth muscle components. The lesions can be isolated lesions predominantly in women or multiple and bilateral in tuberous sclerosis complex with no gender predominance.

KEY POINTS

- The hallmark of autosomal dominant polycystic kidney disease is large kidneys with multiple kidney cysts; other manifestations include hypertension, flank or back pain, nephrolithiasis, hematuria, and infection.
- In patients with autosomal dominant polycystic kidney disease, treatment of hypertension using an ACE inhibitor or an angiotensin receptor blocker is appropriate, but the optimal blood pressure target is unclear.
- Kidney manifestations of tuberous sclerosis complex include renal angiomyolipomas and kidney cysts.

Noncystic Kidney Disorders

Table 33 provides details on noncystic kidney disorders, including autosomal dominant interstitial kidney disease, collagen type IV–related nephropathies, hereditary nephrotic syndromes, and Fabry disease.

Collagen Type IV-Related Nephropathies

These disorders involve mutations to the genes coding for type IV collagen. Type IV collagen is a key component of the glomerular basement membrane (GBM) but is also widely distributed in other organs.

Hereditary Nephritis

Hereditary nephritis (also known as Alport syndrome) is a rare cause of ESKD, with a prevalence of 0.4% among adult U.S. patients. There are three genetic variants: X-linked (80%), autosomal recessive (15%), and autosomal dominant (5%). Female carriers variably develop kidney disease

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TABLE 33. Noncystic Kidney Disorders

Disorder	Inheritance	Gene(s)	Features/Comments
ADIKD (medullary cystic kidney disease)	AD	*UMOD*; *REN*; *MUC*	Rare; medullary cysts may or may not be present; slow progression to ESKD; bland urine sediment; may be associated with gout and anemia
Collagen type IV–related nephropathies			
Hereditary nephritis	X-linked	*COL4A5*	Sensorineural hearing loss; lenticonus (conical deformation of the lens)
	AD or AR	*COL4A3*	Similar phenotype as X-linked with some variability
	AD or AR	*COL4A4*	Similar to *COL4A3*
Thin glomerular basement membrane disease	Primarily AD	*COL4A3*; *COL4A4*	Also known as benign familial hematuria; microscopic or macroscopic hematuria
Hereditary nephrotic syndromes			
Congenital nephropathy (Finnish type)	AR	*NEPH1*; *NEPH2*	Severe perinatal nephrotic syndrome; ESKD; kidney transplantation is only treatment
Familial FSGS	AR or AD	*NEPH2*; *ACTN4*; *TRPC6*	Nephrotic syndrome; ESKD; should be considered in those with prednisone-resistant FSGS
Denys-Drash syndrome	AR	*WT1*	Cause of pediatric nephrotic syndrome; associated with urogenital abnormalities
Fabry disease	X-linked	*GLA*	Premature coronary artery disease; severe neuropathic pain; telangiectasias; angiokeratomas

AD= autosomal dominant; ADIKD = autosomal dominant interstitial kidney disease; AR = autosomal recessive; ESKD = end-stage kidney disease; FSGS = focal segmental glomerulosclerosis.

depending on activity of the X chromosome in somatic renal cells.

Hereditary nephritis is accompanied by sensorineural hearing loss and characteristic ocular findings. Proteinuria, hypertension, and CKD usually develop over time. ESKD occurs between the late teenage years and the fourth decade of life. Diagnosis is confirmed by kidney biopsy. There are no specific therapies for hereditary nephritis. Antiproteinuric therapy with RAAS inhibitors is a mainstay of management. Kidney transplantation is the optimal treatment for ESKD, with no recurrence in the transplanted kidney.

Thin Glomerular Basement Membrane Disease

Thin glomerular basement membrane disease is associated with type IV collagen abnormalities that cause thinning of the GBM, resulting in hematuria. Up to 5% of the population may be affected; 30% to 50% of patients have a family history of hematuria. The disease is characterized by microscopic or macroscopic hematuria, which often initially occurs in childhood. Long-term prognosis is excellent, with rare progression to CKD. Blood pressure control with agents to decrease proteinuria is of benefit.

Fabry Disease

Fabry disease is a rare X-linked inherited disorder of α-galactosidase A deficiency, an enzyme deficiency in the glycosphingolipid pathway, leading to progressive deposit of globotriaosylceramide (Gb3) in lysosomes. Fabry disease should be considered as a cause of CKD of unknown etiology in young adulthood.

Diagnosis includes measurement of leukocyte enzymatic activity, with subsequent genetic confirmation. Screening for the disease is recommended for family members of affected

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patients. Enzyme replacement therapy with recombinant human α-galactosidase A is effective.

KEY POINTS

- Hereditary nephritis (also known as Alport syndrome) is associated with sensorineural hearing loss and lenticonus; proteinuria, hypertension, and chronic kidney disease usually develop over time.
- Thin glomerular basement membrane disease is characterized by microscopic or macroscopic hematuria, which often initially occurs in childhood.
- Fabry disease should be considered as a cause of chronic kidney disease of unknown etiology in young adulthood.

Acute Kidney Injury

Pathophysiology and Epidemiology

Acute kidney injury (AKI) is characterized by rapid loss of kidney function over hours to days, resulting in accumulation of creatinine, urea, and other waste products and/or decreased urine output. It may be associated with sodium and water retention and development of metabolic disturbances. AKI can occur in individuals with previously normal kidney function or in those with preexisting kidney disease.

AKI occurs in approximately 5% to 7% of hospital admissions and up to 30% of ICU admissions. It is associated with significant in-hospital morbidity and mortality. Risk factors include older age, diabetes mellitus, chronic kidney disease (CKD), and states of decreased effective arterial circulation. Although often reversible, AKI can result in incomplete renal recovery with progression to CKD and end-stage kidney disease (ESKD).

Definition and Classification

The Acute Dialysis Quality Initiative (ADQI) developed the RIFLE (Risk, Injury, Failure, Loss, and ESKD) criteria to standardize the definition of AKI. The Acute Kidney Injury Network (AKIN) modified the RIFLE criteria to include less severe AKI (**Table 34**). Due to the need for a single definition for clinical practice and research, the Kidney Disease Improving Global Outcomes (KDIGO) AKI consensus guidelines combined both classification systems and define AKI as an increase in serum creatinine ≥0.3 mg/dL (26.5 µmol/L) within 48 hours, ≥1.5 times baseline (known to have occurred within the previous 7 days), or urine volume <0.5 mL/kg/h for 6 hours.

AKI can be categorized as prerenal, intrinsic, and postrenal (**Table 35**). Prerenal AKI is caused by hypoperfusion of an otherwise normal kidney; postrenal is caused by obstruction of the urinary tract. Intrinsic AKI is caused by disease of the renal parenchyma.

Clinical Manifestations

Clinical manifestations of AKI depend on the cause and severity. AKI is often asymptomatic until severe loss of kidney function occurs. As a result, mild or moderate AKI is often identified by laboratory studies only. Patients can present with oliguria (urine output <400-500 mL/24 h), anuria (urine output <100 mL/24 h), or no change in urine volume. Patients with severe AKI may present with uremic symptoms, including anorexia, nausea, vomiting, muscle cramps, restless legs syndrome, mental status changes, asterixis, seizures, and

TABLE 34. RIFLE and AKIN Criteria for Acute Kidney Injury

RIFLE[a]		AKIN[a]		Both
Stage	**Serum Creatinine Criteria**	**Stage**	**Serum Creatinine Criteria**	**Urine Output Criteria**
R	Increase in S_{Cr} of 1.5-fold from baseline or GFR decrease >25%	1	Increase in S_{Cr} of 1.5-fold from baseline or increase in S_{Cr} of ≥0.3 mg/dL (26.5 µmol/L)	<0.5 mL/kg/h for 6 h
I	Increase in S_{Cr} of 2-fold from baseline or GFR decrease >50%	2	Increase in S_{Cr} of 2-fold from baseline	<0.5 mL/kg/h for 12 h
F	Increase in S_{Cr} >3-fold from baseline or GFR decrease >75% or S_{Cr} ≥4.0 mg/dL (353.6 µmol/L) with an acute rise of ≥0.5 mg/dL (44.2 µmol/L)	3	Increase in S_{Cr} >3-fold from baseline or S_{Cr} ≥4.0 mg/dL (353.6 µmol/L) with an acute rise of ≥0.5 mg/dL (44.2 µmol/L)	<0.3 mL/kg/h for 24 h or anuria for 12 h
L	Persistent kidney failure for >4 wk	—	—	—
E	Persistent kidney failure for >3 mo	—	—	—

AKIN = Acute Kidney Injury Network; GFR = glomerular filtration rate; RIFLE = risk (R), injury (I), failure (F), loss (L), end-stage kidney disease (E); S_{Cr} = serum creatinine.

[a]For AKIN, the increase in serum creatinine must occur in <48 hours. For RIFLE, acute kidney injury should be both abrupt (within 1 to 7 days) and sustained (>24 hours). For AKIN, those who receive dialysis are considered to have met the criteria for stage 3.

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TABLE 35. Causes of Acute Kidney Injury

Category	Examples
Prerenal	
Volume depletion	Kidney losses
	Gastrointestinal fluid losses
	Hemorrhage
	Burns
Decreased cardiac output (cardiopulmonary syndrome)	Heart failure
	Massive pulmonary embolus
	Acute coronary syndrome
Systemic vasodilation	Sepsis
	Anaphylaxis
	Anesthesia
	Cirrhosis
Intrarenal vasoconstriction	Hypercalcemia
	Drugs (NSAIDs, COX-2 inhibitors, amphotericin B, calcineurin inhibitors, contrast agents)
	Hepatorenal syndrome
Efferent arteriolar vasodilation	Renin inhibitors
	ACE inhibitors
	Angiotensin receptor blockers
Intrinsic	
Acute tubular necrosis	Ischemia (may result from prolonged prerenal AKI causes)
	Drugs (aminoglycosides, vancomycin, amphotericin B, pentamidine, cisplatin, foscarnet, tenofovir, carboplatin, ifosfamide, contrast agents, sucrose, immune globulins, mannitol, hydroxyethyl starch, dextran, NSAIDs)
	Pigment (rhabdomyolysis, intravascular hemolysis)
Acute interstitial nephritis	Drugs (β-lactams, penicillin, fluoroquinolones, sulfonamides, rifampin, NSAIDs, COX-2 inhibitors, proton pump inhibitors, 5-aminosalicylates, indinavir, abacavir, allopurinol, phenytoin, triamterene, Chinese herb nephropathy)
	Infection (pyelonephritis, viral nephritides, leptospiroses, *Legionella*)
	Autoimmune (Sjögren syndrome, sarcoidosis, SLE, IgG4-related disease)
	Malignancy (lymphoma, leukemia, multiple myeloma)
Rapidly progressive glomerulonephritis	ANCA-associated vasculitis
	Anti–glomerular basement membrane antibody disease
	Immune complex glomerulonephritis (SLE, endocarditis, postinfectious, cryoglobulinemia, IgA nephropathy, Henoch-Schönlein purpura)
Vascular	Macrovascular (bilateral renal artery stenosis, bilateral renal vein thrombosis, polyarteritis nodosa, abdominal compartment syndrome)
	Microvascular (atheroembolic disease, HUS, TTP, APLS, HELLP, systemic sclerosis, malignant hypertension, clopidogrel, cyclosporine, tacrolimus, mitomycin, sirolimus, ticlopidine, quinine, gemcitabine)
Intratubular obstruction	Monoclonal gammopathy (multiple myeloma)
Crystals	Tumor lysis syndrome
	Drugs (sulfonamides, triamterene, ciprofloxacin, acyclovir, indinavir, methotrexate, orlistat, large doses of vitamin C, sodium phosphate [oral and enemas])
	Toxins (ethylene glycol)

(Continued on the next page)

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TABLE 35. Causes of Acute Kidney Injury *(Continued)*

Category	Examples
Postrenal	
Upper tract obstruction	Nephrolithiasis
	Blood clots
	External compression from tumor, fibrosis, and radiation
Lower tract obstruction	Benign prostatic hyperplasia
	Neurogenic bladder (often related to diabetes mellitus)
	Blood clots
	Cancer
	Urethral stricture

AKI = acute kidney injury; APLS = antiphospholipid antibody syndrome; COX = cyclooxygenase; HELLP = hemolysis, elevated liver enzymes, and low platelets; HUS = hemolytic uremic syndrome; SLE = systemic lupus erythematosus; TTP = thrombotic thrombocytopenic purpura.

CONT. pericarditis. Patients may also develop symptoms from fluid overload, electrolyte disturbances, anemia, and platelet dysfunction.

KEY POINTS

- Acute kidney injury occurs in approximately 5% to 7% of hospital admissions and up to 30% of ICU admissions.
- Kidney Disease Improving Global Outcomes acute kidney injury (AKI) consensus guidelines define AKI as an increase in serum creatinine ≥0.3 mg/dL (26.5 µmol/L) within 48 hours, ≥1.5 times baseline (known to have occurred within the previous 7 days), or urine volume <0.5 mL/kg/h for 6 hours.

Diagnosis

The diagnosis of AKI begins with a detailed history, physical examination, and laboratory/imaging studies to determine whether the cause is prerenal, postrenal, or intrinsic. The history includes a review of possible contributing factors of AKI such as the use of diuretics or nephrotoxic medications, predisposing conditions for AKI, and urinary obstructive symptoms. Drug history includes over-the-counter medications, herbal remedies, and recreational drugs. The physical examination focuses on volume status, signs of systemic disease, and evidence of urinary obstruction.

The diagnosis of AKI is primarily determined by increasing levels of blood urea nitrogen (BUN) and serum creatinine (knowledge of previous serum creatinine measurements can distinguish between AKI and CKD). Although useful, these variables can be influenced by nonrenal factors (**Table 36**). Urinalysis, microscopic evaluation of the urine sediment, and urine indices are extremely beneficial in determining the cause of AKI (**Table 37**).

In patients with oliguria, the fractional excretion of sodium (FE_{Na}) can help differentiate between prerenal AKI and acute tubular necrosis (ATN). FE_{Na} is calculated as $(U_{Sodium} \times P_{Cr})/(U_{Cr} \times P_{Sodium}) \times 100$. FE_{Na} <1% indicates prerenal AKI, whereas FE_{Na} >2% indicates ATN. Despite its usefulness, the FE_{Na} has significant limitations. For example, FE_{Na} <1% can be seen in contrast-induced nephropathy, acute interstitial nephritis, rhabdomyolysis, glomerulonephritis, and early obstruction because the tubular handling of sodium is intact in these conditions. Conversely, FE_{Na} may be >2% in patients who are prerenal and are on diuretics or have adrenal insufficiency, bicarbonaturia, or CKD; this is due to the increased distal tubular delivery of sodium in these conditions. In the setting of diuretics, the fractional excretion of urea (FE_{Urea}), calculated as $(U_{Urea} \times P_{Cr})/(U_{Cr} \times P_{Urea}) \times 100$, is more accurate because urea excretion is not promoted by diuretics and is still retained in volume-depleted states. FE_{Urea} <35% is suggestive of a prerenal state. Kidney biopsy should be considered when other causes of AKI are ruled out or when glomerulonephritis is suspected.

Kidney ultrasonography should be performed to rule out obstructive uropathy as the cause of AKI. Additional useful information includes kidney size, echotexture, and renal

TABLE 36. Causes of Elevated Blood Urea Nitrogen and Serum Creatinine Without Acute Kidney Injury

Elevated Blood Urea Nitrogen
Gastrointestinal bleeding
Protein loading, including albumin infusions
Catabolic steroids
Tetracycline antibiotics
Elevated Serum Creatinine
Medications that block creatinine secretion: cimetidine; trimethoprim
Creatine ethyl ester intake
Substances that interfere with creatinine assay: acetoacetate; cefoxitin; flucytosine

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TABLE 37. Diagnostic Findings in Acute Kidney Injury

Condition	BUN-Creatinine Ratio	Urine Osmolality (mOsm/kg H_2O)	Urine Sodium (mEq/L)	FE_{Na}	Urinalysis and Microscopy
Prerenal	>20:1	>500	<20	<1%	Specific gravity >1.020; normal or hyaline casts
ATN	10:1	~300	>40	>2%[a]	Specific gravity ~1.010; pigmented granular (muddy brown) casts and tubular epithelial cells
AIN	Variable	Variable, ~300	Variable, >40	Variable, >2% or can be low	Mild proteinuria; leukocytes; erythrocytes; leukocyte casts; eosinophiluria
Acute GN	Variable	Variable, >500	Variable, <20	Variable, <1%	Proteinuria; dysmorphic erythrocytes; erythrocyte casts
Intratubular obstruction	Variable	Variable	Variable	Variable	Crystalluria or Bence-Jones proteinuria
Acute vascular syndromes	Variable	Variable	Variable, >20	Variable	Variable hematuria
Postrenal	>20:1	Variable	Variable, >20	Variable	Variable, bland

AIN = acute interstitial nephritis; ATN = acute tubular necrosis; BUN = blood urea nitrogen; FE_{Na} = fractional excretion of sodium; GN = glomerulonephritis.

[a]FE_{Na} can be low in contrast-induced nephropathy and pigment nephropathy.

CONT. vascular status. Decreased kidney size and cortical thickness are characteristic of CKD; however, kidney size can be preserved in patients with long-standing diabetic nephropathy, HIV nephropathy, or amyloidosis. Increased echogenicity is a nonspecific indicator suggestive of renal parenchymal disease that may be useful in differentiating an intrinsic kidney etiology from other potential causes.

KEY POINTS

- In patients with oliguria, the fractional excretion of sodium (FE_{Na}) can help differentiate between prerenal acute kidney injury (AKI) and acute tubular necrosis (ATN); FE_{Na} <1% indicates prerenal AKI, whereas FE_{Na} >2% indicates ATN.
- In the setting of diuretics, a fractional excretion of urea (FE_{Urea}) <35% can be used to diagnose prerenal acute kidney injury.
- Kidney ultrasonography should be performed to rule out obstructive uropathy as the cause of acute kidney injury.

Causes

Prerenal Acute Kidney Injury

Prerenal AKI (also known as prerenal azotemia) is the most common form of AKI in the outpatient setting (see Table 35). Prerenal AKI results from decreased renal perfusion, leading to a reduction in glomerular filtration rate (GFR) with no structural damage to the kidney. Drugs with antiprostaglandin activity such as NSAIDs or those that block the renin-angiotensin system can interfere with the kidney's ability to autoregulate renal blood flow and can decrease GFR in the setting of volume depletion or decreased effective arterial circulation.

Patients with prerenal AKI may have a history of acute volume loss, heart failure, the nephrotic syndrome, liver disease, acute infection, or recent diuretic or NSAID use. Prerenal AKI laboratory findings are listed in Table 36.

Prerenal AKI and ATN lie along a continuum of renal hypoperfusion, and prolongation of the prerenal state can lead to ATN. Management includes discontinuation of nephrotoxins and treatment of the underlying cause.

KEY POINT

- Management of prerenal acute kidney injury includes discontinuation of nephrotoxins and treatment of the underlying cause.

Intrinsic Kidney Diseases

Intrinsic AKI is categorized by injury to the structural components of the kidney, including the tubules (including intratubular obstruction), glomeruli, and interstitium (see Table 35). The important distinction between intrinsic AKI and pre- and postrenal AKI is the presence of structural injury and the primary cause of kidney dysfunction.

Acute Tubular Necrosis

The most common cause of hospital-acquired AKI is ATN, which represents damage and destruction of the renal tubular epithelial cells, and is most commonly caused by ischemia or

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toxins. A careful evaluation of hemodynamics, volume status, and physical findings of associated illness can help determine the cause of ATN. Laboratory findings are listed in Table 37 (**Figure 15**).

Treatment of ATN is supportive, with elimination of predisposing factors. Pharmacologic therapies to prevent or treat ATN have been unsuccessful. Acute dialysis may be necessary to support patients through the course of AKI. Renal recovery is dependent upon the severity of the kidney injury and associated comorbid conditions. Nonoliguric ATN represents a lesser degree of injury than oliguric ATN and has a better prognosis. Complete or partial renal recovery of AKI usually occurs within 1 to 4 weeks. Although patients who require dialysis may recover kidney function, the likelihood decreases the longer they require dialysis.

Ischemic Acute Tubular Necrosis

Patients at risk for ischemic ATN include those with prolonged prerenal AKI (see Table 35). Unlike prerenal AKI, the GFR in ischemic ATN does not improve with restoration of renal blood flow. The loss of GFR is attributed to renal vasoconstriction, tubular obstruction from sloughed cellular material, and backleak of glomerular ultrafiltrate across the exposed tubular basement membrane. Ischemic ATN is frequently reversible, but if the ischemia is severe enough to cause cortical necrosis, irreversible injury can occur.

Renal hypoperfusion without hypotension can result in normotensive ischemic ATN when the normal adaptive responses of the kidney to maintain renal perfusion are impaired. Risk factors for impaired renal autoregulation include older age, atherosclerotic or renovascular disease, hypertension, diabetes, CKD, myeloma kidney, and medications such as ACE inhibitors, angiotensin receptor blockers (ARBs), or NSAIDs. Normotensive ischemic ATN should be suspected in high-risk patients who develop AKI when their blood pressures are lowered below their usual levels, even if the levels remain in the normal range.

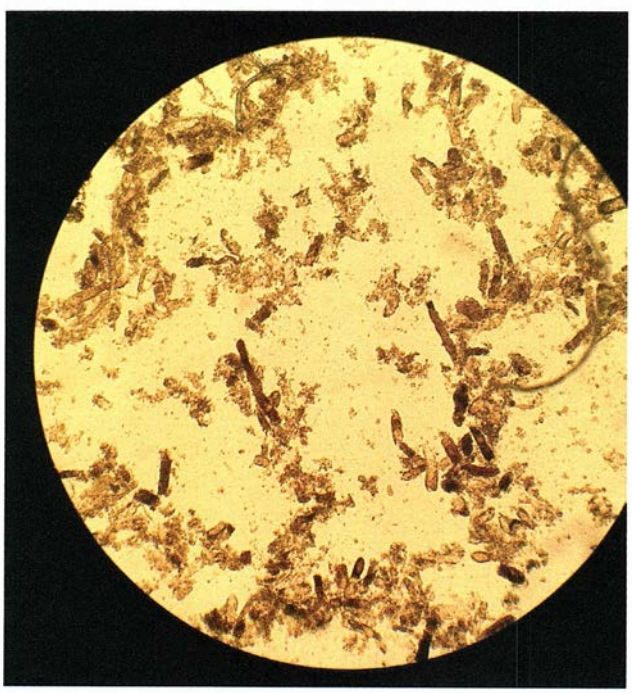

FIGURE 15. Urine sediment showing multiple, coarse granular (muddy brown) casts characteristic of acute tubular necrosis.

Drug-Induced Acute Tubular Necrosis

Recognizing drug-induced ATN is important because eliminating the nephrotoxic agent often leads to renal recovery. Incidence increases in older patients and in patients with decreased effective blood volume, CKD, or concomitant nephrotoxin exposure. Drug-induced ATN can result from hemodynamic changes or direct tubular injury. Exposure to hyperosmolar substances such as intravenous immune globulin, mannitol, or hydroxyethyl starch can cause osmotic nephrosis, a form of ATN that is characterized by vacuolization and swelling of the renal proximal tubular cells.

Common causes of drug-induced ATN are listed in Table 35. Contrast agents and calcineurin inhibitors cause AKI through intrarenal vasoconstriction. Aminoglycosides and anticancer drugs such as cisplatin and carboplatin are directly toxic to the proximal tubular epithelial cells and cause nonoliguric ATN 5 to 10 days after therapy. Amphotericin B causes dose-related AKI through intrarenal vasoconstriction and direct toxicity to proximal tubule epithelium. Liposomal amphotericin B formulations may be associated with less nephrotoxicity. Vancomycin nephrotoxicity is associated with high trough vancomycin levels or high vancomycin dose, concomitant nephrotoxic agents, and prolonged therapy.

Pigment Nephropathy

Myoglobin and hemoglobin are heme pigment–containing proteins that can cause AKI. Causes include trauma, metabolic and electrolyte disorders, endocrinopathies, drugs, toxins, seizures, hyperthermia/hypothermia, compartment syndrome, infections, and excessive exercise. Laboratory findings of rhabdomyolysis-induced AKI include hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, metabolic acidosis, elevated serum creatinine, and elevated muscle enzymes such as creatine kinase (typically >5000 U/L), lactate dehydrogenase (LDH), and aspartate and alanine aminotransferases. The urine dipstick is positive for blood in the absence of erythrocytes. Urine findings include a reddish-brown urine supernatant, myoglobinuria, pigmented granular casts, and FE_{Na} <1%.

Mechanisms of rhabdomyolysis-induced AKI include intravascular volume depletion from fluid sequestration within damaged muscle, renal vasoconstriction, direct and ischemic tubule injury from myoglobin, and tubular obstruction from intraluminal cast formation. Measures to prevent and treat early AKI include aggressive intravenous isotonic fluid resuscitation, correction of the underlying cause, and

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maintenance of urine output >300 mL/h. Further studies are necessary to establish the effectiveness of bicarbonate and mannitol in AKI prevention. Acute dialysis may be indicated for severe AKI with electrolyte and acid-base abnormalities. Most patients recover kidney function.

Less commonly, heme pigment nephropathy occurs when large amounts of heme pigment are released into the circulation due to massive intravascular hemolysis. ATN associated with this form of pigment nephropathy also results from volume depletion, renal vasoconstriction, direct heme protein–mediated cytotoxicity, and intraluminal cast formation. Laboratory findings include anemia, increased LDH, decreased haptoglobin, and increased serum creatinine. The urine dipstick is positive for blood in the absence of erythrocytes. Other urine findings include pigmented granular casts and hemoglobinuria. Both myoglobinuria and hemoglobinuria can cause tea-colored urine and urine dipstick positive for blood; however, hemoglobin produces a reddish-brown color in centrifuged serum and myoglobin does not discolor the serum. Therapy is supportive, with intravenous isotonic fluids and treatment of the underlying cause.

Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) may be associated with drugs, infection, autoimmune diseases, and malignancy (see Table 35). Only 10% to 30% of patients with AIN have the classic triad of fever, rash, and eosinophilia. Laboratory and urine findings for diagnosing AIN are listed in Table 37. Identification of eosinophiluria by using the Hansel stain supports a diagnosis of AIN but has limited specificity. In general, AIN should be suspected in a patient who presents with an elevated serum creatinine and urinalysis with leukocytes, leukocyte casts, and possibly eosinophiluria. A definitive diagnosis requires kidney biopsy.

Drug-induced AIN is the most common type of AIN and should be considered in any patient with unexplained AKI who has been exposed to a potentially offending drug. Drug-induced AIN is characterized by a slowly increasing serum creatinine 7 to 10 days after exposure; however, it can occur within 1 day of exposure if the patient has been exposed previously. Drug-induced AIN can also occur months after exposure, as seen with NSAIDs and proton pump inhibitors. The mainstay of treatment is discontinuation of the medication with close follow-up. If no improvement in kidney function occurs within 5 to 7 days, a kidney biopsy should be considered. Although the evidence for glucocorticoids is limited, a trial may be beneficial if given early in the course of the disease and if kidney biopsy results show minimal interstitial fibrosis. If drug-induced AIN is recognized early and the drug stopped immediately, complete renal recovery usually occurs. Irreversible interstitial fibrosis develops between 14 to 21 days after exposure to the offending drug. AIN can also result from connective tissue diseases and infections such as *Legionella*, which should be considered in the appropriate context.

Acute Glomerulonephritis

Acute glomerulonephritis and rapidly progressive glomerulonephritis are kidney diseases characterized by immune-mediated damage to the glomerular basement membrane (GBM), mesangium, and capillary endothelium that presents as AKI. Kidney function progressively declines over days to weeks, and irreversible damage occurs without prompt treatment.

Urine findings of dysmorphic erythrocytes and erythrocyte casts are pathognomonic (see Table 37). Serologic assays for hepatitis B and C, cryoglobulins, serum complement, and antistreptolysin O, anti-DNase B, antinuclear, anti–double-stranded DNA, anti-GBM, and ANCA antibodies can aid in the diagnosis. Complement levels are low in lupus nephritis, endocarditis, acute postinfectious glomerulonephritis, and cryoglobulinemia. Kidney biopsy is often needed for definitive diagnosis. Treatment depends on the underlying cause.

See Glomerular Diseases for more information.

Acute Vascular Syndromes

Large- and small-vessel causes of intrinsic AKI include bilateral renal artery obstruction (thrombosis, emboli, dissection, and vasculitis), bilateral renal vein thrombosis, thrombotic microangiopathy, and atheroembolic disease (see Table 35). Renal artery and renal vein thrombosis commonly present with flank pain, elevated serum LDH, and hematuria due to renal infarction. Treatment usually consists of anticoagulation and supportive care.

Polyarteritis nodosa (PAN) is a systemic vasculitis primarily affecting medium-sized arteries at points of bifurcation. Microaneurysm formation with rupture can result in hemorrhage, thrombosis, and organ ischemia or infarction. The kidneys, skin, peripheral nerves, joints, muscles, and gastrointestinal tract are commonly affected. AKI is caused by ischemic changes in the glomeruli and renal artery vasculitis. In some cases, PAN is associated with active hepatitis B or C infection. See Systemic Vasculitis in MKSAP 17 Rheumatology for more information.

Thrombotic microangiopathy (TMA) is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and AKI occurring from endothelial injury and glomerular capillary thrombosis. Typical examples are thrombotic thrombocytopenic purpura, hemolytic uremic syndrome (HUS), malignant hypertension, the antiphospholipid antibody syndrome, scleroderma renal crisis, preeclampsia-eclampsia, the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, and drug-induced TMA (such as some chemotherapeutic agents and the anti-vascular endothelial growth factor inhibitors, bevacizumab and sunitinib). Free hemoglobin and LDH levels are elevated, whereas haptoglobin levels are low. Urine sediment may be bland or demonstrate hematuria and proteinuria. In patients with Shiga toxin–associated HUS, peripheral blood smear is used to determine whether the anemia is caused by a microangiopathic hemolytic process. Treatment is directed toward the underlying disease. Scleroderma renal crisis is a type of TMA characterized by the

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acute onset of kidney failure and abrupt onset of moderate to severe hypertension. Urine sediment is usually bland or has mild proteinuria, microscopic hematuria, or rarely erythrocyte casts. Treatment consists of gradual blood pressure control with ACE inhibitors.

Atheroembolic disease can cause irreversible AKI. Patients with atherosclerotic disease may develop atheroembolic AKI several days to weeks after manipulation of the aorta or renal arteries during surgery, angiography, or even spontaneously. Plaque rupture with cholesterol embolization to distal small- and medium-sized arteries causes ischemic end-organ damage through mechanical plugging and inflammation. Atheroemboli can affect the skin, muscle, gastrointestinal tract, liver, and central nervous system in addition to the kidneys. Physical findings include livedo reticularis (**Figure 16**), blue toe syndrome (**Figure 17**), ulcerations, and Hollenhorst plaques on funduscopic examination. Laboratory findings include hypocomplementemia, eosinophilia, and eosinophiluria. Urine may be bland or have minimal proteinuria, occasional microscopic hematuria, or erythrocyte casts. Management is supportive, with secondary prevention of cardiovascular disease (hypertension control, statins, and aspirin).

Intratubular Obstruction

Precipitation of protein or crystals within the tubular lumen can cause AKI. Examples include tubular obstruction from precipitated monoclonal light chains, uric acid from tumor lysis syndrome, calcium oxalate deposition from ethylene glycol, and drugs (see Table 35).

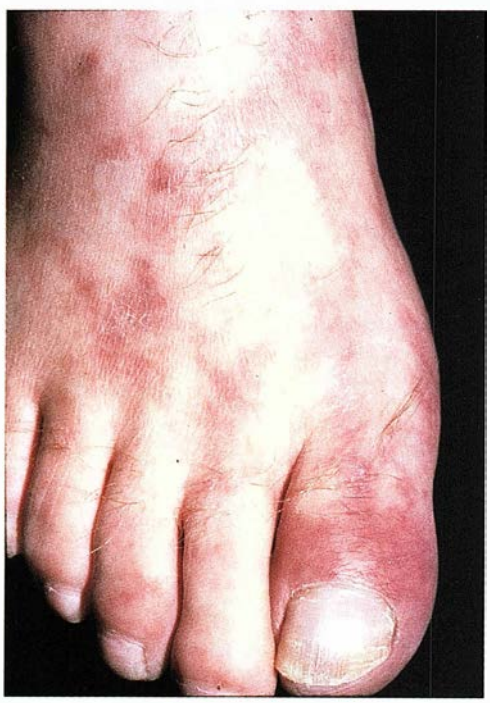

FIGURE 16. Livedo reticularis is a cutaneous reaction pattern that produces a pink, red, or bluish-red, mottled, net-like pattern on the skin. It is caused by slowed blood flow through the superficial cutaneous vasculature and obstruction of capillaries by cholesterol emboli as seen in atheroembolic acute kidney injury. It most commonly affects the lower extremities.

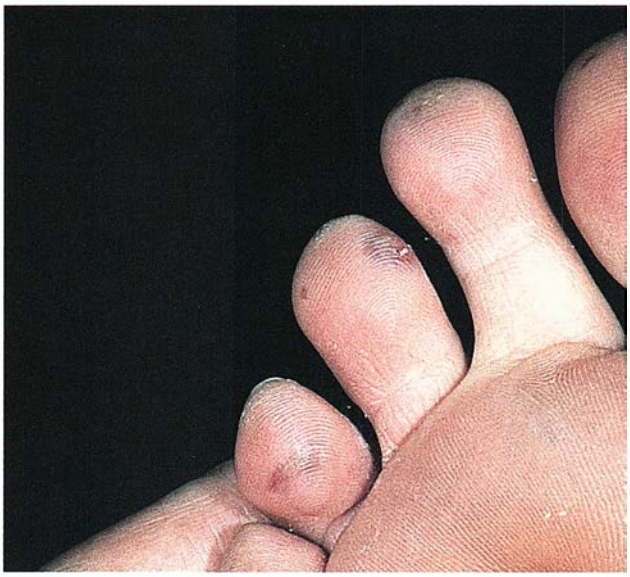

FIGURE 17. Blue toe syndrome presents as a cyanotic toe with necrosis of the skin caused by occlusion of the small vessels from cholesterol emboli as seen in atheroembolic acute kidney injury.

Multiple myeloma can cause several types of kidney disease, with cast nephropathy being the most common form. Cast formation is enhanced by volume depletion, increased urine calcium from hypercalcemia, contrast, NSAIDs, and loop diuretics. The urine is usually bland and the urine dipstick negative or trace positive for protein. The dipstick detects only negatively charged albumin, whereas Bence-Jones proteins are positively charged. The quantification of total protein in the urine leads to the recognition of the discrepancy between the urine dipstick and the actual amount of proteinuria, raising the diagnostic possibility of cast nephropathy. Treatment is directed at treating the myeloma and preventing volume depletion. The role of plasma exchange is controversial. See Kidney Manifestations of Gammopathies for more information.

Ethylene glycol intoxication causes AKI from intratubular precipitation with calcium oxalate crystals, which are often seen on urine microscopy. Ethylene glycol should be suspected in any patient who presents with a high anion gap metabolic acidosis and increased osmolal gap. Treatment includes correction of acidosis, fomepizole, and hemodialysis for severe cases.

Drugs implicated in intratubular obstruction from crystals are listed in Table 35. Hematuria, pyuria, and urine crystals may be present. Predisposing factors include volume depletion, CKD, and changes in urine pH favoring crystal precipitation. AKI is usually reversed after discontinuation of the offending drug. Acute phosphate nephropathy is a potentially irreversible cause of AKI due to oral phosphate–containing bowel preparations. AKI can present weeks to months after

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exposure. Acute phosphate nephropathy causes acute and chronic tubular injury with tubular and interstitial calcium phosphate deposits. Predisposing factors include inadequate hydration, high doses of sodium phosphate, older age, female gender, hypertension, CKD, volume depletion, and use of ACE inhibitors, ARBs, NSAIDs, or diuretics.

KEY POINTS

- Drug-induced acute interstitial nephritis is characterized by a slowly increasing serum creatinine 7 to 10 days after exposure and should be considered in any patient with unexplained acute kidney injury who has been exposed to a potentially offending drug.
- Large- and small-vessel causes of intrinsic acute kidney injury include bilateral renal artery obstruction, bilateral renal vein thrombosis, thrombotic microangiopathy, and atheroembolic disease.
- Intratubular obstruction from precipitated monoclonal light chains, uric acid from tumor lysis syndrome, calcium oxalate deposition from ethylene glycol, and drugs can cause acute kidney injury.

Postrenal Disease

Postrenal AKI results from urinary tract obstruction that is readily reversible if recognized early and corrected promptly (see Table 35). If uncorrected, the elevated tubular pressure can cause CKD and ESKD. Partial or complete obstruction of the urinary tract can occur anywhere from the renal pelvis to the urethral meatus. Obstruction of the upper tract (ureters or renal pelvis) must be bilateral to cause AKI (unless obstruction occurs in a single kidney). Postrenal obstruction should be suspected in patients with a history of benign prostatic hyperplasia, diabetes, nephrolithiasis, abdominal or pelvic surgeries or radiation, pelvic malignancies, or retroperitoneal fibrosis or lymphadenopathy.

The clinical presentation depends upon the site, degree, and rapidity of obstruction. Complete obstruction causes anuria, whereas partial obstruction can present with oliguria, polyuria, unchanged urine output, or fluctuating urine output. Common symptoms of lower tract obstruction include abdominal fullness or pain, urinary frequency, urgency, hesitancy, nocturia, and incomplete voiding. Bladder outlet obstruction (BOO) may reveal a distended bladder on physical examination and should be suspected in patients with prostate enlargement or in the setting of diabetes (neurogenic bladder), pain medications, or anticholinergic medications. Patients with acute ureteral obstruction from nephrolithiasis may present with ureteral colic. In postrenal obstruction, urine sediment is often unremarkable, but microscopic hematuria may be present. Urine chemistries are variable and nondiagnostic (see Table 37).

Evaluation of possible BOO with urinary retention can be diagnosed by a large output of urine volume on bladder catheterization or an elevated postvoid residual bladder volume by ultrasound. Kidney ultrasonography is the modality of choice for diagnosing upper tract obstruction; however, it may not detect early stages of hydronephrosis or obstruction from encasement of the ureter or kidney from retroperitoneal fibrosis or tumor. Noncontrast CT is indicated for suspected nephrolithiasis. Treatment of obstructive uropathy is relief of the obstruction. If the obstruction is relieved within 1 to 2 weeks, recovery of kidney function is excellent.

KEY POINT

- Kidney ultrasonography is the modality of choice for diagnosing upper tract obstruction in patients with postrenal acute kidney injury.

Acute Kidney Injury in Specific Clinical Settings

Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN) is a common cause of AKI in the hospital setting. Contrast agents are thought to cause ATN through renal vasoconstriction and direct cytotoxicity; however, the mechanisms are not completely understood. Predisposing factors include advanced age, CKD, diabetic nephropathy, conditions of decreased renal perfusion (such as heart failure, hypovolemia, and hemodynamic instability), multiple myeloma, concomitant nephrotoxins, high contrast dose, hyperosmolal contrast agents, and intra-arterial route of administration.

The diagnosis of CIN is based on an increase in the serum creatinine within 24 to 48 hours of contrast exposure. Patients may or may not be oliguric and have coarse granular casts and an FE_{Na} <1%. Patients with CIN typically recover kidney function, with the serum creatinine improving within 3 to 7 days. In high-risk patients, strategies to minimize the development of CIN include intravenous volume expansion with isotonic fluids, use of low- or iso-osmolal contrast media, minimization of contrast volume, and discontinuation of potentially nephrotoxic medications. More recent studies do not support the use of acetylcysteine. Prevention of CIN by dialysis immediately after contrast media administration is not recommended.

Cardiorenal Syndrome

The term *cardiorenal syndrome* (CRS) describes heart and kidney disorders whereby dysfunction in one organ precipitates dysfunction in the other. CRS is characterized by worsening kidney function in the setting of diuretic-resistant heart failure with persistent congestion. CRS is categorized into five types: 1) acute heart failure leading to AKI (CRS1), 2) chronic heart failure leading to CKD, 3) AKI leading to acute heart failure, 4) CKD leading to cardiac dysfunction (heart failure, coronary heart disease, arrhythmias), and 5) systemic conditions leading to simultaneous heart and kidney dysfunction (such as sepsis). Mechanisms of AKI in CRS1 include

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neurohumoral activation, increased intra-abdominal pressure leading to venous congestion and increased renal venous pressure, reduced renal perfusion, and right ventricular dysfunction.

Management is challenging because treatment of one organ may cause worsening of the other. Treatment is mostly directed toward improving cardiac function with diuretics, ACE inhibitors or ARBs, vasodilators, and inotropes. Many of these medications may worsen kidney function. Ultrafiltration, or the removal of plasma water through an extracorporeal circuit, has been used in patients unresponsive to diuretics; however, current evidence does not support ultrafiltration over intensive diuretic management. Patients presenting with CKD or AKI at presentation of heart failure have an increased mortality.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a reversible form of AKI that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure. HRS is characterized by marked reduction in GFR and renal perfusion in the absence of other causes of AKI. AKI in HRS is caused by intense renal vasoconstriction with peripheral arterial vasodilation. Tubular function is preserved with no tubular histologic changes, no proteinuria, normal urine sediment, FE_{Na} <1%, and urine sodium concentration <10 mEq/L (10 mmol/L).

Two subtypes of HRS have been identified based on the rapidity of AKI: type 1 HRS is rapidly progressive AKI defined by the doubling of initial serum creatinine to a level >2.5 mg/dL (221 µmol/L) in <2 weeks, usually with a precipitating event; and type 2 HRS is defined as a more gradual decline in kidney function associated with refractory ascites. Diuretic withdrawal and volume expansion are used to exclude a prerenal cause.

See Hepatorenal Syndrome in MKSAP 17 Gastroenterology and Hepatology for more information.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is characterized by the massive release of uric acid, potassium, and phosphate into the blood from rapid lysis of malignant cells. It is typically seen after initiation of cytotoxic therapy for hematologic malignancies with large tumor burden (such as high-grade lymphomas) or high cell counts (such as acute lymphoblastic leukemia), but TLS can also occur spontaneously. AKI results from intratubular precipitation of uric acid and calcium phosphate crystals. Clinical features include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. General principles for the management of patients at high or intermediate risk for or presenting with TLS are aggressive volume expansion, management of hyperkalemia, and preventive therapy for hyperuricemia. Allopurinol decreases uric acid production, and rasburicase (a recombinant urate oxidase) catalyzes enzymatic oxidation of uric acid into water-soluble allantoin. Rasburicase is usually reserved for those at highest risk; it is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because it can induce severe hemolysis and methemoglobinemia. Urine alkalinization in TLS is controversial and can promote calcium phosphate precipitation.

Abdominal Compartment Syndrome

Intra-abdominal hypertension (IAH) is defined as an intra-abdominal pressure (IAP) >12 mm Hg. Abdominal compartment syndrome (ACS) is defined as sustained IAP >20 mm Hg associated with new organ dysfunction. Both IAH and ACS are associated with AKI and increased mortality. ACS occurs in the setting of diminished abdominal wall compliance (abdominal surgery, trauma, prone positioning, respiratory failure, obesity), increased intraluminal contents (gastroparesis, ileus, bowel obstruction), increased intra-abdominal contents (hemoperitoneum, ascites), increased retroperitoneal contents (pancreatitis, retroperitoneal hemorrhage), and capillary leak (secondary to massive fluid resuscitation, coagulopathy, sepsis, burns). Increasing abdominal pressure compresses abdominal viscera and leads to intra-abdominal organ impairment and cardiac, respiratory, and neurologic impairment. Oliguric AKI develops from renal vein and artery compression.

The diagnosis is made by measuring IAP using bladder pressure. Management includes supportive care, management of ascites, correction of positive fluid balance, and abdominal compartment decompression.

KEY POINTS

- Strategies to minimize the development of contrast-induced nephropathy include intravenous volume expansion with isotonic fluids, use of low- or iso-osmolal contrast media, minimization of contrast volume, and discontinuation of potentially nephrotoxic medications.
- Tumor lysis syndrome is characterized by the massive release of uric acid, potassium, and phosphate into the blood from rapid lysis of malignant cells; management of patients at high or intermediate risk includes aggressive volume expansion, management of hyperkalemia, and preventive therapy for hyperuricemia.
- Abdominal compartment syndrome is defined as sustained intra-abdominal hypertension >20 mm Hg associated with new organ dysfunction; oliguric acute kidney injury develops from renal vein and artery compression in this setting.

Management

General Considerations

Successful management of AKI requires early recognition, correction of the cause, and discontinuation of nephrotoxins. Other supportive measures include optimizing hemodynamics and renal perfusion, preventing further kidney injury, and medically treating complications of AKI. Potassium,

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magnesium, and phosphate should be restricted. Supplemental bicarbonate can be used to correct metabolic acidosis. Diuretics should be used for volume overload. Nutrition should be managed carefully to ensure adequate caloric and protein intake.

Acute Dialysis

Dialysis is used to control complications of severe AKI. Several specific types of dialysis used in AKI are intermittent hemodialysis (IHD), peritoneal dialysis (PD), continuous renal replacement therapy (CRRT), and hybrid therapies such as prolonged intermittent renal replacement therapy (PIRRT). Absolute indications for dialysis include hyperkalemia, metabolic acidosis, and pulmonary edema refractory to medical therapy; uremic symptoms; uremic pericarditis; and certain drug intoxications.

IHD is delivered 3 to 6 times a week, 3 to 4 hours per session, through a temporary double-lumen hemodialysis catheter inserted into the internal jugular or femoral vein. Advantages of IHD include rapid correction of electrolyte disturbances (such as hyperkalemia) and rapid removal of drug intoxications. The main disadvantage is the risk of hypotension caused by rapid solute and fluid removal.

CRRT is a slow continuous type of dialysis that is delivered 24 hours a day in the ICU for unstable patients. CRRT removes solutes and fluid much more slowly than IHD. As a result, CRRT is used to treat hemodynamically unstable patients who cannot tolerate IHD due to hypotension or in patients in whom IHD cannot adequately control azotemia, acidosis, and volume overload. CRRT often requires anticoagulation.

PIRRT, also known as sustained low-efficiency dialysis (SLED), is slower than IHD and runs for 8 to 12 hours daily. PIRRT combines advantages of both CRRT and IHD: it allows for the improved hemodynamic stability that gradual solute and volume removal provide in CRRT while utilizing the less expensive technology of conventional IHD. PIRRT is an effective alternative to CRRT in hemodynamically unstable patients.

PD is not thought to be as effective as the other RRTs for management of AKI, although direct clinical comparisons are limited. PD may be useful when the other types of dialysis are unavailable or vascular access cannot be obtained. However, PD requires the insertion of a catheter into the peritoneal cavity, which is often complicated by catheter leakage and malfunction. In addition, PD is associated with increased protein losses and is contraindicated in patients with recent abdominal surgery.

Generally, IHD is used for stable patients with AKI, and CRRT or PIRRT for critically ill patients with unstable hemodynamics, multiorgan failure, or high catabolic states. Randomized clinical trials have not shown a benefit of CRRT over IHD or PIRRT for survival or renal recovery. However, CRRT is preferred in patients with acute liver failure and acute brain injury with increased intracranial pressure because rapid fluid and solute shifts in IHD may worsen cerebral edema.

KEY POINT

- In patients with acute kidney injury, absolute indications for dialysis include hyperkalemia, metabolic acidosis, and pulmonary edema refractory to medical therapy; uremic symptoms; uremic pericarditis; and certain drug intoxications.

Kidney Stones

Epidemiology

Kidneys stones are common, with a lifetime incidence between 7% and 13% and a high recurrence rate in the United States. Without treatment, symptomatic nephrolithiasis will recur in 35% to 50% of patients within 5 years and 75% at 20 years. Asymptomatic stones are commonly seen on abdominal imaging and may progress to symptomatic disease in 11% to 32% within 4 years.

Clinical Manifestations

The classic presenting symptom in patients with kidney stones is paroxysmal waxing and waning pain, termed *renal colic*, which usually occurs in the affected flank or back. The pain radiates to the groin, labium, penis, or testicle as the stone travels down the ureter. Kidney stones can produce abdominal pain and symptoms such as nausea, mimicking an acute abdomen.

Diagnosis

On physical examination, patients with kidney stones typically are restless. Although there may be tenderness in the general region of nephrolithiasis, the abdominal examination may be unremarkable.

A complete blood count, complete metabolic profile, and measurement of kidney function are indicated to rule out infection, electrolyte abnormalities, and acute kidney injury. Urinalysis typically reveals hematuria, although the absence of erythrocytes in the urine does not exclude the diagnosis. Urine crystals on microscopy may suggest the chemical composition of the stone, although this finding may not be definitive.

Radiologic imaging is indicated for diagnosis and to guide management based on stone size and location. Plain abdominal radiography has limited utility due to its inability to detect radiolucent uric acid stones and does not provide as much anatomic information as other modalities. However, it may be useful in assessing stone burden in patients with known radiopaque stones. Noncontrast helical CT has traditionally been the most commonly used imaging technique because it detects most stones, provides anatomic information, and visualizes the entire urinary tract; it may also suggest stone composition

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CONT. and potentially provide alternative diagnoses if nephrolithiasis is not detected. However, CT is associated with significant radiation exposure and is contraindicated in pregnant women. Ultrasonography is increasingly being used as an initial diagnostic study. Although less sensitive than CT for nephrolithiasis, particularly for detecting small stones and ureteral stones, ultrasonography does not expose patients to radiation and is usually more readily available and has a lower cost compared with CT; it is also the preferred modality during pregnancy. A positive ultrasound may therefore be adequate for initial diagnosis in patients with a typical presentation for kidney stones, with more complex testing indicated for those with a high clinical suspicion but a nondiagnostic ultrasound or a more complicated clinical presentation.

KEY POINTS

- Noncontrast helical CT is commonly used to evaluate for nephrolithiasis because it detects most stones, provides anatomic information, visualizes the entire urinary tract, may suggest stone composition, and potentially provides alternative diagnoses.
- HVC Ultrasonography is increasingly being used as an initial diagnostic study for nephrolithiasis due to availability, lack of radiation exposure, and low cost; it is also the preferred modality during pregnancy.

Types of Kidney Stones

Calcium Stones

Approximately 80% of kidney stones contain calcium oxalate, calcium phosphate, or both. Calcium stones are radiopaque on plain radiograph. Hypercalciuria, hyperoxaluria, and hypocitraturia are risk factors for calcium stones.

Hypercalciuria

Hypercalciuria is the most common metabolic risk factor for calcium oxalate stones. In patients with hypercalcemia, increased filtered calcium results in hypercalciuria. However, hypercalciuria is often idiopathic and commonly familial, occurring without associated hypercalcemia.

Hypercalciuria due to hypercalcemia is treated by addressing the cause of increased serum calcium. In patients with other forms of hypercalciuria, thiazide diuretics reduce calcium excretion in the urine by inducing mild hypovolemia, triggering increased proximal sodium reabsorption and passive calcium reabsorption. A low sodium diet enhances the effect thiazides have in promoting calcium reabsorption from the renal tubule. However, restricting dietary calcium intake in patients with hypercalciuria may paradoxically increase the risk of kidney stone formation by causing decreased binding of calcium with oxalate in the gut with increased absorption and excretion of oxalate; therefore, dietary calcium should not be limited unless it is excessive (for example, >2000 mg/d).

Hyperoxaluria

Hyperoxaluria predisposes to calcium oxalate stones and can have several potential causes. Primary hyperoxaluria is a rare inborn error of glyoxylate metabolism resulting in overproduction of oxalate. Excessive dietary oxalate intake (chocolate, spinach, rhubarb, green and black tea) can cause hyperoxaluria. Excessive urinary oxalate may also occur due to significant restriction in dietary calcium intake, which decreases binding of calcium to dietary oxalate in the gut and increases oxalate absorption.

Enteric hyperoxaluria results from malabsorption when excessive free fatty acids in the gastrointestinal lumen bind calcium, increasing free oxalate absorption in the colon. Short bowel syndromes with an intact colon and malabsorptive bariatric procedures (such as Roux-en-Y gastric bypass) are the most common causes of enteric hyperoxaluria.

Avoiding excessive oral intake of oxalate is a primary therapeutic intervention for hyperoxaluria. Specific therapy for enteric hyperoxaluria is oral calcium carbonate or citrate supplementation (up to 4 g/d) to bind intestinal oxalate (the reduction in oxalate absorption counters the potential for increased calcium absorption). Cholestyramine may also be used to decrease oxalate absorption as it binds both oxalate and bile salts in the gut. Patients with primary hyperoxaluria are treated with high-dose pyridoxine.

Hypocitraturia

Urinary citrate inhibits stone formation by binding calcium in the tubular lumen, preventing it from precipitating with oxalate. Hypocitraturia is seen with high animal protein diets and metabolic acidosis from chronic diarrhea, renal tubular acidosis, ureteral diversion, and carbonic anhydrase inhibitors (including seizure medications such as topiramate).

Citrate excretion can be enhanced by alkalinizing the serum with potassium citrate or potassium bicarbonate, which decreases uptake of filtered citrate from the tubular lumen. Increased fruit and vegetable intake also increases citrate excretion, especially in patients who are hypocitraturic.

Struvite Stones

Struvite stones are composed of magnesium ammonium phosphate (struvite) and calcium carbonate-apatite and occur in the presence of urea-splitting bacteria such as *Proteus* or *Klebsiella* in the upper urinary tract. These organisms convert urea to ammonium, which alkalinizes the urine, decreases the solubility of phosphate, and leads to struvite precipitation. Although struvite stones affect less than 10% of patients with kidney stones, they occur more commonly in women and in patients predisposed to chronic or recurrent urinary tract infection, including those with urologic diversions or neurogenic bladder. Struvite stones can rapidly enlarge to fill the entire renal pelvis within weeks to months, taking on a characteristic "staghorn" shape.

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Treatment of infections from urea-splitting organisms is the cornerstone of therapy for preventing struvite stone formation. Once struvite stones develop, antibiotic therapy is less effective, particularly for large stones, due to decreased penetration of antimicrobial agents into the stone, allowing for persistent infection and continued stone growth. Surgical stone removal provides definitive therapy.

Uric Acid Stones

Uric acid stones are uncommon (10% of stones), but the incidence increases in hotter, arid climates due to low urine volumes. The main risk factor is low urine pH, which decreases the solubility of uric acid. Hyperuricosuria is not a consistent finding. Comorbid risk factors for uric acid stones include gout, diabetes mellitus, the metabolic syndrome, and chronic diarrhea. Uric acid stones are radiolucent on plain radiograph but are visualized on CT scan or ultrasound.

Preventive measures include maintaining urine output >2 L/24 h and urine alkalinization to a pH of 6.1 to 7.0. Xanthine oxidase inhibitors (such as allopurinol) may be used in patients with hyperuricosuria (>1000 mg/24 h [59 mmol/d]) and patients without hyperuricosuria who have recurrent uric acid stones despite other treatments.

Cystine Stones

Cystine stones occur in cystinuria, a rare autosomal recessive disorder of proximal tubular transport of dibasic amino acids such as cystine. Patients typically present during adolescence, but earlier and later presentations occur. Cystine forms characteristic hexagonal crystals in the urine, and cystine stones can become large and form staghorn calculi. Treatment includes urine alkalinization to increase cystine solubility, dietary sodium and protein restriction to reduce cystine excretion, and thiol-containing agents (penicillamine, tiopronin, captopril) that increase the solubility of cystine.

KEY POINTS

- Hypercalciuria is the most common risk factor for calcium oxalate stones; management includes thiazide diuretics and a low sodium diet.
- Treatment of urea-splitting *Proteus* or *Klebsiella* infections is the cornerstone of therapy for struvite stones, and surgical stone removal provides definitive therapy.
- The main risk factor for uric acid stones is low urine pH; management may involve increased urine volume, urine alkalinization, and xanthine oxidase inhibitors.

Management

Successful management of nephrolithiasis includes risk factor modification, laboratory and radiologic evaluation, dietary changes, and pharmacologic therapy. Referral to nephrology and/or urology may be necessary to treat recurrent or complicated disease.

Acute Management

Acute management of kidney stones includes analgesia, maintenance of adequate hydration, and evaluation for coincident infection. Although most cases may be managed in the ambulatory setting, hospitalization is typically indicated with ureteral obstruction in the presence of urinary tract infection or in a high-risk kidney (solitary or transplanted) or if adequate analgesia cannot be achieved.

Stone collection for chemical analysis is frequently used to guide subsequent therapy. Although there is limited evidence of effectiveness of therapy guided by stone analysis, physiologic and biochemical information suggest that interventions based on stone composition may be helpful in preventing recurrent stone formation. Therefore, it is reasonable to attempt to obtain a stone or its fragments in the acute setting for biochemical analysis.

Stones up to 10 mm can be managed conservatively, although the likelihood of spontaneous passage decreases with increasing size (**Figure 18**). Medical expulsive therapy with α-blocker therapy (such as tamsulosin) or a calcium channel blocker (such as nifedipine) can aid the passage of small stones (≤10 mm in diameter).

Urologic Management

Urgent urologic consultation is indicated for patients with urosepsis, acute kidney injury, anuria, refractory pain, or large stones requiring surgical removal. Complicated cases, including pyelonephritis, bilateral obstruction, and obstruction of a solitary kidney, may require urgent decompression via percutaneous nephrostomy or ureteral stenting depending on the location of the stone and other clinical circumstances. Urologic referral is also indicated for ambulatory patients who do not pass stones with conservative management or who have stones >10 mm in diameter.

Extracorporeal shock wave lithotripsy (ESWL) can be used for stones in the renal pelvis and proximal ureter, but it is less effective for stones located in the mid/distal ureter or the lower pole calyx, larger stones (>15 mm), and hard stones (calcium oxalate monohydrate or cystine). Potential complications of ESWL include incomplete stone fragmentation, kidney injury, and possibly increased blood pressure or new-onset hypertension. Proximal and mid-ureteral stones can also be managed with a percutaneous antegrade approach or retroperitoneal laparoscopy, but these techniques are typically reserved for large, impacted stones.

Ureteroscopy, in which an endoscopic device is introduced in a retrograde fashion into the ureter through the bladder, is most commonly used in the management of mid-ureteral and distal ureteral stones, using a combination of catheter-based stone disintegration methods (such as laser lithotripsy), stone baskets, and ureteral stent placement.

If ESWL and/or ureteroscopy are unsuccessful or if the patient has large complex stones, percutaneous nephrolithotomy may be necessary. Surgical stone removal is the gold standard for staghorn calculi.

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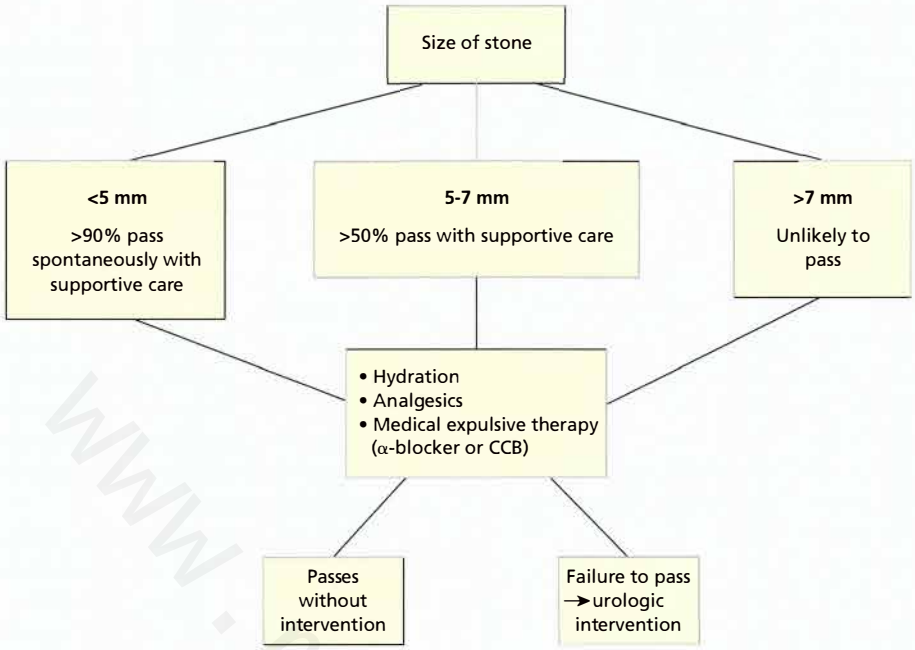

FIGURE 18. Acute management of symptomatic kidney stones. CCB = calcium channel blocker.

TABLE 38. Prevention Strategies for Nephrolithiasis

Stone Type	Treatment
General Stone Advice	
	Fluid intake ≥2 L/d regardless of stone composition; low sodium diet <100 mEq/d (100 mmol/d); age-appropriate calcium intake; consider recommending a low protein diet, 0.8-1 g/kg/d
Calcium[a]	
Idiopathic hypercalciuria	Thiazide diuretics: chlorthalidone, 12.5-25 mg/d, or hydrochlorothiazide, 25 mg twice daily
Hyperoxaluria	All patients: avoid high oxalate foods; reduce soft drink consumption
	Enteric hyperoxaluria: calcium carbonate or citrate, 1-2 g, with meals; cholestyramine, 4 g, with meals
	Primary hyperoxaluria: pyridoxine, 5-20 mg/kg/d
Hypocitraturia	Potassium citrate, 20-30 mEq twice daily; reduce dietary animal protein intake; increase fruit and vegetable intake
Uric Acid	
Urine pH <6.0	Potassium citrate or bicarbonate 40-80 mEq/d (40-80 mmol/d): titrate to urine pH 6.1 to 7.0
Hyperuricosuria	Allopurinol, 100-300 mg/d
Struvite	
Urinary tract infections with urea-splitting organisms	Aggressive treatment of infection; complete removal of stone material
Cystine	
Cystinuria	Potassium citrate or bicarbonate 3-4 mEq/kg/d (3-4 mmol/kg/d) to maintain urine pH >7.0; dietary sodium and protein restriction; chelating agents tiopronin, penicillamine (captopril if hypertension)

[a]The 2014 American College of Physicians Clinical Practice Guideline on the Dietary and Pharmacologic Management to Prevent Recurrent Nephrolithiasis in Adults recommends monotherapy with either a thiazide diuretic, citrate, or allopurinol for patients with calcium composite kidney stones and active disease in which increased fluid intake fails to prevent the recurrence of kidney stones. This recommendation does not apply to patients with hyperparathyroidism or rare causes of nephrolithiasis.

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Risk Factor Evaluation and Prevention Strategies

There is evidence that maintaining fluid intake spread throughout the day to achieve at least 2 L of urine per day is effective in reducing the risk of recurrent nephrolithiasis. Less evidence is available for the efficacy of a low protein diet or other dietary interventions to prevent recurrent kidney stones, although they are frequently recommended. There also is evidence that monotherapy with a thiazide diuretic, citrate, or allopurinol is effective in preventing recurrent nephrolithiasis with composite calcium stones if increased fluid intake fails to reduce the formation of stones.

Some clinicians perform a more extensive metabolic evaluation to help guide therapy in patients with recurrent kidney stones or those that occur in the context of an extensive family history of stone disease. If pursued, patients should be instructed to consume their typical diet and level of fluid intake, with at least two 24-hour urine collections to account for dietary variation. Urine collections should include urine volume, pH, creatinine (to assess adequacy of collection), sodium, calcium, phosphate, citrate, oxalate, and uric acid. In the absence of stone analysis, the 24-hour urine results may be suggestive of a particular stone composition but are not definitive.

Prevention strategies for nephrolithiasis are discussed in **Table 38** on page 70.

KEY POINTS

HVC
- For patients with kidney stones ≤10 mm in diameter, conservative management, including analgesia, hydration, and expulsive therapy, may be attempted.
- Larger stones in the renal pelvis and proximal ureter can be treated with extracorporeal shock wave lithotripsy, whereas mid- and distal ureteral stones can be managed with ureteroscopy.

The Kidney in Pregnancy

Normal Physiologic Changes in Pregnancy

Changes in Hemodynamics

During pregnancy, peripheral vasodilation and loss of response to vasoconstrictive hormones such as angiotensin II and antidiuretic hormone lower blood pressure in the first trimester, reaching maximal effect in the second trimester. Renal sodium and water retention increases plasma volume, which causes increased renal plasma flow and glomerular filtration rate (GFR). Kidney size may increase by up to 1.5 cm. Serum creatinine drops from a normal antepartum value of 0.8 mg/dL (70.7 µmol/L) to 0.5 mg/dL (44.2 µmol/L). Relatively normal serum creatinine levels (>1.0 mg/dL [88.4 µmol/L]) may indicate significant kidney dysfunction.

The increased GFR during pregnancy increases the upper normal limit for proteinuria from 150 mg/24 h to 250 mg/24 h. Patients with preexisting proteinuria may experience worsening proteinuria during pregnancy that can be difficult to differentiate from preeclampsia.

Changes in the Urinary Tract

The urinary system, including the renal pelvis, calices, and ureters, dilates during pregnancy due to the effects of progesterone or mechanical compression of the ureters at the pelvic brim. These normal physiologic changes may be mistaken for obstruction and take several weeks postpartum to resolve. The dilation increases the risk for ascending pyelonephritis; thus, women should have urine culture screening at the first prenatal visit and be treated for asymptomatic bacteriuria (>100,000 colony-forming units/mL).

Changes in Acid-Base Regulation

Progesterone stimulates the respiratory center during pregnancy, causing hyperventilation and respiratory alkalosis, with an average P_{CO_2} of 30 mm Hg (4.0 kPa) and a serum pH of 7.40 to 7.45. The renal response to hypocapnia is increased bicarbonate excretion, resulting in a serum bicarbonate of 18 to 20 mEq/L (18-20 mmol/L).

Changes in Water Homeostasis

While the plasma volume increases during pregnancy, water retention exceeds the concomitant sodium retention, resulting in mild hypo-osmolality and hyponatremia. The plasma osmolality decreases by 8 to 10 mOsm/kg H_2O, and the serum sodium decreases by 4.0 mEq/L (4.0 mmol/L). These hormonally mediated changes in plasma osmolality and serum sodium do not require therapy. Rarely, women develop gestational diabetes insipidus due to increased metabolism of antidiuretic hormone by the placenta, resulting in polyuria, polydipsia, and hypernatremia.

KEY POINTS

- Pregnancy is associated with increased glomerular filtration rate, decreased serum creatinine, decreased blood pressure, and increased proteinuria.
- Dilatation of the urinary system during pregnancy increases the risk for ascending pyelonephritis; therefore, urine culture screening and treatment for asymptomatic bacteriuria are appropriate at the first prenatal visit.
- While the plasma volume increases during pregnancy, water retention exceeds the concomitant sodium retention, resulting in mild hypo-osmolality and hyponatremia.

Hypertension in Pregnancy

Chronic Hypertension

Women with chronic hypertension may experience normal or lower blood pressures during pregnancy. Chronic

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hypertension may be masked during the first trimester due to the physiologic decrease in blood pressure. Hypertension prior to the 20th week of gestation is most consistent with previously undiagnosed chronic hypertension. Chronic hypertension may be primary (formerly known as essential) or secondary.

The 2013 American College of Obstetricians and Gynecologists (ACOG) guidelines on the management of hypertension in pregnancy recommend treating persistent blood pressure >160/105 mm Hg in women with chronic hypertension or >160/110 mm Hg in women with preeclampsia. Blood pressure goals with medications in chronic hypertension during pregnancy were established at 120-160/80-105 mm Hg. The ACOG guidelines did not establish targets in preeclampsia or gestational hypertension. There is controversy over thresholds for initiating therapy and targets for blood pressure with medications. Evidence of end-organ damage from hypertension (for example, kidney dysfunction, intracranial hemorrhage) may necessitate lower thresholds and targets for blood pressure management. Treatment of milder hypertension (<160/105 mm Hg) during pregnancy is controversial, and benefits of treatment have not been established.

All antihypertensive medications cross the placenta. Some antihypertensive medications are absolutely contraindicated during pregnancy, including ACE inhibitors, angiotensin receptor blockers (ARBs), and, likely, renin inhibitors. Women taking ACE inhibitors or ARBs should be counseled about their teratogenicity throughout all trimesters, and these medications should be stopped if pregnancy is anticipated or possible. There is limited clinical experience with nitroprusside, and its use has been associated with fetal cyanide toxicity. Methyldopa and labetalol have been used safely, although monotherapy with methyldopa may not be sufficient. Although less studied, metoprolol and pindolol have also been used, and atenolol and propranolol may have fetal side effects. Calcium channel blockers (such as long-acting nifedipine) can also be used during pregnancy, whereas diuretics may induce oligohydramnios if initiated during pregnancy.

Gestational Hypertension

Hypertension that develops after 20 weeks of pregnancy without preexisting hypertension, proteinuria, or other end-organ damage is defined as gestational hypertension. Seen in 6% of pregnancies, gestational hypertension resolves within 12 weeks of delivery. Hypertension that persists beyond the 12 weeks is considered chronic hypertension.

Of those who develop gestational hypertension, 15% to 25% progress to preeclampsia, and the rate increases to up to 50% in women who develop hypertension before 30 weeks. Gestational hypertension can recur with subsequent pregnancies and is associated with up to approximately a four-fold increased relative risk for the development of chronic hypertension.

KEY POINTS

- Hypertension prior to the 20th week of gestation is most consistent with previously undiagnosed chronic hypertension.
- The American College of Obstetricians and Gynecologists guidelines on the management of hypertension in pregnancy recommend treating persistent blood pressure >160/110 mm Hg in women with preeclampsia or >160/105 mm Hg in women with chronic hypertension.
- Renin-angiotensin system inhibitors are teratogenic and should be discontinued before conception.

Preeclampsia

Preeclampsia is classically defined as new-onset hypertension with proteinuria (≥300 mg/24 h or a urine protein-creatinine ratio ≥300 mg/g) after 20 weeks of pregnancy. Preeclampsia can also be diagnosed in patients without proteinuria if the hypertension is accompanied by other end-organ damage (**Table 39**). Features of severe preeclampsia include any signs of end-organ damage (excluding proteinuria) or a sustained blood pressure >160/110 mm Hg. Preeclampsia risk factors include preeclampsia with a previous pregnancy, family history, nulliparity, multiple gestations, obesity, chronic kidney disease (CKD), chronic hypertension, diabetes mellitus, and thrombophilia (for example, antiphospholipid antibodies). Eclampsia is the presence of generalized tonic-clonic seizures in women with preeclampsia.

Pathophysiology

The pathophysiology of preeclampsia is complex, as suggested by the multiorgan involvement. Early developmental abnormalities in the placental vasculature result in placental hypoperfusion and increased circulating antiangiogenic factors that result in maternal endothelial dysfunction and end-organ damage.

Clinical Manifestations

Fetal injury (such as growth restriction) and maternal end-organ damage may complicate preeclampsia. Symptoms include headache, altered mental status, visual changes, chest and abdominal pain, and nausea. The HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome may complicate preeclampsia in up to 10% to 20% of cases. The cause of HELLP syndrome is unknown, but it may be related to placental factors. However, it likely represents a separate disorder from preeclampsia.

Prevention and Treatment

Only low-dose aspirin initiated at the end of the first trimester has shown efficacy in preventing preeclampsia. Definitive treatment is delivery, including induction of labor in women at or near term. Severe preeclampsia can be considered an indication for delivery regardless of gestational age given the high

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TABLE 39. Diagnostic Criteria for Preeclampsia

Blood pressure	≥140 mm Hg systolic or ≥90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of pregnancy in a woman with a previously normal blood pressure OR ≥160 mm Hg systolic or ≥110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
AND	
Proteinuria	≥300 mg/24 h (or this amount extrapolated from a timed collection) OR Urine protein-creatinine ratio ≥300 mg/g OR Dipstick reading of 1+ (used only if other quantitative methods are not available)
OR	
In the absence of proteinuria, new-onset hypertension with the new onset of any of the following:	
Thrombocytopenia	Platelet count <100,000/μL (100 × 10^9/L)
Kidney dysfunction	Serum creatinine concentration >1.1 mg/dL (97.2 μmol/L) or a doubling of the serum creatinine concentration in the absence of other kidney disease
Impaired liver function	Elevated blood concentrations of liver aminotransaminases to twice the normal concentration
Pulmonary edema	—
Cerebral or visual symptoms	—

With permission from American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122-31. [PMID: 24150027]

CONT. risk of maternal morbidity. Women with mild disease and remote from term are managed with maternal and fetal monitoring and antihypertensive therapy as needed. There is no consensus regarding initiation of therapy; however, most experts initiate treatment at blood pressures >150-160/100-110 mm Hg. Antihypertensive medications do not prevent preeclampsia but reduce stroke and heart failure. Intrapartum and postpartum magnesium sulfate is used for seizure prophylaxis in severe preeclampsia but does not reduce the risk of other preeclampsia complications. Close postpartum follow-up of hypertension is recommended. Proteinuria can take months to resolve.

KEY POINTS

- Preeclampsia is classically defined as new-onset hypertension with proteinuria after 20 weeks of pregnancy.
- Low-dose aspirin initiated at the end of the first trimester has shown efficacy in preventing preeclampsia.
- Definitive treatment of preeclampsia is delivery.

Chronic Kidney Disease in Pregnancy

Women with CKD require preconception counseling because of the greater risk of pregnancy complications such as preeclampsia and declining kidney function when the prepregnancy serum creatinine exceeds 1.4 mg/dL (124 μmol/L). Patients with CKD may develop worsening or new hypertension, increases in chronic proteinuria, and worsening GFR with increasing risk as GFR declines. Patients with more advanced CKD are at risk for worsening CKD and/or acute kidney injury (AKI) requiring dialysis. CKD increases maternal and fetal complications such as gestational hypertension, preterm delivery, preeclampsia, intrauterine growth retardation, and stillbirth. Isolated proteinuria without decreased GFR is also a risk factor for pregnancy complications. Patients with moderate CKD should be advised of the risk of AKI or worsening CKD and the potential need for temporary or permanent dialysis.

Pregnancy is uncommon in dialysis patients because of the more advanced age of many dialysis patients, anovulatory cycles, and comorbid conditions. Diagnosis of pregnancy can be difficult because of elevated β-human chorionic gonadotropin levels due to decreased renal clearance; ultrasonography may be necessary to confirm pregnancy and gestational age. Pregnancy outcomes improve with increased uremic solute clearance through intensive dialysis. Pregnant women on hemodialysis typically receive more than 20 hours of therapy per week on a nearly daily schedule (compared with a three times per week, 9-12 hour/week regimen prior to pregnancy) to maintain blood urea nitrogen levels below 45 to 50 mg/dL (16.1-17.9 mmol/L). Peritoneal dialysis can be technically challenging as the fetus enlarges but can provide adequate clearance with intensified regimens. Additional goals include adequate nutrition, normal electrolytes, blood pressure control, and euvolemia.

Fertility increases after kidney transplantation, although fertility rates remain lower and pregnancy complications higher compared with the general population. Transplant recipients are counseled to wait at least 1 to 2 years after transplant before attempting to conceive. Allograft function (creatinine <1.5 mg/dL [132.6 μmol/L]), immunosuppression regimen, proteinuria (<500 mg/24 h), and other comorbid conditions (such as systemic lupus erythematosus) should be stable prior to conception. Mycophenolate mofetil and sirolimus must be stopped prior

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to conception due to fetal toxicity. Glucocorticoids, cyclosporine, tacrolimus, and azathioprine have been used during pregnancy. Potential complications from glucocorticoids include infection and adrenal insufficiency.

KEY POINTS

- Women with chronic kidney disease require preconception counseling because of the greater risk of pregnancy complications such as preeclampsia and declining kidney function when the prepregnancy serum creatinine exceeds 1.4 mg/dL (124 µmol/L).
- Kidney transplant recipients should wait at least 1 to 2 years after transplantation and be clinically stable before conception.
- Mycophenolate mofetil and sirolimus must be discontinued prior to conception due to fetal toxicity.

Chronic Kidney Disease

Definition and Staging

Chronic kidney disease (CKD) is defined by the presence of abnormalities of kidney structure or function that persist for >3 months (**Table 40**). The Kidney Disease Improving Global Outcomes (KDIGO) group recently established a definition and staging system for CKD based upon the estimated glomerular filtration rate (eGFR) and albuminuria, with stratification of risk based on these parameters (**Figure 19**). This staging system was designed to improve upon the previously published National Kidney Foundation eGFR-based CKD staging system, which did not incorporate albuminuria quantification. Because

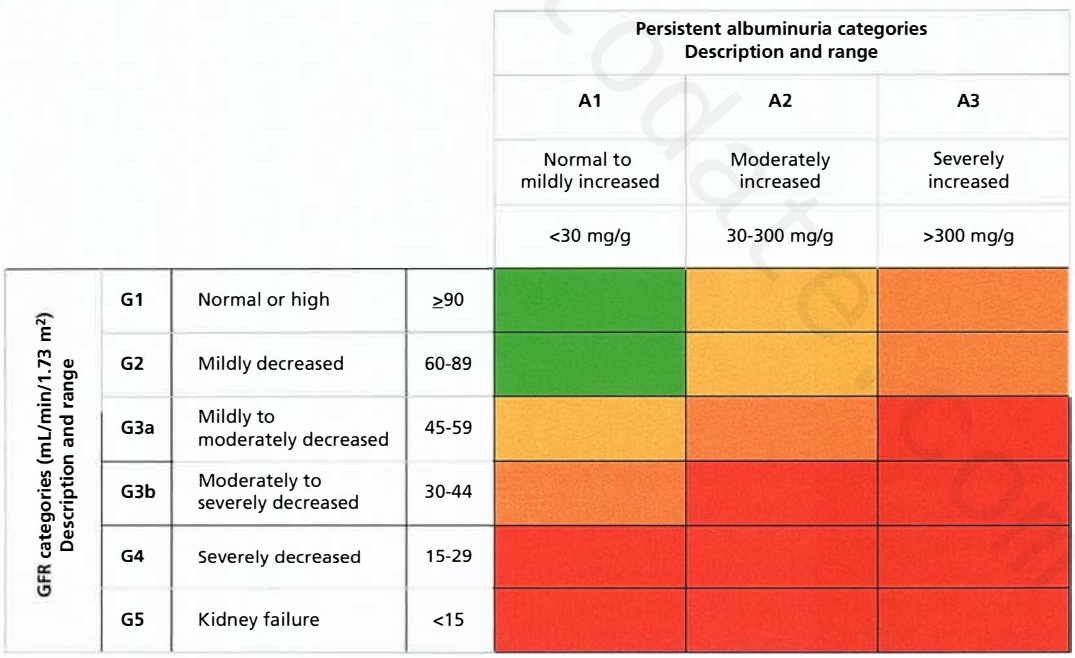
TABLE 40. Criteria for the Diagnosis of Chronic Kidney Disease[a]

Marker of kidney damage	Moderately increased albuminuria or severely increased albuminuria[b]
	Abnormal urine sediment (such as hematuria)
	Electrolyte or other abnormalities caused by tubular dysfunction
	Histologic abnormalities of the kidney
	Structural kidney abnormalities detected by imaging
	Previous kidney transplantation
AND/OR	
Reduced eGFR	<60 mL/min/1.73 m^2

eGFR = estimated glomerular filtration rate.

[a]Must be present for >3 months.

[b]Moderately increased albuminuria (formerly known as microalbuminuria) is defined as a spot urine albumin-creatinine ratio of 30 to 300 mg/g or a 24-hour excretion of 30 to 300 mg/24 h. Severely increased albuminuria (formerly known as macroalbuminuria) is defined as a spot urine albumin-creatinine ratio of >300 mg/g or a 24-hour excretion of >300 mg/24 h.



Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

FIGURE 19. KDIGO chronic kidney disease staging system. Prognosis of chronic kidney disease by glomerular filtration rate and albuminuria category. CKD = chronic kidney disease; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes.

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eGFR and albuminuria are both associated with mortality, cardiovascular disease, and end-stage kidney disease (ESKD), the KDIGO staging system is better able to identify patients at highest risk of adverse outcomes.

Pathophysiology and Epidemiology

Approximately 7% of U.S. adults over the age of 20 years have an eGFR <60 mL/min/1.73 m^2, and prevalence of CKD increases to 12.3% when those with albuminuria are included. Comorbid conditions associated with increased risk of CKD include diabetes mellitus, hypertension, cardiovascular disease, infection with HIV or hepatitis C, and obesity. The demographic factor most strongly associated with increased risk of CKD is age; 35% of Americans over the age of 60 years have CKD. It is unclear if CKD is more prevalent in black persons; however, CKD is more likely to progress to ESKD in black persons.

The most common causes of ESKD in the United States are diabetic nephropathy (45%), hypertension (29%), and glomerulonephritis (5.5%). After steadily increasing for decades, the incidence of ESKD has recently plateaued. Because mortality of patients with ESKD has been declining, the prevalence of ESKD continues to rise.

Screening

Because patients with CKD are often asymptomatic until the eGFR is <30 mL/min/1.73 m^2 and/or when nephrotic-range proteinuria (>3500 mg/g) develops, most cases are not detected unless patients are screened. However, there is controversy regarding which populations should be screened for CKD. The American College of Physicians (ACP) guidelines recommend against screening for CKD in asymptomatic adults without risk factors for CKD. The guidelines also question the value of screening patients with known risk factors because screening asymptomatic adults for CKD has never been demonstrated to improve clinical outcomes. Moreover, the ACP recommends against testing for proteinuria in patients with or without diabetes who are already taking ACE inhibitors or angiotensin receptor blockers (ARBs) because results would not influence therapy. The United States Preventive Services Task Force (USPSTF) concludes that there is insufficient evidence for screening for CKD in asymptomatic adults. The American Society of Nephrology, however, emphasizes the importance of screening all adults for CKD, including, but not limited to, those with a family history of kidney disease and adults with diabetes, hypertension, or cardiovascular disease.

In patients in whom screening is indicated, a serum creatinine measurement to estimate the GFR and a random urine determination of the albumin-creatinine ratio are recommended.

Clinical Manifestations

As CKD progresses, patients often experience fatigue, worsening signs of volume overload and hypertension, and/or pruritus. When eGFR falls below 10 to 15 mL/min/1.73 m^2 (stage G5), most patients develop more overt symptoms of uremia, including fatigue, anorexia, nausea, vomiting, and confusion (which can progress to delirium and obtundation). Uremia can also induce serositis, especially pericarditis and tamponade.

Diagnosis

Current guidelines suggest staging patients with CKD according to the eGFR and albuminuria (see Figure 19). Establishing the cause is important for guiding treatment and estimating prognosis. The cause may also have important implications with regard to outcomes and management after kidney transplantation.

KEY POINTS

- Chronic kidney disease is defined by the presence of abnormalities of kidney structure or function that persist for >3 months.
- The American College of Physicians recommends against screening for chronic kidney disease (CKD) in asymptomatic adults without risk factors for CKD, whereas the American Society of Nephrology emphasizes the importance of screening all adults for CKD.
- Current guidelines suggest staging patients with chronic kidney disease according to the estimated glomerular filtration rate and albuminuria.

Complications and Management

Cardiovascular Disease

Cardiovascular disease is the most common cause of death in patients with CKD. It has also been increasingly recognized that CKD is one of the strongest risk factors for cardiovascular morbidity and mortality, and the risk increases with decreasing eGFR and increasing albuminuria. Cardiac risk factors should be addressed in patients with CKD. However, many of the landmark studies that underpin the approach for preventing and treating cardiovascular disease excluded patients with CKD (and ESKD in particular) and may not be generalizable to patients with CKD.

Hypertension

Optimal management of hypertension is an important component of evaluating and treating patients with CKD. For patients with CKD, the eighth report from the Joint National Committee (JNC 8) recommends a blood pressure target goal of <140/90 mm Hg, which is higher than the JNC 7 recommendation of <130/80 mm Hg. This change was based on several large clinical trials that failed to show a benefit of a lower blood pressure

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target on clinical end points. However, in some studies there was a lower risk of a composite kidney failure end point in patients with elevated proteinuria; therefore, some experts still recommend a lower blood pressure goal of <130/80 mm Hg in patients with heavy proteinuria.

The JNC 8 recommends ACE inhibitors or ARBs as first-line therapy for hypertension in most patients with CKD. The JNC 8 recommends that initial therapy in black patients with CKD and proteinuria be with an ACE inhibitor or ARB; in black patients without proteinuria, treatment options include a diuretic, calcium channel blocker, ACE inhibitor, or ARB. Evidence for a beneficial effect of ACE inhibitors or ARBs in slowing CKD progression is limited to patients with albuminuria >300 mg/g (stage A3). See Hypertension for more information.

Dyslipidemia

CKD is most commonly associated with elevated serum triglyceride levels and lower HDL cholesterol levels. LDL cholesterol levels may vary depending upon clinical factors, including nutritional status. Although dyslipidemia is associated with an increased risk of CKD, it is unclear whether treating patients with CKD with lipid-lowering medications prevents CKD progression.

Studies have demonstrated that treatment with statins in patients with an eGFR <60 mL/min/1.73 m^2 (stage G3-G5 not on dialysis) or an eGFR ≥60 mL/min/1.73 m^2 (stage G1-G2) and albuminuria reduces adverse cardiovascular outcomes to a similar or greater extent than in patients with normal kidney function. Current KDIGO guidelines therefore recommend treatment with statins for patients over age 50 years with an eGFR <60 mL/min/1.73 m^2 and/or albuminuria. However, the efficacy of statins in preventing adverse cardiovascular outcomes in patients with ESKD is less clear, with major studies of treating patients on hemodialysis failing to demonstrate a benefit on cardiovascular morbidity or mortality in patients with ESKD with or without diabetes despite control of LDL cholesterol.

Coronary Artery Disease

Patients with CKD have a markedly increased prevalence of coronary artery disease (CAD). This is explained in part by the high prevalence of risk factors such as diabetes or hypertension; however, CKD itself is independently associated with CAD, and the association increases with lower levels of eGFR and higher levels of albuminuria. Despite this excess risk, patients with CKD are paradoxically less likely to be treated for the prevention of CAD. Moreover, patients with CKD are less likely to receive coronary revascularization procedures.

Laboratory studies for the evaluation of CAD must be interpreted with caution in patients with CKD. Reduced GFR may cause decreased clearance of troponins (troponin T in particular) and creatine kinase, leading to false elevation; troponin I is the least likely to be abnormally increased due to CKD. Cardiac enzymes must also be interpreted in the context of the clinical presentation; stable elevations may reflect chronic myocardial injury in uremia, and acute elevations may represent ischemia.

KEY POINTS

- The eighth report from the Joint National Committee (JNC 8) recommends a blood pressure target goal of <140/90 mm Hg for patients with chronic kidney disease (CKD) and ACE inhibitors or angiotensin receptor blockers as first-line therapy for hypertension in most patients with CKD.
- In patients with chronic kidney disease who have an estimated glomerular filtration rate <60 mL/min/1.73 m^2, treatment of dyslipidemia with statins is recommended.

Chronic Kidney Disease-Mineral and Bone Disorder

As kidney function declines, the normal homeostasis of calcium and phosphorus levels by the kidney becomes compromised, resulting in alterations in bone mineralization. The term *chronic kidney disease-mineral and bone disorder* (CKD-MBD) encompasses these changes that commonly occur in patients with CKD. The KDIGO guidelines for the evaluation and management of CKD-MBD are available online at www.kdigo.org.

Calcium and Phosphorus Homeostasis

Calcium and phosphorus homeostasis is regulated primarily by three hormones: parathyroid hormone (PTH), vitamin D, and fibroblast growth factor 23 (FGF-23). FGF-23 is a peptide secreted by osteocytes and osteoclasts and is one of the earliest indicators of CKD-MBD. As the eGFR declines to 30-60 mL/min/1.73 m^2 (stage G3), FGF-23 levels rise, which increases renal phosphorus excretion and helps maintain normal phosphorus levels. However, measurement of this hormone is not routinely done in clinical practice.

Increased FGF-23 and decreased nephron mass reduce the conversion of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D by renal tubular cells. Reduction in 1,25-dihydroxy vitamin D levels results in lower intestinal absorption of calcium and phosphorus and increased PTH production by the parathyroid glands. Suppression of absorption of calcium and phosphorus in the gut helps mitigate phosphorus retention but contributes to hypocalcemia, especially late in CKD. Hypocalcemia is a potent stimulus for further increases in PTH levels.

Increased plasma PTH occurring as a result of CKD is referred to as *secondary hyperparathyroidism*. Increased PTH levels result in reduced calcium excretion and increased phosphorus excretion by the kidneys and activate osteoclasts, resulting in bone resorption. Early in CKD, the PTH-induced increase in renal phosphorus excretion enables normal phosphorus levels despite reduced renal excretory capacity. However, as CKD progresses, the kidney is unable to compensate for the increased release of phosphorus from bone, and phosphorus levels rise.

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This results in a vicious cycle as phosphorus stimulates PTH production. Key factors in the regulation of calcium homeostasis are summarized in **Figure 20**.

Laboratory Abnormalities

Serum calcium and phosphorus levels typically remain in the normal range until the eGFR drops below 20-30 mL/min/1.73 m^2 (stages G4-G5), at which point the ability of elevated FGF-23 and PTH levels to promote phosphorus excretion becomes overwhelmed and hyperphosphatemia develops. Progressive decline in 1,25-dihydroxy vitamin D levels results in reduced intestinal calcium absorption, and hyperphosphatemia promotes precipitation of calcium and phosphorus in extraskeletal tissues, leading to hypocalcemia.

In addition to reduced conversion of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D, patients with CKD also have a higher prevalence of 25-hydroxy vitamin D deficiency. KDIGO guidelines state that patients with an eGFR of <60 mL/min/1.73 m^2 (stage G3-G5) should be screened for 25-hydroxy vitamin D deficiency and supplemented as per guidelines for the general population.

PTH levels are often elevated in patients with an eGFR <60 mL/min/1.73 m^2 (stage G3-G5) and progressively increase with worsening CKD. KDIGO therefore recommends measuring intact PTH levels in these patients to aid in the detection and management of secondary hyperparathyroidism and its complications.

Vascular Calcification

Numerous studies have documented an increased prevalence of arterial calcification, including the coronary arteries, in patients with CKD; the burden of calcification is highest in patients with ESKD. Arterial calcification reduces vascular compliance and likely contributes to the increased prevalence of left ventricular hypertrophy observed in patients with CKD. Arterial calcification is also strongly associated with cardiovascular and all-cause mortality; KDIGO guidelines therefore suggest treating patients with CKD and arterial calcification as is appropriate for patients in the highest category of cardiovascular risk, although treatments specifically targeted at reducing vascular calcification have not been shown to improve clinical outcomes.

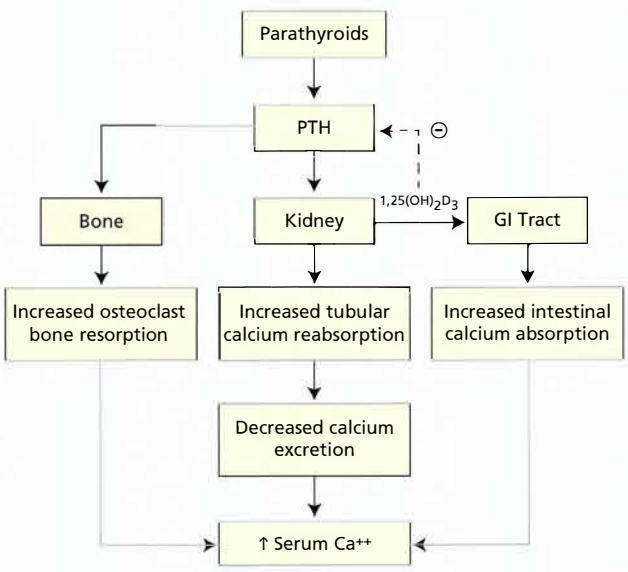

FIGURE 20. Overview of the metabolic systems that maintain calcium homeostasis. PTH stimulates increased $1,25(OH)_2D_3$ synthesis by the kidneys, and $1,25(OH)_2D_3$ causes feedback suppression of PTH production. Ca^{++} = ionized calcium; GI = gastrointestinal; $1,25(OH)_2D_3$ = 1,25-dihydroxy vitamin D_3; PTH = parathyroid hormone; ↑ = increased.

Renal Osteodystrophy

The term *renal osteodystrophy* refers to alteration of bone morphology in patients with CKD, which occurs as part of the systemic disorder of CKD-MBD.

Osteitis Fibrosa Cystica

Osteitis fibrosa cystica is due to abnormally high bone turnover that can occur after prolonged exposure of bone to sustained high levels of PTH in secondary hyperparathyroidism. It is associated with an increased number and activity of osteoblasts and osteoclasts and expansion of osteoid surfaces, resulting in an increased risk of fracture. Patients can be asymptomatic, or they may have bone pain. Classic skeletal changes on radiograph may include subperiosteal resorption of bone, most prominently at the phalanges of the hands.

Adynamic Bone Disease

Adynamic bone disease occurs when there is a lack of bone cell activity and a markedly reduced rate of bone turnover. Histopathologic abnormalities include decreased osteoclast activity with an increase in osteoid, resulting in an increased risk of fracture. Patients have suppressed PTH levels (due to chronic illness or aggressive treatment with vitamin D analogues) and may be asymptomatic or have bone pain. It is important to rule out adynamic bone disease prior to bisphosphonate therapy because these drugs can cause and/or worsen this disease by inhibiting osteoclast activity.

Osteomalacia

Osteomalacia is characterized by decreased mineralization of osteoid at sites of bone turnover. The most common symptoms of osteomalacia include bone pain and tenderness and increased risk of fracture. Although patients with CKD are at increased risk of osteomalacia, CKD does not cause osteomalacia per se, and vitamin D deficiency caused by coexisting factors such as intestinal malabsorption due to gastrointestinal disorders or restricted access to sunlight is often present.

Osteoporosis

Compared with persons with normal kidney function, patients with CKD have many causes of reduced bone density. The diagnosis of osteoporosis therefore cannot be based solely upon reduced bone density detected on dual-energy x-ray

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absorptiometry (DEXA) scan. Because DEXA has poor predictive value for distinguishing histologic subtypes of bone disease in patients with CKD, KDIGO guidelines do not recommend its routine use in patients with CKD.

Management

In patients with CKD prior to dialysis, the primary goal is to maintain laboratory parameters in the normal range. KDIGO guidelines recommend monitoring calcium, phosphorus, intact PTH, and vitamin D levels in patients with an eGFR <60 mL/min/1.73 m^2 (stages G3-G5).

The approach to managing secondary hyperparathyroidism differs depending upon CKD stage. In patients with an eGFR <60 mL/min/1.73 m^2 not on dialysis, KDIGO guidelines suggest attempting to normalize PTH. The first step in managing secondary hyperparathyroidism is to correct 25-hydroxy vitamin D deficiency and normalize the serum calcium and phosphorus, thus eliminating the stimulus for PTH secretion. If PTH levels remain elevated after correction of 25-hydroxy vitamin D deficiency, calcitriol or calcitriol analogues can be used to further suppress PTH, but monitoring for hyperphosphatemia and/or hypercalcemia due to increased absorption of phosphorus and calcium is necessary. Although KDIGO guidelines suggest attempts to normalize PTH in patients with CKD not on dialysis, it is unclear if this approach improves clinical outcomes. The approach to secondary hyperparathyroidism differs somewhat in patients with ESKD on dialysis. Tertiary hyperparathyroidism is the result of the prolonged PTH stimulation needed to maintain normocalcemia. This prolonged stimulation results in increased calcium levels and severe hyperparathyroid hyperplasia and elevated PTH levels that do not respond to phosphate binders and calcitriol therapy. These patients often require parathyroidectomy for definitive treatment. Further information can be found at www.kdigo.org.

Hyperphosphatemia is an important complication in patients with an eGFR <30 mL/min/1.73 m^2, and the severity is directly associated with mortality. Patients with CKD and hyperphosphatemia should be counseled regarding a low phosphate diet, and most patients require phosphate binders.

KEY POINTS

- The first step in managing secondary hyperparathyroidism is to correct 25-hydroxy vitamin D deficiency and normalize the serum calcium and phosphorus, thus eliminating the stimulus for parathyroid hormone secretion.
- Tertiary hyperparathyroidism is the result of the prolonged parathyroid hormone (PTH) stimulation, resulting in increased calcium levels and severe hyperparathyroid hyperplasia and elevated PTH levels that do not respond to phosphate binders and calcitriol therapy; these patients often require parathyroidectomy.

Anemia

The prevalence of anemia increases as CKD progresses due to several factors, including impaired erythropoietin production, erythropoietin resistance, and reduced erythrocyte life span. Iron deficiency may contribute to erythropoietin resistance. Even if patients do not meet criteria for iron deficiency anemia, it is important to optimize iron stores to maximize the response to endogenous erythropoietin. KDIGO recommendations suggest maintaining transferrin saturation levels of >30% and serum ferritin levels of >500 ng/mL (500 µg/L) using either oral or intravenous iron supplementation.

Initial evaluation for the cause of anemia in patients with CKD includes laboratory studies as would be appropriate for patients without CKD. CKD-related anemia is normocytic. CKD as a cause of a normocytic anemia is a diagnosis of exclusion. There is no specific test to establish the diagnosis. Although erythropoietin levels are often decreased in patients with CKD, there is little evidence to support the utility of measuring erythropoietin levels in patients with CKD.

As the eGFR declines below 30 mL/min/1.73 m^2 (stages G4-G5), anemia can become symptomatic. Erythropoiesis-stimulating agents (ESAs) are highly effective in raising hemoglobin concentrations and alleviating symptoms. Although the use of ESAs can avoid the need for transfusion, the optimal strategy for ESA dosing that balances benefits and risks is unknown. These medications are associated with risks and are expensive. Black box warnings for use of ESAs include the risk of increased mortality and/or tumor progression in patients with active malignancy, increased risk of thromboembolic events for postsurgical patients not on anticoagulant therapy, and increased risk of serious cardiovascular events when ESAs are administered to patients with hemoglobin values >11 g/dL (110 g/L) or history of stroke. It is unknown whether these adverse effects are due to the increased hemoglobin or due to direct effects of high ESA doses. Full KDIGO guidelines for the diagnosis and management of CKD-related anemia can be found at www.kdigo.org.

Metabolic Acidosis

Metabolic acidosis is a common and important complication of CKD that occurs due to progressive loss of the ability of the kidneys to regenerate bicarbonate. Large observational studies have demonstrated a strong association between lower bicarbonate levels and adverse clinical outcomes, including CKD progression and mortality. Recent prospective trials have demonstrated slower progression of CKD in patients treated with alkali to increase serum bicarbonate to at least 23 mEq/L (23 mmol/L). For this reason, KDIGO guidelines now suggest treatment of patients with CKD with alkali to maintain serum bicarbonate in the normal range (23-28 mEq/L [23-28 mmol/L]). However, excessive alkali supplementation above the normal range may also be associated with adverse outcomes with metabolic alkalosis. The most common alkali formulations prescribed are sodium bicarbonate and sodium citrate (citrate is metabolized to bicarbonate). Patients with

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CKD who are treated with alkali should be monitored for symptoms of volume overload.

Nephrotoxins

Patients with CKD are at increased risk of acute kidney injury (AKI), and AKI or more indolent kidney injury may promote irreversible CKD progression. The use of potential nephrotoxins should therefore be minimized or avoided in patients with CKD. Patients with CKD should also be counseled to avoid over-the-counter medications such as NSAIDs and to seek medical advice before taking nutritional or herbal preparations because such agents may adversely affect kidney function, can be nephrotoxic, and/or have other harmful effects (**Table 41**). The use of contrast agents in patients with CKD is discussed in the Imaging section of Special Considerations.

Proteinuria

The severity of proteinuria is strongly associated with adverse clinical outcomes, including progression of CKD to ESKD, cardiovascular morbidity, and mortality. Several large prospective randomized controlled studies have demonstrated that ACE inhibitors or ARBs decrease proteinuria and slow the progression of proteinuric kidney diseases. However, there is substantial evidence that using ACE inhibitors, ARBs, or renin inhibitors in combination to treat patients with CKD and proteinuria does not improve clinical outcomes and is associated with increased risk of hypotension and hyperkalemia.

Protein Restriction

Protein-restricted diets have been shown to slow the progression of kidney disease in animal models. The mechanism is thought to be due at least in part to reduced glomerular filtration pressure, preventing progressive injury and fibrosis. In the Modification of Diet in Renal Disease study, no definitive benefit was seen in renal outcomes in patients randomly assigned to the low protein (0.6 g/kg/d) group.

Although there is insufficient evidence to recommend routine use of low protein diets to slow progression of CKD, high protein diets may precipitate or exacerbate symptoms of uremia. Small studies suggest that low protein diets might delay the onset of symptomatic uremia and the need for renal replacement therapy in selected patients.

KEY POINTS

- Chronic kidney disease as a cause of a normocytic anemia is a diagnosis of exclusion; erythropoietin levels are not diagnostic.
- Erythropoiesis-stimulating agents are associated with an increased risk of serious cardiovascular events when administered to patients with hemoglobin values >11 g/dL (110 g/L) or a history of stroke.
- Metabolic acidosis in patients with chronic kidney disease should be treated with alkali to maintain serum bicarbonate in the normal range.
- ACE inhibitors or angiotensin receptor blockers slow progression of chronic kidney disease in patients with proteinuria.

Special Considerations

Imaging

Important risk factors for AKI due to contrast, known as contrast-induced nephropathy (CIN), include severity of CKD, reduced renal perfusion (due to poor cardiac function or

TABLE 41. Over-the-Counter Medications to Avoid or Use With Great Caution in Chronic Kidney Disease

Class	Medication/Supplement	Adverse Effect(s)
Analgesics	NSAIDs (including COX-2 inhibitors)	AKI; hyperkalemia; increased blood pressure
Vasoconstricting decongestants	Pseudoephedrine; ephedrine; phenylephrine; oxymetazoline	Increased blood pressure
Laxatives	Magnesium hydroxide	Hypermagnesemia
	Sodium phosphate (oral or enema)	Hyperphosphatemia
Antacids	Aluminum hydroxide	Aluminum toxicity; osteomalacia
	Magnesium hydroxide	Hypermagnesemia
	Sucralfate	Aluminum toxicity
Nutritional supplements	Creatine	Fluid overload; factitious increase in creatinine; AKI (rarely)
	Germanium	AKI
	Salt substitutes	Hyperkalemia
Herbal remedies	Aristolochia/aristolochic acid	AKI; chronic tubulointerstitial fibrosis
	Ephedra (ma huang)	Increased blood pressure; myocardial infarction; stroke; AKI

AKI = acute kidney injury; COX = cyclooxygenase.

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CONT.

volume depletion), higher dose of contrast, use of early generation high osmolar ionic contrast, repeated doses of contrast, and concomitant use of NSAIDs. The most effective ways to prevent CIN are to avoid contrast by using alternative studies and to correct all modifiable risk factors. Patients with CKD should receive intravenous hydration with isotonic saline or bicarbonate-containing solutions before and after receiving contrast. Although the risk of CIN is clearly increased in patients with CKD, risks and benefits should be judged on a case-by-case basis. See Acute Kidney Injury for more information on CIN.

Gadolinium-containing MRI contrast agents are associated with the risk of nephrogenic systemic fibrosis (NSF) in patients with CKD. NSF is characterized by hardened and thickened skin on the trunk and the extremities, along with widening and fibrosis of the dermis and infiltration with CD34 fibrocytes on skin biopsy. Although most cases have occurred in patients with ESKD, isolated cases have been reported in patients with AKI, cirrhosis, or CKD not on dialysis. Therefore, gadolinium contrast must be avoided in patients with an eGFR <30 mL/min/1.73 m^2 unless there is a compelling clinical indication with informed patient consent. If gadolinium is used, prior nephrology consult should be obtained to assess risks of gadolinium administration and guide the use of dialysis in advanced CKD and ESKD. See MKSAP 17 Dermatology for more information on NSF.

Vaccination

Patients with CKD are at increased risk of infections that can be prevented by vaccination; however, these patients also have impaired immune responses to vaccines. Patients with CKD should receive vaccinations according to guidelines with a few exceptions. Current Centers for Disease Control (CDC) guidelines state that vaccinations in patients with CKD may be more effective when performed before the need for chronic dialysis or kidney transplantation. All susceptible patients with CKD should be vaccinated against hepatitis B virus. Patients with CKD should also receive the 23- and 13-valent pneumococcal vaccines, with revaccination with the 23-valent vaccine after a minimum of 5 years. The influenza vaccine should be administered annually to patients with CKD; importantly, these patients should only receive the inactivated influenza vaccine due to the risks associated with the live vaccine in immunocompromised patients. More information on vaccinations is available at http://itunes.apple.com/us/app/acp-immunization-advisor/id503636536.

Vascular Access

Patients with progressive or severe CKD may ultimately require renal replacement therapy with hemodialysis; vascular access is therefore a major clinical consideration in these patients. Patients who receive hemodialysis via an arteriovenous fistula (AVF) have superior clinical outcomes and fewer vascular complications or episodes of infection compared with arteriovenous grafts (AVGs) or catheters. Therefore, great care should be taken to protect peripheral veins in patients with CKD from venipuncture-induced trauma. Specific measures to protect peripheral veins include restricting phlebotomy, limiting intravenous (IV) catheter sites to hands, and protecting the nondominant arm for possible AVF placement. Because AVF placement can be technically challenging and may require several months for full maturation, referral to an experienced surgeon many months before dialysis is critical.

It is important to avoid peripherally inserted central venous catheters and subclavian catheters on either side due to the risk of sclerosis of peripheral veins and subclavian stenosis in patients at risk of developing ESKD.

In patients with ESKD on dialysis, it is critical to protect the arm with an existing AVF or AVG against trauma from blood pressure measurements, venipuncture, or other procedures. Other veins in the arms should also be protected in case they are needed for future vascular access.

Older Patients

CKD is highly prevalent in the older population, and the incidence of dialysis initiation is increasing most rapidly among patients over the age of 75 years. Management of CKD can be complicated by the high burden of comorbidities; interdisciplinary coordination of care is therefore essential. Particular care needs to be taken when evaluating older patients with impending ESKD. Decisions regarding initiation of renal replacement therapy and/or referral for evaluation for kidney transplantation in an older patient with impending ESKD must take into account comorbid medical conditions, functional status, expected outcomes, and patient preferences regarding goals of care.

KEY POINTS

- Gadolinium-containing MRI contrast agents are associated with the risk of nephrogenic systemic fibrosis and should be avoided in patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2.
- The incidence of dialysis initiation is increasing most rapidly among patients over the age of 75 years; decisions regarding initiation of renal replacement therapy in an older patient with impending end-stage kidney disease must take into account comorbid medical conditions, functional status, expected outcomes, and patient preferences regarding goals of care. HVC

End-Stage Kidney Disease

Although declining in recent years, mortality for U.S. patients initiating dialysis is approximately 10 times higher than for age-matched controls. The most common causes of death in patients with ESKD are cardiovascular disease and infection. Efforts to decrease mortality in this vulnerable population are therefore primarily focused upon preventing cardiovascular and infectious complications.

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Planning for ESKD treatment should begin many months, and ideally more than 1 year, prior to the need for renal replacement because the rate of CKD progression can be unpredictable. Several recent studies have demonstrated no benefit in starting dialysis in asymptomatic patients early based upon an arbitrary eGFR cutoff compared with waiting until patients develop very low eGFR (<8-10 mL/min/1.73 m^2) or clinical indications for dialysis are present.

Patients with an eGFR <30 mL/min/1.73 m^2 should receive education regarding treatment options, including peritoneal dialysis and hemodialysis, transplantation, and non-dialytic management of ESKD. Patients who opt for hemodialysis should be referred for arteriovenous fistula (AVF) placement before their eGFR drops below 15 mL/min/1.73 m^2 (stage G5) to allow sufficient time for AVF maturation. Placement of arteriovenous graft (AVG) or peritoneal dialysis catheters can occur a few weeks prior to therapy but should be planned months ahead.

Suitable candidates for kidney transplantation should be referred for evaluation once their eGFR is <20 mL/min/1.73 m^2. The reasons for timely referral for transplant are twofold. First, the best clinical outcomes occur with "preemptive transplants," in which patients receive the transplant prior to dialysis. Second, because the waiting list for kidneys can be extremely long (>7 years in some parts of the United States), it is important that patients start accruing time on the transplant list as early as possible to maximize the chances that they will receive a transplant while they are still healthy enough to tolerate the procedure and benefit from it.

KEY POINTS

- Suitable candidates for kidney transplantation should be referred for evaluation once their estimated glomerular filtration rate is <20 mL/min/1.73 m^2.
- Preemptive kidney transplants are associated with better clinical outcomes compared with transplantation after dialysis.

Dialysis

Hemodialysis

Most U.S. patients with ESKD receive hemodialysis three times a week during 3.5- to 4-hour in-center sessions. Recent data suggest that more frequent and/or longer dialysis sessions provided in-center or at home may provide some health benefits, including better control of volume and electrolytes (particularly phosphorus). Patients receiving more frequent and/or longer dialysis are also usually able to liberalize their diet with regard to potassium, phosphorus, and fluid intake. Because longer and/or more frequent hemodialysis has not yet been demonstrated to decrease mortality in a randomized controlled trial, the choice of hemodialysis modality and site of dialysis must incorporate patient preference and other factors, including availability of adequate home resources and support.

See Vascular Access for information on vascular access in patients undergoing hemodialysis.

Peritoneal Dialysis

In patients receiving peritoneal dialysis (PD), a dialysate solution is intermittently instilled into the peritoneal cavity via an indwelling catheter, and excess water and solutes are removed by osmosis and diffusion across the peritoneal membrane into the dialysis solution. Clinical outcomes, including mortality, are equivalent for patients on PD compared with hemodialysis, although there is a trend toward superior outcomes for PD in patients with new-onset ESKD who have significant residual kidney function. This may be explained in part by the fact that residual kidney function is preserved longer in patients on PD than in those on hemodialysis. Peritonitis is one of the most important complications of PD and can damage the peritoneum, reducing the efficacy of dialysis. PD-associated peritonitis is uncommon, with one episode of peritonitis every 2 to 3 years, usually caused by bacteria from skin introduced by poor sterile technique and often easily treated with antibiotics.

PD provides patients with more autonomy than in-center hemodialysis but requires that patients or their caregiver be capable of learning to connect/disconnect dialysis bags with a sterile technique and to have access to clean space and sufficient storage for supplies. Absolute contraindications to PD include documented loss of peritoneal function and uncorrectable mechanical defects of the peritoneum or abdominal wall that prevent effective dialysis or increase the risk of infection.

Non-dialytic Therapy

Some patients with ESKD may elect not to initiate dialysis, and others who are already undergoing chronic dialysis may decide to withdraw from treatment. Non-dialytic therapy for patients with ESKD is a viable treatment option that entails active management of symptoms with a primary focus on maximizing quality of life. The life expectancy of some patients with ESKD with advanced age and severe comorbidities can be extremely short and may not be improved by dialysis. Palliative medicine and hospice services can be used to manage symptoms in patients who choose non-dialytic ESKD therapy. In patients with minimal residual kidney function who withdraw from dialysis, most die within 2 weeks.

KEY POINTS

- Clinical outcomes are equivalent for patients on peritoneal dialysis (PD) compared with hemodialysis, although there is a trend toward superior outcomes for PD in patients with new-onset end-stage kidney disease who have significant residual kidney function.
- Non-dialytic therapy for patients with end-stage kidney disease is a viable treatment option that entails active management of symptoms with a primary focus on maximizing quality of life.

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Kidney Transplantation

Patients who receive kidney transplants for treatment of ESKD have markedly improved life expectancy and quality of life, and transplantation is the preferred therapy for eligible candidates. However, there is a severe shortage of available donor organs in the United States. The waiting list for transplants varies markedly by region within the United States. Because the best outcomes occur in patients who receive a preemptive transplant from a living donor, early referral for transplant evaluation to identify suitable living donors is important. If no living donor is available, early transplant listing is essential to minimize waiting time for a transplant.

Patients and donors are carefully screened for potential issues that may affect the safety and/or outcome of the transplant, including the presence of active malignancy, coronary ischemia, or active infection, and to ensure that there are adequate social supports and financial resources available.

Patients are usually managed by transplant nephrologists for at least the first 3 to 6 months posttransplant and subsequently co-managed with general nephrologists and/or internists, especially for comorbidities. The KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Patients can be found at www.kdigo.org.

Immunosuppressive Therapy

Patients with kidney transplants must receive immunosuppressive medications to prevent their immune system from rejecting the kidney allograft. Doses are typically highest immediately after transplant and are tapered gradually over several months to minimize toxicities associated with these medications while maintaining adequate immunosuppression.

The most commonly used immunosuppressants in the immediate posttransplant period for immunosuppression induction are anti-T cell and interleukin-2 receptor blocking antibodies. The most commonly prescribed medications for chronic maintenance immunosuppression include calcineurin inhibitors (tacrolimus or cyclosporine), antimetabolites (mycophenolate mofetil or azathioprine), and glucocorticoids. Although these medications are usually well tolerated, they can have significant side effects (**Table 42**).

TABLE 42. Common Side Effects of Medications Used for Chronic Maintenance Immunosuppression After Kidney Transplantation

Class	Medication	Common Side Effects
Calcineurin inhibitor	Cyclosporine	Hypertension; decreased GFR; dyslipidemia; hirsutism
	Tacrolimus	New-onset diabetes mellitus; decreased GFR; hypertension; gastrointestinal symptoms
Antimetabolite, blocker of de novo purine synthesis	Mycophenolate mofetil	Diarrhea; nausea/vomiting; leukopenia; anemia
	Azathioprine	Leukopenia
mTOR inhibitor	Sirolimus; everolimus	Proteinuria; dyslipidemia; new-onset diabetes mellitus; anemia; leukopenia
Glucocorticoid receptor agonist	Prednisone	Osteopenia; hypertension; edema; new-onset diabetes mellitus

GFR = glomerular filtration rate; mTOR = mammalian target of rapamycin.

Risks of Transplantation

Immediately after kidney transplantation, patients must be monitored closely for acute rejection and postsurgical complications. In the ensuing months, the focus shifts toward minimizing the risks of infection and side effects of medications while maintaining adequate immunosuppression to maintain optimal graft function.

Infection

Patients with kidney transplants are at increased risk for several infections, and the type of organism varies depending upon the time after transplant. In the first month, the most common infectious complications are wound infections and urinary tract infections.

After the first month, opportunistic infections become more important. Cytomegalovirus (CMV) is an important pathogen in kidney transplant patients, and the risk of CMV infection depends upon the serologic status of the kidney donor and recipient at the time of transplant. The highest risk occurs when a seronegative recipient (one who has never had a CMV infection) receives a kidney from a seropositive donor. Signs and symptoms of CMV infection include fever, hepatitis, pneumonitis, and gastrointestinal ulceration. Due to the relatively high incidence of CMV infection posttransplantation, most guidelines suggest that kidney transplant recipients receive prophylactic valganciclovir. Similar to other patients receiving strongly immunosuppressive medications, kidney transplant recipients should also receive prophylaxis against *Pneumocystis jirovecii* pneumonia.

Polyoma BK virus is an opportunistic infection that induces kidney injury in approximately 5% of kidney transplant recipients. The most common clinical manifestation of BK virus infection is an acute or indolent rise in serum creatinine due to BK-induced renal tubular cell injury and tubulointerstitial nephritis or, less commonly, due to ureteral stenosis. Because more intense immunosuppression is associated with higher risk of BK nephropathy, reduction of immunosuppression is the mainstay of prevention and must be balanced with risk of rejection.

Cancer

Immunosuppression of kidney transplant recipients increases the incidence and progression of several types of malignancies.

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The most common malignancies arising in transplant recipients are non-melanoma skin cancers, predominantly squamous cell carcinomas. Therefore, transplant recipients should be carefully screened for skin cancer and educated on the importance of protection from ultraviolet radiation.

Kaposi sarcoma (KS) is much more common in kidney transplant recipients than in the general population. The risk is highest in men of Jewish, Mediterranean, Arabic, Caribbean, or African ancestry, which parallels the regions where human herpesvirus-8, the causative factor in KS, is endemic. The most commonly used approaches to managing KS are reducing the intensity of immunosuppression and switching to sirolimus-based immunosuppression for its antiproliferative effects.

Posttransplant lymphoproliferative disease (PTLD) is caused by unrestricted proliferation of B lymphocytes, which is usually associated with Epstein-Barr virus (EBV) infection and impaired surveillance by T lymphocytes induced by immunosuppression. The most important risk factors for PTLD are the degree of immunosuppression and negative recipient EBV serostatus pretransplant. The most common treatments for PTLD are reduction of immunosuppression and administration of the anti-B-cell antibody rituximab in patients with CD20+ tumors.

Because several other types of cancer are also more prevalent and/or have worse outcomes in kidney transplant recipients, it is important to screen potential kidney recipients and donors for the presence of active malignancy prior to transplant.

Special Considerations in Transplant Recipients

Acute Kidney Injury

Kidney transplant recipients have an increased risk of AKI, which can occur immediately posttransplant or years later. Although acute rejection is an important cause of AKI, it occurs relatively early posttransplant and is less likely to occur after the first few months in patients who are adherent with their immunosuppressant medications. Other common reversible causes of AKI in transplant recipients with a previously functioning graft include volume depletion/prerenal causes, calcineurin inhibitor toxicity, acute interstitial nephritis, acute tubular necrosis, BK nephropathy, and ureteral or bladder outlet obstruction.

Disease Recurrence

Many forms of primary kidney disease can recur in the transplant allograft, including many glomerular diseases. In patients with ESKD due to autoimmune glomerulonephritis, including lupus or ANCA-associated glomerulonephritis, it is important that the disease be quiescent for several months prior to transplant. Some common causes of ESKD such as diabetic nephropathy and IgA nephropathy can recur in the allograft, although they are unlikely to cause allograft failure. However, recurrence of some primary kidney diseases, including focal segmental glomerulosclerosis and thrombotic microangiopathy, can worsen allograft outcomes and may warrant aggressive treatment.

Cardiovascular Disease

Because cardiovascular disease is the most common cause of death in kidney transplant recipients, aggressive management of cardiac risk factors is warranted (See Complications and Management, Cardiovascular Disease). Immunosuppressive medications, including calcineurin inhibitors, sirolimus, and glucocorticoids, contribute to dyslipidemia. Although clinical studies on the efficacy of statins in preventing cardiovascular mortality have yielded conflicting results, a large proportion of kidney transplant recipients receive these medications. KDIGO guidelines state that fluvastatin, atorvastatin, rosuvastatin, pravastatin, or simvastatin may be used in transplant recipients. Cyclosporine increases serum levels of statins; therefore, clinicians should consider reducing the dose of statins in patients taking cyclosporine.

Bone Disease

Kidney transplant recipients are at increased risk of bone disease due to several factors, including secondary or tertiary hyperparathyroidism, side effects of immunosuppressive medications, and high prevalence of vitamin D deficiency. Glucocorticoids can cause osteopenia and/or osteonecrosis, and tacrolimus can induce phosphate wasting. Secondary hyperparathyroidism usually improves after kidney transplantation but may not fully resolve and should be managed as described in the Chronic Kidney Disease-Mineral and Bone Disorder section.

Vaccination

Patients with CKD should receive all appropriate vaccinations prior to transplantation as outlined in the Vaccination section of Special Considerations. Most transplant centers avoid immunizations in the first 3 to 6 months after transplant when patients are more immunosuppressed and less likely to have an adequate response to immunization, with the exception of the influenza vaccine, which can be given within 1 month of transplantation in unvaccinated patients in the setting of an influenza outbreak. Vaccination using live attenuated viruses is generally contraindicated in kidney transplant recipients.

Nonadherence

Successful transplant outcomes depend heavily upon the ability of patients to adhere to medications, scheduled appointments, dietary advice, and abstinence from smoking or illicit drug use. It is therefore critical that patients be evaluated prior to transplant for adherence to medical therapy and adequacy of social support. Lack of medical insurance and financial resources is also an important factor that can prevent patients from being able to afford immunosuppressive medications. A multidisciplinary team approach that includes psychiatric services, nursing, and social work is therefore essential to promote patient adherence.

Risks of Kidney Donation

Persons who wish to be considered for living kidney donation must undergo extensive testing to ensure that they have

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normal kidney function and excellent health with low risk of future kidney or cardiac disease. In the United States, potential donors must be assigned an Independent Living Donor Advocate who is not directly affiliated with the transplant center or team and who advocates solely for the interests of the donor. Although long-term donor outcomes are generally excellent and similar to healthy non-donor controls, potential donors must be fully educated regarding short-term surgical risks and potential long-term risks, especially if they have a family history of kidney disease or are from racial or ethnic groups with increased susceptibility to kidney disease.

KEY POINTS

- Wound and urinary tract infections are most common in the first month following kidney transplantation; after the first month, opportunistic infections with cytomegalovirus, *Pneumocystis jirovecii*, and polyoma BK virus are most common.
- Immunosuppression of kidney transplant recipients increases the incidence and progression of several types of malignancies, including non-melanoma skin cancers, Kaposi sarcoma, and posttransplant lymphoproliferative disease.
- The dose of statins should be reduced in kidney transplant recipients taking cyclosporine.

Complications of End-Stage Kidney Disease

Cardiovascular Disease

The most common cause of death in patients with ESKD is arrhythmia/sudden cardiac death. The reasons for this propensity are unclear, but important factors include abnormalities in serum electrolyte concentrations that may rapidly change during hemodialysis, chronic fluid overload that likely contributes to high prevalence of left ventricular hypertrophy and cardiac fibrosis, and uremic toxins. Arterial calcification may also promote cardiac disease due to reduced vascular compliance and other factors. It is therefore important to attenuate electrolyte disturbances, especially hyperkalemia, to avoid rapid changes in extracellular potassium during dialysis, which may precipitate arrhythmias. Also, promoting adherence to dietary fluid restriction may prevent intradialytic hypotension caused by rapid fluid removal during dialysis, which can cause cardiovascular and central nervous system injury.

Infection

Infection is the second-leading cause of death in patients with ESKD. Catheter-associated bacteremia and sepsis contribute to morbidity and mortality. Patients with suspected bacteremia due to infection of a tunneled cuffed catheter should have blood cultures drawn and receive empiric antibiotics while awaiting culture results. Indications for immediate catheter removal are listed in **Table 43**. Afebrile patients who have received at least 48 hours of appropriate antibiotics and who do not have an indication for immediate catheter removal can safely have their catheter exchanged over a guidewire to minimize venous trauma associated with de novo catheter placement. Attempting to salvage a hemodialysis catheter in a patient with bacteremia is rarely advisable due to poor rates of success, except in patients in whom the risks outweigh benefits.

TABLE 43. Indications for Immediate Removal of Cuffed Tunnel Hemodialysis Catheters in Patients With Known or Suspected Catheter-Related Bacteremia

Severe sepsis
Hemodynamic instability
Evidence of metastatic infection
Infection of catheter exit site or tunnel
Persistent fever and/or bacteremia >48-72 h despite adequate antibiotic coverage and no other suspected source
Infection due to high risk and difficult-to-cure organisms, including *Staphylococcus aureus*, *Pseudomonas*, or fungi

Acquired Cystic Kidney Disease

Acquired kidney cysts often develop in patients with severe CKD and are frequently detected during routine kidney ultrasound or incidentally noted on abdominal CT or MRI scan. Acquired cystic kidney disease becomes more common and progresses during the course of ESKD, and some studies suggest that it may affect >50% of patients who have had ESKD for >3 years. The epithelial cells lining these cysts may undergo malignant transformation by poorly understood mechanisms. Patients with ESKD have a markedly increased risk for renal cell carcinoma. Although current guidelines do not support routine screening for renal cell carcinoma in all patients with CKD, a high level of suspicion is warranted in patients with symptoms such as new-onset gross hematuria or unexplained flank pain.

KEY POINT

- Complications of end-stage kidney disease include cardiovascular disease, infection, and acquired cystic kidney disease.

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 43-year-old man is evaluated during a routine physical examination. He has no current symptoms and no prior medical history. Family history is notable for diabetes mellitus and hypertension in two first-degree relatives. He takes no medications.

On physical examination, initial blood pressure measurement is 144/86 mm Hg; repeat measurement after 5 minutes of rest are 136/86 mm Hg and 134/88 mm Hg. BMI is 32. The remainder of the examination is normal.

Laboratory studies show normal serum creatinine and plasma glucose levels.

In addition to lifestyle modifications, which of the following is the most appropriate next step in the management of this patient's blood pressure?

(A) Initiate a low-dose ACE inhibitor
(B) Initiate low-dose chlorthalidone
(C) Order ambulatory blood pressure monitoring
(D) Recheck blood pressure in 1 year

Item 2

A 74-year-old woman is evaluated for a 1-week history of intermittent painless gross hematuria. She has a 3-year history of stage G4/A3 chronic kidney disease due to diabetic nephropathy, a 12-year history of type 2 diabetes mellitus, diabetic retinopathy, and hypertension. Medications are lisinopril, furosemide, insulin glargine, and insulin lispro.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 128/85 mm Hg, pulse rate is 76/min, and respiration rate is 15/min. BMI is 28. The lungs are clear. There are no abdominal masses or costovertebral angle tenderness. There is no edema.

Laboratory studies:

Creatinine	2.6 mg/dL (230 µmol/L)
Estimated glomerular filtration rate	23 mL/min/1.73 m^2
Urinalysis	2+ protein; 25-50 erythrocytes/hpf; 0 leukocytes/hpf; no erythrocyte casts

Which of the following is the most appropriate diagnostic test to perform in this patient?

(A) Contrast-enhanced CT of the abdomen and pelvis
(B) Gadolinium-enhanced MRI of the abdomen and pelvis
(C) Radiography of the abdomen and pelvis
(D) Ultrasonography of the abdomen and pelvis

Item 3

A 45-year-old man is evaluated during a new patient visit. He immigrated to the United States from Serbia 4 years ago and was diagnosed with Balkan endemic nephropathy at that time. His kidney function has remained stable, and his only symptoms are mild nocturia and urinary frequency. Medical history is otherwise unremarkable. He takes no medications.

On physical examination, temperature is 37.1 °C (98.7 °F), blood pressure is 138/82 mm Hg, pulse rate is 76/min, and respiration rate is 12/min. BMI is 26. The remainder of the examination is normal.

Laboratory studies:

Hemoglobin	9.6 g/dL (96 g/L)
Electrolytes	Normal
Creatinine	1.7 mg/dL (150.1 µmol/L)
Glucose	Normal
Estimated glomerular filtration rate	35 mL/min/1.73 m^2
Urinalysis	Specific gravity 1.005; 2+ glucose; 10-20 erythrocytes/hpf

An increased risk of which of the following is most likely in this patient?

(A) Diabetes mellitus
(B) Intracranial cerebral aneurysm
(C) Renal cell carcinoma
(D) Transitional cell carcinoma

Item 4

A 64-year-old man is evaluated for a 6-week history of intermittent red-colored urine. He notes fatigue but otherwise feels well. Medical history includes hypertension, mechanical mitral valve replacement due to myxomatous degeneration, and calcium oxalate nephrolithiasis. He is a current smoker with a 60-pack-year history. Medications are amlodipine, warfarin, and aspirin.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 112/72 mm Hg, and pulse rate is 98/min. BMI is 30. Examination of the heart reveals a metallic click with a grade 2/6 cardiac systolic murmur that radiates to the axilla. The lungs are clear. There is no costovertebral angle tenderness. The remainder of the examination is unremarkable.

Urinalysis is dipstick positive for 3+ blood, 1+ protein, and no leukocyte esterase or nitrites; on microscopic examination, there are no cells or casts, although calcium oxalate crystals are seen.

Which of the following is the most likely cause of this patient's clinical findings?

(A) Bladder cancer
(B) Glomerulonephritis
(C) Hemoglobinuria
(D) Nephrolithiasis

Item 5

A 62-year-old man is evaluated during a follow-up visit for hypertension. His clinic blood pressure readings during the

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past year have been persistently above 140/90 mm Hg, and home blood pressure readings have been in the range of 150-170/90-96 mm Hg. He reports no symptoms. Medical history is otherwise unremarkable. Medications are maximal doses of lisinopril, nifedipine, and atenolol.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 168/100 mm Hg in both arms with no orthostasis, pulse rate is 60/min, and respiration rate is 16/min. BMI is 29. Retinal examination shows copper wiring of the arteries. An S_4 is heard on cardiac auscultation. There are no bruits heard over the carotids or abdomen. Neurologic and peripheral vascular examinations are normal. There is no edema.

Laboratory studies:

Creatinine	1.5 mg/dL (132.6 µmol/L)
Potassium	4.1 mEq/L (4.1 mmol/L)
Estimated glomerular filtration rate	45 mL/min/1.73 m²
Urinalysis	No protein, blood, or cells

Electrocardiogram shows left ventricular hypertrophy with repolarization abnormalities. Kidney ultrasound is normal.

Which of the following is the most appropriate next step in management?

(A) Add chlorthalidone
(B) Add clonidine transdermal patch
(C) Add minoxidil
(D) Switch nifedipine to amlodipine

Item 6

A 68-year-old man is evaluated for a 6-month history of progressive dyspnea on exertion, dizziness on standing, lower extremity edema, and burning pain with numbness in his extremities. He also notes intermittent loose stools up to 6 times daily. Medical history is otherwise unremarkable, and he takes no medications. He is current with scheduled health maintenance screening interventions, and laboratory studies obtained 3 years ago for an insurance physical examination were normal.

On physical examination, temperature is normal, pulse rate is 90/min, and respiration rate is 20/min. Blood pressure is 140/70 mm Hg sitting; upon standing, blood pressure drops to 90/60 mm Hg with dizziness. BMI is 27. Estimated central venous pressure is 7 cm H_2O. Decreased breath sounds are heard at the lung bases bilaterally. Heart examination does not reveal a rub or gallop. Abdominal examination reveals mild hepatosplenomegaly. On neurologic examination, there is impaired touch and vibration sense in a glove and stocking distribution. Bilateral lower extremity edema is noted to the level of the ankles.

Laboratory studies:

Albumin	2.8 g/dL (28 g/L)
Creatinine	1.6 mg/dL (141.4 µmol/L)
Electrolytes	Normal
Fasting plasma glucose	98 mg/dL (5.4 mmol/L)
Urinalysis	3+ protein; no blood or cells
Urine protein-creatinine ratio	4800 mg/g

Which of the following is the most likely diagnosis on kidney biopsy?

(A) AL amyloidosis
(B) Diabetic nephropathy
(C) Myeloma nephropathy
(D) Primary focal segmental glomerulosclerosis

Item 7

A 55-year-old woman is evaluated for persistent hyperkalemia. She is asymptomatic. Medical history is significant for type 2 diabetes mellitus complicated by nephropathy and peripheral neuropathy; she also has hypertension. Medications are insulin, rosuvastatin, amlodipine, amitriptyline, and aspirin.

On physical examination, temperature is 36.3 °C (97.4 °F), blood pressure is 130/72 mm Hg, pulse rate is 64/min, and respiration rate is 18/min. BMI is 32. Estimated central venous pressure is 6.0 cm H_2O. There is hyperesthesia of the feet bilaterally but no edema. The remainder of the examination is unremarkable.

Laboratory studies:

Creatinine	1.9 mg/dL (168 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	5.1 mEq/L (5.1 mmol/L)
Chloride	112 mEq/L (112 mmol/L)
Bicarbonate	18 mEq/L (18 mmol/L)
Glucose	142 mg/dL (7.9 mmol/L)
Phosphorus	4.5 mg/dL (1.5 mmol/L)
Estimated glomerular filtration rate	27 mL/min/1.73 m²
Urinalysis	pH 5.0

Which of the following is the most likely cause of this patient's metabolic findings?

(A) Kidney failure
(B) Type 1 (hypokalemic distal) renal tubular acidosis
(C) Type 2 (proximal) renal tubular acidosis
(D) Type 4 (hyperkalemic distal) renal tubular acidosis

Item 8

A 37-year-old woman is evaluated for an episode of blood in her urine. She notes the passage of red-colored urine that resolved spontaneously and was not associated with her menstrual cycle. She reports having had several similar episodes in the past. She has no other symptoms such as abdominal pain or dysuria. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, the patient is afebrile. Blood pressure is 128/78 mm Hg, pulse rate is 82/min, and respiration rate is 13/min. Cardiopulmonary and abdominal examinations are normal. There is no flank tenderness to palpation. The remainder of the examination is unremarkable.

Laboratory studies show a normal complete blood count and metabolic profile and a serum creatinine level of 0.9 mg/dL (79.6 µmol/L). Dipstick urinalysis is positive for blood and protein but is negative for leukocyte esterase and nitrites.

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Microscopy of the urine sediment is shown.



Which of the following is the most appropriate next step in the evaluation of this patient?

(A) Cystoscopy
(B) Evaluation for glomerular disease
(C) Noncontrast helical abdominal CT
(D) Serum creatine kinase measurement

Item 9

A 22-year-old woman is evaluated for persistent hematuria initially discovered following treatment of a urinary tract infection. She is asymptomatic. Family history is significant for persistent hematuria in her father and brother without kidney failure. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 110/74 mm Hg, pulse rate is 74/min, and respiration rate is 16/min. BMI is 22. Hearing is normal, and examination of the eyes is unremarkable. Cardiopulmonary examination is normal. Skin examination shows no lesions. Neurologic examination is unremarkable.

Laboratory studies:

Blood urea nitrogen	18 mg/dL (6.4 mmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)
Urinalysis	pH 5.0; 2+ blood; no protein; 10-20 erythrocytes/hpf

Kidney ultrasound shows normal-sized kidneys without evidence of obstruction or cysts.

Which of the following is the most likely diagnosis?

(A) Fabry disease
(B) Hereditary nephritis
(C) Thin glomerular basement membrane disease
(D) Tuberous sclerosis complex

Item 10

A 51-year-old man is evaluated during a follow-up visit for management of newly diagnosed hypertension and diabetes mellitus. He has started a program of lifestyle modification for his diabetes but has not yet started antihypertensive therapy. He is currently taking no medications.

On physical examination, blood pressure is 148/92 mm Hg, and pulse rate is 76/min. BMI is 33. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 1.5 mg/dL (132.6 µmol/L) (estimated glomerular filtration rate of 52 mL/min/1.73 m^2) and a serum potassium level of 4.2 mEq/L (4.2 mmol/L); a urine dipstick demonstrates no hematuria or proteinuria, and a spot urine protein-creatinine ratio is 50 mg/g.

Which of the following is the most appropriate antihypertensive treatment for this patient?

(A) Hydrochlorothiazide
(B) Lisinopril
(C) Lisinopril and amlodipine
(D) Lisinopril and hydrochlorothiazide
(E) Lisinopril and losartan

Item 11

A 73-year-old man is evaluated during a routine examination. He feels well but notes a gradual weight gain of 9.1 kg (20 lb) over the past 5 years. He reports his blood pressure to be around 155/85 mm Hg on several determinations at his local pharmacy. Medical history is significant for mild benign prostatic hyperplasia, gout, and hyperlipidemia. Medications are atorvastatin and as-needed colchicine.

On physical examination, blood pressure is 158/87 mm Hg, pulse rate is 85/min, and respiration rate is 12/min. BMI is 29. Cardiac examination is normal, and the remainder of the physical examination is unremarkable.

Laboratory studies show a normal chemistry panel; a urine dipstick demonstrates no blood or protein.

An electrocardiogram shows no evidence of left ventricular hypertrophy.

Which of the following is the most appropriate next step in management?

(A) Doxazosin
(B) Hydrochlorothiazide
(C) Metoprolol
(D) Lifestyle modifications
(E) Repeat blood pressure determination in 6 months

Item 12

A 24-year-old man is evaluated in the hospital for progressively worsening kidney function. He was admitted 5 days ago with fevers and was diagnosed with endocarditis with methicillin-resistant *Staphylococcus aureus*. Intravenous vancomycin was started and adjusted daily to target levels of 15 to 20 µg/mL (10.4-13.8 µmol/L). Since admission, his fevers have resolved, but his serum creatinine level has gradually increased. Medical history includes two previous admissions for staphylococcal endocarditis treated with prolonged courses of antibiotics. He has occasionally used injection drugs, including heroin, during the past 4 years. His only medication is vancomycin.

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H CONT.

On physical examination, temperature is 37.3 °C (99.2 °F), blood pressure is 110/70 mm Hg, pulse rate is 92/min, and respiration rate is 18/min. BMI is 22. Cardiac examination is notable for a soft diastolic murmur along the left sternal border. There is trace lower extremity edema. There is no skin rash or arthritis.

Laboratory studies:

C3	Low
C4	Normal
Creatinine	2.8 mg/dL (247.5 µmol/L) (1.5 mg/dL [132.6 µmol/L] on admission)
Cryoglobulins	Negative
Urinalysis	3+ blood; 2+ protein; 30-40 erythrocytes/hpf; 10-15 leukocytes/hpf; erythrocyte casts

Transthoracic ultrasound shows moderate aortic regurgitation without vegetations (confirmed on transesophageal ultrasound). Kidney ultrasound shows normal-sized, mildly echogenic kidneys. Doppler study of the renal arteries and veins is normal.

Which of the following is the most appropriate management?

(A) Initiate glucocorticoids
(B) Schedule a kidney biopsy
(C) Switch vancomycin to daptomycin
(D) Continue current therapy

Item 13

A 58-year-old man is evaluated during a follow-up visit for a 15-year history of hypertension. Medical history is significant for hypertensive nephropathy. He states that he feels well and is without current complaints. Medications are lisinopril and hydrochlorothiazide.

On physical examination, the patient is afebrile, blood pressure is 138/82 mm Hg, pulse rate is 83/min, and respiration rate is 12/min. BMI is 29. Cardiovascular examination is unremarkable. The lungs are clear. There is no peripheral edema.

Laboratory studies are significant for a serum creatinine level of 1.7 mg/dL (150.3 µmol/L) and a urine albumin-creatinine ratio of 200 mg/g.

Which of the following is the most appropriate management?

(A) Add losartan
(B) Increase lisinopril dose
(C) Replace lisinopril with amlodipine
(D) Continue current medications

Item 14

A 20-year-old woman is evaluated during a new-patient visit for persistent dipstick-positive hematuria initially discovered 2 years ago when she was evaluated for a possible urinary tract infection. Two subsequent urinalyses have shown dipstick-positive hematuria and 10-15 erythrocytes/hpf on microscopic examination without other abnormalities. She has not noted any episodes of gross hematuria or other urinary tract symptoms. She reports no fever, rash, or arthritis. Family history is notable for her mother and maternal aunt who have hematuria; there is no family history of kidney disease. Medical history is otherwise negative, and the patient takes no medications.

On physical examination, the patient is afebrile, blood pressure is 118/78 mm Hg, pulse rate is 64/min, and respiration rate is 14/min. BMI is 22. The remainder of the physical examination is normal.

Laboratory studies:

Complements (C3 and C4)	Normal
Creatinine	0.6 mg/dL (53 µmol/L)
Hepatitis B and C serologies	Negative
Antinuclear antibodies	Negative
ANCA	Negative
Urinalysis	2+ blood; no protein; 10-15 erythrocytes/hpf; no casts
Urine protein-creatinine ratio	110 mg/g

Kidney ultrasound is normal.

Which of the following is the most appropriate management?

(A) Abdominal CT with contrast
(B) Cystoscopy
(C) Kidney biopsy
(D) Serial kidney function and urine protein determinations
(E) Urine cytology

Item 15

A 48-year-old woman is evaluated during a follow-up visit for hypertension. Blood pressure measurements taken at the past three visits have been in the range of 135 to 146 mm Hg systolic and 86 to 92 mm Hg diastolic. Twenty-four hour ambulatory blood pressure monitoring shows an overall mean blood pressure of 136/84 mm Hg; daytime readings average 138/85 mm Hg, and nighttime readings average 130/82 mm Hg. She has no other pertinent personal or family history. She takes no medications.

On physical examination, blood pressure is 146/92 mm Hg, and pulse rate is 76/min. BMI is 29. The remainder of the examination is unremarkable.

Laboratory studies show a normal chemistry panel; a urine dipstick demonstrates no protein.

Which of the following is the most appropriate next step in management?

(A) Begin lisinopril
(B) Begin melatonin
(C) Recheck blood pressure in the office in 6 months
(D) Recheck blood pressure in the office in 1 year
(E) Repeat 24-hour ambulatory blood pressure monitoring in 1 year

Item 16

A 36-year-old man is evaluated following his second episode of nephrolithiasis. His initial kidney stone occurred

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6 months ago and passed spontaneously. The stone was recovered and on analysis was found to be a pure uric acid stone. He was advised to increase his urine output to at least 2 L/d and has been adherent to this recommendation. His second episode occurred last week. He again passed the stone spontaneously, which was submitted for analysis and shown to be a pure uric acid stone. Medical history is significant for type 2 diabetes mellitus, but he has never had evidence of gout. Medications are metformin and rosuvastatin.

On physical examination, temperature is 36.9 °C (98.5 °F), blood pressure is 135/87 mm Hg, pulse rate is 78/min, and respiration rate is 12/min. BMI is 31. There is no costovertebral angle tenderness. No joint abnormalities or gouty tophi are noted.

Laboratory studies:

Electrolytes	Normal
Kidney function studies	Normal
Urate	7.6 mg/dL (0.45 mmol/L)
Urinalysis	pH 5.8; no blood; no cells or crystals
24-Hour uric acid excretion	850 mg/24 h (5 mmol/24 h)

In addition to continuing oral hydration, which of the following is the most appropriate next step in therapy?

(A) Allopurinol
(B) Cholestyramine
(C) Hydrochlorothiazide
(D) Urine alkalinization

Item 17

A 45-year-old man is evaluated during a routine follow-up visit. Medical history is significant for difficult-to-control hypertension, type 2 diabetes mellitus complicated by proliferative retinopathy and sensory and autonomic neuropathy, and chronic kidney disease. He has no new symptoms. Medications are lisinopril, amlodipine, hydrochlorothiazide, and insulin.

On physical examination, temperature is 36.9 °C (98.4 °F), blood pressure is 180/100 mm Hg in both arms, pulse rate is 66/min, and respiration rate is 14/min. BMI is 34. There is bilateral lower extremity edema to the mid calf.

Laboratory studies are significant for a serum creatinine level of 2.2 mg/dL (194.5 µmol/L), a serum potassium level of 4.2 mEq/L (4.2 mmol/L), and a urine protein-creatinine ratio of 4000 mg/g.

Which of the following is the most appropriate treatment?

(A) Add aliskiren
(B) Add clonidine
(C) Add minoxidil
(D) Switch hydrochlorothiazide to furosemide

Item 18

An 85-year-old man arrives with his daughter to discuss options for end-stage kidney disease (ESKD) management. He has stage G5/A3 chronic kidney disease due to diabetic nephropathy and hypertension. History is also significant for a 3-year history of Alzheimer disease and heart failure with a left ventricular ejection fraction of 35%. Medications are aspirin, losartan, furosemide, carvedilol, and calcium acetate. The patient is a resident of a nursing facility.

On physical examination, the patient appears comfortable but is not oriented to place or time. Temperature is 37.0 °C (98.6 °F), blood pressure is 142/70 mm Hg, pulse rate is 82/min, and respiration rate is 18/min. BMI is 21. The lungs are clear. There is trace bipedal edema. The remainder of the examination is unremarkable.

Laboratory studies are notable for a blood urea nitrogen level of 82 mg/dL (29.3 mmol/L), a serum creatinine level of 5.1 mg/dL (450.8 µmol/L), and an estimated glomerular filtration rate of 9 mL/min/1.73 m^2.

Which of the following is the most appropriate recommendation for management of this patient's ESKD?

(A) Hemodialysis in a dialysis unit
(B) Hemodialysis at the nursing facility
(C) Nocturnal peritoneal dialysis
(D) Non-dialytic therapy

Item 19

A 48-year-old woman is evaluated during a follow-up visit for newly diagnosed hypertension, confirmed by multiple measurements at home and in the office. Medical history is notable for hyperlipidemia, for which she takes atorvastatin. Lifestyle modifications have been recommended.

On physical examination, blood pressure is 160/92 mm Hg, and pulse rate is 64/min. BMI is 32. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 1.1 mg/dL (97.2 µmol/L), a fasting plasma glucose level of 114 mg/dL (6.3 mmol/L), and a serum potassium level of 4.0 mEq/L (4.0 mmol/L); a urine dipstick demonstrates no blood or protein.

Which of the following is most likely to be effective in controlling this patient's hypertension?

(A) Amlodipine
(B) Lisinopril
(C) Losartan
(D) Lisinopril and amlodipine
(E) Losartan and lisinopril

Item 20

A 55-year-old woman is evaluated during a follow-up visit for elevated blood pressure noted on several previous clinic visits. She checks her blood pressure at home with a device checked in the clinic for accuracy and reports measurements typically in the "120s over 80s." She is asymptomatic except for occasional palpitations associated with episodes of anxiety. Medical history is notable for depression, for which she takes citalopram.

On physical examination, blood pressure is 152/88 mm Hg, and pulse rate is 88/min. BMI is 24. The remainder of the examination is unremarkable.

Laboratory studies show a normal chemistry panel; a urine dipstick demonstrates no blood or protein.

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A resting electrocardiogram is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) 24-Hour ambulatory blood pressure monitoring
(B) 24-Hour urine testing for fractionated metanephrines
(C) Ambulatory electrocardiography
(D) Echocardiography
(E) Plasma aldosterone-plasma renin ratio

Item 21

A 65-year-old man is hospitalized for an ischemic, nonhealing right lower extremity ulcer with associated biopsy-proven osteomyelitis. On hospital day 1, he was started on cefazolin and underwent angiography and stenting of the iliac artery using a low osmolar contrast agent. On day 2, he became febrile and was switched to vancomycin and gentamicin based on culture sensitivity data. On day 3, his fever resolved and his serum creatinine was at baseline (1.5 mg/dL [132.6 µmol/L]). On day 10, his serum creatinine increased to 3.0 mg/dL (265.2 µmol/L) with a urine output of 0.5 mL/kg/h. Medical history is notable for type 2 diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, and chronic kidney disease. Medications are rosuvastatin, amlodipine, carvedilol, aspirin, insulin, vancomycin, and gentamicin.

On physical examination, blood pressure is 150/78 mm Hg, and pulse rate is 72/min. There is no rash. The lower extremities have decreased peripheral pulses. The right foot has a 1-cm clean-appearing ulcer on the tip of the second toe. The remainder of the physical examination is normal.

Laboratory studies on day 10:

Hemoglobin	11.2 g/dL (112 g/L)
Leukocyte count	8500/µL (8.5×10^9/L) with 58% polymorphonuclear leukocytes, 20% lymphocytes, 3% eosinophils
Creatinine	3.0 mg/dL (265.2 µmol/L) (baseline, 1.5 mg/dL [132.6 µmol/L])
Urine sodium	40 mEq/L (40 mmol/L)
Fractional excretion of sodium	2.1%
Urinalysis	Specific gravity 1.012; pH 5.5; trace blood; trace protein; 1-3 normal-appearing erythrocytes/hpf; granular casts; tubular epithelial cells

Kidney ultrasound is normal.

Which of the following is the most likely cause of this patient's acute kidney injury?

(A) Cefazolin
(B) Cholesterol emboli
(C) Contrast
(D) Gentamicin

Item 22

A 59-year-old man is evaluated during a follow-up visit for a 6-year history of end-stage kidney disease and a 20-year history of hypertension. He had a kidney transplant 3 months ago with an unremarkable postoperative course. Current medications are tacrolimus, mycophenolate mofetil, nifedipine, losartan, valganciclovir, and prednisone, 5 mg/d.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 165/95 mm Hg, pulse rate is 86/min, and respiration rate is 14/min. BMI is 28. There are no oral lesions. There is no jugular venous distention. Heart sounds are normal. The lungs are clear. The abdomen is nontender with no bruits. There is a well-healed scar in the right lower abdomen over the kidney allograft. There is 1+ peripheral edema.

Laboratory studies are notable for a serum creatinine level of 1.0 mg/dL (88.4 µmol/L).

Monitoring for which of the following complications is indicated in this patient?

(A) Hyperphosphatemia
(B) Hyperthyroidism
(C) Hypoparathyroidism
(D) New-onset diabetes mellitus and dyslipidemia

Item 23

A 36-year-old man is evaluated in the emergency department for right flank pain of 2 days' duration and an episode of gross hematuria. He reports no fever, nausea, or gastrointestinal symptoms. He has no other pertinent medical history, and he takes no medications. Family history is notable for a father with kidney stones.

On physical examination, the patient is in moderately painful discomfort. Temperature is 37.1 °C (98.7 °F), blood pressure is 123/76 mm Hg, pulse rate is 78/min, and respiration rate is 12/min. BMI is 21. There is no costovertebral angle tenderness. The abdomen is normal without rebound or guarding. The remainder of the examination is unremarkable.

Laboratory studies show a normal complete blood count, electrolyte panel, and kidney function. Urinalysis is significant for large blood on dipstick and >50,000 erythrocytes/hpf.

Noncontrast abdominal CT scan reveals a 12-mm stone in the right renal pelvis.

Which of the following is the most appropriate management?

(A) Mechanical stone removal
(B) Nifedipine
(C) Oral glucocorticoids
(D) Tamsulosin

Item 24

A 54-year-old woman is evaluated for fatigue, anorexia, polyuria, and nocturia of several weeks' duration. She had otherwise felt well until the onset of her current symptoms. Medical history is significant for autoimmune pancreatitis diagnosed 1 year ago, treated with a prednisone taper that was completed 8 months ago with resolution of her symptoms. She takes no medications.

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On physical examination, temperature is 36.2 °C (97.2 °F), blood pressure is 110/58 mm Hg, pulse rate is 72/min, and respiration rate is 16/min. BMI is 25. Estimated central venous pressure is 7 cm H_2O. The lungs are clear. There are no murmurs or extra heart sounds. Abdominal examination is unremarkable. There is no edema.

Laboratory studies:

Blood urea nitrogen	56 mg/dL (20 mmol/L)
Creatinine	5.2 mg/dL (459.7 µmol/L)
Serum free light chain ratio	Normal
Urinalysis	pH 5.0; 1+ protein; 3-5 erythrocytes/hpf; 5-10 leukocytes/hpf; occasional leukocyte casts

Chest radiograph is normal. Kidney ultrasound shows slightly enlarged kidneys without evidence of obstruction.

Which of the following is the most likely diagnosis?

(A) ANCA-associated vasculitis
(B) Anti–glomerular basement membrane antibody disease
(C) IgG4-related interstitial nephritis
(D) Lupus nephritis

Item 25

A 46-year-old woman is evaluated in the emergency department for fatigue and weakness of 5 days' duration. The patient also reports recurrent lower extremity swelling. She is vague when asked about medication or drug use.

On physical examination, blood pressure is 108/62 mm Hg, pulse rate is 98/min, and respiration rate is 16/min. Upon standing, systolic blood pressure decreases by 15 mm Hg, and pulse rate increases by 10/min. BMI is 26. The remainder of the examination is unremarkable, with no evidence of lower extremity edema.

Laboratory studies:

Serum bicarbonate	29 mEq/L (29 mmol/L)
Serum creatinine	1.2 mg/dL (106.1 µmol/L)
Serum potassium	3.1 mEq/L (3.1 mmol/L)
Urine chloride	53 mEq/L (53 mmol/L)
Urine potassium	25 mEq/L (25 mmol/L)
Urine sodium	42 mEq/L (42 mmol/L)

Which of the following is the most appropriate diagnostic test to perform next?

(A) 24-Hour urine free cortisol excretion
(B) Plasma aldosterone-plasma renin ratio
(C) Serum thyroid-stimulating hormone level
(D) Urine diuretic screening

Item 26

A 77-year-old woman is evaluated 4 months following a left middle cerebral artery ischemic stroke. The severity of her stroke required prolonged initial hospitalization and a 3-month stay in a rehabilitation center before returning home. Residual deficits include dense right-sided hemiparesis and dysphagia requiring oral feeding with thickened liquids. Medical history is otherwise significant for hypertension and diabetes mellitus. Current medications are aspirin, chlorthalidone, lisinopril, tolterodine, and insulin.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 136/86 mm Hg, and pulse rate is 86/min. BMI is 18. The general medical examination is unremarkable. Neurologic examination reveals dysarthria, left-sided facial droop, 1/5 strength in the right arm and leg, and bilateral distal sensory neuropathy.

Laboratory studies:

Hemoglobin A_{1c}	7.2%
Albumin	2.4 g/dL (24 g/L)
Blood urea nitrogen	12 mg/dL (4.3 mmol/L) (4 months ago: 28 mg/dL [10 mmol/L])
Creatinine	0.8 mg/dL (70.7 µmol/L) (4 months ago: 1.4 mg/dL [123.8 µmol/L])
Urinalysis	Normal

Which of the following is the most likely cause of this patient's decreased serum creatinine level?

(A) Decrease in muscle mass
(B) Improvement in diabetic kidney disease
(C) Initiation of chlorthalidone
(D) Initiation of lisinopril

Item 27

A 60-year-old man is evaluated during a routine visit. He has stage G4/A3 chronic kidney disease due to membranous glomerulopathy. He received treatment with cyclosporine and prednisone and received rituximab 2 years ago. Current medications are lisinopril, atorvastatin, furosemide, and calcium carbonate/vitamin D. He received the complete hepatitis B immunization series, pneumococcal polysaccharide, tetanus and diphtheria combined with acellular pertussis, and influenza immunizations 6 months ago.

On physical examination, vital signs are normal. BMI is 27. The remainder of the examination is noncontributory.

Which of the following is an appropriate approach to pneumococcal vaccination in this patient?

(A) Administer the pneumococcal conjugate vaccine now
(B) Administer the pneumococcal conjugate vaccine in 6 months
(C) Administer the pneumococcal polysaccharide and pneumococcal conjugate vaccines in 6 months
(D) Repeat the pneumococcal polysaccharide vaccine now

Item 28

A 26-year-old woman is evaluated for muscle weakness developing over the past several months. She has no focal symptoms and states that she otherwise feels well. Medical history is unremarkable, and there is no pertinent family history. She takes no medications.

On physical examination, blood pressure is 98/62 mm Hg, pulse rate is 98/min, and respiration rate is 16/min. BMI is 19. There is no lower extremity edema. The remainder of the examination is unremarkable.

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Laboratory studies:

Serum electrolytes:	
Sodium	142 mEq/L (142 mmol/L)
Potassium	3.1 mEq/L (3.1 mmol/L)
Chloride	120 mEq/L (120 mmol/L)
Bicarbonate	15 mEq/L (15 mmol/L)
Serum creatinine	1.2 mg/dL (106.1 µmol/L)
Urine electrolytes:	
Sodium	18 mEq/L (18 mmol/L)
Potassium	8.0 mEq/L (8.0 mmol/L)
Chloride	32 mEq/L (32 mmol/L)
Urine pH	5.0
Urine dipstick	No blood or protein

Which of the following is the most likely cause of this patient's acid-base and electrolyte abnormalities?

(A) Bulimia nervosa
(B) Gitelman syndrome
(C) Laxative abuse
(D) Surreptitious diuretic use
(E) Type 1 (hypokalemic distal) renal tubular acidosis

Item 29

A 65-year-old man is evaluated during a follow-up visit for a preemptive living donor kidney transplant 6 months ago, with a postoperative course complicated by an episode of acute cellular rejection requiring antithymocyte antibody induction. He has done well since then. He has a 10-year history of chronic kidney disease due to diabetic nephropathy and a 35-year history of type 1 diabetes mellitus. Basal cell carcinoma was removed from his nose 2 years ago. Current medications are tacrolimus, mycophenolate mofetil, valganciclovir, and prednisone, 5 mg/d.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 135/78 mm Hg, pulse rate is 80/min, and respiration rate is 14/min. BMI is 22. There is no lymphadenopathy. Actinic keratoses are present on the forehead. The lungs are clear. The abdomen is nontender without organomegaly. The kidney allograft in the left pelvis is nontender with a well-healed scar. There is no peripheral edema.

Laboratory studies show a serum creatinine level of 1.2 mg/dL (106.1 µmol/L).

In addition to age- and sex-appropriate screening, which of the following should this patient be evaluated for?

(A) Colon cancer
(B) Lung cancer
(C) Prostate cancer
(D) Skin cancer
(E) No additional screening

Item 30

A 68-year-old woman is hospitalized for coronary artery bypass surgery for multi-vessel coronary artery disease. Medical history includes atherosclerotic cardiovascular disease, hypertension, type 2 diabetes mellitus, hyperlipidemia, and chronic kidney disease. Home medications are simvastatin, lisinopril, furosemide, amlodipine, aspirin, and glimepiride.

On physical examination, blood pressure is 150/82 mm Hg, and pulse rate is 76/min. BMI is 25. The remainder of the physical examination is unremarkable.

Laboratory studies are significant for a baseline serum creatinine level of 2.3 mg/dL (203.3 µmol/L), with an estimated glomerular filtration rate (eGFR) of 25 mL/min/1.73 m^2.

Which of the following is considered the strongest predictor of the development of acute kidney injury in the perioperative period for this patient?

(A) Baseline eGFR
(B) BMI
(C) Hypertension
(D) Perioperative lisinopril use
(E) Perioperative statin use

Item 31

A 72-year-old woman is evaluated for a 3-year history of progressively worsening low back pain involving the lumbar spine, sacroiliac joints, and hips. She reports progressive difficulty with rising from a squat and climbing stairs. She also has had several spontaneous fractures over the past year. At the time of presentation, she cannot walk without support. Medical history is also notable for type 2 diabetes mellitus, hypertension, and hyperlipidemia. Medications are glipizide, quinapril, rosiglitazone, atorvastatin, and hydrocodone/acetaminophen.

On physical examination, blood pressure is 147/84 mm Hg, and pulse rate is 82/min. There is a small swelling over the proximal phalanx of the left index finger. There is tenderness upon palpation of the ribs. Examination of the joints and spine is normal. Decreased strength in the proximal muscles of the lower limbs is noted.

Laboratory studies:

Albumin	3.9 g/dL (39 g/L)
Alkaline phosphatase	436 U/L
Calcium	9.0 mg/dL (2.3 mmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)
Phosphorus	1.7 mg/dL (0.55 mmol/L)
Intact parathyroid hormone	22 pg/mL (22 ng/L)
1,25-Dihydroxy vitamin D	5.0 pg/mL (12 pmol/L)
25-Hydroxy vitamin D	40 ng/mL (99.8 nmol/L)
24-Hour urine phosphate	1.4 g/24 h (45 mmol/24 h) (normal range, 0.4-1.3 g/24 h [12.9-42 mmol/24 h])

Which of the following is the most likely cause of this patient's hypophosphatemia?

(A) Nutritional vitamin D deficiency
(B) Oncogenic osteomalacia
(C) Primary hyperparathyroidism
(D) X-linked hypophosphatemic rickets

Item 32

A 47-year-old man is admitted to the medical ICU with severe sepsis, multi-lobar pneumonia, and acute respiratory distress syndrome. He developed oliguric acute kidney injury on hospital day 3; he has produced only 240 mL of

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urine over the past 24 hours despite adequate intravenous hydration. He is mechanically ventilated and requires 80% FIO_2. Medical history is unremarkable, and current medications are piperacillin/tazobactam, vancomycin, norepinephrine, vasopressin and propofol infusions, and a proton pump inhibitor.

On physical examination the patient is intubated and sedated. Temperature is 38.5 °C (101.3 °F), blood pressure is 95/60 mm Hg, and pulse rate is 130/min. Estimated central venous pressure is 14 cm H_2O. There is no rash. Generalized anasarca is noted. Examination of the chest reveals coarse breath sounds and inspiratory crackles throughout both lungs.

Laboratory studies:

Blood urea nitrogen	103 mg/dL (36.8 mmol/L)
Creatinine	4.3 mg/dL (380.1 µmol/L)
Electrolytes	
Sodium	137 mEq/L (137 mmol/L)
Potassium	6.0 mEq/L (6.0 mmol/L)
Chloride	97 mEq/L (97 mmol/L))
Bicarbonate	16 mEq/L (16 mmol/L)
Phosphorus	7.2 mg/dL (2.33 mmol/L)
Serum pH	7.2
Urinalysis	3+ blood; 0-2 erythrocytes/hpf; multiple granular casts and tubular epithelial cells

Which of the following is the most appropriate treatment for this patient's kidney failure?

(A) Initiate continuous renal replacement therapy
(B) Initiate intermittent hemodialysis
(C) Initiate slow continuous ultrafiltration
(D) Start a furosemide infusion

Item 33

A 50-year-old man is hospitalized with acute onset of shortness of breath and fatigue. In the emergency department, he coughed up a large quantity of blood followed by hypoxic respiratory failure, for which he was intubated.

On physical examination, the patient is well developed. He is afebrile; blood pressure is 140/90 mm Hg, and heart rate is 98/min. There is no jugular venous distension. Coarse crackles are heard in the lung fields. There is trace lower extremity edema. The remainder of the physical examination is normal.

Laboratory studies:

Hemoglobin	9.0 g/dL (90 g/L)
Blood urea nitrogen	38 mg/dL (13.6 mmol/L)
Creatinine	3.2 mg/dL (282.9 µmol/L)
Liver chemistry tests	Normal
Urinalysis	3+ blood; 2+ protein; 20-30 erythrocytes/hpf; 5-10 leukocytes/hpf
Urine protein-creatinine ratio	2200 mg/g

A chest radiograph shows bilateral pulmonary infiltrates.

A kidney biopsy is performed, which shows necrotizing, crescentic glomerulonephritis with linear staining of IgG along the glomerular basement membrane.

Which of the following is the most likely diagnosis?

(A) Anti-glomerular basement membrane antibody disease
(B) Cardiorenal syndrome
(C) Membranous nephropathy
(D) Microscopic polyangiitis

Item 34

A 54-year-old woman is evaluated during a follow-up visit for chronic osteomyelitis. She has type 2 diabetes mellitus complicated by nephropathy and peripheral neuropathy and was recently diagnosed with osteomyelitis of the left foot associated with a chronic neuropathic ulcer. Bone biopsy and culture demonstrated methicillin-sensitive *Staphylococcus aureus*, and 1 week ago she was started on oral high-dose trimethoprim-sulfamethoxazole and rifampin based on sensitivity data for a planned 6-week course of therapy. Medical history is also significant for hypertension. Medications are trimethoprim-sulfamethoxazole, rifampin, glipizide, and atorvastatin.

On physical examination today, temperature is 37.2 °C (99.0 °F), blood pressure is 126/66 mm Hg, and pulse rate is 78/min. Chest, heart, and abdominal examinations are unremarkable. There is loss of sensation to light touch on the feet bilaterally to the ankles. The ulcer overlying the first metatarsal head on the plantar aspect of the left foot is clean and dry.

Current laboratory studies:

Blood urea nitrogen	28 mg/dL (10 mmol/L) (pretreatment baseline: 26 mg/dL [9.3 mmol/L])
Creatinine	1.8 mg/dL (159.1 µmol/L) (pretreatment baseline: 1.4 mg/dL [123.8 µmol/L])
Potassium	4.7 mEq/L (4.7 mmol/L)

Which of the following is the most appropriate management?

(A) Discontinue rifampin
(B) Discontinue trimethoprim-sulfamethoxazole
(C) Order a urine eosinophil test
(D) Continue current therapy

Item 35

A 57-year-old man is evaluated in the emergency department for a 3-day history of left inguinal pain and gross hematuria. He reports no history of kidney stones or kidney disease. Medical history is notable for hypertension and dyslipidemia. Medications are amlodipine and atorvastatin.

On physical examination, temperature is 37.2 °C (98.9 °F), blood pressure is 129/78 mm Hg, pulse rate is 96/min, and respiration rate is 12/min. BMI is 24. There is no left costovertebral angle tenderness.

Laboratory studies show normal complete blood count, serum electrolytes, blood urea nitrogen, and serum creatinine. Dipstick urinalysis reveals 3+ blood, trace protein, and

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negative leukocyte esterase and nitrites. Urine microscopy shows 1-2 leukocytes/hpf, too numerous to count erythrocytes, and no casts.

A kidney ultrasound shows normal-appearing kidneys, no hydronephrosis, and no nephrolithiasis.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Doppler ultrasonography of the renal veins
(B) Kidney biopsy
(C) Noncontrast helical abdominal CT
(D) Urine culture

Item 36

A 72-year-old man is admitted to the ICU with a 3-day history of worsening shortness of breath and edema. He is found to have pulmonary edema with severe hypoxia requiring intubation and mechanical ventilation. Medical history is significant for ischemic cardiomyopathy, coronary artery disease, myocardial infarction, hypertension, hyperlipidemia, and benign prostatic hyperplasia. Medications on admission are aspirin, lisinopril, carvedilol, atorvastatin, and as-needed furosemide.

On physical examination, the patient is afebrile, blood pressure is 92/60 mm Hg, and pulse rate is 112/min. Estimated central venous pressure is 14 cm H_2O. Diffuse crackles are heard throughout both lung fields. Cardiovascular examination reveals an S_3 gallop. There is lower extremity edema to the knees.

A dobutamine infusion is started. A urinary catheter is inserted, and he is given intravenous furosemide with a urine output of 230 mL over the next 4 hours.

Laboratory studies:

Blood urea nitrogen	76 mg/dL (27.1 mmol/L)
Serum creatinine	3.0 mg/dL (265.2 µmol/L) (baseline: 1.9 mg/dL [168 mmol/L])
Serum electrolytes	Normal
Urine sodium	64 mEq/L (64 mmol/L)
Fractional excretion of sodium	1.9%
Fractional excretion of urea	8.8%
Urinalysis	Specific gravity 1.018; pH 5.5; 1+ protein; 1-2 erythrocytes/hpf; 2-4 leukocytes/hpf; moderate hyaline and fine granular casts

Which of the following is the most likely diagnosis?

(A) Acute interstitial nephritis
(B) Acute tubular necrosis
(C) Obstructive uropathy
(D) Prerenal acute kidney injury

Item 37

A 24-year-old woman is evaluated for fever, lower extremity edema, and worsening malar rash. She was diagnosed with systemic lupus erythematosus 2 years ago. Her initial evaluation showed normal kidney function, trace proteinuria, and an otherwise normal urinalysis; periodic monitoring of her kidney function and urinalysis has been unchanged. She has been treated with hydroxychloroquine and prednisone, 5 mg/d, since the time of her diagnosis with good control of her symptoms. Medical history is otherwise unremarkable, and she takes no additional medications.

On physical examination, blood pressure is 140/92 mm Hg. A malar rash is present. Mild erythema and effusion in the left knee and bilateral wrist joints are noted. The remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	9.2 g/dL (92 g/L)
C3	Low
C4	Low
Creatinine	1.0 mg/dL (88.4 µmol/L)
Liver chemistry tests	Normal
Anti-double stranded DNA antibodies	Elevated
Urinalysis	3+ blood; 2+ protein; 20-30 erythrocytes/hpf; 5-10 leukocytes/hpf
Urine protein-creatinine ratio	2200 mg/g

A kidney biopsy shows a diffuse proliferative glomerulonephritis with immunofluorescence microscopy showing granular deposits in the subendothelial, mesangial, and subepithelial areas (IgG, IgM, IgA, C3, and C1q), which are confirmed by electron microscopy, and is classified as class IV lupus nephritis.

Which of the following is the most appropriate treatment?

(A) Increase prednisone
(B) Increase prednisone and add mycophenolate mofetil
(C) Increase prednisone and perform plasmapheresis
(D) Continue current therapy and rebiopsy in 3 months

Item 38

A 70-year-old woman is evaluated during a new-patient visit. She is asymptomatic. Medical history is significant for osteoporosis and borderline blood pressure elevations; she was advised by her previous physician to periodically check her blood pressures at home. She reports that over the past year these readings have been consistently between 140 and 150 mm Hg systolic and 82 and 86 mm Hg diastolic. She follows a low salt diet and exercises regularly three times a week. Family history is notable for both parents who were diagnosed with hypertension after the age of 65 years. Medications are alendronate and calcium with vitamin D.

On physical examination, temperature is 36.9 °C (98.4 °F), pulse rate is 68/min, and respiration rate is 14/min. Blood pressure is 146/86 mm Hg, with a repeat measurement of 148/86 mm Hg; there are no orthostatic changes.

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Laboratory studies show a serum creatinine level of 0.7 mg/dL (61.9 µmol/L) and a serum potassium level of 4.0 mEq/L (4.0 mmol/L); urinalysis is normal.

Electrocardiogram is normal.

Which of the following is the most appropriate next step in management?

(A) Begin hydrochlorothiazide
(B) Begin lisinopril
(C) Obtain echocardiography
(D) Continue clinical observation

Item 39

A 25-year-old man is evaluated for dark-colored urine for 2 days, swelling of the face and hands for 1 day, and severe headaches this morning. He reports having an upper respiratory tract infection 1 week ago with fever, sore throat, and swollen glands, but had otherwise felt well. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 180/90 mm Hg, pulse rate is 88/min, and respiration rate is 14/min. Cardiopulmonary and abdominal examinations are normal. No skin rash or arthritis is present. There is bilateral lower extremity edema to the mid shins.

Laboratory studies:

Albumin	3.3 g/dL (33 g/L)
C3	Low
C4	Normal
Creatinine	1.4 mg/dL (124 µmol/L)
Antistreptolysin O antibodies	Elevated
Urinalysis	3+ blood; 2+ protein; too numerous to count erythrocytes/hpf; 10-15 leukocytes/hpf; numerous erythrocyte casts
Urine protein-creatinine ratio	1900 mg/g
Rapid streptococcal antigen test	Positive

Which of the following is the most likely diagnosis?

(A) IgA nephropathy
(B) Infection-related glomerulonephritis
(C) Lupus nephritis
(D) Small-vessel vasculitis

Item 40

A 54-year-old woman is hospitalized for management of acute kidney injury. Medical history is significant for obesity but is otherwise unremarkable. She reports that she was seen in a weight loss clinic 1 month ago and was prescribed an unknown weight reduction drug, which she has been taking since that time. She takes no other medications.

On physical examination, blood pressure is 140/70 mm Hg, and pulse rate is 72/min. BMI is 40. Estimated central venous pressure is 10 cm H_2O. There are crackles at the lung bases. Heart examination is unremarkable. There is lower extremity edema to the mid-calf bilaterally. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 5.1 mg/dL (450.8 µmol/L). Urinalysis is dipstick positive for trace protein, and urine sediment is notable for 0-2 erythrocytes/hpf, 0-5 leukocytes/hpf, and numerous calcium oxalate crystals.

Kidney ultrasound demonstrates normal-sized kidneys with slightly increased echogenicity and no hydronephrosis. Kidney biopsy demonstrates deposition of calcium oxalate crystals within the tubules and the interstitium.

Which of the following is the most likely cause of this patient's acute kidney injury?

(A) Aristolochic acid
(B) Ephedrine
(C) Orlistat
(D) Phentermine

Item 41

A 35-year-old man is evaluated in the emergency department for dyspnea of 24 hours' duration. He also reports progressive lower extremity edema for 1 month. He has no other pertinent personal or family medical history, and he takes no medications.

On physical examination, the patient is afebrile, blood pressure is 120/78 mm Hg, pulse rate is 100/min, and respiration rate is 22/min. Oxygen saturation on ambient air is 88%. BMI is 25. The chest is clear. Examination of the heart is unremarkable. There is bilateral lower extremity pitting edema to the knees. The remainder of the examination is normal.

Laboratory studies:

Albumin	1.8 g/dL (18 g/L)
Creatinine	1.1 mg/dL (97.2 µmol/L)
Urinalysis	Negative for blood; 3+ protein; no cells
Urine protein-creatinine ratio	5500 mg/g

Chest radiograph is normal. CT angiogram of the chest shows a right pulmonary artery embolism.

The patient is started on supplemental oxygen and heparin.

Which of the following is the most likely underlying diagnosis?

(A) Acute interstitial nephritis
(B) Membranous glomerulopathy
(C) Poststreptococcal glomerulonephritis
(D) Thrombotic microangiopathy

Item 42

A 32-year-old man is evaluated during a follow-up visit for high blood pressure. During a recent insurance

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examination, his blood pressure was 180/80 mm Hg. He rechecked his blood pressure in a pharmacy, and it was 138/80 mm Hg. Medical history is unremarkable. Family history is notable for both parents who have hypertension; his father experienced a stroke at age 60 years. The patient takes no medications. He has a 10-pack-year history of smoking but stopped smoking 5 years ago. He is asymptomatic, exercises regularly, and follows a heart-healthy, low salt diet.

On physical examination, temperature is 36.8 °C (98.3 °F), blood pressure is 190/90 mm Hg, pulse rate is 90/min, and respiration rate is 14/min. BMI is 28. Blood pressure taken 5 minutes later is 160/80 mm Hg. The blood pressure readings are symmetric in all four limbs, with no postural drop. Retinal examination is normal. Cardiovascular examination is normal.

Laboratory studies show normal serum creatinine and electrolyte levels, and a urinalysis is unremarkable.

Electrocardiogram is normal.

Ambulatory blood pressure monitoring results:

Average blood pressure	121/81 mm Hg
Systolic blood pressure readings >140 mm Hg	15%
Diastolic blood pressure readings >90 mm Hg	20%
Awake/sleep blood pressure decrease	16%/12%

Which of the following is the most appropriate next step in management?

(A) Order echocardiography
(B) Order a plasma aldosterone-plasma renin ratio
(C) Start amlodipine
(D) Continue clinical follow-up

Item 43

A 72-year-old man was diagnosed with colon cancer 12 months ago, and surgical resection was performed. He presented with metastatic lesions to the liver 2 months ago, for which he was started on a chemotherapy regimen that includes oxaliplatin with 5-fluorouracil and leucovorin with bevacizumab. He has been experiencing progressive headaches and lower extremity swelling over the past 3 weeks. He reports no diarrhea, mental status changes, or shortness of breath.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 180/120 mm Hg, pulse rate is 80/min, and respiration rate is 16/min. BMI is 32. There is 2+ pedal edema.

Laboratory studies show a hemoglobin level of 7.5 g/dL (75 g/L), a platelet count of 90,000/μL (90×10^9/L), and a serum creatinine level of 2.2 mg/dL (194 μmol/L); a peripheral blood smear shows numerous schistocytes.

Which of the following is the most likely cause of this patient's clinical picture?

(A) 5-Fluorouracil
(B) Bevacizumab
(C) Leucovorin
(D) Oxaliplatin

Item 44

A 54-year-old woman is evaluated during a follow-up visit for stage G4/A3 chronic kidney disease due to diabetic nephropathy. She is asymptomatic except for mild fatigue and peripheral edema and reports a good appetite. Medications are ramipril, furosemide, and calcium acetate.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 128/73 mm Hg, pulse rate is 80/min, and respiration rate is 14/min. BMI is 29. Pallor and pale mucous membranes are noted. There is no jugular venous distention. There is no pericardial friction rub. The lungs are clear. There is no asterixis. Neurologic examination is normal.

Laboratory studies are significant for a serum creatinine level of 2.6 mg/dL (229.8 μmol/L) and an estimated glomerular filtration rate of 19 mL/min/1.73 m^2 (1 year ago: 30 mL/min/1.73 m^2).

After discussing the goals of care, the patient wishes to explore renal replacement options and kidney transplantation.

Which of the following is the most appropriate management?

(A) Nephrologist referral now
(B) Nephrologist referral in 6 months
(C) Repeat creatinine measurement in 2 weeks
(D) Continue current management

Item 45

A 54-year-old woman is evaluated during a follow-up examination. She has a 22-year history of type 2 diabetes mellitus complicated by sensory neuropathy and proliferative retinopathy, for which she has received laser photocoagulation. She also has hypertension and hyperlipidemia. Medications are metformin, glipizide, atorvastatin, and lisinopril, 20 mg/d.

On physical examination, temperature is normal, blood pressure is 132/78 mm Hg, pulse rate is 72/min, and respiration rate is 12/min. BMI is 29. Cardiopulmonary and abdominal examinations are normal. There is no lower extremity edema. There is decreased sensation to monofilament testing in the feet.

Laboratory studies:

Hemoglobin A_{1c}	6.8%
Creatinine	1.2 mg/dL (106.1 μmol/L) (2 years ago: 0.8 mg/dL [70.7 μmol/L])
Electrolytes	Normal
Urine albumin-creatinine ratio	460 mg/g (5 years ago: <30 mg/g)

Which of the following is the most appropriate management of this patient's hypertension?

(A) Add amlodipine
(B) Add losartan
(C) Reduce lisinopril dose
(D) Continue current therapy

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Item 46

A 54-year-old man is hospitalized for necrotizing pancreatitis. His course has been complicated by acute respiratory distress syndrome requiring ventilator support. He is hemodynamically unstable and requires an intravenous norepinephrine infusion to maintain a mean arterial blood pressure of 65 mm Hg. On the third hospital day, he develops increasing norepinephrine and oxygen requirements and increasing ventilator airway pressures, and he becomes oliguric. Medications are propofol and fentanyl.

On physical examination, blood pressure is 80/60 mm Hg, pulse rate is 92/min, and respiration rate is 12/min. Estimated central venous pressure is 12 cm H_2O. Heart sounds are normal. There are diffuse pulmonary crackles. The abdomen is modestly distended and tense. Bilateral lower extremity and flank edema are present.

Laboratory studies:

Hemoglobin	9.0 g/dL (90 g/L)
INR	2.0
Creatinine	2.1 mg/dL (185.6 µmol/L) (on admission, 0.9 mg/dL [79.6 µmol/L])
Urine sodium	<10 mEq/L (10 mmol/L)
Urinalysis	Specific gravity 1.022; pH 6.0; 0-1 erythrocytes/hpf; 0-2 leukocytes/hpf; occasional hyaline casts

Kidney ultrasound reveals normal-sized kidneys and no hydronephrosis.

Which of the following is the most appropriate next step in management?

(A) Bladder pressure measurement
(B) Erythrocyte transfusion to a target hemoglobin of 11 g/dL (110 g/L)
(C) Isotonic saline bolus, 500 mL
(D) Pulmonary artery catheter placement

Item 47

A 68-year-old woman is evaluated for myalgia and generalized weakness. Medical history is significant for hypertension, hyperlipidemia, hypothyroidism, and chronic kidney disease. One week ago, she was hospitalized with symptoms of a transient ischemic attack. Carotid ultrasound revealed 50% stenosis of her left internal carotid. Her serum creatinine level during hospitalization was 1.5 mg/dL (132.6 µmol/L), and her thyroid-stimulating hormone level was 18 µU/mL (18 mU/L). She states that she had not been regularly adherent with her medications prior to admission, but that since discharge she has been taking her medications as prescribed. Current medications are aspirin, high-dose atorvastatin, lisinopril, hydrochlorothiazide, and levothyroxine.

On physical examination, blood pressure is 152/78 mm Hg, and pulse rate is 82/min. She is not orthostatic. Skin turgor is normal. The lung fields are clear. Cardiovascular examination reveals a left carotid bruit and a fourth heart sound. There is diffuse tenderness to palpation of the major muscle groups. Trace lower extremity edema is present.

Laboratory studies:

Complete blood count	Normal
Creatinine	3.0 mg/dL (265.2 µmol/L)
Electrolytes:	
Sodium	132 mEq/L (132 mmol/L)
Potassium	5.6 mEq/L (5.6 mmol/L)
Chloride	100 mEq/L (100 mmol/L)
Bicarbonate	22 mEq/L (22 mmol/L)
Phosphorus	6.0 mg/dL (1.9 mmol/L)
Urinalysis	4+ blood; 0-1 erythrocytes/hpf; 0-2 leukocytes/hpf; numerous granular casts

Which of the following medications is the most likely cause of this patient's acute kidney injury?

(A) Atorvastatin
(B) Hydrochlorothiazide
(C) Levothyroxine
(D) Lisinopril

Item 48

A 42-year-old man is evaluated during a follow-up visit for chronic kidney disease due to vesicoureteral reflux that progressed to end-stage kidney disease 10 years ago; he has been receiving hemodialysis for 5 years. He is anuric but feels well and reports no other symptoms. Medical history is otherwise unremarkable.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 145/95 mm Hg, pulse rate is 85/min, and respiration rate is 14/min. BMI is 26. The lungs are clear. The abdominal examination is normal, and there is no costovertebral angle tenderness. The remainder of the examination is normal.

An abdominal ultrasound was recently performed to evaluate a complaint of abdominal discomfort, which has since resolved. This study was remarkable for bilateral small echogenic kidneys with innumerable cysts and a 4-cm mass in the right renal parenchyma.

Which of the following is the most likely diagnosis?

(A) Hemorrhagic kidney cyst
(B) Renal angiomyolipoma
(C) Renal cell carcinoma
(D) Transitional cell carcinoma

Item 49

A 45-year-old man is evaluated during an annual routine health maintenance visit. History is notable for type 2 diabetes mellitus (diet controlled) diagnosed 3 months ago. Family history is significant for his father who developed end-stage kidney disease due to diabetes at age 68 years. He reports no symptoms and takes no medications.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 135/78 mm Hg, pulse rate is 70/min, and respiration rate is 12/min. BMI is 31. Cardiac

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examination reveals no murmur or gallop. The lungs are clear. There is 1+ peripheral edema.

Laboratory studies show a serum creatinine level of 1.0 mg/dL (88.4 µmol/L).

Which of the following is the most appropriate next step in management?

(A) Measure urine albumin excretion
(B) Order kidney ultrasonography
(C) Perform dipstick urinalysis
(D) Start an angiotensin receptor blocker

Item 50

A 65-year-old man is evaluated for a slowly rising serum creatinine level from 0.8 mg/dL (70.7 µmol/L) to 1.4 mg/dL (124 µmol/L) noted on laboratory testing over the past 8 months. Medical history is significant for benign prostatic hyperplasia and gastroesophageal reflux disease. He feels well and has no current symptoms. Medications are tamsulosin and omeprazole.

On physical examination, temperature is 37.1 °C (98.7 °F), blood pressure is 134/84 mm Hg, pulse rate is 76/min, and respiration rate is 12/min. BMI is 26. There is no rash. The remainder of the examination is unremarkable.

Laboratory studies:

Complete blood count with differential	Normal
Blood urea nitrogen	38 mg/dL (13.6 mmol/L)
Creatinine	1.4 mg/dL (124 µmol/L)
Electrolytes	Normal
Urinalysis	Positive for protein; no blood, glucose, leukocyte esterase, or nitrites; <3 erythrocytes/hpf; 3-5 leukocytes/hpf; no casts or crystals
Urine protein-creatinine ratio	470 mg/g

Kidney ultrasound shows normal-sized kidneys without hydronephrosis or calculi.

Which of the following is the most appropriate next step in management?

(A) Discontinue omeprazole
(B) Discontinue tamsulosin
(C) Order a 24-hour urine collection for creatinine clearance and proteinuria
(D) Perform duplex ultrasonography

Item 51

A 56-year-old woman is hospitalized for acute decompensated heart failure. Medical history is significant for ischemic cardiomyopathy, coronary artery disease, hypertension, and hyperlipidemia. Medications on admission are aspirin, lisinopril, carvedilol, spironolactone, rosuvastatin, and as-needed furosemide.

Baseline medications are continued, and intravenous diuretics are started resulting in a 2.0-kg negative fluid balance over the initial 36 hours with improvement of her symptoms. However, her serum creatinine level increased to 1.5 mg/dL (132.6 µmol/L) from her baseline of 1.2 mg/dL (106.1 µmol/L).

On physical examination, the patient is afebrile, blood pressure is 112/82 mm Hg, pulse rate is 68/min, and respiration rate is 16/min. Oxygen saturation is 92% on 2 L oxygen by nasal cannula. Estimated central venous pressure is 12 cm H_2O. Examination of the lungs reveals bibasilar crackles, improved from admission. Cardiac examination reveals an S_3 gallop. There is lower extremity edema to the mid-calf.

In addition to continuing her baseline medications, which of the following is the most appropriate next step in management?

(A) Add nesiritide and continue intravenous diuretics
(B) Continue intravenous diuretics
(C) Discontinue intravenous diuretics and begin ultrafiltration
(D) Hold intravenous diuretics for 24 hours

Item 52

A 32-year-old woman is evaluated during a follow-up visit. She is at 12 weeks' gestation of her first pregnancy. Her pregnancy has been uncomplicated except for persistently elevated blood pressures measured at her obstetric visits. She otherwise feels well. She has no urinary symptoms such as dysuria, hematuria, or foamy urine. She did not receive routine medical care prior to her pregnancy. Family history is notable for hypertension in her parents and one older sibling. Her only medication is a prenatal vitamin.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 154/93 mm Hg, pulse rate is 87/min, and respiration rate is 16/min. BMI is 24. Funduscopic and neurologic examinations are normal. Chest and cardiac examinations are normal. Abdominal examination is unremarkable. There is trace lower extremity edema.

Laboratory studies show normal liver chemistries and kidney function. A complete blood count is normal except for a hemoglobin level of 10.9 g/dL (109 g/L). Urinalysis is normal.

Which of the following is the most likely diagnosis?

(A) Chronic hypertension
(B) Gestational hypertension
(C) Normal pregnancy
(D) Preeclampsia

Item 53

A 65-year-old man is evaluated in the emergency department for polyuria, polydipsia, and nocturia. Medical history is notable for diabetes mellitus, for which he takes metformin. He has a 45-pack-year history of smoking and does not drink alcohol.

On physical examination, the patient is alert and oriented. Blood pressure is 110/70 mm Hg supine and 100/65 mm Hg standing, pulse rate is 88/min supine and 95/min standing, and respiration rate is 20/min. BMI

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is 20. Occasional expiratory wheezing is noted in the right posterior lung field.

Laboratory studies:

Blood urea nitrogen	30 mg/dL (10.7 mmol/L)
Total cholesterol	250 mg/dL (6.48 mmol/L)
Electrolytes:	
Sodium	130 mEq/L (130 mmol/L)
Potassium	4.5 mEq/L (4.5 mmol/L)
Chloride	92 mEq/L (92 mmol/L)
Bicarbonate	24 mEq/L (24 mmol/L)
Glucose	800 mg/dL (44.4 mmol/L)
Plasma osmolality	319 mOsm/kg H_2O

Chest radiograph shows a 2-cm cavitary mass in the right upper lobe.

Which of the following conditions is the most likely cause of this patient's hyponatremia?

(A) Adrenal insufficiency
(B) Hyperglycemia
(C) Hyperlipidemia
(D) Reset osmostat
(E) Syndrome of inappropriate antidiuretic hormone secretion

Item 54

A 76-year-old woman is evaluated in the emergency department for altered sensorium. Medical records indicate a history of osteoarthritis. Listed medications are acetaminophen, naproxen, aspirin, and tramadol.

On physical examination, the patient is not communicative. Temperature is 36.5 °C (97.7 °F), blood pressure is 108/62 mm Hg, pulse rate is 104/min, and respiration rate is 12/min. BMI is 24. Lung examination reveals no crackles or wheezing. Neurologic examination is remarkable for somnolence but with appropriate responsiveness to noxious stimuli.

Laboratory studies:

Creatinine	1.2 mg/dL (106.1 µmol/L)
Electrolytes:	
Sodium	139 mEq/L (139 mmol/L)
Potassium	3.9 mEq/L (3.9 mmol/L)
Chloride	102 mEq/L (102 (mmol/L)
Bicarbonate	26 mEq/L (26 mmol/L)
Arterial blood gas studies:	
pH	7.30
P_{CO_2}	55 mm Hg (7.3 kPa)
P_{O_2}	65 mm Hg (8.6 kPa)

Overdose of which of the following is the most likely cause of this patient's findings?

(A) Acetaminophen
(B) Aspirin
(C) Naproxen
(D) Tramadol

Item 55

A 65-year-old woman is hospitalized for pneumonia and sepsis. She has no pertinent personal or family medical history and takes no medications.

On physical examination, the patient is intubated and mechanically ventilated. Temperature is 39.0 °C (102.2 °F), blood pressure is 90/60 mm Hg, pulse rate is 100/min, and respiration rate is 24/min. Estimated central venous pressure is 6 cm H_2O. Central venous oxygen saturation is 60%.

Intravenous fluid resuscitation is to be initiated.

Which of the following resuscitation therapies is contraindicated in this patient?

(A) Albumin
(B) Hydroxyethyl starch
(C) Isotonic crystalloids
(D) Lactated Ringer solution

Item 56

A 76-year-old woman is diagnosed with non–ST-elevation myocardial infarction and is scheduled for urgent coronary angiography. History is significant for type 2 diabetes mellitus, hypertension, and chronic kidney disease. Medications are lisinopril, atorvastatin, furosemide, amlodipine, metoprolol, insulin, aspirin, and heparin.

On physical examination, blood pressure is 152/84 mm Hg, pulse rate is 82/min, and respiration rate is 14/min. There is no jugular venous distention. Cardiac examination reveals regular rhythm with an S_1 but no murmurs. The lungs are clear. There is mild lower extremity edema at the ankles.

Laboratory studies are significant for a serum creatinine level of 2.0 mg/dL (176.8 µmol/L) and an estimated glomerular filtration rate of 30 mL/min/1.73 m^2; urinalysis reveals 2+ protein.

In addition to discontinuing diuretic therapy, which of the following is the most appropriate periprocedural management of this patient?

(A) Begin intravenous isotonic saline
(B) Begin oral *N*-acetylcysteine
(C) Begin prophylactic hemodialysis within 2 hours after procedure
(D) Discontinue lisinopril for at least 24 hours before procedure

Item 57

A 57-year-old man is evaluated for a diagnosis of acute kidney injury. He was diagnosed with gastroesophageal reflux disease 3 weeks ago and was prescribed omeprazole. Several days ago he noticed lower extremity swelling and decreased frequency of urination. Laboratory evaluation showed a serum creatinine level of 2.2 mg/dL (194.5 µmol/L). Medical history is otherwise unremarkable, and he takes no other medications. He reports no allergies.

On physical examination, the patient is afebrile, blood pressure is 135/77 mm Hg, pulse rate is 88/min, and respiration rate is 12/min. There is no rash. Cardiac examination and estimated central venous pressure are normal. The lungs are clear. Lower extremity edema to the ankles is present bilaterally.

Dipstick urinalysis reveals blood and trace protein, and urine sediment is notable for 5-10 erythrocytes/hpf, 10-20 leukocytes/hpf, and 1 leukocyte cast.

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In addition to discontinuing omeprazole, which of the following is the most appropriate next step in management?

(A) Kidney biopsy
(B) Oral glucocorticoids
(C) Repeat kidney function testing in 5 to 7 days
(D) Urine eosinophil testing

Item 58

A 53-year-old woman is evaluated during a follow-up visit for recurrent urinary tract infections. She has been treated for three episodes of urinary tract infection with *Klebsiella* over the past 4 months. Despite an initial response to antibiotics, her urinary tract symptoms return once the antibiotics are stopped. She has no systemic symptoms, including fever or chills. Medical history is otherwise unremarkable. She currently takes no medications.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 124/74 mm Hg, pulse rate is 72/min, and respiration rate is 12/min. BMI is 22. There is no costovertebral angle tenderness to palpation. The remainder of the examination is unremarkable.

Urine dipstick reveals a pH of 9.0 and is positive for leukocyte esterase and nitrites; urine microscopy shows 8-10 leukocytes/hpf and many coffin-lid–shaped crystals consistent with struvite.

Kidney ultrasound shows a 1.2-cm irregularly shaped stone in the left renal pelvis.

Which of the following is the most appropriate next step in management?

(A) Chronic antibiotic therapy
(B) Low phosphate diet
(C) Stone removal
(D) Urine acidification

Item 59

A 28-year-old man is evaluated for a 2-month history of progressive lower extremity edema, weight loss, and fatigue. Medical history is significant for recreational use of inhaled cocaine; he denies injection drug use. He has no other known medical issues and takes no medications.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 130/90 mm Hg, pulse rate is 90/min, and respiration rate is 20/min. BMI is 28. Temporal wasting is present. The lungs are clear. Cardiac examination is normal, and no pericardial rub is detected. There is no hepatosplenomegaly or evidence of ascites on abdominal examination. The lower extremities show edema to the knees bilaterally. Skin and joint examinations are normal. Mild asterixis is noted.

Laboratory studies:

Albumin	2.5 g/dL (25 g/L)
Liver chemistry studies	Normal
Blood urea nitrogen	98 mg/dL (35 mmol/L)
Creatinine	6.8 mg/dL (601.1 µmol/L)
Urinalysis	1+ blood; 3+ protein; 5 erythrocytes/hpf; 0-2 leukocytes/hpf
Urine protein-creatinine ratio	3700 mg/g

Kidney ultrasound shows mildly enlarged and echogenic kidneys without obstruction.

Kidney biopsy results are indicative of the collapsing variant of focal segmental glomerulosclerosis (FSGS).

Which of the following tests is most likely to establish the cause of this patient's FSGS?

(A) Hepatitis B and C serologies
(B) HIV antibody test
(C) Serum and urine electrophoresis
(D) Treponemal antibody test

Item 60

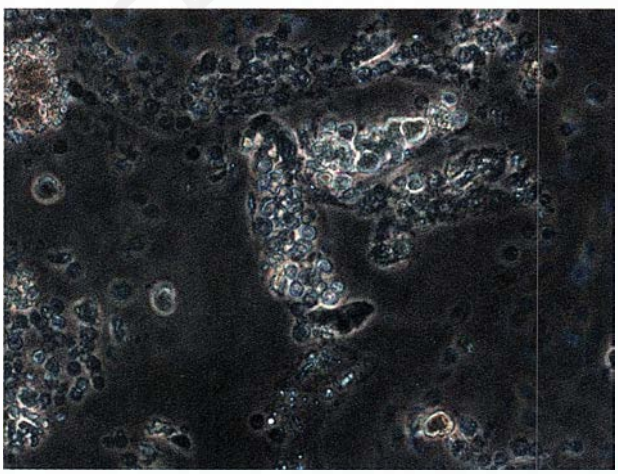
A 60-year-old woman is evaluated for a 3-week history of fever, fatigue, and arthralgia. She also notes intermittent low back pain and weight loss of 4.5 kg (10 lb) during the past 2 months. She reports no dysuria or night sweats. Medical history is significant for urinary tract infections once every 1 to 2 years and osteoarthritis. She has a 25-pack-year smoking history but stopped 15 years ago. Her only medication is as-needed ibuprofen.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 152/94 mm Hg, pulse rate is 92/min, and respiration rate is 16/min. BMI is 26. Lung, heart, and abdominal examinations are normal. There is no costovertebral angle tenderness. Skin examination reveals nonblanching erythematous palpable papules and macules on the lower legs.

Laboratory studies:

Creatinine	1.8 mg/dL (159.1 µmol/L) (baseline: 0.9 mg/dL [79.6 µmol/L])
Urinalysis	2+ blood; 2+ protein; positive for leukocyte esterase; 20-30 erythrocytes/hpf; 5-10 leukocytes/hpf; no crystals

Urine microscopy results are shown.



Which of the following is the most appropriate next step in management?

(A) Antibiotics
(B) Cystoscopy

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(C) Kidney biopsy
(D) Kidney ultrasonography

Item 61

A 52-year-old woman is evaluated in the hospital following admission for gastroenteritis and hyponatremia. She reports a 5-day history of diarrhea, nausea, and vomiting, and had been drinking water to maintain hydration. On evaluation in the emergency department earlier today, she was noted to be mildly volume contracted with an initial serum sodium level of 114 mEq/L (114 mmol/L) with normal plasma glucose and minimally elevated blood urea nitrogen levels. Her mental status was normal. She was given 2 liters of normal saline and admitted to the hospital. Medical history is unremarkable, and she takes no medications.

On physical examination, the patient feels better. Temperature is normal, blood pressure is 120/70 mm Hg, pulse rate is 84/min, and respiration rate is 16/min. BMI is 22. Estimated central venous pressure is 6 cm H_2O. Cardiopulmonary examination is unremarkable, and the abdomen is mildly tender to palpation diffusely. The neurologic examination is normal.

Current laboratory studies:

Blood urea nitrogen	14 mg/dL (5 mmol/L)
Creatinine	1.0 mg/dL (88.4 µmol/L)
Electrolytes:	
Sodium	128 mEq/L (128 mmol/L)
Potassium	4.0 mEq/L (4.0 mmol/L)
Chloride	94 mEq/L (94 mmol/L)
Bicarbonate	24 mEq/L (24 mmol/L)
Glucose	90 mg/dL (5 mmol/L)

Which of the following is the most appropriate management of this patient's hyponatremia?

(A) Desmopressin intravenously
(B) Desmopressin intravenously with 5% dextrose
(C) Fluid restriction of 800 mL/d
(D) Fluid restriction of 800 mL/d and salt tablets
(E) No additional intervention

Item 62

A 40-year-old woman is evaluated during a follow-up visit for a diagnosis of autosomal dominant polycystic kidney disease (ADPKD). She is asymptomatic but is questioning whether she should be screened for a brain aneurysm. Medical history is otherwise significant for hypertension treated with enalapril. Family history is notable for her father who has ADPKD and is on hemodialysis and her paternal grandmother who died of chronic kidney disease, although she does not know the type. She is not aware of any family history of stroke or other neurologic abnormalities. She works as an administrator in an office.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 140/90 mm Hg, pulse rate is 80/min, and respiration rate is 15/min. BMI is 22. Cardiovascular, pulmonary, and neurologic examinations are normal. On abdominal examination, nontender masses are palpable bilaterally.

Which of the following is the most appropriate screening regimen for this patient?

(A) One-time MR angiography now
(B) One-time MR angiography at age 50 years
(C) MR angiography now and every 5 years
(D) No screening

Item 63

A 65-year-old woman is evaluated in the emergency department for dysuria, urgency, and polyuria occurring for 4 days. She has no neurologic symptoms. Medical history is significant for depression. Her only medication is fluoxetine, which was started 8 weeks ago.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 140/90 mm Hg, pulse rate is 85/min, and respiration rate is 15/min. BMI is 30. Cardiovascular, pulmonary, and neurologic examinations are normal. Mild tenderness to palpation of the mid lower abdomen is noted. There is no costovertebral angle tenderness.

Laboratory studies:

Blood urea nitrogen	10 mg/dL (3.6 mmol/L)
Creatinine	1.0 mg/dL (88.4 µmol/L)
Electrolytes:	
Sodium	123 mEq/L (123 mmol/L)
Potassium	4.0 mEq/L (4.0 mmol/L)
Chloride	91 mEq/L (91 mmol/L)
Bicarbonate	24 mEq/L (24 mmol/L)
Glucose	120 mg/dL (6.7 mmol/L)
Plasma osmolality	260 mOsm/kg/H_2O
Urine sodium	40 mEq/L (40 mmol/L)
Urine osmolality	600 mOsm/kg/H_2O
Urinalysis	Too numerous to count leukocytes/hpf

Antibiotics for a urinary tract infection are started.

In addition to discontinuing fluoxetine, which of the following is the most appropriate management of this patient's hyponatremia?

(A) Fluid restriction
(B) Hypertonic saline infusion
(C) Isotonic saline infusion
(D) Oral demeclocycline
(E) Tolvaptan

Item 64

A 76-year-old woman is evaluated during a follow-up visit for hypertension. She notes fluctuating home blood pressure measurements, with systolic blood pressure measurements in the range of 140 to 150 mm Hg. History is notable for osteoporosis, hip fracture and subsequent hip replacement, and vertebral fracture. Medications are amlodipine, alendronate, calcium, and vitamin D.

On physical examination, the patient appears frail; she has difficulty climbing onto the examination

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table and requires assistance. Average blood pressure is 152/76 mm Hg based on two measurements, which is consistent with home measurements taken over the past few weeks. Pulse rate is 64/min. BMI is 19. It takes her 20 seconds to walk 6 meters. The remainder of the examination is unremarkable.

Laboratory studies show a normal chemistry panel; a urine dipstick demonstrates no protein.

Which of the following is the most appropriate next step in management?

(A) Add chlorthalidone
(B) Add lisinopril
(C) Obtain 24-hour ambulatory blood pressure monitoring
(D) Continue current regimen

Item 65

A 45-year-old woman was hospitalized 2 days ago after attempting suicide with an overdose of a benzodiazepine. She is now asymptomatic. Medical history is significant for bipolar disorder, treated with lithium for the past 15 years. She has a 45-pack-year history of smoking and drinks 3 to 4 beers daily.

On physical examination, blood pressure is 142/74 mm Hg supine and 140/80 mm Hg standing, pulse rate is 82/min, and respiration rate is 15/min. BMI is 25. Examination of the heart, lungs, and abdomen is normal. There is no peripheral edema.

Laboratory studies:

Electrolytes:	
Sodium	125 mEq/L (125 mmol/L)
Potassium	3.5 mEq/L (3.5 mmol/L)
Chloride	85 mEq/L (85 mmol/L)
Bicarbonate	27 mEq/L (27 mmol/L)
Plasma osmolality	263 mOsm/kg H_2O
Urine sodium	42 mEq/L (42 mmol/L)
Urine osmolality	600 mOsm/kg H_2O

Which of the following is the most likely diagnosis?

(A) Beer potomania
(B) Lithium-induced renal toxicity
(C) Primary polydipsia
(D) Syndrome of inappropriate antidiuretic hormone secretion

Item 66

A 34-year-old woman is evaluated for laboratory abnormalities discovered as part of an evaluation for joint pain. She describes the pain as being diffuse and associated with chronically dry eyes and mouth. She also notes recent-onset mild nocturia. Medical history is otherwise negative, and she takes acetaminophen daily for her joint pain.

On physical examination, vital signs are normal. BMI is 23. Mucous membranes and conjunctivae are dry, and mild parotid enlargement is present. There is no evidence of joint inflammation. The remainder of the examination is unremarkable.

Laboratory studies:

Creatinine	0.9 mg/dL (79.6 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	3.1 mEq/L (3.1 mmol/L)
Chloride	118 mEq/L (118 mmol/L)
Bicarbonate	12 mEq/L (12 mmol/L)
Glucose	74 mg/dL (4.1 mmol/L)
Urinalysis	pH 7.0; no blood, glucose, protein, erythrocytes, or leukocytes

Which of the following is the most likely cause of this patient's laboratory findings?

(A) Acetaminophen
(B) Type 1 (hypokalemic distal) renal tubular acidosis
(C) Type 2 (proximal) renal tubular acidosis
(D) Type 4 (hyperkalemic distal) renal tubular acidosis

Item 67

A 65-year-old woman is evaluated during a follow-up visit. She has end-stage kidney disease due to IgA nephropathy; she started peritoneal dialysis 3 months ago. She also has a 10-year history of hypertension. She has done well since starting dialysis, is without current complaints, and has recently resumed exercising regularly. She has three adult children who are encouraging her to explore kidney transplantation and are willing to be evaluated as kidney donors; however, the patient feels that she is "too old." Medications are amlodipine, ramipril, calcitriol, epoetin alfa, and calcium acetate.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 135/75 mm Hg, pulse rate is 72/min, and respiration rate is 14/min. BMI is 27. The peritoneal dialysis catheter site is nontender without induration or exudate. Cardiac examination reveals normal heart sounds. The lungs are clear. The abdomen is nontender. There is no peripheral edema.

Which of the following kidney replacement strategies is most likely to provide this patient with the best long-term survival?

(A) Change from peritoneal dialysis to hemodialysis
(B) Continue peritoneal dialysis
(C) Continue peritoneal dialysis and evaluate for transplant in 2 to 3 years
(D) Refer for transplant evaluation now

Item 68

A 49-year-old woman is evaluated during a follow-up visit for a 5-year history of stage G3b/A2 chronic kidney disease (CKD) and a 15-year history of hypertension. Medical history is otherwise unremarkable. She is a never-smoker. Family history is notable for her mother who developed end-stage kidney disease due to hypertension at age 60 years. Medications are lisinopril, amlodipine, and hydrochlorothiazide.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 134/85 mm Hg, pulse rate is 73/min, and respiration rate is 12/min. BMI is 24. There is

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no jugular venous distention. An S_4 gallop is heard. The lungs are clear. There is no peripheral edema. The remainder of the examination is unremarkable.

Laboratory studies are notable for a serum creatinine level of 2.1 mg/dL (185.6 µmol/L), an estimated glomerular filtration rate of 31 mL/min/1.73 m^2, and a urine albumin-creatinine ratio of 20 mg/g.

Which of the following is the most appropriate management?

(A) Begin a low protein diet
(B) Lower blood pressure to <130/80 mm Hg
(C) Switch hydrochlorothiazide to furosemide
(D) No changes to current therapy

Item 69

A 65-year-old man is evaluated during a follow-up visit for stage G3b/A3 chronic kidney disease due to diabetic nephropathy. He reports doing well with good baseline exercise tolerance and no shortness of breath. Medical history is also significant for type 2 diabetes mellitus and hypertension. Medications are basal bolus insulin and lisinopril.

On physical examination, temperature is normal, blood pressure is 145/75 mm Hg, pulse rate is 82/min, and respiration rate is 16/min. BMI is 28. There is no jugular venous distention. The lungs are clear.

Laboratory studies:

Bicarbonate	Normal
Creatinine	1.9 mg/dL (168 µmol/L)
Potassium	4.0 mEq/L (4.0 mmol/L)
Estimated glomerular filtration rate	42 mL/min/1.73 m^2
Urine protein-creatinine ratio	3900 mg/g

Kidney ultrasound shows mildly echogenic kidneys that are of normal size with no obstruction.

Which of the following is the most appropriate treatment?

(A) Add an angiotensin receptor blocker
(B) Increase lisinopril dose
(C) Replace lisinopril with amlodipine
(D) No change in current medications

Item 70

A 43-year-old man is evaluated in the emergency department for abdominal pain. He has a history of alcohol abuse, with repeated episodes of acute intoxication requiring medical therapy. He also has a history of several episodes of acute pancreatitis, but no history of seizure disorder. He takes no medications.

On physical examination, temperature is 37.4 °C (99.3 °F), blood pressure is 112/66 mm Hg, and pulse rate is 76/min. BMI is 20. There is no evidence of trauma or head injury. There is no evidence of ascites. The abdomen is tender to palpation. Neurologic examination reveals normal pupillary and corneal reflexes, normal muscle tone, and a downgoing plantar reflex.

Laboratory studies:

Blood urea nitrogen	28 mg/dL (10 mmol/L)
Calcium	8.6 mg/dL (2.2 mmol/L)
Creatinine	1.2 mg/dL (106.1 µmol/L) (baseline, 0.8 mg/dL [70.7 µmol/L])
Electrolytes:	
Sodium	135 mEq/L (135 mmol/L)
Potassium	4.9 mEq/L (4.9 mmol/L)
Chloride	96 mEq/L (96 mmol/L)
Bicarbonate	12 mEq/L (12 mmol/L)
Ethanol	62 mg/dL (0.062 g/dL)
Glucose	72 mg/dL (4 mmol/L)
Lactate	0.8 mEq/L (0.8 mmol/L)
Plasma osmolality	293 mOsm/kg H_2O
Phosphorus	3.7 mg/dL (1.2 mmol/L)
Urinalysis	pH 5.5; specific gravity 1.020; no blood, ketones, or cells

Which of the following is the most likely cause of this patient's acidosis?

(A) Acute kidney injury
(B) Alcoholic ketoacidosis
(C) D-Lactic acidosis
(D) Rhabdomyolysis

Item 71

A 50-year-old man is evaluated in the hospital for fatigue, joint pain, and skin lesions. His symptoms started 2 weeks ago with fever and sore throat, which subsided in 2 days. Fatigue and joint pain were noted 1 day after the onset of sore throat, which worsened over the subsequent days. Four days after the onset of symptoms, he noted dark red spots on his ankles and shins, which spread to involve his legs, thighs, and buttocks; the skin lesions were not painful or itchy. He also notes intermittent central abdominal pain, crampy in nature and not related to food. He has hypertension that was previously well controlled with lisinopril and hydrochlorothiazide.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 170/84 mm Hg, pulse rate is 78/min, and respiration rate is 14/min. BMI is 28. Examination of the joints shows tenderness and increased warmth in the knees, ankles, and elbows without effusions. Cardiac and lung examinations are normal. There is mild guarding around the periumbilical area on abdominal examination.

The appearance of the skin is shown (see top of next page).

Laboratory studies:

Albumin	3.1 g/dL (31 g/L)
Complements (C3 and C4)	Normal
Creatinine	1.8 mg/dL (159 µmol/L)
Hepatitis B antibody profile	Negative
Hepatitis C antibody profile	Negative
Urinalysis	3+ blood; 2+ protein; 50-100 erythrocytes/hpf; 10-15 leukocytes/hpf; few erythrocyte casts
Urine protein-creatinine ratio	2200 mg/g

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Lupus serologies, antistreptolysin O antibodies, ANCA, and anti-glomerular basement membrane antibodies are pending. Blood cultures are pending. Stool occult blood test is positive.

Which of the following is the most likely diagnosis?

(A) Cryoglobulinemic vasculitis
(B) Endocarditis
(C) IgA vasculitis
(D) Systemic lupus erythematosus

Item 72

A 23-year-old woman is evaluated in the emergency department for generalized weakness and lightheadedness of 4 hours' duration. She has had no previous contact with the health care system and takes no medications.

On physical examination, blood pressure is 120/80 mm Hg supine and 105/70 mm Hg sitting, and pulse rate is 95/min supine and increases to 108/min upon standing. BMI is 26. Skin turgor is poor. Multiple dental caries are present. There is no jugular venous distention. Cardiac examination reveals a regular rhythm with no murmurs. The lungs are clear. Bowel sounds are hyperactive. The abdomen is soft, nontender, and nondistended.

Laboratory studies:

Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	2.8 mEq/L (2.8 mmol/L)
Chloride	90 mEq/L (90 mmol/L)
Bicarbonate	36 mEq/L (36 mmol/L)
Urine studies:	
Sodium	45 mEq/L (45 mmol/L)
Potassium	42 mEq/L (42 mmol/L)
Chloride	5.0 mEq/L (5.0 mmol/L)
pH	7.0

Which of the following is the most likely cause of this patient's hypokalemia?

(A) Bartter syndrome
(B) Hypokalemic periodic paralysis
(C) Sjögren syndrome
(D) Vomiting

Item 73

A 35-year-old woman is evaluated in the emergency department for new-onset lower extremity edema. She notes a 1-week history of progressive shortness of breath and fatigue. She attended a picnic 10 days ago and subsequently developed bloody diarrhea, which has largely subsided. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 190/90 mm Hg, pulse rate is 100/min, and respiration rate is 20/min. BMI is 27. There is no skin rash. Cardiopulmonary examination is normal. The abdomen is diffusely tender but without rebound. Bilateral lower extremity edema is noted to the level of the mid calves. On neurologic examination, mental status is normal, and there are no other focal findings.

Laboratory studies:

Hemoglobin	7.0 g/dL (70 g/L)
Platelet count	50,000/μL (50×10^9/L)
Creatinine	7.2 mg/dL (636.5 μmol/L)
Urinalysis	2+ blood; 1+ protein; 0-2 erythrocytes/hpf; 0-2 leukocytes/hpf

Which of the following is the most appropriate next step in diagnosis?

(A) ADAMTS13 activity level
(B) Kidney biopsy
(C) Peripheral blood smear
(D) Urine protein electrophoresis

Item 74

A 28-year-old woman is evaluated in the emergency department for right flank pain of several days' duration and an episode of gross hematuria. She is in her 24th week of pregnancy, which has been uncomplicated, and she has had regular obstetric care. She reports no fevers or chills, abdominal pain, changes in bowel habits, dysuria, or urinary frequency. Family history is notable for her mother with kidney stones. Her only medication is a prenatal vitamin.

On physical examination, the patient is in moderately painful distress localized to the right flank area. Temperature is 37.0 °C (98.6 °F), blood pressure is 118/68 mm Hg, pulse rate is 78/min, and respiration rate is 12/min. BMI is 28. She has a

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gravid uterus, and the abdominal examination is otherwise unremarkable. There is no costovertebral angle or suprapubic tenderness. The remainder of the examination is normal.

Urinalysis shows large blood and >50,000 erythrocytes/hpf but is otherwise normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Abdominal MRI
(B) Bilateral kidney ultrasonography
(C) Low-dose noncontrast helical CT
(D) Plain abdominal radiography
(E) Transvaginal ultrasonography

Item 75

A 28-year-old man is evaluated for recurrent nephrolithiasis. Medical history is significant for Crohn disease complicated by multiple small bowel strictures requiring resection. He began developing kidney stones 3 years ago following his last bowel surgery. Analysis of the stones has consistently shown calcium oxalate, and he has been adherent to a low oxalate diet, oral hydration to maintain urine output of at least 2 L/d, and intake of 2 g of calcium carbonate with each meal. However, he has continued to have periodic episodes of kidney stones. Medical history is otherwise unremarkable. Medications are infliximab and calcium carbonate.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 131/78 mm Hg, pulse rate is 84/min, and respiration rate is 12/min. BMI is 22. The abdominal examination shows healed surgical incisions and is otherwise unremarkable. The remainder of the examination is normal.

Laboratory studies, including complete blood count, electrolytes, and kidney function, are normal. Urinalysis is normal; 24-hour urine chemical analysis shows normal levels of calcium, citrate, and uric acid, but elevated oxalate.

Plain abdominal radiographs show multiple small stones in both kidneys.

Which of the following is the most appropriate additional treatment for this patient?

(A) Cholestyramine
(B) Hydrochlorothiazide
(C) Potassium citrate
(D) Pyridoxine

Item 76

An 80-year-old woman is evaluated in the emergency department for tinnitus, confusion, and unsteady gait. She also has had dry heaves and vomiting for the past few days. Her family notes progressive decline in her overall functional status over the preceding 2 weeks. Medical history is notable for hypertension and osteoarthritis. Medications are lisinopril, hydrochlorothiazide, and aspirin.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 140/68 mm Hg, pulse rate is 96/min, and respiration rate is 24/min. Estimated central venous pressure is 4.0 cm H_2O. Abdominal examination is unremarkable.

Laboratory studies:

Electrolytes:	
Sodium	142 mEq/L (142 mmol/L)
Potassium	3.2 mEq/L (3.2 mmol/L)
Chloride	100 mEq/L (100 mmol/L)
Bicarbonate	20 mEq/L (20 mmol/L)
Arterial blood gases:	
pH	7.56
P_{CO_2}	22 mm Hg (2.9 kPa)

Chest radiograph is normal.

Which of the following is the most likely diagnosis?

(A) Respiratory alkalosis with chronic compensation
(B) Respiratory alkalosis and increased anion gap metabolic acidosis
(C) Respiratory alkalosis and metabolic alkalosis
(D) Respiratory alkalosis, increased anion gap metabolic acidosis, and metabolic alkalosis

Item 77

A 53-year-old woman is evaluated during a routine follow-up visit. Medical history is significant for hypertension and chronic active hepatitis B infection. Her hepatitis B infection has been treated with tenofovir for the past 5 years with suppression of her serum hepatitis B DNA levels. She currently notes mild generalized weakness but otherwise feels well. Medications are ramipril and tenofovir.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 136/79 mm Hg, pulse rate is 70/min, and respiration rate is 14/min. BMI is 22. Abdominal examination shows a normal-sized liver and no splenomegaly. The remainder of the examination is normal.

Laboratory studies:

Bicarbonate	21 mEq/L (21 mmol/L)
Creatinine	1.2 mg/dL (106.1 µmol/L) (3 years ago: 0.8 mg/dL [70.7 µmol/L])
Glucose	87 mg/dL (4.8 mmol/L)
Phosphorus	2.2 mg/dL (0.71 mmol/L)
Urinalysis	1+ protein; 2+ glucose; no cells or casts

Which of the following is the most likely cause of this patient's kidney findings?

(A) Hypertensive nephropathy
(B) Membranoproliferative glomerulonephritis
(C) Membranous glomerulopathy
(D) Tubulointerstitial disease

Item 78

A 37-year-old man is evaluated in the emergency department for nausea and vomiting of 12 hours' duration. The patient states that he has been drinking large amounts of alcohol for several weeks and has eaten very little for the past week. His last alcoholic drink was more than 24 hours ago. He also reports intermittent diarrhea for the past

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2 months. History is notable for chronic alcoholism. He takes no medications.

On physical examination, the patient is cachectic. Blood pressure is 100/65 mm Hg, and pulse rate is 105/min. BMI is 17. Proximal muscle wasting is noted. There is no evidence of jaundice or ascites. The liver is enlarged and mildly tender. There is no asterixis. Neurologic examination is unremarkable.

While awaiting the results of laboratory studies, the patient is given intravenous saline with dextrose and vitamins. His respiration rate becomes markedly diminished, and he requires intubation. His laboratory studies return and show the following:

Laboratory studies:

Albumin	3.0 g/dL (30 g/L)
Calcium	8.0 mg/dL (2.0 mmol/L)
Electrolytes:	
Sodium	132 mEq/L (132 mmol/L)
Potassium	3.4 mEq/L (3.4 mmol/L)
Chloride	90 mEq/L (90 mmol/L)
Bicarbonate	32 mEq/L (32 mmol/L)
Magnesium	1.7 mg/dL (0.7 mmol/L)
Phosphorus	1.5 mg/dL (0.48 mmol/L)

Which of the following is the most likely cause of this patient's respiratory failure?

(A) Hypocalcemia
(B) Hypokalemia
(C) Hypomagnesemia
(D) Hyponatremia
(E) Hypophosphatemia

Item 79

A 57-year-old woman is evaluated during a preoperative physical examination for a total left knee replacement. Medical history is significant for osteoarthritis; her only medication is over-the-counter ibuprofen, which she takes multiple times daily for pain relief.

On physical examination, blood pressure is 152/90 mm Hg, and pulse rate is 64/min. BMI is 34. Severe osteoarthritic changes are noted in the left knee. Trace pitting edema in the ankles is noted. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 1.2 mg/dL (106.1 µmol/L) and a serum potassium level of 5.1 mEq/L (5.1 mmol/L); urine dipstick demonstrates no blood or protein.

Which of the following is the most appropriate next step in the management of this patient's blood pressure?

(A) Begin a low-dose ACE inhibitor
(B) Begin low-dose hydrochlorothiazide
(C) Discontinue ibuprofen
(D) Obtain a plasma aldosterone-plasma renin ratio

Item 80

A 64-year-old man is hospitalized with confusion, nausea, and dizziness. He has not felt well for weeks. Medical history is notable for hypertension, atrial fibrillation, and hyperlipidemia. He had a superior mesenteric artery embolus 2 years ago and had a resection of a large segment of his small bowel. He has chronic diarrhea. Medications are rosuvastatin, metoprolol, warfarin, and enalapril. His wife confirms that he takes no additional medications, including over-the-counter drugs or supplements.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 108/60 mm Hg, pulse rate is 96/min, and respiration rate is 18/min. BMI is 22. He is confused to place and time and is easily distractible. The remainder of the physical examination is noncontributory.

Laboratory studies:

Blood urea nitrogen	14 mg/dL (5 mmol/L)
Electrolytes:	
Sodium	140 mEq/L (140 mmol/L)
Potassium	3.8 mEq/L (3.8 mmol/L)
Chloride	106 mEq/L (106 mmol/L)
Bicarbonate	20 mEq/L (20 mmol/L)
Glucose	90 mg/dL (5 mmol/L)
Lactate	Normal
Arterial blood gases:	
pH	7.37
P_{CO_2}	36 mm Hg (4.8 kPa)
Plasma osmolality	296 mOsm/kg H_2O

Which of the following is the most likely diagnosis?

(A) D-Lactic acidosis
(B) Ethylene glycol or methanol poisoning
(C) Propylene glycol toxicity
(D) Pyroglutamic acidosis

Item 81

A 70-year-old woman is evaluated in the emergency department for acute-onset fever and rigors that began during hemodialysis. She has end-stage kidney disease due to chronic glomerulonephritis. She started hemodialysis 1 month ago via a right internal jugular tunneled cuffed catheter. A left forearm arteriovenous fistula was placed 1 week ago. Medications are labetalol, sevelamer, epoetin alfa, and calcitriol.

On physical examination, temperature is 37.9 °C (100.2 °F), blood pressure is 145/95 mm Hg, pulse rate is 95/min, and respiration rate is 20/min. BMI is 23. Examination of the right internal jugular catheter site reveals no tenderness, induration, or discharge. The left forearm arteriovenous fistula is nontender with a clean, well-healed surgical incision. There is no heart murmur. The lungs are clear. The remainder of the physical examination is unremarkable.

Laboratory studies are notable for a leukocyte count of 13,000/µL (13×10^9/L) and a plasma lactate level of 1.0 mEq/L (1.0 mmol/L). Blood cultures are pending.

A chest radiograph is normal.

Which of the following is the most appropriate next step in management?

(A) Begin vancomycin
(B) Begin vancomycin and ceftazidime
(C) Exchange dialysis catheter over a wire
(D) Remove dialysis catheter and observe

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Item 82

A 66-year-old woman is hospitalized for nausea and vomiting, worsening dyspnea on exertion, and weakness of 4 days' duration. Medical history is notable for heart failure, COPD, and hypertension. Medications are carvedilol, amlodipine, albuterol, and tiotropium inhalers.

On physical examination, blood pressure is 108/65 mm Hg, pulse rate is 98/min, and respiration rate is 20/min. Oxygen saturation is 91% on ambient air. BMI is 36. Cardiovascular examination demonstrates an S_1 and no jugular venous distention. Lung examination demonstrates no wheezing or crackles. There is 1+ pitting edema in the ankles. The remainder of the physical examination is normal.

Laboratory studies:

Bicarbonate	29 mEq/L (29 mmol/L)
Potassium	3.0 mEq/L (3.0 mmol/L)
Arterial blood gas studies:	
pH	7.47
P_{CO_2}	44 mm Hg (5.9 kPa)
P_{O_2}	70 mm Hg (9.3 kPa)

A chest radiograph shows flattened diaphragms and a narrow cardiac silhouette.

Which of the following is the most appropriate next step in management?

(A) Administer 0.9% saline intravenously
(B) Administer furosemide intravenously
(C) Measure urine chloride level
(D) Measure urine sodium level

Item 83

A 42-year-old woman is evaluated in the emergency department for an episode of blood in her urine associated with right-sided abdominal pain. She reports no dysuria, urgency, or frequency. She notes a history of chronic, nonlocalized abdominal discomfort, but has no history of urinary tract infections. She otherwise has been healthy. Family history indicates that her mother and father are both alive without medical problems, as are three brothers and one sister. She is sexually active, and her only medication is an oral contraceptive.

On physical examination, the patient is in mild distress. Temperature is 37.0 °C (98.6 °F), blood pressure is 150/100 mm Hg, pulse rate is 88/min and regular, and respiration rate is 15/min. BMI is 30. Cardiovascular and pulmonary examinations are normal. There is no costovertebral angle tenderness. On abdominal examination, there is diffuse tenderness to moderate palpation without rebound. There are palpable masses in the right and left abdomen, with increased discomfort with palpation on the right.

Laboratory studies:

Hematocrit	42%
Leukocyte count	8500/μL (8.5×10^9/L)
Blood urea nitrogen	25 mg/dL (8.9 mmol/L)
Creatinine	2.0 mg/dL (176.8 μmol/L)
Urinalysis	Too numerous to count erythrocytes/hpf; 3-5 leukocytes/hpf
Human chorionic gonadotropin	Negative

Which of the following is the most likely diagnosis?

(A) Autosomal dominant polycystic kidney disease
(B) Renal cell carcinoma
(C) Renal vein thrombosis
(D) Urinary tract infection

Item 84

A 42-year-old man is hospitalized to begin chemotherapy for recently diagnosed Burkitt-like lymphoma. He is started on aggressive intravenous volume repletion with isotonic sodium chloride and allopurinol. Three days into receiving hyper-CVAD therapy (cyclophosphamide, vincristine, doxorubicin, dexamethasone), he develops decreasing urine output to 0.6 mL/kg/h. His only other medication is as-needed ondansetron.

On physical examination, blood pressure is 130/72 mm Hg. There is lymphadenopathy involving the cervical and submental chains and supraclavicular areas bilaterally, as well as bulky axillary and inguinal lymphadenopathy. Heart rate and rhythm are regular. Lungs are clear. The spleen is palpable approximately 4 cm below the left costal margin. There is no hepatomegaly. There is no edema, cyanosis, or clubbing of the extremities.

Laboratory studies:

Blood urea nitrogen	22 mg/dL (7.9 mmol/L)
Calcium	7.3 mg/dL (1.8 mmol/L) (baseline, 8.7 mg/dL [2.2 mmol/L])
Creatinine	1.3 mg/dL (114.9 μmol/L) (baseline, 0.9 mg/dL [79.6 μmol/L])
Phosphorus	6.5 mg/dL (2.1 mmol/L) (baseline, 3.3 mg/dL [1.1 mmol/L])
Potassium	5.1 mEq/L (5.1 mmol/L) (baseline, 4.3 mEq/L [4.3 mmol/L])
Urate	14 mg/dL (0.83 mmol/L) (pretreatment level, 6.2 mg/dL [0.37 mmol/L])
Urinalysis	pH 5.5; multiple urate crystals

Which of the following is the most appropriate treatment?

(A) Begin hemodialysis
(B) Begin urine alkalinization
(C) Increase allopurinol dose
(D) Substitute rasburicase for allopurinol

Item 85

A 20-year-old woman is seen during a follow-up visit for hematuria. She was evaluated 1 week ago for hematuria of 5 days' duration. She recalled having a sore throat around the time of onset of hematuria, but no fever, dysuria, flank pain, or other symptoms. Urinalysis at that time showed too numerous to count erythrocytes/hpf with a few erythrocyte casts. Laboratory studies at that time showed the following: normal complement levels, a serum creatinine level of 0.7 mg/dL (61.9 μmol/L), negative antinuclear antibodies and ANCA, and a urine protein-creatinine ratio of 1100 mg/g. Kidney ultrasound was normal. She has been healthy, and her only medication is an oral contraceptive pill.

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On physical examination, temperature is 37.1 °C (98.7 °F), blood pressure is 130/80 mm Hg, pulse rate is 78/min, and respiration rate is 16/min. BMI is 22. Mild pharyngeal congestion is noted. There is no edema. The remainder of the physical examination, including skin, joints, and nasal and oral mucosa, is normal.

Current laboratory studies show a urinalysis with 5-10 erythrocytes/hpf without casts, a serum creatinine level of 0.6 mg/dL (53 µmol/L), and a urine protein-creatinine ratio of 100 mg/g.

Which of the following is the most appropriate next step in management?

(A) ACE inhibitor therapy
(B) Kidney biopsy
(C) Oral glucocorticoids
(D) Continued observation

Item 86

A 35-year-old woman is evaluated during a follow-up visit. She is at 37 weeks' gestation of her first pregnancy. Preeclampsia was diagnosed at 32 weeks when she was found to be hypertensive with mild proteinuria; she was previously normotensive. Her subsequent prenatal obstetric and laboratory monitoring has remained stable, and she is without symptoms. Medical history is otherwise unremarkable, and her only medication is a prenatal vitamin.

On physical examination, temperature is 36.9 °C (98.4 °F), blood pressure is 148/85 mm Hg, pulse rate is 87/min, and respiration rate is 12/min. BMI is 27. Examination of the lungs and heart is normal. The abdomen shows expected changes of pregnancy but is otherwise normal. There is trace bipedal edema. The remainder of the examination is unremarkable.

Laboratory studies are significant for a normal platelet count, blood urea nitrogen, serum creatinine, electrolyte panel, and liver chemistry studies.

Which of the following is the most appropriate next step in management?

(A) Antihypertensive therapy
(B) Aspirin therapy
(C) Delivery of the baby
(D) Glucocorticoids
(E) Continued monitoring until term

Item 87

A 40-year-old man is seen in follow-up for evaluation of proteinuria detected on urinalysis as part of an insurance physical examination. He is otherwise asymptomatic. Medical history is significant for obesity but is otherwise unremarkable with no prior kidney disease. He takes no medications.

On physical examination, patient is afebrile, blood pressure is 155/105 mm Hg, pulse rate is 74/min, and respiration rate is 14/min. BMI is 38. Cardiopulmonary and abdominal examinations are unremarkable. There is no arthritis, rash, or lower extremity edema.

Laboratory studies:

Albumin	4.2 g/dL (42 g/L)
Complements (C3 and C4)	Normal
Creatinine	1.0 mg/dL (88.4 µmol/L)
Antinuclear antibodies	Negative
Hepatitis B surface antigen	Negative
Hepatitis C antibodies	Negative
HIV antibodies	Negative
Urinalysis	3+ protein; no blood or cells
Urine protein-creatinine ratio	2000 mg/g

Kidney biopsy shows enlarged glomeruli with focal segmental sclerosis; immunofluorescence is nonspecific, and electron microscopy shows mild foot process effacement.

In addition to starting an ACE inhibitor, which of the following is the most appropriate additional next step in management?

(A) Prednisone
(B) Rapid plasma reagin test
(C) Tacrolimus
(D) Weight loss

Item 88

A 77-year-old woman was evaluated in the hospital for worsening kidney function. She presented 14 days ago with substernal chest pain and underwent coronary catheterization that showed left anterior descending arterial thrombosis that was treated with balloon angioplasty and stenting. Hospital course was uneventful, and she was discharged 11 days ago. She now presents for a follow-up evaluation. Medical history is significant for hypertension, type 2 diabetes mellitus, and stage 3A chronic kidney disease. She has a 90-pack-year smoking history and continues to smoke. Current medications are aspirin, lisinopril, atorvastatin, clopidogrel, metoprolol, and insulin.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 140/86 mm Hg sitting and 134/78 mm Hg standing, and pulse rate is 66/min sitting and 70/min standing. BMI is 28. The lungs are clear, and the heart and abdominal examinations are normal. There is no lower extremity edema.

Skin findings of the lower extremities are shown (see top of next page).

Laboratory studies:

Blood urea nitrogen	48 mg/dL (17.1 mmol/L)
Creatinine	3.1 mg/dL (274 µmol/L) (baseline: 1.3 mg/dL [114.9 µmol/L])
Urinalysis	1+ blood; 2+ protein; positive for leukocyte esterase; 5-10 erythrocytes/hpf; 10-15 leukocytes/hpf with eosinophils; no casts or crystals

Which of the following is the most likely diagnosis?

(A) Acute interstitial nephritis
(B) Atheroembolism
(C) Contrast-induced nephropathy
(D) Polyarteritis nodosa

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Item 89

A 57-year-old man is evaluated for treatment of newly diagnosed hypertension. History is notable for hyperlipidemia, which is treated with moderate-dose simvastatin. The patient is black.

On physical examination, blood pressure is 151/94 mm Hg, and pulse rate is 72/min. BMI is 28. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 1.0 mg/dL (88.4 µmol/L), a fasting plasma glucose level of 104 mg/dL (5.8 mmol/L), and a serum potassium level of 4.5 mEq/L (4.5 mmol/L); a urine dipstick demonstrates no blood or protein.

In addition to recommending lifestyle modifications, which of the following is the most appropriate initial antihypertensive therapy for this patient?

(A) Amlodipine
(B) Diltiazem
(C) Hydrochlorothiazide
(D) Lisinopril

Item 90

A 24-year-old man is hospitalized following an attempted suicide by overdose.

On physical examination, the patient has trouble staying awake and does not respond to questions. Temperature is 37.0 °C (98.6 °F), blood pressure is 146/96 mm Hg, pulse rate is 112/min, and respiration rate is 22/min. BMI is 28. The general medical examination is normal. On neurologic examination, his pupils react to light and are symmetric. Deep tendon reflexes are slightly diminished but symmetric.

Laboratory studies:

Blood urea nitrogen	28 mg/dL (10 mmol/L)
Creatinine	2.2 mg/dL (194.5 µmol/L)
Electrolytes:	
Sodium	136 mEq/L (136 mmol/L)
Potassium	4.0 mEq/L (4.0 mmol/L)
Chloride	96 mEq/L (96 mmol/L)
Bicarbonate	12 mEq/L (12 mmol/L)
Glucose	90 mg/dL (5 mmol/L)
Plasma osmolality	314 mOsm/kg H_2O
Serum ethanol	Undetectable
Arterial blood gases:	
pH	7.24
P_{CO_2}	28 mm Hg (3.7 kPa)
P_{O_2}	102 mm Hg (13.6 kPa)

Additional toxicology studies are pending.

Intravenous hydration and fomepizole are administered, and emergent hemodialysis is planned.

Which of the following is the most appropriate additional management intervention in this patient?

(A) Activated charcoal gastric decontamination
(B) Intravenous ethanol
(C) Intravenous sodium bicarbonate
(D) No additional therapy

Item 91

A 61-year-old woman is evaluated during a routine health maintenance visit. She has no symptoms or concerns at this time. She has stage G4/A1 chronic kidney disease due to autosomal dominant polycystic kidney disease and a 22-year history of hypertension. Medications are fosinopril, furosemide, and sodium bicarbonate.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 129/72 mm Hg, pulse rate is 84/min, and respiration rate is 14/min. BMI is 28. Bilateral flank fullness is noted. The lungs are clear. There is no peripheral edema.

Laboratory studies:

Calcium	9.0 mg/dL (2.3 mmol/L)
Creatinine	2.8 mg/dL (247.5 µmol/L)
Phosphorus	3.5 mg/dL (1.13 mmol/L)
Intact parathyroid hormone	450 pg/mL (450 ng/L)
25-Hydroxy vitamin D	42 ng/mL (104.8 nmol/L)

Which of the following is the most appropriate next step in management?

(A) Bisphosphonate therapy
(B) Dual-energy x-ray absorptiometry scan
(C) Oral calcitriol
(D) Parathyroidectomy

Item 92

A 38-year-old man is evaluated in the emergency department for acute abdominal pain. Medical history

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CONT.

is significant for excessive alcohol use and recurrent acute pancreatitis. He drinks six beers daily. He takes no medications.

On physical examination, the patient is in acute distress and indicates epigastric pain. Temperature is 38.0 °C (100.4 °F), blood pressure is 160/88 mm Hg, pulse rate is 88/min, and respiration rate is 20/min. BMI is 25. Chest and heart examinations are normal. The abdomen is slightly distended, with tenderness to minimal palpation in the epigastric area. There is no peripheral edema.

Laboratory studies:

Leukocyte count	10,000/μL (10×10^9/L)
Blood urea nitrogen	15 mg/dL (5.4 mmol/L)
Creatinine	1.2 mg/dL (106.1 μmol/L)
Electrolytes:	
Sodium	128 mEq/L (128 mmol/L)
Potassium	4.0 mEq/L (4.0 mmol/L)
Chloride	99 mEq/L (99 mmol/L)
Bicarbonate	24 mEq/L (24 mmol/L)
Glucose	90 mg/dL (5 mmol/L)
Lipase	620 U/L
Plasma osmolality	290 mOsm/kg H_2O
Urine osmolality	400 mOsm/kg H_2O

Which of the following is the most likely cause of this patient's hyponatremia?

(A) Adrenal insufficiency
(B) Pseudohyponatremia
(C) Psychogenic polydipsia
(D) Syndrome of inappropriate antidiuretic hormone secretion

Item 93

A 25-year-old woman is evaluated for an acute onset of swelling of the lower extremities and a 9.1-kg (20 lb) weight gain over 10 days. She notes that her urine output has diminished and that her urine appears "frothy." Medical history is significant for an unknown kidney problem as a child that resolved with medical therapy. She currently takes no medications.

On physical examination, temperature is normal, blood pressure is 100/70 mm Hg, pulse rate is 74/min, and respiration rate is 14/min. BMI is 22. Anasarca is present. Decreased breath sounds are noted at both lung bases. Cardiac examination is normal. Abdominal distention with edema of the abdominal wall is present. There is no skin rash or joint swelling.

Laboratory studies:

Albumin	1.2 g/dL (12 g/L)
Creatinine	1.1 mg/dL (97.2 μmol/L)
Urinalysis	3+ protein; 0-2 erythrocytes/hpf; 0-2 leukocytes/hpf
Urine protein-creatinine ratio	10,500 mg/g

Kidney biopsy results reveal normal-appearing glomeruli on light microscopy with immunofluorescence staining showing no immune complex deposition; electron microscopy results are pending.

Which of the following is the most appropriate treatment?

(A) Cyclophosphamide
(B) Lisinopril
(C) Prednisone
(D) No pharmacologic treatment

Item 94

A 19-year-old man is evaluated in the emergency department for weakness and inability to walk that began shortly after a 5-mile run. In the morning, he had a related episode of weakness of both lower limbs that lasted for 1 hour and resolved spontaneously. He also notes about a 5.0-kg (11-lb) weight loss over the past 7 months, episodes of palpitations, and heat intolerance. He was previously in good health. He takes no medications.

On physical examination, blood pressure is 150/90 mm Hg, pulse rate is 106/min, and respiration rate is 20/min. BMI is 18. The thyroid is enlarged. There is a fine tremor of the outstretched hands. There is symmetric muscle weakness with areflexia in the lower and upper extremities. The remainder of the examination is unremarkable.

Laboratory studies:

Electrolytes:	
Sodium	142 mEq/L (142 mmol/L)
Potassium	2.0 mEq/L (2.0 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	24 mEq/L (24 mmol/L)

Which of the following is the most likely diagnosis?

(A) Bartter syndrome
(B) Hypokalemic periodic paralysis
(C) Primary hyperaldosteronism
(D) Sjögren syndrome

Item 95

A 33-year-old woman seeks preconception counseling. She and her partner plan to conceive a child within the next few months. She stopped taking her oral contraceptive several months ago. She has a 3-year history of hypertension treated successfully with losartan. Her home blood pressure measurements are typically in the range of 110-115/70-75 mm Hg. She feels well and has no specific complaints. Medical history is otherwise normal, and family history is notable for hypertension in her parents. Medications are losartan, 50 mg/d, and a prenatal vitamin.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 112/71 mm Hg, pulse rate is 87/min, and respiration rate is 16/min. BMI is 23. The remainder of the examination, including neurologic examination, is normal.

Laboratory studies, including complete blood count, liver chemistries, kidney function studies, and urinalysis, are normal.

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Which of the following is the most appropriate next step in management?

(A) Continue losartan at current dose
(B) Decrease losartan dose to 25 mg/d
(C) Stop losartan and monitor blood pressure
(D) Switch losartan to labetalol

Item 96

A 45-year-old man is evaluated for increased urination and thirst of several months' duration. He also notes twice-nightly nocturia during this time period. Medical history is significant for bipolar disorder diagnosed 20 years ago that has been successfully treated with lithium.

On physical examination, blood pressure is 110/70 mm Hg supine and 105/65 mm Hg standing, pulse rate is 88/min supine and 95/min standing, and respiration rate is 20/min. BMI is 25. Examination of the lymph nodes, chest, heart, and abdomen is normal.

Laboratory studies:

Blood urea nitrogen	24 mg/dL (8.6 mmol/L)
Creatinine	1.5 mg/dL (132.6 µmol/L)
Electrolytes:	
Sodium	144 mEq/L (144 mmol/L)
Potassium	4.5 mEq/L (4.5 mmol/L)
Chloride	115 mEq/L (115 mmol/L)
Bicarbonate	24 mEq/L (24 mmol/L)
Glucose	90 mg/dL (5 mmol/L)
Plasma osmolality	320 mOsm/kg H_2O
Urine osmolality	240 mOsm/kg H_2O

Which of the following is the most appropriate diagnostic test to perform next?

(A) Cosyntropin stimulation test
(B) Serum thyroid-stimulating hormone measurement
(C) Urine sodium measurement
(D) Water restriction test

Item 97

A 45-year-old man is evaluated in the emergency department for proximal muscle weakness worsening over the course of the day. Medical history is significant for non-anuric end-stage kidney disease, hypertension, and hyperlipidemia. Medications are lisinopril, atorvastatin, amlodipine, aspirin, and sevelamer. He missed his regular hemodialysis session yesterday and has not been dialyzed for 3 days.

On physical examination, blood pressure is 170/90 mm Hg, and pulse rate is 77/min. Estimated central venous pressure is 10 cm H_2O. Cardiac examination reveals a regular rhythm with an S_1 but no murmurs. The lungs are clear. There is 2+ edema of the lower extremities.

Laboratory studies are significant for a plasma glucose level of 110 mg/dL (6.1 mmol/L) and a serum potassium level of 8.0 mEq/L (8.0 mmol/L).

An electrocardiogram shows peaked T waves.

Emergent hemodialysis is planned.

In addition to intravenous calcium gluconate, which of the following is the most appropriate next step in treatment?

(A) Intravenous glucose and insulin
(B) Intravenous high-dose bumetanide
(C) Intravenous sodium bicarbonate
(D) Oral sodium polystyrene sulfonate in sorbitol

Item 98

A 60-year-old woman is evaluated during a follow-up visit for hypertension. History is also notable for hyperlipidemia. She tolerates her medications well except for minor pedal edema since starting her antihypertensive medication. She is active and plays tennis three times per week. Current medications are amlodipine, 5 mg/d, and rosuvastatin.

On physical examination, the average of two blood pressure measurements is 152/86 mm Hg, which is consistent with measurements she has obtained at home over the past 3 months. Pulse rate is 64/min. BMI is 22. Trace pedal edema is noted. The remainder of the examination is unremarkable.

Laboratory studies show a normal chemistry panel; a urine dipstick demonstrates no protein.

Which of the following is the most appropriate next step in management?

(A) Add lisinopril
(B) Add metoprolol
(C) Increase amlodipine to 10 mg/d
(D) Continue current regimen

Item 99

A 54-year-old man is evaluated for elevated blood pressure noted recently at a local health fair. He has no other medical history and takes no medications.

On this visit and on two subsequent nurse visits, the patient's blood pressure measurements are less than 140/90 mm Hg. BMI is 34. Cardiac examination reveals an S_4 gallop. The remainder of the examination is normal.

Laboratory studies show a normal chemistry panel, and a urine dipstick demonstrates no blood or protein.

Electrocardiogram demonstrates evidence of left ventricular hypertrophy.

Which of the following is the most appropriate next step in management?

(A) Ambulatory blood pressure monitoring
(B) Lisinopril
(C) Plasma aldosterone-plasma renin ratio
(D) Repeat blood pressure measurement in 6 months

Item 100

A 46 year-old woman is evaluated in the emergency department for difficulty catching her breath, generalized weakness, and paresthesias of the hands and feet. Medical history is significant for hypertension and generalized

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anxiety disorder. Medications are hydrochlorothiazide and paroxetine.

On physical examination, the patient appears anxious and is breathing rapidly. Temperature is 36.5 °C (97.7 °F), blood pressure is 108/62 mm Hg, pulse rate is 104/min, and respiration rate is 24/min. Oxygen saturation on ambient air is 99%. BMI is 24. There is no stridor, crackles, or wheezing on lung examination. The remainder of the physical examination is normal.

Laboratory studies:

Bicarbonate	21 mEq/L (21 mmol/L)
Arterial blood gas studies:	
pH	7.58
P_{CO_2}	22 mm Hg (2.9 kPa)
P_{O_2}	103 mm Hg (13.7 kPa)

Which of the following is the most likely acid-base disorder in this patient?

(A) Metabolic alkalosis and acute respiratory compensation
(B) Metabolic alkalosis and chronic respiratory compensation
(C) Respiratory alkalosis and acute metabolic compensation
(D) Respiratory alkalosis and chronic metabolic compensation

Item 101

A 58-year-old woman is evaluated during a follow-up visit for a 5-year history of stage G3b/A1 chronic kidney disease caused by analgesic nephropathy. History is also notable for hypertension. She takes amlodipine and no longer uses analgesics.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 132/78 mm Hg, pulse rate is 82/min, and respiration rate is 14/min. BMI is 26. Cardiac examination reveals no murmur, rub, or gallop. The lungs are clear.

Laboratory studies:

Creatinine	1.8 mg/dL (159.1 µmol/L)
Electrolytes:	
Sodium	140 mEq/L (140 mmol/L)
Potassium	5.4 mEq/L (5.4 mmol/L)
Chloride	110 mEq/L (110 mmol/L)
Bicarbonate	18 mEq/L (18 mmol/L)
Arterial blood gases:	
pH	7.36
P_{CO_2}	35 mm Hg (4.7 kPa)
Estimated glomerular filtration rate	33 mL/min/1.73 m^2

Which of the following is the most appropriate treatment?

(A) Intravenous sodium bicarbonate
(B) Oral potassium citrate
(C) Oral sodium bicarbonate
(D) Continue current therapy

Item 102

A 35-year-old man is evaluated in the hospital for acute kidney injury. He presented with worsening fatigue, decreased urination, and progressive swelling in the ankles occurring over the course of 2 to 3 weeks. Laboratory studies at the time of diagnosis showed a serum creatinine level of 6.7 mg/dL (592.3 µmol/L) (baseline of 0.9 mg/dL [79.6 µmol/L] 1 year ago). Medical history is significant for a 3-year history of inflammatory bowel disease that has been well controlled with daily mesalamine therapy. He does not take any over-the-counter drugs.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 118/67 mm Hg, pulse rate is 60/min, and respiration rate is 16/min. BMI is 20. Cardiac examination is normal. The lungs show crackles at the bases bilaterally. There is lower extremity edema to the mid calf. The remainder of the examination is normal.

Dipstick urinalysis shows 1+ protein but is otherwise normal. Urine microscopy shows 2-3 erythrocytes/hpf, 5-10 leukocytes/hpf, and leukocyte casts. Urine protein-creatinine ratio is 1060 mg/g. Urine cultures are negative.

Kidney ultrasound shows normal-sized kidneys with mildly increased parenchymal echogenicity, no hydronephrosis, and no renal calculi.

Which of the following is the most likely cause of this patient's acute kidney injury?

(A) Interstitial nephritis
(B) Lupus nephritis
(C) Membranous glomerulopathy
(D) Rapidly progressive glomerulonephritis

Item 103

A 41-year-old woman is evaluated during a routine obstetrics visit. She is in the third trimester of her first pregnancy. Her previous visits have been unremarkable, with blood pressures within the normal range for pregnancy. She has noticed mild shortness of breath with exertion and mild peripheral edema in her lower extremities. She reports no urinary changes. Medical history is notable for type 1 diabetes mellitus; she reports well-controlled blood sugars. Family history is notable for her mother who has hypertension. Medications are insulin and prenatal vitamins.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 162/112 mm Hg, pulse rate is 87/min, and respiration rate is 16/min. BMI is 28. Cardiac examination reveals a grade 2/6 crescendo-decrescendo murmur at the right upper sternal border and an S_3 gallop. Estimated central venous pressure is 14 cm H_2O. Bibasilar crackles are noted at the lung bases bilaterally. The patient has a gravid uterus and an otherwise unremarkable abdominal examination. There is trace lower extremity edema.

Laboratory studies are significant for a platelet count of 75,000 µL (75×10^9/L); a comprehensive metabolic profile with liver chemistry tests, peripheral blood smear, and urinalysis are normal.

Which of the following is the most likely diagnosis?

(A) Chronic hypertension
(B) HELLP syndrome

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(C) Normal changes of pregnancy
(D) Preeclampsia

Item 104

A 69-year-old woman is evaluated during a follow-up visit for stage G4/A1 chronic kidney disease due to hypertensive nephrosclerosis. History is also significant for peripheral arterial disease with right femoral-popliteal bypass 1 year ago. Medications are metoprolol, atorvastatin, aspirin, and calcium acetate.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 132/89 mm Hg, pulse rate is 61/min, and respiration rate is 13/min. BMI is 27. There is an audible S_4 gallop and reduced pedal pulses. The lungs are clear. The lower extremities are warm with normal capillary refill. There is no peripheral edema.

Laboratory studies:

Albumin	4.2 g/dL (42 g/L)
Calcium	8.3 mg/dL (2.1 mmol/L)
Creatinine	2.6 mg/dL (229.8 µmol/L)
Phosphorus	6.9 mg/dL (2.23 mmol/L)
Intact parathyroid hormone	95 pg/mL (95 ng/L)
Estimated glomerular filtration rate	22 mL/min/1.73 m^2

Review of a previous chest radiograph is remarkable for a heavily calcified aorta but is otherwise clear.

In addition to dietary counseling regarding a low phosphate diet, which of the following is the most appropriate treatment?

(A) Calcitriol
(B) Calcium carbonate
(C) Cinacalcet
(D) Sevelamer

Item 105

A 72-year-old man is evaluated for a 3-month history of slowly progressive anemia and fatigue. He has a 3-year history of end-stage kidney disease and receives hemodialysis three times weekly. Prior to starting hemodialysis he was able to maintain adequate iron stores with oral iron therapy. Erythropoietin for symptomatic anemia was initiated 3 years ago with the onset of dialysis; he responded well, with an increase in his hemoglobin level to 11 g/dL (110 g/L) and a decrease in symptoms. There have been no changes in his medications, which consist of erythropoietin, three times weekly; oral iron sulfate, 325 mg three times daily; lisinopril; metoprolol; nifedipine; sevelamer; and aspirin.

On physical examination, the patient is afebrile. Blood pressure is 144/94 mm Hg, pulse rate is 76/min, and respiration rate is 16/min. The lungs are clear. There is no edema.

Laboratory studies:

Hemoglobin	9.8 g/dL (98 g/L)
Ferritin	80 ng/mL (80 µg/L)
Transferrin saturation	12%

Which of the following is the most appropriate management?

(A) Administer intravenous iron
(B) Increase erythropoietin dose
(C) Increase oral iron dose
(D) Measure erythropoietin level

Item 106

A 52-year-old man is evaluated for a recent diagnosis of membranous glomerulopathy (MG). He presented with a 1-month history of increasing lower extremity edema and was found to have nephrotic-range proteinuria. Evaluation included normal serum complement levels; negative serologies for antinuclear antibodies, hepatitis B, and hepatitis C; and negative serum protein electrophoresis. Kidney biopsy showed changes consistent with MG; staining for antibodies to the phospholipase A_2 receptor (PLA_2R) was negative. Medical history is otherwise significant for hypertension. He is up-to-date with recommended health maintenance interventions. He has a 25-pack-year smoking history and is a current smoker. His only medication is ramipril.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 140/80 mm Hg, pulse rate is 68/min, and respiration rate is 14/min. BMI is 31. Pulmonary and abdominal examinations are normal. There is lower extremity edema to the knees bilaterally.

Which of the following is the most appropriate next diagnostic step?

(A) Chest radiography
(B) PET/CT of the chest
(C) Whole body CT
(D) No additional testing

Item 107

A 57-year-old man is hospitalized with *Streptococcus viridans* endocarditis; intravenous ceftriaxone for 6 weeks will be initiated. History is significant for stage G5/A2 chronic kidney disease due to IgA nephropathy and hypertension. Placement of a left forearm arteriovenous fistula occurred 12 days ago. He does not yet require dialysis. Medications are lisinopril, furosemide, and sevelamer.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 128/84 mm Hg, pulse rate is 77/min, and respiration rate is 17/min. BMI is 25. A grade 3/6 holosystolic murmur is present at the left sternal border. There is no pericardial rub. The arteriovenous fistula has a palpable thrill. The lungs are clear. There is no asterixis. There is no peripheral edema.

Which of the following is the most appropriate vascular access for antibiotic administration?

(A) A peripherally inserted central catheter line
(B) A single-lumen catheter in the left subclavian vein
(C) A single-lumen catheter in the right internal jugular vein
(D) The arteriovenous fistula

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Item 108

A 32-year-old woman is evaluated in the emergency department 30 minutes after a motor vehicle accident in which she struck her head on the steering wheel. She is awake and conversant and has no major symptoms aside from a mild headache. She is at 23 weeks' gestation of her second pregnancy. She has been receiving routine prenatal care, and her pregnancy has been uncomplicated. Her only medication is a prenatal vitamin.

On physical examination, the patient is in neck immobilization. Temperature is 37.1 °C (98.7 °F), blood pressure is 111/63 mm Hg, pulse rate is 76/min, and respiration rate is 12/min. BMI is 24. There is a contusion on the upper forehead but no other evidence of trauma. The abdomen shows normal changes of pregnancy but is otherwise normal. The remainder of the physical and neurologic examinations is unremarkable.

Initial laboratory studies show a serum sodium level of 131 mEq/L (131 mmol/L); the remainder of the electrolytes, blood urea nitrogen, and serum creatinine are normal.

Which of the following is the most likely cause of this patient's decrease in her serum sodium level?

(A) Cerebral salt wasting
(B) Normal physiologic changes of pregnancy
(C) Pituitary apoplexy
(D) Syndrome of inappropriate antidiuretic hormone secretion

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Answers and Critiques

Item 1 Answer: D

Educational Objective: Manage prehypertension.

In addition to lifestyle modifications, rechecking blood pressure in 1 year is appropriate for this patient with prehypertension. Although the eighth report of the Joint National Committee (JNC) did not address prehypertension, JNC 7 defined prehypertension as a systolic blood pressure of 120-139 mm Hg or a diastolic blood pressure of 80-89 mm Hg in the absence of preexisting end-organ disease (for example, diabetes mellitus, chronic kidney disease, or cardiovascular disease). Lifestyle modifications, including a low salt diet and exercise regimen, can be used to effectively reduce blood pressure in patients with prehypertension. Patients with prehypertension may also adopt the DASH (Dietary Approaches to Stop Hypertension) diet, which emphasizes vegetables, fruits, whole grains, legumes, and low-fat dairy products and limits sweets, red meat, and saturated/total fat, along with dedicated weight loss planning. Appropriate follow-up for those with prehypertension occurs at annual visits. The mean blood pressure in this patient (even accounting for the potential of inaccurate technique upon initial check-in) falls within the prehypertensive range, making lifestyle modifications and follow-up in 1 year the appropriate management. If blood pressures measuring 140/90 mm Hg or greater were documented, this would require repeat measurements for at least three visits over the period of at least 1 week of more to establish a diagnosis of hypertension.

Although there is an increased risk of stroke and cardiovascular disease for every level of blood pressure above 115/75 mm Hg and an increased risk of the development of hypertension, treatment of prehypertension using pharmacologic therapy (such as an ACE inhibitor or diuretic) has not yet been demonstrated to reduce this risk.

Ambulatory blood pressure monitoring records blood pressures periodically during normal activities. It is indicated primarily for diagnosis of suspected white coat hypertension (persistently elevated blood pressure readings in the office without evidence of end-organ damage) or to confirm a poor response to antihypertensive medication. It may also be useful in assessing for masked hypertension (evidence of end-organ damage without apparent elevated blood pressures) or for evaluating episodic or resistant hypertension. It is not indicated for this patient with evidence of prehypertension.

KEY POINT

- Prehypertension is managed with lifestyle modifications and annual follow-up visits to monitor blood pressure.

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Item 2 Answer: D

Educational Objective: Select the most appropriate imaging modality for a patient with chronic kidney disease.

Ultrasonography of the abdomen and pelvis is appropriate for this patient with chronic kidney disease (CKD). She requires imaging studies to evaluate her kidneys and genitourinary tract in order to rule out a structural lesion or tumor as the source of gross hematuria. Ultrasonography is an appropriate initial screening test because it can provide necessary information without exposure to the risks associated with the administration of contrast agents in patients with severe CKD who are at increased risk of contrast-induced nephropathy (CIN) and gadolinium-induced nephrogenic systemic fibrosis (NSF).

This patient has risk factors for CIN (older age, elevated serum creatinine, diabetes mellitus); therefore, a contrast-enhanced CT to evaluate for lesions of the kidneys and genitourinary tract as a cause of her hematuria should be performed only if similar information cannot be obtained from tests that entail less risk to the patient.

The use of gadolinium in MRI studies is relatively contraindicated in patients with an estimated glomerular filtration rate of less than 30 mL/min/1.73 m^2 due to the increased risk of NSF. Although most NSF cases have occurred in patients with end-stage kidney disease, there have been isolated case reports occurring in patients with stage G4 CKD. Gadolinium-enhanced MRI is therefore contraindicated in these patients unless there is a compelling clinical indication and the patient is fully informed of the risk of NSF.

Radiography of the abdomen and pelvis may be a reasonable test to rule out nephrolithiasis. However, the patient does not have symptoms suggestive of nephrolithiasis, and a plain radiograph would not provide information to determine whether there are structural lesions in the kidneys or genitourinary tract.

KEY POINT

- Ultrasonography is an appropriate imaging modality for patients with chronic kidney disease to avoid adverse events such as contrast-induced nephropathy or nephrogenic systemic fibrosis.

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Item 3 Answer: D

Educational Objective: Identify the increased risk for transitional cell carcinoma in patients with Balkan endemic nephropathy.

This patient has Balkan endemic nephropathy (BEN) and is at increased risk for transitional cell carcinoma. BEN is a slowly progressive tubulointerstitial disease that has recently been linked to aristolochic acid. Aristolochic acid is a nephrotoxic alkaloid from the plant *Aristolochia clematis*, which is endemic to the Balkan region and is sometimes a component of herbal therapies used for weight loss. BEN is believed to be due to exposure to low levels of aristolochic acid over years, compared with more acute toxicity associated with ingestion of herbal preparations. Characteristics of BEN include chronic kidney disease due to tubulointerstitial injury, tubular dysfunction (polyuria and decreased concentrating ability, glucosuria without hyperglycemia, and tubular proteinuria), and anemia. Because aristolochic acid is also mutagenic, patients with BEN are at increased risk for transitional cell carcinomas of the renal pelvis, ureters, and bladder. Therefore, annual surveillance with urine cytology is recommended.

Although this patient has glucosuria, BEN is not associated with an increased incidence of diabetes mellitus. The glucosuria is due to a tubular defect, resulting in glucosuria with normoglycemia.

Intracranial cerebral aneurysms are associated with autosomal dominant polycystic kidney disease, which is characterized by large kidneys with multiple kidney cysts.

Patients with BEN are at higher risk for transitional cell carcinoma, not renal cell carcinoma.

KEY POINT

- Patients with Balkan endemic nephropathy are at increased risk for transitional cell carcinomas of the renal pelvis, ureters, and bladder.

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Item 4 Answer: C

Educational Objective: Diagnose hemoglobinuria.

This patient most likely has hemoglobinuria, possibly due to intravascular hemolysis from his mechanical mitral valve, whose dysfunction is suggested by the finding of mitral regurgitation on physical examination. Fragmentation hemolysis in this setting manifests as a microangiopathic hemolytic anemia with thrombocytopenia and is accompanied by the release of free hemoglobin into the circulation. Free hemoglobin is partially bound by haptoglobin but may also be filtered into the urine, producing a red color. Heme reacts with peroxidase in the urine dipstick, causing a false-positive result for blood. Hemoglobinuria is distinguished from true hematuria by the absence of erythrocytes on urine microscopy. Similar findings on urinalysis will also occur with the release of myoglobin into the circulation, usually from muscle injury (rhabdomyolysis). Myoglobin is a small molecule relative to hemoglobin, is not bound within the circulation by haptoglobin, and is readily filtered through the kidneys, resulting in red-colored urine. It also reacts with peroxidase in the urine dipstick indicating blood, although microscopic examination will also be negative for erythrocytes.

Bladder cancer is a concern in a patient with a significant smoking history presenting with a finding of red urine. However, the urine color change in bladder cancer is due to bleeding into the urinary tract, and erythrocytes would be seen on urinalysis.

Glomerulonephritis may be associated with bleeding into the urine and would be suspected if erythrocytes, particularly acanthocytes (dysmorphic erythrocytes), were found on urine microscopic examination. Proteinuria may also be found in glomerulonephritis, although this patient's proteinuria is relatively mild and may result from tubular damage caused by hemoglobin toxicity.

Nephrolithiasis often presents with true hematuria in association with acute flank pain radiating to the ipsilateral groin, with or without costovertebral angle tenderness. Despite his history of nephrolithiasis, this patient does not have suggestive clinical symptoms and has no evidence of erythrocytes on urinalysis, making this an unlikely diagnosis.

KEY POINT

- Hemoglobinuria is distinguished from true hematuria by the absence of erythrocytes on urine microscopy.

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Item 5 Answer: A

Educational Objective: Treat a patient with uncontrolled hypertension.

The addition of chlorthalidone is the most appropriate next step in management in this patient who has uncontrolled hypertension with evidence of end-organ damage (left ventricular hypertrophy, chronic kidney disease, and retinopathy) despite being on three medications. However, he does not meet the definition of resistant hypertension, which is defined by blood pressure readings not at target despite three agents, one of which must be a diuretic. Persistent volume expansion, even if not sufficient to produce clinically evident edema, contributes significantly to hypertension; because of this, use of diuretics is almost always required to achieve adequate blood pressure control in patients with resistant blood pressure. Therefore, the addition of a diuretic such as chlorthalidone is appropriate for this patient before other drugs are added. Chlorthalidone is often preferred over other

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thiazide-type diuretics primarily due to its higher potency and longer duration of action.

Although limited data exist regarding the most effective medication regimen for patients requiring multi-drug therapy, a reasonable approach is to use medications recommended by hypertension treatment guidelines that have different mechanisms of action, with consideration of other agents with an antihypertensive effect indicated for treatment of comorbid conditions (such as a β-blocker for atrial fibrillation). For example, in addition to diuretic therapy, the combination of a long-acting dihydropyridine calcium channel blocker with an ACE inhibitor or angiotensin receptor blocker is often effective and generally well tolerated.

Vasodilator agents (hydralazine or minoxidil) and centrally acting agents (clonidine or guanfacine) may be effective, although side effects are common. Therefore, these medications are more commonly used as add-on therapy to other guideline-recommended agents and would not be an appropriate choice in this patient who is not currently on a diuretic. Additionally, minoxidil promotes sodium retention and is almost always given with a diuretic. Its use in this patient who is not taking a diuretic would not be appropriate.

Switching from nifedipine to amlodipine would not be expected to significantly improve blood pressure because both drugs are in the same class.

KEY POINT

- Diuretics are almost always required to achieve adequate blood pressure control in patients with resistant blood pressure.

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Item 6 Answer: A

Educational Objective: Diagnose AL amyloidosis with kidney manifestations.

AL amyloidosis secondary to a plasma cell dyscrasia is the most likely diagnosis. Amyloid consists of randomly oriented fibrils composed of various proteins that form organized β-pleated sheets within the tissues; amyloid resulting from monoclonal lambda or kappa light chains is termed *AL amyloid*. AL amyloid may present with nonspecific systemic symptoms such as fatigue or weight loss, but most commonly presents with symptoms associated with infiltration of different organ systems. These may include restrictive cardiomyopathy, peripheral neuropathy, hepatosplenomegaly, and, less commonly, cutaneous purpura and macroglossia. In amyloidosis involving the kidney, glomerular lesions tend to be prominent and present with proteinuria, often in the nephrotic range. However, amyloid deposits may also be found in tubular basement membranes, the interstitial space, and blood vessels. Findings on biopsy show deposits that stain apple green on Congo red staining under a polarizing microscope; these deposits are also visible on electron microscopy. In this patient, the presence of the nephrotic syndrome, autonomic symptoms (diarrhea and postural hypotension), and sensory neuropathy is highly suggestive of AL amyloidosis.

Although diabetes mellitus may present with similar systemic manifestations, such as autonomic and peripheral neuropathy and the nephrotic syndrome, these manifestations are typically seen after many years of diabetes, and this patient does not have evidence of diabetes on his current laboratory studies or on prior studies.

Myeloma nephropathy results from filtering of myeloma light chains with minimal albumin, with the light chains accumulating in the renal tubule causing tubular injury and typically forming casts (cast nephropathy). Filtered light chains are often not detected on routine dipstick testing and require identification with urine electrophoresis. The degree of albuminuria seen in this patient is less consistent with the findings typically seen in myeloma nephropathy.

Primary focal segmental glomerulosclerosis is a kidney-limited disease and is not associated with the systemic manifestations exhibited in this patient.

KEY POINT

- In amyloidosis involving the kidney, glomerular lesions tend to be prominent and present with proteinuria, often in the nephrotic range.

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Item 7 Answer: D

Educational Objective: Diagnose type 4 (hyperkalemic distal) renal tubular acidosis.

Type 4 (hyperkalemic distal) renal tubular acidosis (RTA) is the most likely cause of this patient's metabolic findings. Type 4 (hyperkalemic distal) RTA is caused by aldosterone deficiency or resistance. Primary aldosterone deficiency is seen in primary adrenal deficiency (Addison disease), and relative aldosterone deficiency may be seen in the syndrome of hyporeninemic hypoaldosteronism in which there is diminished renin release by the kidney. This occurs most commonly in patients with mild to moderate kidney disease due to diabetic nephropathy (such as this patient) or chronic interstitial nephritis (such as in systemic lupus erythematosus or AIDS). It may also be associated with acute glomerulonephritis, specific drugs that impair renin release (NSAIDs and calcineurin inhibitors), tubulointerstitial disease, and drugs that reduce aldosterone production (ACE inhibitors, cyclooxygenase inhibitors, and heparin). Patients with type 4 (hyperkalemic distal) RTA typically present with hyperkalemia, a normal anion gap metabolic acidosis, and impaired urine acidification, but with the ability to maintain the

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urine pH to <5.5. The specific cause can be differentiated by measurement of plasma renin activity, serum aldosterone, and serum cortisol. Initial treatment includes correction of the underlying cause if possible, with discontinuation of offending medications. Replacement of mineralocorticoids with fludrocortisone is indicated for patients with documented deficiency and should be considered for those with hyporeninemic hypoaldosteronism unless hypertension or heart failure is present.

Although kidney failure may cause hyperkalemia and metabolic acidosis, the acidosis associated with kidney failure more commonly reflects an increase in the anion gap with impaired organic acid excretion.

Type 1 (hypokalemic distal) RTA results from a defect in urine acidification in the distal tubule with impaired excretion of hydrogen ions and a normal anion gap metabolic acidosis. However, this tubular defect also results in potassium wasting and hypokalemia, which are not present in this patient.

Type 2 (proximal) RTA involves a defect in regenerating bicarbonate in the proximal tubule and is characterized by hypokalemia, glycosuria (in the setting of normal plasma glucose), low-molecular-weight proteinuria, and renal phosphate wasting, none of which is present in this patient.

KEY POINT

- Patients with type 4 (hyperkalemic distal) renal tubular acidosis typically present with hyperkalemia, a normal anion gap metabolic acidosis, and impaired urine acidification, but with the ability to maintain the urine pH to <5.5.

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Item 8 Answer: B

Educational Objective: Differentiate between glomerular and nonglomerular hematuria.

Evaluation for glomerular disease is the most appropriate next step for this patient. An initial step in evaluating hematuria is assessing whether the likely source of bleeding is from the glomerulus or elsewhere in the urinary tract. Glomerular hematuria is typically characterized by brown- or tea-colored urine with dysmorphic erythrocytes (or acanthocytes) and/or erythrocyte casts on urine sediment examination, although some glomerular disorders may cause gross hematuria. Other findings suggestive of a glomerular source include proteinuria. Nonglomerular bleeding typically presents with isomorphic erythrocytes in the urine without evidence of glomerular dysfunction. Glomerular causes of hematuria include inflammatory processes such as glomerulonephritis that may lead to rapid declines in kidney function but may also include more benign or indolent diseases such as thin glomerular basement membrane disease, IgA nephropathy, and other forms of chronic glomerulonephritis. The clinical presentation in this asymptomatic patient with normal kidney function and apparent recurrent episodes of gross hematuria is consistent with IgA nephropathy as a cause of her hematuria.

Cystoscopy is used to evaluate for lower urinary tract causes of nonglomerular bleeding. It is not an appropriate next step in this patient with evidence of glomerular bleeding and no other risk factors for lower urinary tract pathology.

Noncontrast helical abdominal CT can be used to detect kidney stones or other potential causes of nonglomerular hematuria. However, this patient's presentation is not suggestive of nephrolithiasis, and she has evidence of a glomerular source of her hematuria. Additionally, the preferred method of kidney imaging in younger patients, particularly women of childbearing age, is ultrasonography due to decreased radiation exposure.

Measurement of serum creatine kinase levels is useful in evaluating for rhabdomyolysis. This diagnosis should be suspected when dipstick urinalysis is positive for heme with a negative microscopic urinalysis for erythrocytes; however, this patient has evidence of erythrocytes in her urine. Additionally, she does not have a clinical history consistent with rhabdomyolysis, and her urine studies suggest a glomerular cause of her hematuria.

KEY POINT

- Glomerular hematuria typically features brown- or tea-colored urine with dysmorphic erythrocytes (or acanthocytes) and/or erythrocyte casts on urine sediment examination.

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Item 9 Answer: C

Educational Objective: Diagnose thin glomerular basement membrane disease.

The most likely diagnosis is thin glomerular basement membrane (GBM) disease, an inherited type IV collagen abnormality that causes thinning of the GBM and results in hematuria. The disorder may affect up to 5% of the population, and 30% to 50% of patients report a family history of hematuria. The disease is characterized by microscopic or macroscopic hematuria that may be first discovered in young adults. Diagnosis is usually based on the history of persistent hematuria, normal kidney function, and positive family history of hematuria without kidney failure; biopsy is not typically required. Long-term prognosis for kidney function is excellent, with rare progression to chronic kidney disease (CKD).

Fabry disease is a rare X-linked inherited disorder in which there is deficiency of α-galactosidase A (an enzyme in the glycosphingolipid pathway) that leads to progressive deposit of globotriaosylceramide (Gb3) in lysosomes. This

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disorder may present as CKD in young adulthood. Other associated clinical features include premature coronary artery disease, severe neuropathic pain, telangiectasias, and angiokeratomas. Because Fabry disease is X-linked and this patient has no other clinical findings of this disorder, it is not a likely diagnostic consideration.

Hereditary nephritis (also known as Alport syndrome), also a heritable disorder of type IV collagen, is a rare cause of end-stage kidney disease with a prevalence of 0.4% among adult U.S. patients. Most cases are X-linked (80%) and are associated with sensorineural hearing loss and lenticonus (conical deformation of the lens), with proteinuria, hypertension, and kidney failure developing over time. The remaining cases are autosomal recessive (15%) or autosomal dominant (5%) and may also be associated with hearing loss. Female carriers variably develop kidney disease depending on activity of the X chromosome in somatic renal cells. The prevalence of this disorder and the patient's gender make this a less likely possibility.

Tuberous sclerosis complex (TSC) results from mutations in genes coding for proteins that have a tumor-suppressing effect. Disruption of these gene products allows abnormal cell proliferation in different tissues, including the skin, brain, lung, liver, and kidney. Mild TSC may be detected in adulthood. Renal angiomyolipomas are a characteristic kidney lesion in TSC and occur in 75% of patients on imaging. The lack of evidence of other lesions suggestive of TSC and her normal kidney ultrasound make this an unlikely diagnosis in this patient.

KEY POINT

- Diagnosis of thin glomerular basement membrane disease is usually based on the history of persistent hematuria, normal kidney function, and positive family history of hematuria without kidney failure.

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Item 10 Answer: B

Educational Objective: Treat stage 1 hypertension in a patient with diabetes mellitus and chronic kidney disease.

The ACE inhibitor lisinopril is appropriate antihypertensive therapy for this patient. He was recently diagnosed with diabetes mellitus and stage 1 hypertension (defined as a systolic blood pressure of 140-159 mm Hg and/or a diastolic blood pressure of 90-99 mm Hg) and is now noted to have chronic kidney disease (CKD). There is evidence that in patients with hypertension and CKD, regardless of diabetes status, renin-angiotensin system agents (ACE inhibitor or angiotensin receptor blocker [ARB]) have a protective effect on kidney function. Based on this evidence, the eighth report of the Joint National Committee (JNC 8) recommends the use of these agents in patients with hypertension and CKD, with or without diabetes. The blood pressure goal recommended by the JNC 8 and the American Diabetes Association is <140/90 mm Hg for adult patients with hypertension and diabetes.

Recommendations for more aggressive blood pressure goals of <130/80 mm Hg in this population have recently been tempered by the lack of efficacy in reducing mortality with lower blood pressure goals and an increase in adverse events related to antihypertensive agents. Thus, initial combination therapy is not warranted in this case. Furthermore, the combination of two renin-angiotensin system agents for antihypertensive management in the setting of diabetes and moderately increased albuminuria (formerly known as microalbuminuria) has not been shown to improve outcomes and is associated with higher rates of hyperkalemia and other adverse events.

KEY POINT

- The eighth report of the Joint National Committee recommends an ACE inhibitor or angiotensin receptor blocker for patients with hypertension and chronic kidney disease, with or without diabetes mellitus.

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Item 11 Answer: D

Educational Objective: Recommend lifestyle modifications in a patient with newly diagnosed hypertension.

Lifestyle modification is the most appropriate next step in management for this 73-year-old patient with likely stage 1 hypertension based on consistently elevated blood pressure determinations. He has no evidence of end-organ manifestations on history or physical examination. Therefore, lifestyle modifications, including a low sodium diet; a diet such as DASH (Dietary Approaches to Stop Hypertension) that emphasizes vegetables, fruits, whole grains, legumes, and low-fat dairy products and limits sweets, red meat, and saturated/total fat; weight loss irrespective of diet; and exercise, are the most appropriate initial management strategies. The most effective lifestyle modification is salt restriction to 1500 mg/d, which lowers blood pressure by an average of 7/3 mm Hg. The eighth report of the Joint National Committee (JNC 8) recommends a blood pressure goal of <150/90 mm Hg for those ≥60 years of age. Because his blood pressure measurements have been around 155/85 mm Hg, salt restriction alone as part of lifestyle modifications may be enough to avoid the use of medications to achieve the treatment goal for this 73-year-old patient.

Although the α-blocker doxazosin may be considered for its dual blood pressure–lowering effect and its effect on urinary frequency, its use as first-line therapy for persistent hypertension following lifestyle modification should be

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decided while considering its adverse effect profile (such as orthostatic hypotension) and its increased incidence of heart failure that was noted in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

This patient may ultimately require medical treatment; because he has gout, the angiotensin receptor blocker (ARB) losartan may be preferred not only for its benefits in lowering blood pressure but also for its uricosuric effect. This is in contrast to thiazide diuretics such as hydrochlorothiazide, which increases serum urate.

β-Blockers such as metoprolol are no longer recommended as primary initial therapy for hypertension given their side-effect profiles, which includes higher cardiovascular-related events and mortality compared with ARBs.

Because this patient has evidence of persistently elevated blood pressures and likely stage 1 hypertension, a 6-month follow-up of his blood pressures without intervention is not appropriate.

KEY POINT

- Lifestyle modifications are indicated for all patients with hypertension, which can produce reductions in blood pressure that are equivalent to antihypertensive agents.

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Item 12 Answer: D

Educational Objective: Manage infection-related glomerulonephritis.

The most appropriate management for this patient is to continue current therapy. This patient with methicillin-resistant *Staphylococcus aureus* endocarditis is found to have worsening kidney function since hospitalization. The differential diagnosis includes infection-related glomerulonephritis (IRGN), drug-induced nephrotoxicity, acute interstitial nephritis (AIN), and septic emboli. The finding of a nephritic urine sediment (erythrocytes, erythrocyte casts, and proteinuria) in an azotemic patient with an active infection suggests IRGN. IRGN is an immune complex–mediated disease most frequently associated with nonstreptococcal infections, with the antigen in the immune complex derived from the infectious agent. Immune complexes deposit in the subepithelial area and activate complement with recruitment of inflammatory cells, leading to a proliferative GN. The likelihood of IRGN is high in this patient given the low C3 complement, the absence of cryoglobulins, and the lack of clinical findings suggestive of other causes on the differential diagnosis.

Glucocorticoids are not typically used in IRGN because there is usually improvement with control of the associated infection.

A kidney biopsy is not indicated because the probability of IRGN is high. However, biopsy would be appropriate if this patient's kidney function fails to improve with treatment of the underlying infection.

Drug-induced tubular toxicity (for example, with vancomycin) typically occurs after 7 to 10 days of antibiotic therapy and the urine sediment does not show cells, unlike in this patient. Antibiotic-induced AIN is typically associated with mild proteinuria, erythrocytes, leukocytes, and leukocyte casts on urinalysis. Eosinophiluria, recurrence of fevers, rash, and peripheral eosinophilia may also be seen and typically occur after 7 to 10 days of therapy, none of which is present in this patient. Therefore, switching vancomycin to daptomycin is not appropriate.

KEY POINT

- Management of infection-related glomerulonephritis typically only consists of treatment of the underlying infection.

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Item 13 Answer: D

Educational Objective: Treat a patient who has chronic kidney disease and hypertension.

The most appropriate management for this patient with hypertension and chronic kidney disease (CKD) is to continue the current medication regimen. Although hypertension is a common cause of CKD, hypertension is also highly prevalent in patients with CKD not caused by hypertension. The presence of hypertension in CKD promotes progression of underlying kidney disease and increases cardiovascular risk. Therefore, optimal management of hypertension is an important component of evaluating and treating all patients with CKD. For patients with CKD, the eighth report from the Joint National Committee (JNC 8) recommends a blood pressure target goal of <140/90 mm Hg using a medication regimen that includes an ACE inhibitor or angiotensin receptor blocker (ARB). In general, there is insufficient evidence to justify lower blood pressure goals unless patients have severely increased albuminuria, usually defined as >300 mg/g (stage A3), which is not present in this patient. His hypertension is currently at target goal, and he is taking an ACE inhibitor. Therefore, no changes to his medications are needed at this time.

The addition of the ARB losartan is inappropriate because the patient is already at goal blood pressure. Furthermore, studies have demonstrated that combination ACE inhibitor/ARB therapy worsens clinical outcomes and should not be used to treat patients with CKD.

Increasing this patient's lisinopril dose is unnecessary at this time because the patient is already at goal blood pressure.

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Replacing lisinopril with amlodipine is not indicated because the JNC 8 guidelines recommend the use of an ACE inhibitor (such as lisinopril) or ARB as first-line therapy for hypertension in patients with CKD, and not dihydropyridine calcium channel blockers, which have a lower renoprotective effect. Additionally, this patient is at the recommended blood pressure goal.

KEY POINT

- For patients with chronic kidney disease, the eighth report from the Joint National Committee recommends a blood pressure target goal of <140/90 mm Hg using a medication regimen that includes an ACE inhibitor or angiotensin receptor blocker.

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Item 14 Answer: D

Educational Objective: Manage isolated hematuria.

Serial kidney function and urine protein determinations are appropriate for this young patient with asymptomatic microhematuria. The evaluation of asymptomatic hematuria is somewhat different in younger patients as compared with older patients. In the former, hematuria is likely from mild glomerular disease (such as IgA nephropathy and genetic disorders such as collagen mutations). In older patients, structural changes, stones, infection, and cancers predominate. This young patient presents with asymptomatic microhematuria and has a family history of hematuria (without kidney failure) on her mother's side. Serologic and imaging studies are normal, there are no structural abnormalities of the kidney (such as kidney stones), and infection is unlikely based on the urinalysis. She likely has a familial hematuric syndrome, which is typically associated with either X-linked or somatic mutations of type IV collagen. In female carriers of X-linked hereditary nephritis (Alport syndrome), kidney failure may occur later in life. Thus, annual measurements of blood pressure, kidney function, and urine protein are reasonable (although there are no consensus guidelines defining the frequency of testing).

Cystoscopy is usually performed in patients with hematuria who are older than 35 years of age or who have risk factors for lower urinary tract malignancy (such as smoking, aniline dye, or cyclophosphamide exposure). This patient is at low risk for urinary tract malignancy and therefore does not have an indication for cystoscopy or urine cytology. Similarly, an abdominal CT could identify a renal malignancy that might have been missed on kidney ultrasound, which is not indicated in this young patient.

A kidney biopsy is often performed in a patient with unexplained abnormalities on urinalysis (such as hematuria or proteinuria) in the presence of evidence of kidney failure in order to establish the diagnosis and guide therapy. However, this patient has normal kidney function and stable microhematuria without other clear risk factors for progressive kidney disease. Therefore, kidney biopsy is not currently indicated.

KEY POINT

- Patients with isolated hematuria with a family history of hematuria may require serial measurements of kidney function and urine protein because kidney failure may occur later in life.

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Item 15 Answer: A

Educational Objective: Treat a patient with hypertension based on ambulatory blood pressure monitoring.

Initiation of a low-dose ACE inhibitor with follow-up in 2 weeks is appropriate for this patient with hypertension. Lower thresholds for the definition of hypertension exist for measurements obtained in the ambulatory setting. In general, blood pressure averages ≥135/85 mm Hg by ambulatory blood pressure monitoring or home monitoring meet most consensus panels' definition of hypertension, and nighttime hypertension is defined by average values >125/75 mm Hg. This is to reflect the typical blood pressure drop from daytime to nighttime (during sleep) of approximately 15%, noted in both normotensive and hypertensive patients. A lack of blood pressure drop of at least 10% ("non-dipping") is independently associated with left ventricular hypertrophy, cardiovascular events, moderately increased albuminuria (formerly known as microalbuminuria), and a more rapid rate of decline in glomerular filtration rate. This patient has hypertension defined by ambulatory readings and is a non-dipper with nighttime hypertension; therefore, pharmacologic therapy is indicated.

Although it has been shown that melatonin release is diminished in non-dippers and in small studies melatonin can lower nighttime blood pressure, there are no large trials with cardiovascular end points to recommend this therapy.

Observation is appropriate in the setting of prehypertension or white coat hypertension; however, this patient has confirmed hypertension and requires pharmacologic therapy.

KEY POINT

- Blood pressure averages ≥135/85 mm Hg by ambulatory blood pressure monitoring or home monitoring meet most consensus panels' definition of hypertension and should be treated with pharmacologic therapy.

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Item 16 Answer: D

Educational Objective: Manage uric acid nephrolithiasis with adequate urine output and urine alkalinization.

Urine alkalinization is the most appropriate treatment for this patient with uric acid nephrolithiasis not adequately treated with increased urine output. Uric acid is an uncommon cause of nephrolithiasis (approximately 10% of cases). It is more common in hot arid climates where low urine output and acidic urine (low urine pH) are more likely. These two factors, particularly low urine pH, markedly increase the risk of uric acid stones by favoring the development of insoluble uric acid from the relatively soluble urate salt. Elevated serum urate levels, gout, and associated hyperuricosuria are other risk factors, although many patients with uric acid stones do not have these risk factors. Other comorbid risk factors for uric acid stones include diabetes mellitus, the metabolic syndrome, and chronic diarrhea. Oral hydration to maintain a urine output of at least 2 L/d is the mainstay of therapy. If this is inadequate, the next treatment is urine alkalinization (usually with potassium citrate or potassium bicarbonate) to increase the solubility of uric acid.

Treatment with xanthine oxidase inhibitors such as allopurinol to lower uric acid production is usually reserved for patients with refractory disease despite adequate urine output and urine alkalinization or those with very high 24-hour urine uric acid levels (>1000 mg/24 h [5.9 mmol/24 h]). Therefore, allopurinol is not the next treatment of choice in this patient with mild uricosuria who has not undergone a trial of urine alkalinization.

Cholestyramine binds bile salts and oxalate in the gut and is sometimes used as a treatment for kidney stones related to hyperoxaluria but would likely not benefit this patient with uric acid stones.

Thiazide diuretics, such as hydrochlorothiazide, decrease hypercalciuria by increasing proximal sodium reabsorption and passive calcium reabsorption in the kidney. However, this is a strategy for treating calcium-based nephrolithiasis and is not effective for uric acid stones.

KEY POINT

- Management of uric acid nephrolithiasis includes adequate urine output, urine alkalinization, and xanthine oxidase inhibitors if needed to decrease uric acid production.

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Item 17 Answer: D

Educational Objective: Treat resistant hypertension by switching a thiazide diuretic to a loop diuretic in a patient with chronic kidney disease.

Switching hydrochlorothiazide to furosemide is the most appropriate next step in this patient. Uncontrolled hypertension in a patient who is already on three drugs, one of which is a diuretic, is defined as resistant hypertension. The approach to patients with resistant hypertension centers around lifestyle changes (particularly salt reduction and optimizing medication adherence) and choosing appropriate drug combinations. In patients with diabetic nephropathy and chronic kidney disease (CKD), ACE inhibitors or angiotensin receptor blockers should be used as an initial therapy given the established benefit of these agents in patients with diabetes mellitus and proteinuria. Most patients will require a second medication, and diuretic therapy is typically used in patients with CKD because persistent volume expansion contributes significantly to hypertension. Although thiazide diuretics are frequently used as initial therapy, they are generally less effective when the glomerular filtration rate drops below 30 mL/min/1.73 m^2. When this occurs, loop diuretics tend to be more effective and should be used instead of (or added to) thiazide diuretics. The dosage of loop diuretics depends on the sodium intake and the severity of CKD. Generally, furosemide doses of 40 to 80 mg once or twice daily is initiated with a salt-restricted diet and adjusted according to the response.

Adding a second inhibitor of the renin-angiotensin system such as aliskiren increases the risk of acute kidney injury and hyperkalemia without any benefit on renal and cardiovascular end points; therefore, combination therapy with renin-angiotensin inhibitors should not be used.

The centrally acting agent clonidine and the vasodilator minoxidil are potent antihypertensives sometimes used in cases of resistant hypertension if maximal doses of more conventional agents are unsuccessful. However, this patient is not currently on optimal triple therapy, and both agents also increase the risk of orthostatic hypotension in those with autonomic neuropathy, such as this patient. Moreover, the use of minoxidil without adequate diuresis will worsen salt and water retention and should be avoided.

KEY POINT

- In the setting of chronic kidney disease stage 4 and greater (glomerular filtration rate <30 mL/min/1.73 m^2), thiazide diuretics lose potency, and loop diuretics may often be required.

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Item 18 Answer: D

Educational Objective: Recommend non-dialytic therapy for a very elderly patient who has end-stage kidney disease and a high burden of comorbid conditions and poor functional status.

The most appropriate next step in the management of this patient's end-stage kidney disease (ESKD) is to recommend non-dialytic therapy. Dialysis may be beneficial in prolonging life with a good quality in many older patients; therefore, age itself is not always an absolute limiting factor in deciding whether dialysis is appropriate for a specific older patient. However, studies have shown that very elderly patients with a high burden of comorbid conditions and poor functional status may live as long or longer with non-dialytic therapy that is focused on alleviating symptoms and maximizing quality of life. Moreover, most nursing facility residents have a progressive decline in functional status after starting dialysis. Therefore, in this very elderly resident with multiple comorbidities who lives in a nursing facility, pursuing non-dialytic therapy is the most appropriate recommendation. The option of non-dialytic care should not be seen as refusal to provide care or provision of a lower level of care than those receiving dialysis, but rather as an appropriate recommendation based on expected outcomes in these patients. Palliative medicine and hospice services can be helpful in managing patients who choose this mode of therapy.

In older patients who choose to pursue dialysis, there are few definitive data regarding outcomes with hemodialysis versus peritoneal methods, although hemodialysis is typically chosen more frequently by older adults. However, neither modality is appropriate in the patient given his advanced age and other clinical circumstances.

KEY POINT

- Very elderly patients who have end-stage kidney disease with a high burden of comorbid conditions and poor functional status may live as long or longer with non-dialytic therapy that is focused on alleviating symptoms and maximizing quality of life.

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Item 19 Answer: D

Educational Objective: Treat a patient with stage 2 hypertension using combination therapy.

Combination therapy with the ACE inhibitor lisinopril and the calcium channel blocker (CCB) amlodipine is appropriate for this patient with stage 2 hypertension, which is defined as a systolic blood pressure ≥160 mm Hg and/or a diastolic blood pressure ≥100 mm Hg. There is general agreement among hypertension societies that a single agent is unlikely to control blood pressure in patients who are >20/10 mm Hg above target blood pressure. In this circumstance, initial therapy may include a combination of two agents either separately or in a fixed-dose pill. A combination of two agents at moderate doses is often more successful at achieving blood pressure goals than one blood pressure agent at maximal dose and minimizes the side effects that are more commonly noted at higher doses. Several combination regimens are appropriate, including the combination of a thiazide diuretic with an ACE inhibitor or angiotensin receptor blocker (ARB), or an ARB with a CCB; these combinations have been supported by both the eighth report from the Joint National Committee (JNC 8) and the European Society of Hypertension as reasonable approaches to management. However, there is evidence from the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial that a reduced rate of cardiovascular events may occur with the combination of an ACE inhibitor and CCB compared to an ACE inhibitor and thiazide. The combination of a thiazide and CCB is also an effective strategy for blood pressure lowering, although there is less evidence of the effectiveness of this regimen compared with other combination therapies.

There is general consensus that the dual use of renin-angiotensin-aldosterone agents (ACE inhibitor, ARB, or the direct renin inhibitor aliskiren) should not be used because of evidence showing that combining these medications is not associated with improved cardiovascular or renal end points and results in increased adverse events, including hypotension and hyperkalemia.

Given this patient's degree of hypertension (measurement of 160/92 mm Hg at her current visit), it is unlikely that a single agent will achieve her treatment goal of <140/90 mm Hg. Therefore, combination therapy is indicated as initial treatment.

KEY POINT

- Combination antihypertensive therapy is appropriate for patients who are >20/10 mm Hg above their target blood pressure goal.

Bibliography

Jamerson K, Weber MA, Bakris GL, et al; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008 Dec 4;359(23):2417-28. [PMID: 19052124]

Item 20 Answer: A

Educational Objective: Diagnose white coat hypertension using ambulatory blood pressure monitoring.

Ambulatory blood pressure monitoring (ABPM) is appropriate to evaluate this patient for white coat hypertension. ABPM is accomplished with a device that typically measures blood pressure every 15 to 20 minutes during the day

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and every 30 to 60 minutes at night. White coat hypertension is defined as blood pressure readings in the office ≥140/90 mm Hg and out-of-office readings that average <135/85 mm Hg. Prevalence may be as high as 10% to 20% of patients diagnosed with hypertension. This patient's blood pressure measurements have been elevated in the office but normal at home and require further documentation with 24-hour ABPM. If she has normal blood pressure at home, her blood pressure would be classified as white coat hypertension, which does not pose an increased risk of cardiovascular events but does increase her risk of future development of hypertension. Conversely, hypertension documented by ABPM is associated with a higher risk of cardiovascular death compared with hypertension determined in the office or at home. A summary of interpretation of office-based, ABPM, and self-recorded blood pressure readings is **shown**.

Interpretation of Blood Pressure Readings

Blood Pressure Category	Office-Based Readings (mm Hg)	24-Hour Ambulatory Readings (mm Hg)	Self-Recorded (mm Hg)
Hypertension (Nonelderly)	Systolic ≥140 or diastolic ≥90	≥135/85	≥135/85
White Coat Hypertension	≥140/90	<135/85	<135/85
Masked Hypertension	<140/90	>135/85	>135/85

Urine testing for fractionated metanephrines is used to evaluate for pheochromocytoma as a secondary cause of hypertension. Pheochromocytoma is generally suspected in patients with the symptom triad of episodic headache, sweating, and tachycardia associated with coincident increases in blood pressure. Similar symptoms may be seen with episodes of anxiety and panic attacks, which occur with increased frequency in patients with depression, as is present in this patient. However, these symptoms are not associated with significant blood pressure elevations when caused by anxiety or panic attacks. Documentation of consistent symptoms with accompanying blood pressure elevations would increase consideration of pheochromocytoma; however, testing for this diagnosis would not be indicated in the absence of this relationship, and further assessment for anxiety and panic attacks would be indicated.

Ambulatory electrocardiography or echocardiography would not be the appropriate next steps given the lack of other cardiovascular examination findings; palpitations are common and a nonspecific finding in possible hypertension.

Plasma aldosterone-plasma renin ratio would not be appropriate given this patient's normal laboratory findings and the lack of a firm diagnosis of hypertension.

KEY POINT

- Ambulatory blood pressure monitoring is useful to evaluate patients for white coat hypertension.

Bibliography

Pierdomenico SD, Cuccurullo F. Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta analysis. Am J Hypertens. 2011 Jan;24(1):52-8. [PMID: 20847724]

Item 21 Answer: D

Educational Objective: Diagnose aminoglycoside-induced nephrotoxicity.

This patient has developed acute kidney injury (AKI) from gentamicin. Aminoglycoside-induced AKI typically presents as nonoliguric acute tubular necrosis (ATN) with granular casts in the urine sediment and a fractional excretion of sodium >1%. The serum creatinine characteristically rises 5 to 10 days after starting therapy. Hypokalemia and hypomagnesemia can also occur with aminoglycoside toxicity due to kidney potassium and magnesium wasting. Recognizing drug-induced ATN is important because eliminating the nephrotoxic agent often leads to renal recovery. Incidence increases in older patients and in patients with decreased effective blood volume, chronic kidney disease, or concomitant nephrotoxin exposure.

Cephalosporins, such as cefazolin, can cause AKI from acute interstitial nephritis. Urine findings include leukocytes, erythrocytes, and leukocyte casts. Fever, maculopapular rash, peripheral eosinophilia, and eosinophiluria can also occur. Onset of AKI after drug exposure ranges from 3 to 5 days with a second exposure, to as long as several weeks to months with a first exposure. This patient does not have any features of acute interstitial nephritis. Furthermore, cefazolin was discontinued prior to the elevation in serum creatinine.

Cholesterol embolism occurs in patients with atherosclerotic disease after undergoing an invasive vascular procedure or receiving an anticoagulant or thrombolytic agent within the past several months. Emboli from ruptured atheromatous plaques occlude small and medium arterioles, causing ischemia and inflammation with organ dysfunction. Clinical features include rash (livedo reticularis), AKI, purple discoloration of the toes, bowel ischemia, neurologic manifestations, and eosinophilia. This patient does not have findings of embolic phenomena.

Iodinated contrast can induce vasospasm and cause ischemic injury or direct damage to the kidneys. Low osmolar contrast is thought to be safer than high osmolar contrast. Contrast-induced nephropathy (CIN) is defined as either an increase in serum creatinine of 0.5 mg/dL (44.2 µmol/L) or an increase in serum creatinine of 25% from baseline at 48 hours after contrast administration. This patient had no change in the serum creatinine level at 48 hours, making CIN an unlikely diagnosis.

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KEY POINT

- Aminoglycoside-induced acute kidney injury typically presents as nonoliguric acute tubular necrosis with granular casts in the urine sediment and a fractional excretion of sodium >1%, and the serum creatinine characteristically rises 5 to 10 days after starting therapy.

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Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. Crit Care Med. 2008 Apr;36(4 suppl):S216-23. [PMID: 18382197]

Item 22 Answer: D

Educational Objective: Monitor complications of immunosuppressive medications used in kidney transplantation.

New-onset diabetes mellitus and dyslipidemia should be monitored in this patient. Although kidney transplant recipients have improved clinical outcomes compared with patients who remain on dialysis, they require lifelong immunosuppression to prevent rejection of the transplanted kidney. In addition to increasing the risk of hypertension, infection, and certain malignancies, these medications can predispose patients to metabolic complications that should be anticipated by clinicians. Kidney transplant recipients are predisposed to new-onset diabetes after transplantation (often referred to as NODAT). Medications that promote development of NODAT include glucocorticoids, tacrolimus, and the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus. Dyslipidemia is also a common complication posttransplantation, and commonly used immunosuppressive medications that promote dyslipidemia include cyclosporine and mTOR inhibitors. Because cardiovascular disease is the leading cause of death among kidney transplant recipients, it is important to aggressively treat modifiable cardiac risk factors, including diabetes and dyslipidemia. It is important to emphasize that many medications, including some statins, can significantly alter the pharmacokinetics of immunosuppressant medications. Clinicians should therefore never change medication regimens in kidney transplant recipients without ensuring that there will be no adverse drug interactions.

Although hypophosphatemia is commonly observed in the posttransplant period, which is due in part to residual secondary hyperparathyroidism, hyperphosphatemia is not commonly observed unless there is severely impaired allograft function.

Hyperthyroidism is not a common complication of kidney transplantation or of immunosuppressive medications typically used in kidney transplant recipients.

Many patients have residual hyperparathyroidism after transplant that can be slow to resolve; hypercalcemia is relatively commonly observed posttransplant but hypocalcemia is uncommon. Therefore, hypoparathyroidism is unlikely in this patient.

KEY POINT

- Kidney transplant recipients require lifelong immunosuppression and must be monitored for metabolic complications such as diabetes mellitus and dyslipidemia.

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Item 23 Answer: A

Educational Objective: Recommend mechanical stone removal for a patient with a large (>10 mm) kidney stone.

Mechanical removal is the most appropriate management of this patient's 12-mm kidney stone located in the right renal pelvis. Large (>10 mm) stones are less likely than smaller stones to pass on their own, with or without use of medications to facilitate stone passage. Mechanical stone removal in the renal pelvis is often achieved with shock wave lithotripsy. Stones in the ureter may be addressed with either shock wave lithotripsy or ureteroscopy (often with ureteroscopic lithotripsy), usually depending on the specific location and size of the stone. Percutaneous antegrade ureteroscopy or retroperitoneal laparoscopy is generally reserved for impacted stones or other situations in which less invasive techniques would likely not be successful. Currently, open stone removal is rarely performed. Other indications for mechanical stone removal include stones <10 mm in size that have failed to pass with medical therapy. Involvement of a urologist is recommended for patients with nephrolithiasis who have urosepsis, acute kidney injury, anuria, or refractory pain, as well as those who are at high risk of complications such as having a single kidney, because more invasive interventions may be required in these situations.

Uncomplicated kidney stones <10 mm in size may usually be treated with conservative management (including hydration, analgesia, observation, and periodic re-evaluation) and medical expulsive therapy, which usually consists of either an α-blocker (such as tamsulosin) or calcium channel blocker (such as nifedipine). Although some clinicians may also treat with glucocorticoids in addition to medical expulsive therapy to decrease inflammation and swelling to facilitate stone passage, the effectiveness of this approach has not been documented.

KEY POINT

- Mechanical stone removal is appropriate for patients with large (>10 mm) kidney stones or those with smaller stones who have failed medical management or have complicated nephrolithiasis (urosepsis, acute kidney injury, anuria, refractory pain).

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Item 24 Answer: C

Educational Objective: Diagnose IgG4-related interstitial nephritis.

The most likely diagnosis is IgG4-related interstitial nephritis. This patient has a history of autoimmune pancreatitis and now presents with acute kidney injury. Her urinalysis is most consistent with a tubulointerstitial pattern, with mild proteinuria and the presence of inflammatory cells. This history and clinical presentation suggest the possibility of IgG4-related interstitial nephritis. Systemic IgG4-related disease is an uncommon disorder characterized by infiltration of different organs by lymphoplasmacytic infiltrates of IgG4-positive plasma cells with resultant fibrosis associated with elevated serum IgG4 levels. Autoimmune pancreatitis is one form of IgG-related disease, although other organs such as the kidney may be affected, most commonly as interstitial nephritis. IgG4-related interstitial nephritis may present with acute or chronic kidney failure as well as renal mass-like lesions on imaging. As with other IgG4-related diseases, almost all patients with IgG4-related kidney disease will have elevated serum IgG4 levels, and the kidneys may be diffusely enlarged on imaging due to cellular infiltration. Definitive diagnosis requires kidney biopsy with staining for IgG4-positive plasma cells. Treatment is similar to other IgG4-related diseases using immunosuppression with glucocorticoids.

ANCA-associated vasculitis and anti-glomerular basement membrane antibody disease typically cause rapidly progressive glomerulonephritis with significant proteinuria and hematuria in the sediment, occasionally with erythrocyte casts, none of which is present in this patient.

Lupus nephritis is primarily a glomerular lesion with significant proteinuria in the context of other clinical findings suggestive of systemic lupus erythematosus. This patient's clinical presentation is therefore less consistent with this diagnosis.

KEY POINT

- IgG4-related disease is characterized by infiltration of different organs by lymphoplasmacytic infiltrates of IgG4-positive plasma cells with resultant fibrosis associated with elevated serum IgG4 levels.

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Saeki T, Kawano M. IgG4-related kidney disease. [erratum in: Kidney Int. 2014 Jun;85(6):1472.] Kidney Int. 2014 Feb;85(2):251-7. [PMID: 24107849]

Item 25 Answer: D

Educational Objective: Diagnose diuretic-related metabolic alkalosis.

Urine diuretic screening is appropriate for this patient. The first step when assessing a patient with metabolic alkalosis is to clinically assess the patient's volume status. This patient has metabolic alkalosis as implied by the elevated serum bicarbonate and is hypovolemic as evidenced by the orthostatic blood pressure and pulse changes. Such a patient would be expected to have low urine concentrations of sodium and chloride. However, this patient's urine electrolytes show increased excretion of sodium and chloride despite the evident hypovolemia. These findings suggest the presence of active diuretic use or a renal tubular defect that impairs handling of sodium and chloride, such as Bartter and Gitelman syndromes. These rare autosomal recessive genetic disorders of renal sodium and chloride transporters clinically mimic loop diuretic and thiazide diuretic use, respectively, but should be considered only after diuretic use has been eliminated with negative urine diuretic screening.

Measurement of 24-hour urine free cortisol excretion is a standard test for diagnosing Cushing syndrome, which is characterized by proximal muscle weakness, hypokalemia, hypertension, and diabetes mellitus. These findings are not present in this patient.

Plasma aldosterone plasma renin ratio is unlikely to be helpful in this situation. Although primary hyperaldosteronism is characterized by hypokalemia and metabolic alkalosis, the absence of hypertension makes this diagnosis unlikely. Finally, diuretics and Gitelman and Bartter syndromes are associated with various degrees of volume contraction and secondary hyperaldosteronism. Plasma aldosterone and renin activity levels will not differentiate these disorders.

Thyroid dysfunction is not associated with acid-base abnormalities and may be associated with hypokalemia only in rare and severe cases such as thyrotoxic periodic paralysis, in which attacks of profound generalized weakness occur suddenly with preserved consciousness.

KEY POINT

- Diuretic use can mimic the metabolic alkalosis findings of inherited kidney disorders of sodium and chloride handling such as Bartter and Gitelman syndromes.

Bibliography

Medford-Davis L, Rafique Z. Derangements of potassium. Emerg Med Clin North Am. 2014 May;32(2):329-47. [PMID: 24766936]

Item 26 Answer: A

Educational Objective: Identify decreased muscle mass as a cause of decreased serum creatinine.

Decreased muscle mass is the most likely cause of this patient's decreased serum creatinine level. She has likely lost significant muscle mass as a consequence of stroke with paralysis, causing immobility and inability to maintain oral protein intake. She has severe protein-calorie malnutrition, as is evidenced by a low BMI and a severely depressed serum albumin level. Because creatinine is derived from the metabolism of creatine, a constituent of skeletal muscle, any condition that results in decreased muscle mass would be expected to cause long-term decreases in the serum creatinine level in the absence of any change in kidney function.

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Acute, but transient, decreases in creatinine have also been documented in some patients with chronic kidney disease and diabetes mellitus following ischemic stroke.

Diabetic kidney disease is chronically progressive, with rapidity of kidney function decline dependent on type 1 or 2 status, blood pressure and glycemic control, and reduction in proteinuria through use of renin-angiotensin system blockade. There is no known means of reversing diabetic kidney disease, and spontaneous improvement is unlikely.

Chlorthalidone, a thiazide diuretic, likely decreases blood pressure primarily by its effect on endothelial cells but can also result in volume contraction and mild hypovolemia, which generally results in increased, not decreased, serum creatinine.

Lisinopril, an ACE inhibitor, decreases the production of angiotensin II, resulting in decreased arterial blood pressure (systemic effect) and efferent arteriolar dilation (local effect). Both of these processes decrease pressure across the glomerular vascular bed, and thus the glomerular filtration rate. Consequently, serum creatinine is expected to increase by 25% to 30% with appropriate dosing of an ACE inhibitor.

KEY POINT

- Any condition that results in decreased muscle mass would be expected to cause long-term decreases in the serum creatinine level in the absence of any change in kidney function.

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Haider DG, Ferrari J, Mittermayer F, et al. A transient improvement in renal function occurs after ischemic stroke. Ren Fail. 2012;34(1):7-12. [PMID: 22023107]

Item 27 Answer: B

Educational Objective: Provide appropriate pneumococcal vaccinations for a patient with chronic kidney disease.

This patient should receive the pneumococcal conjugate vaccine in 6 months. Because infection is a leading cause of death in patients with chronic kidney disease (CKD) and end-stage kidney disease, proper vaccination to prevent infections should improve patient outcomes. The Advisory Committee on Immunization Practices (ACIP) recommends pneumococcal vaccination for all patients with severe CKD. This patient with stage G4/A3 CKD should receive the 13-valent pneumococcal conjugate vaccine (PCV-13) 1 or more years after the 23-valent pneumococcal polysaccharide vaccine (PPSV-23). A second dose of PPSV-23 should be administered 5 or more years after the first dose. Because this patient was immunized with PPSV-23 6 months ago, he should receive PVC-13 in 6 months and PPSV-23 in 4 years and 6 months.

Other immunocompromising conditions that are indications for pneumococcal vaccination are anatomic and functional asplenia, congenital or acquired immunodeficiency (including B- or T-lymphocyte deficiency, complement deficiencies, and phagocytic disorders excluding chronic granulomatous disease), HIV infection, the nephrotic syndrome, leukemia, lymphoma, Hodgkin lymphoma, generalized malignancy, multiple myeloma, solid-organ transplant, and iatrogenic immunosuppression (including long-term systemic glucocorticoids and radiation therapy).

For patients younger than 65 years of age with CKD who have not been previously immunized against invasive pneumococcal disease, the ACIP recommends that PCV-13 be administered first followed by PPSV-23 no sooner than 8 weeks later.

KEY POINT

- The Advisory Committee on Immunization Practices recommends pneumococcal vaccination with both the 13-valent pneumococcal conjugate and 23-valent pneumococcal polysaccharide vaccines for all patients with severe chronic kidney disease.

Bibliography

Kim DK, Bridges CB, Harriman KH; Advisory Committee on Immunization Practices. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older: United States, 2015. Ann Intern Med. 2015 Feb 3;162(3):214-23. doi:10.7326/M14-2755

Item 28 Answer: C

Educational Objective: Identify laxative abuse as a cause of metabolic acidosis.

Laxative abuse is the most likely cause of this patient's acid-base and electrolyte abnormalities. She has a normal anion gap metabolic acidosis in the setting of physical examination findings consistent with low/normal extracellular fluid status and low/normal blood pressure. The etiology of a normal anion gap metabolic acidosis is typically due to either the inability of the kidney to excrete acid (renal tubular acidosis) or loss of bicarbonate, usually through the gastrointestinal tract. Differentiating the cause of a normal anion gap metabolic acidosis may be accomplished by measurement of the urine anion gap, which is calculated as follows: $(U_{Na} + U_{K} - U_{Cl})$. The urine anion gap is a surrogate method of estimating the ability of the kidney to excrete an acid load. The normal physiologic response to systemic acidosis is an increase in urine acid excretion resulting in an increase in urine ammonium, which is difficult to measure clinically. However, because ammonium carries a positive charge, chloride is excreted into the urine in equal amounts with ammonium to maintain electrical neutrality. Therefore, the amount of chloride in the urine reflects the amount of ammonium present, with a positive urine anion gap suggesting a kidney source of acid loss, and a negative urine anion gap is consistent with gastrointestinal bicarbonate loss. The negative urine anion gap in this patient (-6 mEq/L [6 mmol/L]) indicates a gastrointestinal cause of her normal anion gap metabolic acidosis, and laxative abuse is a likely explanation. In addition, hypokalemia combined with low urine potassium

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indicates appropriate renal compensation to attempt to retain filtered potassium.

The vomiting associated with bulimia nervosa leads to loss of gastric acid with a resulting metabolic alkalosis, not metabolic acidosis.

Active diuretic use leads to kidney potassium wasting and a metabolic alkalosis, as does Gitelman syndrome, a defect that mimics the clinical picture of thiazide diuretic use.

Renal causes of normal anion gap metabolic acidosis are due to specific defects in renal handling of bicarbonate reclamation or in hydrogen ion secretion. Type 1 (hypokalemic distal) renal tubular acidosis is caused by a defect in hydrogen secretion by the distal tubule and is associated with a positive urine anion gap, a high urine potassium secretion, and hypokalemia.

KEY POINT

- Normal anion gap metabolic acidosis can be caused by gastrointestinal bicarbonate loss induced by laxative abuse.

Bibliography

Roerig JL, Steffen KJ, Mitchell JE, Zunker C. Laxative abuse: epidemiology, diagnosis and management. Drugs. 2010 Aug 20;70(12):1487-503. [PMID: 20687617]

Item 29 Answer: D

Educational Objective: Evaluate for malignancy in a kidney transplant recipient.

In addition to age- and sex-appropriate screening, this kidney transplant recipient should be evaluated for skin cancer. Patients who receive kidney transplants are at increased risk of malignancy compared with the general population, and this risk is attributable, at least in part, to the effects of immunosuppressive medications. Kidney transplant patients are at particularly high risk for squamous cell carcinomas (SCC) of the skin and posttransplant lymphoproliferative disease. Unlike in the general population, SCC is more common than basal cell carcinoma and accounts for approximately 90% of skin cancers in organ recipients. Some studies have shown that transplant recipients have more than a 200-fold increased risk of SCC compared with the general population. Moreover, SCC occurring in a transplant recipient is much more likely to metastasize than in non-transplant patients. Transplant recipients, particularly those with fair skin, should therefore be closely monitored for the development of precancerous or cancerous lesions and promptly treated.

Although kidney transplant recipients are at moderately increased risk for colon and lung cancer, insufficient data support more aggressive screening for these cancers than in the general population. Similarly, male kidney transplant recipients are not at increased of prostate cancer, so risk versus harm of screening should be approached as for the general population.

KEY POINT

- Kidney transplant patients are at particularly high risk for squamous cell carcinomas of the skin and posttransplant lymphoproliferative disease and should be evaluated for these diseases, in addition to age- and sex-appropriate screening.

Bibliography

Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011 Nov 2;306(17):1891-901. [PMID: 22045767]

Item 30 Answer: A

Educational Objective: Recognize the risk factors for acute kidney injury after cardiac surgery.

This patient's baseline estimated glomerular filtration rate (eGFR) is considered the strongest predictor of the development of acute kidney injury (AKI) in the perioperative period. An elevated preoperative serum creatinine level and the presence of chronic kidney disease (CKD) are the strongest nonmodifiable predictors of the development of AKI after cardiac surgery. This patient has severe kidney disease with an elevated baseline serum creatinine level of 2.3 mg/dL (203.3 μmol/L), with an eGFR of 25 mL/min/1.73 m^2 and stage 4 CKD. Other nonmodifiable risk factors for post–cardiac surgery AKI include advanced age, female gender, reduced left ventricular function or the presence of heart failure, insulin-dependent diabetes mellitus, peripheral vascular disease, and COPD.

Some observational studies have shown a BMI >30 to be a predictor of AKI post–cardiac surgery. However, the strength of the data is weak, and this patient has a BMI of 25.

Hypertension has not been shown to be a strong predictor for the development of AKI post–cardiac surgery.

Lisinopril and simvastatin have not been established as medications that increase the risk of AKI post–cardiac surgery. In fact, some observational studies indicate that they may have renoprotective properties and should be continued in the perioperative setting.

KEY POINT

- Preexisting chronic kidney disease is the strongest nonmodifiable predictor of the development of acute kidney injury after cardiac surgery.

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Thakar CV. Perioperative acute kidney injury. Adv Chronic Kidney Dis. 2013 Jan;20(1):67-75. [PMID: 23265598]

Item 31 Answer: B

Educational Objective: Diagnose oncogenic osteomalacia.

This patient's findings of bone pain and hypophosphatemia with kidney phosphate wasting in the setting of

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inappropriately low serum concentration of 1,25-dihydroxy vitamin D, normal 25-hydroxy vitamin D concentration, and elevated alkaline phosphatase are consistent with oncogenic osteomalacia. The swelling of the finger is consistent with a mesenchymal tumor. Oncogenic osteomalacia is typically caused by benign mesenchymal tumors of vascular or skeletal origin. Overexpression of fibroblast growth factor–23 by these tumors is associated with decreased resorption of phosphate in the renal tubules with resultant hypophosphatemia and hyperphosphaturia. The tubular defect also impairs calcitriol synthesis. Chronic hypophosphatemia causes abnormal mineralization of bone, increased alkaline phosphatase, and, in the longer term, osteomalacia and associated fractures. Removal of the tumor leads to reversal of the biochemical abnormalities and healing of the bone disease.

Nutritional vitamin D deficiency results in low serum calcium levels and low 25-hydroxy vitamin D concentration, and it does not cause kidney phosphate wasting as seen in this patient.

Primary hyperparathyroidism is defined by an elevated parathyroid hormone level, elevated serum calcium level, and increased 1,25-dihydroxy vitamin D, all of which are absent in this patient.

X-Linked hypophosphatemic rickets can present with the same biochemical markers as noted in this case. However, it usually presents with typical signs of rickets in young children, and clinical expression of this condition in adulthood would not be expected.

KEY POINT

- Oncogenic osteomalacia is characterized by bone pain and hypophosphatemia with kidney phosphate wasting in the setting of low 1,25-dihydroxy vitamin D and normal 25-hydroxy vitamin D concentrations.

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Imel EA, Econs MJ. Approach to the hypophosphatemic patient. J Clin Endocrinol Metab. 2012 Mar;97(3):696-706. [PMID: 22392950]

Item 32 Answer: A

Educational Objective: Treat acute kidney injury with continuous renal replacement therapy.

Continuous renal replacement therapy (CRRT) is the most appropriate treatment for this patient who has hemodynamic instability and oliguric acute kidney injury (AKI) with laboratory and urinary findings consistent with acute tubular necrosis (ATN). CRRT is indicated for treatment of electrolyte abnormalities (hyperkalemia, hyperphosphatemia), metabolic acidosis, and volume overload as seen in this patient. CRRT represents a spectrum of dialysis modalities specifically developed for the management of critically ill patients with AKI who cannot tolerate traditional intermittent hemodialysis due to hemodynamic instability, or in whom intermittent hemodialysis cannot control volume or metabolic derangement. CRRT is performed continuously (24 hours/day) through a venovenous access. Venous access is obtained by placing a large double-lumen catheter into either the internal jugular, femoral, or subclavian vein, as would be done for hemodialysis. There are several variations of CRRT that may involve diffusion-based solute removal (dialysis) or convection-based solute and water removal (filtration).

The major advantage of CRRT over intermittent hemodialysis is its slower rate of solute and fluid removal per unit of time, resulting in better hemodynamic tolerance. Therefore, CRRT is the preferred method of renal replacement therapy for critically ill unstable patients such as the patient in this case. Furthermore, the continuous nature of the therapy allows for better control of volume, acid-base, electrolytes, and azotemia.

Slow continuous ultrafiltration is a type of extracorporeal therapy by which plasma water is removed continuously. Although this therapy will help with fluid overload, it will not correct the azotemia or electrolyte and acid-base abnormalities in this patient.

Starting a furosemide infusion in this patient will not correct the electrolyte or acid-base abnormalities. Furthermore, in the setting of ATN with oliguria, furosemide is unlikely to be effective in volume removal.

KEY POINT

- Continuous renal replacement therapy is preferred for critically ill, unstable patients with acute kidney injury because it provides a slower rate of solute and fluid removal per unit of time, resulting in better hemodynamic tolerance.

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Item 33 Answer: A

Educational Objective: Diagnose anti-glomerular basement membrane antibody disease.

The most likely diagnosis is anti–glomerular basement membrane (GBM) antibody disease. This 50-year-old patient has pulmonary-renal syndrome, including hemoptysis followed by hypoxic respiratory failure and kidney failure with an active urine sediment with protein, erythrocytes, and leukocytes, suggesting an underlying glomerulonephritis. The differential diagnosis of pulmonary-renal syndrome includes small-vessel vasculitis (ANCA associated), anti-GBM antibody disease (Goodpasture syndrome), and rarely, other autoimmune diseases such as cryoglobulinemic vasculitis, systemic lupus erythematosus, and IgA vasculitis. Anti-GBM antibody disease is an autoimmune disease caused by antibodies directed against the noncollagenous domain of type IV collagen that bind to the GBM, inciting an inflammatory response resulting in damage to the GBM and the formation of a proliferative

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and often crescentic glomerulonephritis. The same process occurs with the basement membrane of pulmonary capillaries, leading to pulmonary hemorrhage. Serologies show normal complement levels and elevated levels of anti-GBM antibodies in the serum. On kidney biopsy, there is a proliferative glomerulonephritis, often with many crescents (shown, left panel). There is linear deposition of immunoglobulin along the GBM by immunofluorescence, but no electron-dense deposits on electron microscopy (shown, right panel). Treatment is immunosuppressive therapy with cyclophosphamide and glucocorticoids, combined with daily plasmapheresis to remove circulating anti-GBM antibodies.

Although heart failure can be associated with pulmonary edema and hemoptysis with acute kidney injury (cardiorenal syndrome), such patients typically show signs of severe volume overload and normal urine sediment, unlike this patient.

Membranous nephropathy is associated with the nephrotic syndrome with a low serum albumin level, which is not seen in this patient. The nephrotic syndrome alone is not typically associated with pulmonary disease, although it can be complicated with venous thromboembolic manifestations such as pulmonary embolism. However, this patient's pulmonary presentation with significant hemoptysis and infiltrates on chest radiograph is not consistent with pulmonary emboli as the cause of his respiratory failure.

Microscopic polyangiitis is the most common cause of pulmonary-renal syndrome. However, in the absence of a serum ANCA level or evidence of peripheral vasculitic lesions (for example, palpable purpura), it is not possible to clinically differentiate this disease from anti-GBM antibody disease. A kidney biopsy is diagnostic, showing little or no immune deposits in microscopic polyangiitis ("pauci-immune glomerulonephritis"). In this patient, extensive linear deposition of IgG along the GBM is noted, which is classic of anti-GBM antibody disease.

KEY POINT

- Anti–glomerular basement membrane (GBM) antibody disease is an autoimmune disease caused by antibodies directed against the noncollagenous domain of type IV collagen that bind to the GBM.

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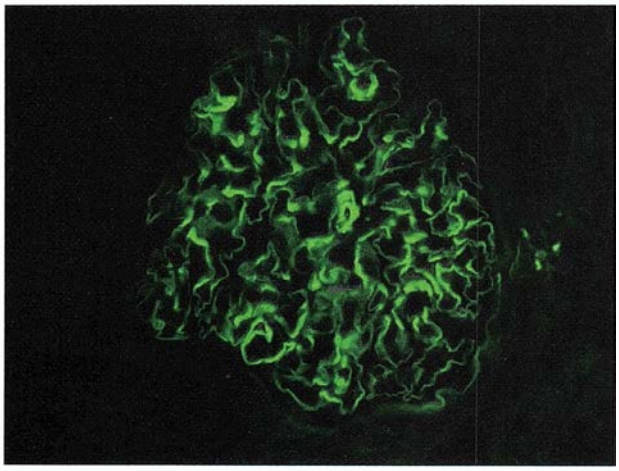
Item 34 Answer: D

Educational Objective: Manage elevated serum creatinine due to trimethoprim.

Continuing this patient's current antibiotic therapy is the most appropriate management. Creatinine is normally filtered by the kidney from the serum, although a smaller amount is also secreted by the proximal tubule. In patients with more advanced chronic kidney disease (CKD), such as this patient, up to 50% of urine creatinine may be secreted instead of being filtered through the glomerulus. Trimethoprim is known to interfere with creatinine secretion without affecting the glomerular filtration rate (GFR) and can cause increases in serum creatinine of up to 0.5 mg/dL (44.2 µmol/L); this rise in serum creatinine therefore does not reflect a drop in actual kidney function. This effect is reversible upon discontinuation of the medication. Trimethoprim also inhibits the epithelial sodium channel in the collecting tubule, effectively acting as a potassium-sparing diuretic and potentially increasing the serum potassium level. The risk of hyperkalemia is therefore increased when using trimethoprim-containing antibiotics, particularly in patients who are on high-dose trimethoprim, who have underlying CKD that may predispose to hyperkalemia, or who are taking a medication with a potassium-sparing effect (such as an ACE inhibitor or angiotensin receptor blocker). Because of this, trimethoprim should be used with caution



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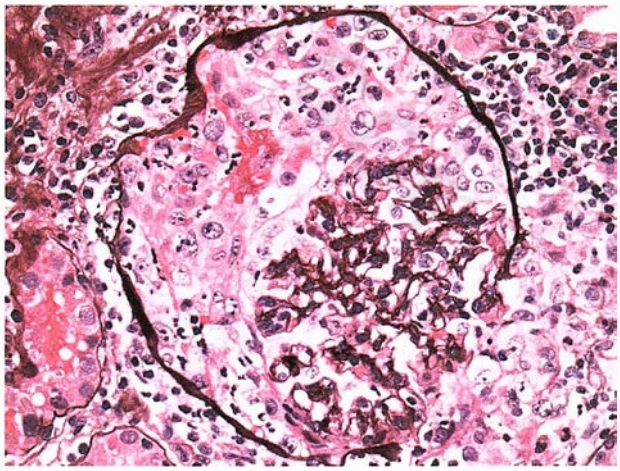

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and with close monitoring in patients with any of these underlying risk factors who require its use for treating infection. This patient's potassium level is within the normal range, and continued close monitoring during her antibiotic therapy is indicated.

Rifampin may cause red or orange discoloration of the urine but is not associated with a decreased GFR, an increase in serum creatinine, or hyperkalemia.

Urine eosinophil testing by means of special stains has been used classically to diagnose acute interstitial nephritis, which is a diagnostic consideration in a patient taking sulfa drugs. However, testing for urine eosinophils is neither sensitive nor specific for this diagnosis, which recent literature suggests may only be definitively made on the basis of kidney biopsy.

KEY POINT

- Trimethoprim is known to interfere with creatinine secretion without affecting the glomerular filtration rate and can cause increases in serum creatinine of up to 0.5 mg/dL (44.2 µmol/L); this rise therefore does not reflect a drop in actual kidney function.

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Item 35 Answer: C

Educational Objective: Evaluate a patient with suspected nephrolithiasis using noncontrast helical abdominal CT.

Noncontrast helical abdominal CT is the most appropriate diagnostic test to perform next in this patient with a clinical presentation consistent with nephrolithiasis. The findings of unilateral pain combined with hematuria without inflammation on urinalysis suggest nephrolithiasis, and the location of the pain in the inguinal region suggests that the stone may be in the distal ureter. Ultrasonography is increasingly used as an initial study for evaluation of suspected nephrolithiasis because of increased availability, lack of radiation exposure, and lower cost than CT; it is also the study of choice in pregnant patients. However, ultrasonography is less sensitive than CT for detecting kidney stones in the distal ureter or for evaluating other potential nonurologic conditions that may be responsible for the pain. Given this patient's clinical picture that is consistent with nephrolithiasis but with a negative ultrasound for kidney stones, further imaging with noncontrast helical abdominal CT is indicated. Additionally, the absence of hydronephrosis on ultrasound does not rule out nephrolithiasis.

Although renal vein thrombosis can cause hematuria, this diagnosis is less likely given the location of this patient's pain, normal kidney function, and lack of proteinuria. Therefore, Doppler ultrasonography of the renal veins is inappropriate.

Kidney biopsy may be appropriate for patients with suspected glomerulonephritis. Glomerulonephritis typically presents with evidence of decreased kidney function with inflammation and glomerular damage seen as variable proteinuria, hematuria, and possibly dysmorphic erythrocytes and erythrocyte casts on urinalysis. However, this patient's clinical history and laboratory findings are not consistent with glomerulonephritis, and kidney biopsy is not indicated.

Urine cultures are appropriate to diagnose a urinary tract infection or pyelonephritis. However, a urinary tract infection is unlikely in this patient given the absence of dysuria and a urinalysis negative for significant leukocytes, leukocyte esterase, or nitrites.

KEY POINT

- Ultrasonography and noncontrast helical CT of the abdomen are testing options for evaluation of suspected nephrolithiasis; CT is indicated if initial ultrasound testing is negative in a patient with a high clinical suspicion for kidney stones.

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Item 36 Answer: D

Educational Objective: Diagnose prerenal acute kidney injury in a patient taking diuretics.

The most likely diagnosis is prerenal acute kidney injury (AKI). AKI occurs most commonly in the setting of true volume depletion or decreased effective blood volume as seen in this patient with decreased cardiac output. In patients with AKI and oliguria, the fractional excretion of sodium (FE_{Na}) may be helpful in differentiating between prerenal AKI and AKI from renal tubular cell damage or acute tubular necrosis (ATN). The FE_{Na} measures the percent of filtered sodium excreted in the urine and is calculated as $(U_{Sodium} \times P_{Cr})/(U_{Cr} \times P_{Sodium}) \times 100$. It is considered a more accurate measurement of kidney sodium avidity in prerenal states than the urine sodium concentration because these individuals are both sodium and water avid, which may cause an elevated urine sodium concentration despite kidney sodium retention. However, the FE_{Na} is less reliable when diuretics are being used because the urine sodium may not accurately reflect attempts by the kidney to retain sodium. Because urea is less sensitive to the effects of diuretics, the fractional excretion of urea (FE_{Urea}) may be more useful in this setting. The FE_{Urea} is calculated as $(U_{Urea} \times P_{Cr})/(U_{Cr} \times P_{Urea}) \times 100$, with values <35% suggesting a prerenal state. In this patient, the FE_{Na} is higher than expected in a prerenal state at 1.9%, but the FE_{Urea} is only 8.8%, suggesting an underlying prerenal state.

The urine sediment of a patient with acute interstitial nephritis will typically reflect inflammation with leukocytes,

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erythrocytes, or leukocyte casts, none of which is seen in this patient's urine sediment.

The urine sediment in patients with ATN will usually show evidence of tubular damage with sloughed tubular epithelial cells or coarse granular casts. These are not present in this patient, making ATN less likely.

Although this patient has a history of benign prostatic hyperplasia, postrenal obstruction is unlikely due to the presence of an indwelling urinary catheter.

KEY POINT

- Because urea is less sensitive to the effects of diuretics, the fractional excretion of urea may be more useful in this setting to identify the cause of acute kidney injury.

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Item 37 Answer: B

Educational Objective: Treat lupus nephritis with combination immunosuppressive therapy.

Increasing prednisone and adding mycophenolate mofetil are indicated for this patient with class IV lupus nephritis (LN). LN occurs in up to 70% of patients with systemic lupus erythematosus (SLE), with the presence of anti-double-stranded DNA antibodies being a marker for risk. All patients with SLE should be evaluated for possible nephritis at the time of diagnosis, with individualized surveillance based on the presence and degree of kidney abnormalities on laboratory studies. Patients who develop LN typically present with extrarenal symptoms of SLE at the time of diagnosis of LN. Glomerular disorders associated with SLE are classified into six different patterns based upon kidney biopsy histopathology, although there may be some overlap between classes in an individual patient, and some patients may evolve from one class to another. Patients with class I or II LN may have minimal or no kidney findings, and those with classes III and IV present with varying degrees of the nephritic syndrome. Patients with class V LN present predominantly with proteinuria. Class VI is the end stage of long-standing LN. This patient is experiencing a major lupus flare with arthritis, rash, fevers, and class IV LN on kidney biopsy. Class IV LN represents diffuse glomerular involvement and is the most common and severe form of nephritis associated with lupus. It is also associated with elevated anti-double stranded DNA antibody levels and hypocomplementemia, particularly during periods of active disease. Most patients with class III and all patients with class IV LN benefit from aggressive combination immunosuppressive therapy. The optimal initial therapy is to increase glucocorticoid doses (typically an intravenous pulse followed by a tapering oral dose), which is accompanied by either intravenous cyclophosphamide or mycophenolate mofetil.

The use of glucocorticoids alone has been associated with an inferior outcome compared with alkylating agents or antimetabolites in combination with glucocorticoids for patients with LN requiring treatment.

The addition of plasmapheresis to immunosuppressive therapy has not been shown to improve outcomes in patients with LN.

The patient has a high probability of worsening kidney function if not aggressively treated in view of the class IV LN, and any delay engenders the risk of irreversible kidney failure.

KEY POINT

- Most patients with class III lupus nephritis and all patients with class IV lupus nephritis benefit from aggressive combination immunosuppressive therapy.

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Item 38 Answer: D

Educational Objective: Manage elevated blood pressure in an older patient.

Continued clinical observation is appropriate for this older patient with elevated blood pressure measurements. The eighth report of the Joint National Committee (JNC 8) recommends that pharmacologic treatment be initiated to lower blood pressure in patients aged ≥60 years who have systolic blood pressure persistently ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg, and treat to a goal of systolic <150 mm Hg and diastolic <90 mm Hg. This recommendation is based on good-quality evidence that a blood pressure goal of <150/90 mm Hg reduces the risk of cardiovascular events, but there appears to be no added benefit with lower targets (140-149 mm Hg). Therefore, in this 70-year-old patient in whom multiple readings have not shown blood pressure above this threshold for treatment, continued clinical observation with periodic blood pressure determinations and evaluation for potential end-organ damage associated with hypertension is recommended.

Pharmacologic treatment, such as a thiazide diuretic or an ACE inhibitor, is not indicated at this time.

Although echocardiography is more sensitive for detecting left ventricular hypertrophy than electrocardiography, it is not indicated for evaluation of possible hypertension or as an initial study in patients with documented hypertension in the absence of another indication (such as clinical evidence of heart failure).

KEY POINT

- The eighth report of the Joint National Committee recommends a treatment goal of <150/90 mm Hg for patients with hypertension who are ≥60 years.

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Item 39 Answer: B

Educational Objective: Diagnose infection-related glomerulonephritis.

This patient likely has infection-related glomerulonephritis (IRGN) following a streptococcal infection. Supportive evidence includes preceding symptoms of an upper respiratory tract infection suggestive of streptococci (rapid streptococcal antigen test is positive and antistreptolysin O antibodies are elevated), followed by the nephritic syndrome in 1 week, and low C3 levels with normal C4 levels (suggesting an alternative pathway of complement activation, which is typical of IRGN). Most patients will show spontaneous resolution of nephritis with conservative management (antibiotics, blood pressure management, and diuretics).

IgA nephropathy (IgAN) is the most common form of glomerulonephritis. Asymptomatic microscopic hematuria with or without proteinuria is the most common presentation of IgAN, and episodic gross hematuria following an upper respiratory tract infection is a classic presentation. Kidney manifestations usually occur concomitantly with the respiratory infection in IgAN ("synpharyngitic" nephritis), as opposed to the typical 7- to 10-day latent period with IRGN. Moreover, complement levels are typically normal in IgAN, whereas C3 is typically low and C4 is normal in IRGN.

Lupus nephritis may occasionally be precipitated by infections. Patients with lupus typically experience systemic manifestations such as rash and arthritis, although kidney-limited disease is sometimes seen. Both C3 and C4 complement levels are depressed in this condition due to the classical pathway of complement being activated. In IRGN, C3 is typically depleted, with normal levels of C4 due to activation of the alternative pathway of complement.

Small-vessel vasculitis is also associated with glomerulonephritis. However, there are frequently other clinical findings of vasculitis present, and complement levels are typically normal.

KEY POINT

- Infection-related glomerulonephritis is characterized by preceding symptoms of an upper respiratory tract infection suggestive of streptococci, followed by the nephritic syndrome and low C3 levels with normal C4 levels.

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Item 40 Answer: C

Educational Objective: Identify orlistat as a cause of acute kidney injury.

This patient has acute oxalate nephropathy most likely caused by orlistat. Orlistat is thought to cause acute kidney injury (AKI) through enteric hyperoxaluria. Orlistat blocks fat uptake and results in the production of calcium soaps from unabsorbed fat in the small bowel. Calcium soaps reduce the availability of free enteric calcium, preventing binding of oxalate in the gut by calcium, and allowing for increased intestinal uptake of oxalate and subsequent renal oxalate excretion. Excessive renal oxalate excretion predisposes to development of oxalate crystals within the tubules and interstitium as seen in this patient, causing intratubular obstruction and acute kidney injury. Volume depletion and preexisting kidney disease appear to increase the risk of developing orlistat-associated nephropathy.

Aristolochic acid is present in some herbal preparations and weight loss supplements and can cause nephropathy. This condition is characterized by extensive, primarily interstitial, fibrosis with tubular loss, which is not seen on this patient's kidney biopsy. Patients with this condition are also at increased risk for urothelial malignancies.

Ephedrine is associated with nephrolithiasis, and analysis of the stones reveals the presence of ephedrine, norephedrine, and pseudoephedrine. Patients may also have rhabdomyolysis. These findings are not found in this patient, making this an unlikely cause of her AKI.

Phentermine is not known to cause AKI or other kidney disorders.

KEY POINT

- Orlistat may be a cause of acute kidney injury by triggering acute oxalate nephropathy, particularly in patients with volume depletion or chronic kidney disease.

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Weir MA, Beyea MM, Gomes T, et al. Orlistat and acute kidney injury: an analysis of 953 patients. Arch Intern Med. 2011 Apr 11;171(7):703-4. [PMID: 21482850]

Item 41 Answer: B

Educational Objective: Diagnose membranous glomerulopathy.

The most likely diagnosis is membranous glomerulopathy (MG). This patient has evidence of the nephrotic syndrome, with significant protein loss in the urine, hypoalbuminemia, and edema. He also has a pulmonary embolism, a common complication of the nephrotic syndrome. The clinical presentation of MG is indistinguishable from other causes of the nephrotic syndrome, although the propensity for venous thromboembolism, and particularly renal vein thrombosis, is much higher in MG than other disorders associated with the nephrotic syndrome, such as focal

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segmental glomerulosclerosis or minimal change glomerulopathy. The pathophysiology of hypercoagulability in the nephrotic syndrome is not well understood, nor has the mechanism underlying the higher propensity for thromboembolism in MG been well defined. The risk appears to be inversely related to the serum albumin level in MG, and prophylactic anticoagulation is frequently given to patients with MG with a serum albumin level of ≤2.8 g/dL (28 g/L). MG is the most common cause of idiopathic nephrotic syndrome in adult white persons but may also be associated with infections, systemic lupus erythematosus, medications, and certain malignancies. Definitive diagnosis is by kidney biopsy.

The hypercoagulable state is associated with the nephrotic syndrome only, not other kidney syndromes such as acute interstitial nephritis or poststreptococcal glomerulonephritis. Additionally, these disorders typically present with evidence of inflammation on urinalysis and kidney failure, neither of which is present in this patient.

The site of thrombosis in thrombotic microangiopathy is the microvasculature, leading to clinical manifestations such as microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction (including kidney failure). Large-vessel thrombosis does not occur as is present in this case.

KEY POINT

- Although the clinical presentation of membranous glomerulopathy is indistinguishable from other causes of the nephrotic syndrome, the propensity for thromboembolic events is much higher.

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Item 42 Answer: D

Educational Objective: Manage white coat hypertension.

Continued clinical follow-up is appropriate for this patient with white coat hypertension. He has high blood pressure readings in the clinic; however, his ambulatory blood pressure monitor (ABPM) readings do not meet the definition of hypertension. The diagnosis of white coat hypertension is applied to patients with average blood pressure readings ≥140/90 mm Hg in the office and average readings <135/85 mm Hg as determined by ABPM. Daytime (awake) average above 140/90 mm Hg and nighttime (asleep) average above 125/75 mm Hg are also used to diagnose hypertension on ABPM. Analysis of nocturnal readings compared to daytime reading is also helpful. Compared with daytime readings, nocturnal readings are approximately 15% lower ("dipping"). A non-dipping status (failure to drop nocturnal blood pressure by <10%) is associated with more cardiovascular events compared with dipping. This patient dips appropriately at night. Patients with white coat hypertension may have an elevated cardiovascular risk compared with normotensive patients. Moreover, such patients are also at a higher risk for sustained hypertension. Therefore, close observation for sustained hypertension and end-organ damage is recommended in patients with white coat hypertension.

Echocardiography is more sensitive than electrocardiography in detecting evidence of left ventricular hypertrophy. However, it is not used for the diagnosis of hypertension unless there is evidence of end-organ damage or if the information would help guide subsequent treatment. In this patient with a normal ABPM study without evidence of cardiac disease, echocardiography is not indicated.

Evaluation for secondary causes of hypertension such as primary hyperaldosteronism is not indicated in this patient without evidence of sustained hypertension and a normal serum potassium level.

Drug therapy is not recommended unless sustained hypertension or evidence of end-organ damage is present.

KEY POINT

- In patients with white coat hypertension, close observation for the emergence of sustained hypertension or end-organ damage is recommended; drug therapy is not usually required.

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Item 43 Answer: B

Educational Objective: Diagnose thrombotic microangiopathy caused by chemotherapy.

Bevacizumab is the most likely cause of this patient's clinical picture. This patient presents with classic features of thrombotic microangiopathy (TMA), including microangiopathic hemolytic anemia, a low platelet count, and kidney dysfunction. Chemotherapeutic agents known to be associated with TMA include mitomycin C, gemcitabine, tyrosine kinase inhibitors, mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus), and anti-vascular endothelial growth factor (VEGF) inhibitors. VEGF inhibitors are an important class of drugs used in treating metastatic cancer, and they are able to induce a form of microangiopathy very similar to preeclampsia/eclampsia that is associated with severe hypertension and kidney failure. VEGF inhibition by endogenous factors is thought to play a key role in development of preeclampsia/eclampsia, and two VEGF inhibitors, bevacizumab and sunitinib, have been linked to TMA, which typically subsides after stopping the drug. Patients typically present with an insidious onset of kidney failure and hypertension (new or exacerbated). There tends to be a variable amount of proteinuria and a relatively bland urine sediment. The cancer is

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not typically overt (to differentiate from cancer-associated TMA, in which there are widely metastatic lesions at the time of diagnosis of TMA). Plasmapheresis is not usually effective for treatment of VEGF inhibitor–associated TMA and is not indicated.

The other chemotherapeutic agents (5-fluorouracil, leucovorin, oxaliplatin) being administered are not associated with TMA.

KEY POINT

- Two anti-vascular endothelial growth factor inhibitors, bevacizumab and sunitinib, have been linked to thrombotic microangiopathy, which typically subsides after stopping the drug.

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Item 44 Answer: A

Educational Objective: Appropriately time the referral of a patient with chronic kidney disease to a nephrologist.

Nephrologist referral and kidney transplant evaluation should occur now. This patient has severe chronic kidney disease (CKD) and will likely require dialysis within the next 1 to 2 years. All patients with stage G4 or G5 CKD should be referred to a nephrologist for evaluation and optimization of metabolic parameters and preparation for dialysis. Because proper preparation for dialysis can take many months, especially if an arteriovenous fistula must be created for hemodialysis, timely referral is important. Hemodialysis and peritoneal dialysis have similar clinical outcomes; choice of modality should be guided by patient preference, willingness, and ability to participate in self-care. All patients who are willing to consider kidney transplant and do not have absolute medical contraindications should be referred for transplant evaluation once their estimated glomerular filtration rate is below 20 mL/min/1.73 m^2 because they are then eligible to be placed on a waiting list for a transplant. This is especially important because the waiting list is several years long in most parts of the United States, and early listing maximizes the chances of surviving until transplant. Also, if a living donor is identified, it is possible that the patient may receive a preemptive transplant before requiring dialysis. It is important to refer patients with CKD to a nephrologist early in the course of the disease for evaluation because late referral is associated with increased mortality.

Waiting to refer to a nephrologist for 6 months will delay proper preparation for dialysis therapy, dialysis access placement, and transplant evaluation.

Rechecking serum creatinine in 2 weeks is not indicated because this patient has long-standing CKD that is unlikely to be significantly improved after 2 weeks, and this approach will unnecessarily delay referral to a nephrologist.

Continuing current management is incorrect because the patient requires timely preparation for renal replacement therapy and transplant referral, and delays in nephrology referral for patients with severe CKD are associated with increased risk of mortality.

KEY POINT

- All patients with stage G4 or G5 chronic kidney disease should be referred to a nephrologist for management, and referral for transplant evaluation is indicated once the estimated glomerular filtration rate is below 20 mL/min/1.73 m^2.

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Smart NA, Titus TT. Outcomes of early versus late nephrology referral in chronic kidney disease: a systematic review. Am J Med. 2011 Nov;124(11):1073-80.e2. [PMID: 22017785]

Item 45 Answer: D

Educational Objective: Manage diabetic nephropathy.

Continuing this patient's current therapy is the most appropriate management. This patient has long-standing type 2 diabetes mellitus complicated by proliferative retinopathy and neuropathy. She has worsening proteinuria accompanied by a slow decline in kidney function over several years. Her blood pressure is within the desired range, and she is receiving an ACE inhibitor. Continued management is therefore appropriate. With adequate blood pressure control and use of an ACE inhibitor (or angiotensin receptor blocker [ARB]), progression of diabetic nephropathy is slowed but not eliminated. A maximally tolerated dose of an ACE inhibitor or ARB should be tried in an attempt to lower proteinuria as much as possible.

Calcium channel blockers are effective antihypertensive medications in patients with diabetic nephropathy and hypertension, although they do not have the same degree of renoprotection as either ACE inhibitors or ARBs. Because this patient's blood pressure is well controlled and she is already on an ACE inhibitor, there is no indication for the addition of amlodipine.

Adding an ARB (such as losartan) to an ACE inhibitor has not been shown to improve kidney outcomes, and dual angiotensin system inhibition increases the risk of hyperkalemia and acute kidney injury. It is therefore not recommended, even in patients with significant proteinuria on monotherapy with an ACE inhibitor or ARB.

Both ACE inhibitors and ARBs exert their renoprotective effect by decreasing glomerular hyperfiltration by reducing the glomerular filtration rate (GFR). In most patients with normal to moderately impaired kidney function, this medication-induced decrease in GFR is well tolerated, although this may result in a slight increase in the serum creatinine. Given this patient's mild increase in serum creatinine and normal serum electrolytes, there is no indication for reducing the dose of her ACE inhibitor lisinopril, which is beneficial in treating her hypertension and proteinuria.

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KEY POINT

- Adequate blood pressure control and use of an ACE inhibitor or angiotensin receptor blocker has been shown to slow the progression of diabetic nephropathy.

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Item 46 Answer: A

Educational Objective: Diagnose abdominal compartment syndrome.

Bladder pressure measurement is the most appropriate next step in management. Abdominal compartment syndrome (ACS) should be suspected in patients with oliguria or increasing serum creatinine levels who have had abdominal surgery, who have received massive fluid resuscitation, who have a tense abdomen, or who have liver or pancreatic disease with ascites. ACS is typically defined as new organ dysfunction with an intra-abdominal pressure >20 mm Hg. This patient is developing ACS manifested by increased hemodynamic instability, worsening respiratory failure with increased airway pressures and increasing difficulty with oxygenation, a tense abdomen on examination, and oliguric kidney failure. Diagnosis of intra-abdominal hypertension and ACS is accomplished by transduction of bladder pressure. Although medical treatment (diuresis, dialysis, management of ascites) can be tried, surgical decompression of the abdomen is often necessary to definitively treat ACS.

There are no data to support that transfusing patients with severe sepsis to a hemoglobin level above 10 g/dL (100 g/L) improves outcomes. The current Surviving Sepsis Guidelines recommend that, once tissue hypoperfusion has resolved and in the absence of serious comorbidities, erythrocytes should only be transfused when hemoglobin decreases to <7.0 g/dL (70 g/L).

Although this patient's urine sodium is <10 mEq/L (10 mmol/L), clinically he is not intravascularly volume depleted. Therefore, further volume resuscitation is not indicated because it may contribute to worsening organ dysfunction by increasing intra-abdominal pressure.

There is no evidence that hemodynamic monitoring with a pulmonary artery catheter improves clinical outcomes in patients with acute respiratory distress syndrome, and it may be associated with harm.

KEY POINT

- Abdominal compartment syndrome should be suspected in patients with oliguria or increasing serum creatinine levels who have had abdominal surgery, who have received massive fluid resuscitation, who have a tense abdomen, or who have liver or pancreatic disease with ascites.

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Item 47 Answer: A

Educational Objective: Diagnose statin-induced rhabdomyolysis.

The most likely diagnosis is statin-induced rhabdomyolysis associated with atorvastatin therapy as a cause of this patient's acute kidney injury (AKI). This is supported by her symptoms of muscle weakness, physical examination findings, AKI, and urinalysis with blood but no erythrocytes. Myoglobin released from damaged muscle cause renal tubular obstruction, direct nephrotoxicity, intrarenal vasoconstriction, and AKI. Statin-induced rhabdomyolysis is a rare occurrence, and routine testing of muscle enzymes following initiation of statin therapy is not recommended. However, further evaluation is indicated in patients presenting with suggestive symptoms and clinical findings, as in this patient. Risk factors for development of statin-induced myositis include advanced age, female gender, preexisting chronic kidney disease (CKD), diabetes mellitus, hypothyroidism, high-dose statin therapy, and use of medications metabolized through cytochrome P450 3A4, which may increase serum levels of statins (lovastatin, simvastatin, atorvastatin) metabolized through this pathway. Treatment includes discontinuation of the statin, hydration, and management of any associated electrolyte abnormalities.

Hydrochlorothiazide can cause symptoms of weakness from volume depletion, hyponatremia, or hypokalemia. This patient has no evidence of volume depletion on examination, and her serum potassium level is elevated. Although she has hyponatremia, it is mild and does not explain her symptoms or urinalysis findings.

Although hypothyroidism may be associated with myalgia and elevations of serum muscle enzymes, rhabdomyolysis is rare, and initiation of levothyroxine therapy is not associated with worsening muscle symptoms. This patient's lack of myalgia at the time of hospitalization and mild degree of hypothyroidism make hypothyroid myopathy an unlikely diagnosis.

ACE inhibitors such as lisinopril can cause AKI in certain settings such as hypovolemia or renal artery stenosis. However, this patient's clinical presentation and laboratory findings are not consistent with AKI associated with ACE inhibitor therapy.

KEY POINT

- Risk factors for the development of statin-induced rhabdomyolysis include advanced age, female gender, preexisting chronic kidney disease, diabetes mellitus, hypothyroidism, high-dose statin therapy, and use of medications metabolized through cytochrome P450 3A4.

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Item 48 Answer: C

Educational Objective: Diagnose acquired cystic kidney disease and renal cell carcinoma in a patient with end-stage kidney disease.

The most likely diagnosis is renal cell carcinoma. The patient has acquired cystic kidney disease (ACKD), which becomes more common and progresses during the course of end-stage kidney disease (ESKD); the incidence of ACKD rises dramatically as time on dialysis increases. Patients with ACKD typically have a large number of small bilateral kidney cysts and reduced kidney size. For unclear reasons, patients with ACKD have an approximately 30-fold increased risk for developing renal cell carcinoma; despite this, routine screening for this malignancy is not recommended. However, clinicians should have a high level of suspicion for renal cell carcinoma in patients with ESKD who have flank pain or hematuria that may be suggestive of the diagnosis. Despite the relatively high prevalence of renal cell carcinoma in patients with ACKD, it is an uncommon cause of death in patients with ESKD.

The hallmark of autosomal dominant polycystic kidney disease (ADPKD) is large kidneys with multiple kidney cysts, usually originating in the renal collecting duct. Most patients with ADPKD have a positive family history for cystic kidney disease and/or chronic kidney disease. Diagnosis may be complicated by the fact that a hemorrhagic kidney cyst is usually indistinguishable from a solid renal mass on ultrasound. However, in this patient without a family history, small kidneys on ultrasound, and cysts scattered throughout the renal parenchyma, ADPKD with a hemorrhagic renal cyst is unlikely.

Renal angiomyolipomas and bilateral renal cysts are associated with tuberous sclerosis complex (TSC). However, because this is an autosomal dominant disease, there is almost always a positive family history. Additionally, TSC is a systemic disorder with lesions typically present in various organs and tissues and would be a far less common cause of kidney tumors in a patient with ESKD.

Transitional cell or urothelial carcinomas arise from the mucosal surfaces of the urethra, bladder, and ureters and may also occur in the renal pelvis and calyces; in the upper urinary tract, transitional cell carcinomas also tend to be multifocal and only uncommonly form mass lesions within the kidney. This patient's mass is located in the renal parenchyma, and there is not an increased risk of transitional cell carcinoma with ACKD, making this a less likely diagnosis.

KEY POINT

- Acquired cystic kidney disease is associated with a large number of small bilateral kidney cysts, reduced kidney size, and a markedly increased risk for developing renal cell carcinoma.

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Item 49 Answer: A

Educational Objective: Screen a patient with risk factors for chronic kidney disease.

Urine albumin excretion measurement is appropriate for this patient with risk factors for chronic kidney disease (CKD). Patients with diabetes mellitus are at a markedly increased risk of CKD, and treatment of patients with diabetes and moderately increased albuminuria (formerly known as microalbuminuria) using ACE inhibitors or angiotensin receptor blockers (ARBs) can reduce the risk of progression to overt nephropathy. Moreover, determining the level of albuminuria and estimated glomerular filtration rate is important for detecting the presence of CKD and accurately staging CKD if present. CKD staging has important implications with regard to clinical prognosis. Guidelines differ among several medical organizations regarding the optimal approach to CKD screening. Whereas the American College of Physicians guidelines state that there is insufficient evidence to support or discourage screening for CKD in persons with CKD risk factors such as diabetes, the National Kidney Foundation and the American Diabetes Association support screening for kidney disease in all patients with diabetes.

There is no evidence to support the value of kidney ultrasonography in persons who have no clinical evidence of kidney disease and no family history of genetic kidney disease such as autosomal dominant polycystic kidney disease.

Dipstick urinalysis is not sufficiently sensitive to detect the presence of moderately increased albuminuria; the results are semiquantitative, and estimations of proteinuria can be significantly affected by urine concentration.

Although ARBs have been demonstrated to reduce the risk of progression from moderately increased albuminuria to overt diabetic nephropathy, no studies have demonstrated a beneficial effect of these medications in patients who do not have increased urine albumin excretion or existing hypertension. It remains unknown whether ARBs or ACE inhibitors are protective in patients with moderately increased albuminuria due to etiologies other than diabetic nephropathy.

KEY POINT

- Patients with risk factors for chronic kidney disease should be screened using laboratory studies, most commonly determining the estimated glomerular filtration rate and urine testing for protein or albumin.

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Item 50 Answer: A

Educational Objective: Treat interstitial nephritis by discontinuing a medication.

Discontinuing omeprazole is appropriate in this patient who may have interstitial nephritis as a cause of chronic tubulointerstitial disease. In contrast to acute kidney injury, chronic tubulointerstitial disease develops over months to years and is a cause of slowly declining kidney function. Chronic tubulointerstitial disease most commonly results from previous injury due to an episode of acute interstitial nephritis, but it can also result from ongoing, subacute interstitial nephritis and other glomerular, vascular, or obstructive diseases that may cause irreversible injury to the tubules and interstitium, even with treatment or resolution of the initial disease process. Symptoms and physical examination findings in patients with chronic tubulointerstitial disease can be minimal or absent unless an active associated disease is present; therefore, the diagnosis is often discovered by abnormalities detected on laboratory testing done for other purposes. This patient was noted to have progressively worsening kidney function, with the only abnormality being mild leukocytosis on urinalysis and subnephrotic-range proteinuria. Evaluation of chronic tubulointerstitial disease is focused on identification of potentially treatable causes. Because proton pump inhibitors are associated with interstitial nephritis, discontinuation of omeprazole is appropriate in this patient.

Although any drug may cause interstitial nephritis, there are no case reports of tamsulosin-induced interstitial nephritis. Stopping tamsulosin may exacerbate the benign prostatic hyperplasia, which could lead to postrenal acute kidney injury.

A 24-hour urine collection may be useful for measuring kidney function and quantifying proteinuria but would not be helpful in establishing the cause of this patient's declining kidney function.

Duplex ultrasonography can be useful for diagnosing renal artery stenosis, but this patient's clinical features of pyuria, mild proteinuria, normal blood pressure, and symmetric kidney size are not consistent with renal artery disease, making this study unnecessary.

KEY POINT

- Proton pump inhibitors are a potentially treatable cause of chronic tubulointerstitial disease.

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Chang YS. Hypersensitivity reactions to proton pump inhibitors. Curr Opin Allergy Clin Immunol. 2012 Aug;12(4):348-53. [PMID: 22744268]

Item 51 Answer: B

Educational Objective: Treat a patient with cardiorenal syndrome.

Continuing intravenous diuretic therapy is the most appropriate next step in management. In acute decompensated heart failure, elevated renal venous pressure can cause distended renal venules with increased tubular fluid pressure and backleak, leading to venous congestion and cardiorenal syndrome (CRS). This patient has CRS, defined as a change in function of either the heart or kidneys that may influence the function of the other organ system. CRS is categorized into five types: 1) acute heart failure leading to acute kidney injury (AKI) (CRS1), 2) chronic heart failure leading to chronic kidney disease (CKD), 3) AKI leading to acute heart failure, 4) CKD leading to cardiac dysfunction (heart failure, coronary artery disease, arrhythmias), and 5) systemic conditions leading to simultaneous heart and kidney dysfunction (such as sepsis). Management of CRS may be challenging because treatment of one organ system may cause worsening of the other. In patients with heart failure–related CRS, treatment is directed toward improving cardiac function and fluid balance, which may optimize kidney function. However, it is common to see mild to moderate worsening of kidney function associated with treatment of volume overload until fluid balance is achieved. In general, diuresis in heart failure should be maintained until fluid retention (as seen by elevated central venous pressure and peripheral edema) is resolved, even if this results in asymptomatic mild to moderate decreases in kidney function that are followed closely.

Nesiritide, a recombinant human B-type natriuretic peptide that acts as a vasodilator, is available for treatment of selected patients with acute decompensated heart failure. However, there is no evidence that nesiritide improves kidney function when used in this setting and is therefore an inappropriate addition to therapy for this purpose.

Ultrafiltration, or the removal of plasma water through an extracorporeal circuit, has been used in patients unresponsive to diuretics; however, this patient has responded to diuretic therapy, and ultrafiltration is not indicated at present.

Excessive concern about precipitating kidney failure can lead to underutilization of diuretics and persistent volume overload, which may reduce the efficacy of ACE inhibitors and increase the risk of carvedilol-induced decompensated heart failure.

KEY POINT

- In patients with heart failure–related cardiorenal syndrome, treatment is directed toward improving cardiac function and fluid balance, which may optimize kidney function.

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Item 52 Answer: A

Educational Objective: Diagnose chronic hypertension in a pregnant patient.

Chronic hypertension is the most likely diagnosis. Hypertension prior to the 20th week of gestation is most

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consistent with previously undiagnosed chronic hypertension, which may go undetected in healthy women because of a minimal need for medical evaluation prior to pregnancy. As in nonpregnant patients, chronic hypertension may be primary (formerly known as essential) or secondary. This patient presents at the 12th week of gestation with persistently elevated blood pressures since her pregnancy was discovered, suggesting that her hypertension predated her pregnancy, and is likely primary because she has no other clinical features or laboratory study results to suggest a different cause. The 2013 American College of Obstetricians and Gynecologists (ACOG) guidelines recommend treating persistent blood pressure elevations of >160/105 mm Hg in women with chronic hypertension, with a goal blood pressure with medical therapy in these patients being 120-160/80-105 mm Hg.

The diagnosis of gestational hypertension requires consistent hypertension after the 20th week of gestation without preexisting hypertension or features of preeclampsia and must resolve within 12 weeks of delivery. Because this patient is persistently hypertensive early in her pregnancy, gestational hypertension is not likely.

Normal physiologic changes associated with pregnancy include increased cardiac output and decreased systemic vascular resistance and blood pressure. Blood pressure elevations to the level seen in this patient are not normally seen in pregnancy, when blood pressures are usually much lower.

Preeclampsia requires the combination of new-onset hypertension after 20 weeks of pregnancy and end-organ damage such as proteinuria, kidney dysfunction, thrombocytopenia, abnormal liver chemistry tests, pulmonary edema, and cerebral or visual symptoms.

KEY POINT

- Hypertension prior to the 20th week of gestation is most consistent with previously undiagnosed chronic hypertension, which may go undetected in healthy women because of a minimal need for medical evaluation prior to pregnancy.

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Item 53 Answer: B

Educational Objective: Diagnose hyperosmolar hyponatremia.

The most likely diagnosis is hyperosmolar hyponatremia, caused by this patient's significantly elevated plasma glucose level. The patient's elevated plasma osmolality indicates the presence of a hyperosmolar state. Hyperglycemia causes the osmotic translocation of water from the intracellular to the extracellular fluid compartment, which results in a decrease in the serum sodium level by approximately 1.6 mEq/L (1.6 mmol/L) for every 100 mg/dL (5.6 mmol/L) increase in the plasma glucose above 100 mg/dL (5.6 mmol/L). Hyperosmolar hyponatremia can also be the result of exogenously administered solutes such as mannitol or sucrose.

Pseudohyponatremia is caused by significant hyperlipidemia or the presence of paraproteins in the serum. In these situations, the laboratory measurement of plasma glucose is erroneously low, and the plasma osmolality is normal. This patient has a high plasma osmolality, which is not seen in pseudohyponatremia.

Hypothyroidism, adrenal insufficiency, and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) are associated with hypo-osmolar hyponatremia caused by a decrease in the excretion of free water and are not compatible with the patient's hyperosmolality. Although lung cancer is a common cause of SIADH and may be present in this patient with a lung mass, his laboratory studies are not consistent with this being the cause of his hyponatremia.

Reset osmostat refers to a downward setting of the level at which sensors of plasma osmolality trigger the release of antidiuretic hormone and is associated with quadriplegia, tuberculosis, advanced age, pregnancy, psychiatric disorders, and chronic malnutrition. This lowered setpoint leads to stable, mild hypo-osmolar hyponatremia, which is inconsistent with this patient's findings.

KEY POINT

- Hyperglycemia causes the osmotic translocation of water from the intracellular to the extracellular fluid compartment, which results in a decrease in the serum sodium level by approximately 1.6 mEq/L (1.6 mmol/L) for every 100 mg/dL (5.6 mmol/L) increase in the plasma glucose above 100 mg/dL (5.6 mmol/L).

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Item 54 Answer: D

Educational Objective: Identify tramadol overdose as a cause of respiratory acidosis.

Tramadol, a weak opioid agonist, is the most likely cause of this patient's respiratory findings. She has primary respiratory acidosis characterized by an elevation in P_{CO_2}, a decrease in pH, and a slight increase in bicarbonate. This patient has laboratory findings that suggest an acute onset. For each 10 mm Hg (1.3 kPa) increase in P_{CO_2}, serum bicarbonate increases acutely by 1.0 to 2.0 mEq/L (1.0-2.0 mmol/L) due to the extracellular-to-intracellular shift of hydrogen ions as an immediate compensatory mechanism. Later, renal compensation leads to increased bicarbonate generation, and, after 24 to 48 hours, leads to an increase in serum bicarbonate of 3.0 to 4.0 mEq/L (3.0-4.0 mmol/L) for every 10 mm Hg (1.3 kPa) increase in P_{CO_2}. Primary respiratory acidosis is due to decreased effective ventilation, often noted with opioid overdose, leading to hypercapnia and retention of hydrogen

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ions. Respiratory acidosis can also result from intrinsic lung pathology or from processes that impede ventilation.

The early phase of acetaminophen overdose is often not associated with any acid-base abnormality. After 72 to 96 hours, patients will often develop an increased anion gap metabolic acidosis related to lactic acidosis. This patient's anion gap is only 11 with no evidence of a metabolic acidosis, making acetaminophen overdose an unlikely cause of her acid-base disorder.

Although decreased respiratory drive can occur in the setting of salicylate intoxication in the later stages, it is more commonly associated with a mixed acid-base abnormality, including an increased anion gap acidosis and respiratory alkalosis, making this an unlikely diagnosis for this patient.

NSAID overdose typically presents with azotemia and hyperkalemia in addition to an increased anion gap metabolic acidosis (primarily a lactic acidosis), making this diagnosis unlikely in this patient.

KEY POINT

- Primary respiratory acidosis is due to decreased effective ventilation, often noted with opioid overdose, leading to hypercapnia and retention of hydrogen ions.

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Adrogué HJ, Madias NE. Secondary responses to altered acid-base status: the rules of engagement. J Am Soc Nephrol. 2010 Jun;21(6):920-3. [PMID: 20431042]

Item 55 Answer: B

Educational Objective: Identify hydroxyethyl starch as a cause of acute kidney injury and increased mortality.

Resuscitation therapy with hydroxyethyl starch (HES) is most likely to lead to the development of acute kidney injury (AKI). This patient has septic shock and requires fluid resuscitation to prevent or limit multi-organ failure and reduce mortality. Repetitive fluid challenges are performed by giving a 500- to 1000-mL bolus of crystalloid over short intervals while assessing response to target central venous pressure. Most patients need 4 to 6 L of fluid in the first 6 hours, and a frequent error is underestimating the intravascular volume deficit and the amount of fluid required. The fluid input is typically greater than output owing to vasodilation and capillary leak. HES is a synthetic colloid that is associated with an increased risk of AKI, increased requirement of renal replacement therapy, a trend toward increased blood product transfusion, and increased mortality. HES accumulates in the proximal renal tubular epithelial cell, resulting in vacuolization and swelling of the proximal renal tubular cell, tubular obstruction and injury, and an osmotic nephrosis. As a result, the 2013 Surviving Sepsis Campaign recommends against using any HES in patients with severe sepsis.

Volume resuscitation can be achieved with either crystalloid or colloid solutions. The crystalloid solutions are lactated Ringer solution and 0.9% sodium chloride; the colloid solutions include albumin. Evidence from randomized trials and meta-analyses have found no convincing difference between using crystalloid solutions such as normal saline and lactated Ringer and albumin solutions in the treatment of severe sepsis or septic shock; however, colloid is far more expensive.

KEY POINT

- Hydroxyethyl starch is associated with an increased risk of acute kidney injury, increased requirement of renal replacement therapy, a trend toward increased blood product transfusion, and increased mortality and is not recommended in patients with severe sepsis.

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Item 56 Answer: A

Educational Objective: Manage a patient at risk for contrast-induced nephropathy.

In addition to discontinuing diuretic therapy, the most appropriate periprocedural management for this patient is to begin intravenous isotonic saline. She is at risk for contrast-induced nephropathy (CIN), and administration of intravenous isotonic saline (1-1.5 mL/kg/h) 3 to 12 hours before the procedure and continued for 6 to 24 hours afterward has been shown to decrease the incidence of CIN in high-risk patients. Risk factors include age older than 75 years, diabetes mellitus, chronic kidney disease, conditions of decreased renal perfusion, and concurrent use of nephrotoxic drugs. Therefore, this patient is at high risk for CIN. In addition to intravenous isotonic saline, other strategies to minimize the risk for CIN include discontinuation of potentially nephrotoxic medications, minimization of contrast volume, and use of low- or iso-osmolal contrast media. The benefit of hydration regimens utilizing isotonic sodium bicarbonate is comparable to isotonic sodium chloride and is not considered to be of significant benefit relative to normal saline.

The benefit of *N*-acetylcysteine in patients at risk for CIN remains controversial, and results from trials are inconsistent. It is therefore not recommended as routine treatment to prevent CIN.

Prophylactic hemodialysis has not been shown to provide benefit compared with medical therapy alone for patients at risk for CIN.

Discontinuation of ACE inhibitors or angiotensin receptor blockers has not been clearly shown to decrease the risk of CIN. Although ACE inhibitors should be discontinued in most cases of acute kidney injury, they can be continued in patients with stable kidney function.

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KEY POINT

- Administration of intravenous isotonic saline is appropriate for patients at risk for contrast-induced nephropathy.

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Item 57 Answer: C

Educational Objective: Evaluate kidney function in a patient with acute interstitial nephritis.

In addition to discontinuing omeprazole, repeat kidney function testing in 5 to 7 days is the most appropriate management for this patient with acute interstitial nephritis (AIN). AIN is a condition in which kidney dysfunction results from infiltration of inflammatory cells into the kidney interstitium. It may be associated with drugs, infection, autoimmune diseases, and malignancy, with drug-induced AIN being the most common. Many patients with AIN may be asymptomatic or present with mild, nonspecific symptoms; only 10% to 30% have the classic triad of fever, rash, and eosinophilia. Urinalysis may reveal mild proteinuria, leukocytes, erythrocytes, and leukocyte casts. Drug-induced AIN should be considered in any patient exposed to a potentially offending drug who presents with unexplained acute kidney injury (AKI). Drug-induced AIN is characterized by a slowly increasing serum creatinine 7 to 10 days after exposure; however, it can occur within 1 day of exposure if the patient has been exposed previously. Drug-induced AIN can also occur months after exposure, often with NSAIDs and proton pump inhibitors (PPIs). This patient has a clinical picture consistent with AIN based on clinical and laboratory evidence of kidney injury and urinalysis showing erythrocytes, leukocytes, and leukocyte casts after recently being started on the PPI omeprazole. Discontinuation of the offending agent is the mainstay of therapy. In patients with mild elevations of serum creatinine and minimal clinical findings, stopping the causative drug with close follow-up is usually adequate therapy.

Kidney biopsy is usually not necessary to diagnose AIN, particularly in patients with a consistent clinical and laboratory picture, as seen in this patient. However, kidney biopsy may be indicated in situations where there are inconsistent clinical and laboratory findings, or if kidney function does not improve immediately upon stopping the offending agent.

The role of glucocorticoids in AIN is controversial, with conflicting evidence of benefit in clinical studies. Glucocorticoids are therefore generally reserved for patients who have not responded to discontinuation of the offending agent.

The presence of urine eosinophils detected by Hansel staining of the urine sediment has been classically associated with the diagnosis of AIN but is not specific because they may be associated with other causes of AKI (such as glomerulonephritis), and the absence of urine eosinophils does not exclude AIN. Therefore, this testing is not clinically useful in this patient.

KEY POINT

- Discontinuation of the offending agent is the mainstay of therapy for drug-induced acute interstitial nephritis.

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Item 58 Answer: C

Educational Objective: Treat a patient with struvite nephrolithiasis by removing the stone.

The most appropriate next step in management is to remove the struvite stone in the left renal pelvis. Struvite stones are composed of magnesium ammonium phosphate and occur only when ammonium production is increased, which elevates the urine pH and decreases the solubility of phosphate. This is most commonly a consequence of chronic upper urinary tract infection (UTI) with a urease-producing organism, such as *Proteus* or *Klebsiella*. Struvite stones can grow rapidly and become large, filling the entire renal pelvis and taking on a characteristic "staghorn" shape. Although struvite stones affect less than 10% of patients with kidney stones, they occur more commonly in women and in patients predisposed to chronic or recurrent UTI, including those with urologic diversions or neurogenic bladder.

Although treatment of the initial upper UTI is important to prevent struvite stone development, once struvite stones are formed, they are difficult to treat medically, including with chronic antibiotics. Antibiotics may not penetrate the stone, and colonizing bacteria may create an alkaline environment within the stone that promotes continued or recurrent UTI, stone growth, and chronic inflammatory damage to the kidney. Because of this, stone removal is indicated in most cases, and kidney outcomes have been shown to be improved when struvite stones are removed compared with medical therapy. Removal is commonly by percutaneous nephrolithotomy, shock wave lithotripsy, or a combination of both procedures.

Dietary phosphate reduction and urine acidification would be expected to discourage struvite stone formation but are of minimal effectiveness once struvite stones have developed.

KEY POINT

- In most patients with known struvite stones, removal of the stones is indicated.

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Item 59 Answer: B

Educational Objective: Evaluate for HIV infection in a patient with focal segmental glomerulosclerosis.

The most appropriate test to perform is an HIV antibody test in this patient with focal segmental glomerulosclerosis (FSGS). FSGS is the cause of idiopathic nephrotic syndrome in 25% of cases. FSGS may also be secondary to another process, including hyperfiltration injury to the glomerulus as may occur in chronic hypertension, diabetes mellitus, and conditions in which kidney mass is reduced (progressive kidney disease, obesity, sickle cell disease, reflux nephropathy, or after nephrectomy). Direct injury to podocytes may also cause FSGS as seen with certain drugs (pamidronate, interferon) and infections, including HIV. This patient's kidney biopsy results are indicative of the collapsing variant of FSGS, which is classic for HIV-associated glomerulopathy. Therefore, evaluation for HIV infection as a cause of this patient's FSGS is the most appropriate next diagnostic step. In the early stages of HIV-associated glomerulopathy, antiretroviral therapy and angiotensin system blockers may halt disease progression, thus an early diagnosis is important.

Hepatitis B is typically associated with membranous glomerulopathy, and hepatitis C with cryoglobulinemic glomerulonephritis. Serum and urine electrophoresis can be used to test for monoclonal gammopathies. The treponemal antibody test is used to test for syphilis, which is typically associated with membranous nephropathy. None of these disorders is associated with the collapsing glomerulopathy seen on this patient's kidney biopsy.

KEY POINT

- HIV infection is typically associated with the collapsing form of focal segmental glomerulosclerosis; in the early stages, antiretroviral therapy and angiotensin system blockers may halt disease progression.

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Item 60 Answer: C

Educational Objective: Diagnose glomerulonephritis.

Kidney biopsy is the most appropriate next step in management. This patient has worsening kidney function and new hypertension associated with significant abnormalities on urinalysis, including proteinuria, leukocytes indicating inflammation, hematuria with dysmorphic erythrocytes (acanthocytes), and erythrocyte casts on microscopy. These findings strongly suggest glomerulonephritis. Constitutional symptoms such as fever and arthralgia, as well as nonblanching rash (palpable purpura) and weight loss, further suggest vasculitis as the most likely etiology. Urgent serologic evaluation and kidney biopsy are indicated to diagnose the cause of glomerulonephritis and guide management.

Although this patient has a history of urinary tract infection (UTI), reports fever, and has leukocytes on her urinalysis, her specific lack of symptoms of UTI or other findings consistent with this diagnosis (no costovertebral angle tenderness or bacteria on microscopic urinalysis) make this a less likely diagnosis. UTI would also not be expected to lead to development of hypertension or kidney failure. Therefore, antibiotics are not indicated.

Cystoscopy is typically used to evaluate for hematuria due to a bladder source, such as bladder cancer. The hematuria associated with a bladder source of bleeding is usually structurally normal compared with the dysmorphic erythrocytes seen in this patient; acanthocytes suggest a glomerular source of bleeding. Also, a bladder source of bleeding, such as a malignancy, would not explain the other findings seen on her urinalysis (significant proteinuria, leukocytosis) or her new hypertension and kidney failure, making cystoscopy an inappropriate next step in management.

Kidney ultrasonography can identify structural abnormalities, including nephrolithiasis. However, in this patient with a clinical picture consistent with acute glomerulonephritis, kidney imaging would not be of high diagnostic yield.

KEY POINT

- Urgent serologic evaluation and kidney biopsy are indicated to diagnose the cause of glomerulonephritis and guide management.

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Item 61 Answer: B

Educational Objective: Manage overcorrection of sodium in a patient with severe asymptomatic hyponatremia at risk for osmotic demyelination syndrome.

Desmopressin intravenously with 5% dextrose is the most appropriate treatment. The patient presented with a 5-day history of gastroenteritis symptoms and severe hyponatremia with a normal neurologic examination. She has chronic asymptomatic hyponatremia that was likely from volume depletion, causing an appropriate elevation in antidiuretic hormone (ADH) secretion, which caused the hyponatremia by retaining the free water she was drinking to maintain hydration. Volume repletion in the hospital led to suppression of ADH production with a subsequent water diuresis, leading to rapid correction. Rapid correction in chronic asymptomatic hyponatremia increases the risk for osmotic demyelination syndrome (ODS), especially in women, which may be delayed for a few days after overcorrection. Overcorrection is considered to be an increase of >8.0 mEq/L (8.0 mmol/L) of

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the serum sodium within the first 24 hours or >16 mEq/L (16 mmol/L) within the first 48 hours. Desmopressin will terminate the water diuresis, and if given alone will maintain the serum sodium around the current level of 128 mEq/L (128 mmol/L), which still represents overcorrection. Desmopressin intravenously with 5% dextrose will stop the water diuresis and further lower the serum sodium. The 5% dextrose should be given in sufficient volume to reverse the serum sodium level to 120 mEq/L (120 mmol/L) over the first 24 hours and then allowing slow correction.

Fluid restriction alone is inappropriate because the serum sodium will continue correction toward normal and increase the risk of ODS, as will fluid restriction with salt tablets, which will increase the rate of correction.

Providing no further intervention would not reverse the overcorrection, and the patient's serum sodium would likely continue to return to normal, further increasing her risk for ODS.

KEY POINT

- Overcorrection of chronic asymptomatic hyponatremia is associated with the development of osmotic demyelination syndrome and should be reversed using desmopressin with 5% dextrose.

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Item 62 Answer: D

Educational Objective: Manage intracranial cerebral aneurysm screening in a patient with autosomal dominant polycystic kidney disease.

No screening is necessary for this asymptomatic patient with autosomal dominant polycystic kidney disease (ADPKD). Intracranial cerebral aneurysms (ICAs) can be detected in 10% to 12% of patients with ADPKD, and a ruptured ICA resulting in a subarachnoid or intracerebral hemorrhage is the most serious extrarenal complication of ADPKD. The prevalence of ICA is higher in patients with ADPKD who have a family history of known ICA or hemorrhagic stroke. Therefore, screening using MR angiography is currently only recommended for patients with ADPKD thought to be at high risk, including those with a family history of aneurysm or subarachnoid hemorrhage or those with a previous rupture. In addition, patients with ADPKD who have high-risk occupations in which a rupture would affect the lives of others (such as driving a school bus) should be screened. There are no differences in screening recommendations based on age. Therefore, there is no indication for screening for ICA in this patient with no symptoms suggestive of possible ICA, no family history of known ICA or hemorrhage, and a low-risk occupation.

KEY POINT

- For patients with autosomal dominant polycystic kidney disease, screening for intracranial cerebral aneurysms using MR angiography is only recommended for those with a family history of aneurysm or subarachnoid hemorrhage, those with a previous rupture, or those with high-risk occupations in which a rupture would affect the lives of others.

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Item 63 Answer: A

Educational Objective: Treat chronic hyponatremia.

In addition to discontinuing fluoxetine, fluid restriction is the appropriate treatment for this patient. She is euvolemic and has hyponatremia with a decreased plasma osmolality and an inappropriately increased urine osmolality. This clinical and laboratory presentation is highly suggestive of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). SIADH has many causes, including various drugs such as selective serotonin reuptake inhibitors like fluoxetine. The initial treatment of asymptomatic patients with SIADH includes management of the underlying cause if possible and free water restriction (in practical terms, fluid restriction) without limiting sodium intake. Discontinuation of fluoxetine should result in resolution of the SIADH with normalization of the serum sodium. In the interim, fluid restriction with a decrease in intake less than urine output will result in a gradual increase in the serum sodium.

Although the serum sodium is significantly decreased, she has no specific neurologic symptoms, which suggests that the hyponatremia is chronic. Rapid normalization of this patient's serum sodium with hypertonic saline would place her at risk for osmotic demyelination syndrome, which may result in severe neurologic symptoms such as paraplegia, dysarthria, dysphagia, diplopia, and locked-in syndrome. Because of this risk, treatment with hypertonic saline is usually limited to patients with severely symptomatic hyponatremia (such as mental status changes or seizures) to rapidly increase the serum sodium.

Treatment with isotonic saline may correct hyponatremia if it is secondary to hypovolemia, but this patient is euvolemic and most likely has SIADH. In this patient, isotonic saline alone, without concomitant fluid restriction, results in volume expansion but may not correct and may possibly worsen the hyponatremia because of inappropriate retention of the water associated with the infusion.

Oral demeclocycline results in renal resistance to antidiuretic hormone and can be effective in treating patients with SIADH. However, it has been associated with acute kidney injury and is generally reserved for patients who have failed other therapies. It should be used with caution in patients with preexisting kidney or liver disease.

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Tolvaptan, a vasopressin receptor antagonist, results in the excretion of electrolyte free water and is effective in raising the serum sodium in patients with SIADH. It should be used with caution in the treatment of severe, symptomatic hyponatremia, which is not seen in this patient, and as a last resort when other treatments have failed. Because severe liver injury has been reported with its use, the FDA recommends that it not be used in patients with liver disease and that it be used for no more than 30 days.

KEY POINT

- The initial treatment of asymptomatic patients with syndrome of inappropriate antidiuretic hormone secretion includes management of the underlying cause if possible and fluid restriction without limiting sodium intake.

Bibliography

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Item 64 Answer: D

Educational Objective: Manage stage 1 hypertension in an older, frail patient.

Continuing the current treatment regimen with the calcium channel blocker amlodipine is appropriate. This 76-year-old patient has stage 1 hypertension and systolic blood pressure measurements in the range of 140 to 150 mm Hg. The treatment goal recommended in the eighth report of the Joint National Committee (JNC 8) for patients with hypertension who are ≥60 years is <150/90 mm Hg. Although she is near this goal, the benefits of further blood pressure reduction must be balanced with the potential risks of increasing a dose, changing the antihypertensive agent, or adding additional antihypertensive agents. Importantly, a recent study defining frailty as the inability to walk 6 meters in less than 8 seconds demonstrated no association with hypertension and mortality, and, in those who were unable to complete the walk test, a reduction in mortality was noted with increased blood pressure. This suggests that the risk of complications, morbidity, and mortality related to lower blood pressure in frail individuals may supersede the potential benefit of lower blood pressure goals.

Although 24-hour ambulatory blood pressure monitoring may be more accurate in defining this patient's blood pressure, home blood pressure monitoring is a reasonable alternative because it is less expensive. Furthermore, additional information is not likely to influence therapy.

KEY POINT

- The risk of complications, morbidity, and mortality related to lower blood pressure in frail individuals may supersede the potential benefit of lower blood pressure goals.

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Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. Arch Intern Med. 2012 Aug 13;172(15):1162-8. [PMID: 22801930]

Item 65 Answer: D

Educational Objective: Diagnose the syndrome of inappropriate antidiuretic hormone secretion.

This patient's history and clinical presentation are most consistent with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). On physical examination, she is clinically euvolemic. The appropriate physiologic response to hypo-osmolality in a euvolemic patient is suppression of antidiuretic hormone (ADH) with resultant increase in free water clearance, with urine osmolality less than plasma osmolality. In contrast, this patient demonstrates evidence for increased ADH with hyponatremia and urine osmolality significantly and inappropriately greater than plasma osmolality in spite of her euvolemic status and no apparent stimulus for ADH release.

Because water excretion is, in part, solute dependent, severe limitations in solute intake decrease free water excretion, and hyponatremia may develop in this setting with only modest increases in fluid intake. This syndrome is termed *beer potomania* when observed in patients with chronic alcohol abuse and low solute intake. This patient's relatively high urine osmolality makes beer potomania an unlikely diagnosis.

The most common renal consequence of chronic lithium ingestion is nephrogenic diabetes insipidus; this disorder presents with polyuria and hypernatremia, which are not seen in this patient.

Primary polydipsia should always be considered in the differential diagnosis of patients with mental illness and hyponatremia, particularly those with schizophrenia who are taking psychotropic drugs. Primary polydipsia presents with hyponatremia, decreased plasma osmolality, and decreased urine osmolality, reflecting suppressed ADH levels in response to water overload. Patients with primary polydipsia may also present with abnormalities of ADH regulation such as transient stimulation of ADH release during psychotic episodes and increased renal response to ADH so that at the same levels of ADH, patients who are psychotic may have higher urine osmolalities and a downward resetting of the osmostat that regulates ADH release. Thus, the urine of patients who are psychotic and have primary polydipsia may not be as dilute as would be expected. The significant elevation in urine osmolality makes SIADH the more likely diagnosis in this patient.

KEY POINT

- The syndrome of inappropriate antidiuretic hormone secretion is associated with clinical euvolemia, hypo-osmolar hyponatremia, and urine osmolality inappropriately greater than plasma osmolality.

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Item 66 Answer: B

Educational Objective: Diagnose type 1 (hypokalemic distal) renal tubular acidosis.

The most likely diagnosis is type 1 (hypokalemic distal) renal tubular acidosis (RTA), which results from a defect in urine acidification in the distal tubule with impaired excretion of hydrogen ions, most commonly caused by decreased activity of the proton pump in distal tubular cells. Because of the inability to excrete hydrogen ions, patients develop a metabolic acidosis with compensatory hyperchloremia, resulting in a normal anion gap (8 mEq/L [8 mmol/L] in this patient) and the inability to acidify urine below a pH of 6.0, even after an acid load. The urine pH is therefore almost always inappropriately elevated for the degree of acidemia, and there is a positive urine anion gap. The same defects also cause potassium wasting, and the increased proximal resorption of citrate that occurs with metabolic acidosis leads to hypocitraturia and increased risk of calcium phosphate kidney stones and nephrocalcinosis. Type 1 (hypokalemic distal) RTA is associated with genetic causes, autoimmune disorders, nephrocalcinosis/hypercalciuria, dysproteinemias, drugs/toxins, and tubulointerstitial disease; this patient likely has sicca complex secondary to Sjögren syndrome and kidney involvement with interstitial nephritis.

Acetaminophen is associated with pyroglutamic acidosis (also known as 5-oxoprolinuria), which causes an increased anion gap metabolic acidosis and is less likely to cause a pure normal anion gap metabolic acidosis.

Type 2 (proximal) RTA involves a defect in regenerating bicarbonate in the proximal tubule and is characterized by a normal anion gap metabolic acidosis, hypokalemia, glycosuria (without hyperglycemia), low-molecular-weight proteinuria, and renal phosphate wasting. However, distal urine acidification mechanisms are intact, and the urine pH is usually less than 5.5 without alkali therapy. This patient's high urine pH, absence of glycosuria, and normal urinalysis are inconsistent with type 2 (proximal) RTA.

Type 4 (hyperkalemic distal) RTA is associated with a urine pH <5.5 and hyperkalemia as a result of hypoaldosteronism, neither of which is seen in this patient.

KEY POINT

- Type 1 (hypokalemic distal) renal tubular acidosis results from a defect in urine acidification in the distal tubule with impaired excretion of hydrogen ions.

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Item 67 Answer: D

Educational Objective: Understand the risks and benefits of kidney transplantation.

Kidney transplantation would be the most likely strategy to provide this patient with the best long-term survival. Although there is an increase in short-term morbidity and mortality following transplantation, there is strong evidence that kidney transplantation decreases mortality and improves quality of life over the long term. Even though increased recipient age is also associated with reduced patient and allograft survival than younger patients after transplant, carefully selected older patients also benefit from kidney transplantation, and many centers therefore do not have an absolute age cutoff for transplant recipients. Moreover, this patient has family members who are willing to be evaluated as living kidney donors, and kidneys from living donors have superior outcomes compared with kidneys from deceased donors. Therefore, referral for possible kidney transplant in this otherwise healthy patient would be most likely to improve her long-term survival.

There is no clinical indication for this patient to change from peritoneal dialysis to hemodialysis, and clinical outcomes, including mortality and quality of life, are approximately equivalent between these modalities. The choice between peritoneal dialysis and hemodialysis should therefore be driven by patient-specific factors and patient preference if dialysis is pursued.

There is evidence that risk of graft loss and overall mortality are increased in patients who have been treated with dialysis prior to transplant, and that this risk of graft loss and overall mortality increase with the length of dialysis prior to transplant. Therefore, continuing dialysis and reevaluating for possible transplant in 2 to 3 years would not be an optimal management strategy in this otherwise good candidate for transplantation.

KEY POINT

- Kidney transplantation decreases long-term mortality and improves quality of life compared with dialysis.

Bibliography

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Item 68 Answer: D

Educational Objective: Manage blood pressure and diet to slow progression of chronic kidney disease.

Maintaining the current antihypertensive regimen and a standard protein diet is appropriate in this patient to help slow progression of her chronic kidney disease (CKD).

Although earlier, small studies suggested that low protein diets may slow CKD progression, the landmark Modification of Diet in Renal Disease study did not detect a significant protective effect of protein-restricted diets in

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preventing progression of kidney disease. However, low protein diets may delay onset of symptomatic uremia in patients with late-stage CKD (stage G4/G5).

The eighth report from the Joint National Committee (JNC 8) recommends a target blood pressure of <140/90 mm Hg with ACE inhibitors or angiotensin receptor blockers as first-line agents for treatment of hypertension in patients with CKD. This patient currently meets this recommended goal with an ACE inhibitor as part of her regimen. Although previously recommended by several organizations, there are currently insufficient data to support targeting blood pressures lower than 140/90 mm Hg to prevent progression of kidney disease with the possible exception of patients with severe proteinuria (stage A3 or an albumin-creatinine ratio >300 mg/g), in which some randomized controlled trials have suggested the benefit of a lower blood pressure goal of <130/80 mm Hg.

Volume expansion may contribute to hypertension in CKD; therefore, maintaining normal volume status is important for long-term blood pressure control. Although the diuretic effect of thiazides becomes less effective as the glomerular filtration rate drops, often requiring a switch to a loop diuretic, this patient is clinically euvolemic and with adequate blood pressure control. Additionally, diuretics themselves do not alter progression of proteinuria or CKD. Therefore, there is no indication for switching diuretic therapy in this patient.

KEY POINT

- The eighth report from the Joint National Committee recommends a target blood pressure of <140/90 mm Hg and ACE inhibitors or angiotensin receptor blockers as first-line agents for treatment of hypertension in patients with chronic kidney disease.

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Item 69 Answer: B

Educational Objective: Treat a patient who has chronic kidney disease and proteinuria.

The most appropriate treatment for this patient is to increase the dose of the ACE inhibitor lisinopril. He has chronic kidney disease (CKD) with nephrotic-range proteinuria (urine protein-creatinine ratio >3500 mg/g or a urine protein excretion >3500 mg/24 h) and inadequately controlled hypertension. Increasing lisinopril should decrease his blood pressure and result in some decrease in proteinuria. Although many clinicians are hesitant to escalate the dose of an ACE inhibitor or angiotensin receptor blocker (ARB) in patients with significant CKD, careful upward titration is generally well tolerated with close clinical follow-up. The eighth report from the Joint National Committee (JNC 8) recommends lowering blood pressure to <140/90 mm Hg, although some experts recommend a lower blood pressure goal of <130/80 mm Hg in patients with heavy proteinuria.

Recent studies have demonstrated that although adding an ARB to an ACE inhibitor usually decreases proteinuria, combination therapy does not improve clinical outcomes and increases the risk of acute kidney injury and hyperkalemia.

Most patients with CKD, and those with CKD and proteinuria in particular, should be treated with an ACE inhibitor or ARB as preferred initial medications due to their demonstrated ability to slow CKD progression. Therefore, replacing lisinopril with the calcium channel blocker amlodipine is not appropriate in this case.

Continuing this patient's current therapy would not improve blood pressure control or decrease proteinuria.

KEY POINT

- Blood pressure control using an ACE inhibitor or angiotensin receptor blocker is the therapy of choice in patients with chronic kidney disease.

Bibliography

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Item 70 Answer: B

Educational Objective: Diagnose alcoholic ketoacidosis.

The most likely diagnosis is alcoholic ketoacidosis. This patient has an increased anion gap metabolic acidosis of 27, and ketoacidosis due to acute ethanol intoxication is the most likely cause. Alcoholic ketoacidosis occurs in patients with chronic ethanol abuse and liver disease and develops following an episode of acute intoxication, at which time the ingested ethanol may have already been extensively metabolized, leading to low or normal serum ethanol levels. Ethanol is oxidized to acetaldehyde and then to acetic acid, during which process the electron-carrier coenzyme nicotinamide adenine dinucleotide (NAD^+) is reduced to NADH in increasing amounts. Simultaneously, rising catecholamine levels cause lipolysis with subsequent generation of free fatty acids and ketone bodies, such as acetoacetate. The high ratio of NADH to NAD^+ leads to increased reduction of acetoacetate to β-hydroxybutyrate. Because the nitroprusside reagent in the serum and urine ketone assays detects only acetoacetate, these tests may be falsely negative due to decreased acetoacetate levels despite the presence of increased levels of the ketone β-hydroxybutyrate, as in this case. Definitive diagnosis may require direct measurement of β-hydroxybutyrate levels in the serum, which is available in some laboratories.

Acute kidney injury can lead to an increased anion gap metabolic acidosis due to the accumulation of acidic

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metabolic by-products and phosphates and sulfates. However, this degree of anion gap would not be expected in this patient who is mildly prerenal with a normal serum phosphorus level.

D-Lactic acidosis is an uncommon cause of increased anion gap metabolic acidosis that is typically identified in patients with small-bowel bacterial overgrowth. Bacterial production of D-lactic acid is undetectable by the serum lactate assay, which recognizes only the L enantiomer. However, this disorder is not associated with chronic alcohol use and would not be a likely diagnostic consideration in this patient.

Rhabdomyolysis is a diagnostic consideration in a patient with a history of alcohol abuse and an anion gap metabolic acidosis, but this condition is frequently associated with hyperkalemia, hyperphosphatemia, hypocalcemia, and a urinalysis positive for blood with no erythrocytes visible on urine microscopy.

KEY POINT

- Alcoholic ketoacidosis occurs in patients with chronic ethanol abuse, frequently with associated liver disease, and develops following an episode of acute intoxication.

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Item 71 Answer: C

Educational Objective: Diagnose IgA vasculitis.

The most likely diagnosis is IgA vasculitis (Henoch-Schönlein purpura). This patient presents with fatigue, joint pain, abdominal pain, petechial/purpural skin lesions, and glomerulonephritis following an upper respiratory tract infection. The differential diagnosis of vasculitis with glomerulonephritis includes infection-related vasculitis (such as endocarditis), cryoglobulinemia, systemic lupus erythematosus, ANCA-associated vasculitis, and IgA vasculitis. Although serologic tests and blood cultures are pending, the patient most likely has IgA vasculitis based on the presence of the tetrad of palpable purpura, arthralgia, abdominal pain, and glomerulonephritis. Although no diagnostic serologic tests for this condition exist, normal complement levels support this diagnosis. Diagnosis is confirmed with biopsy of the affected organ.

Infection-related glomerulonephritis such as endocarditis activates the alternative pathway of complement with low C3 and normal C4 levels. The classical pathway of complement is activated with cryoglobulinemic vasculitis (C4, and sometimes C3, is depressed) and systemic lupus erythematosus (both C3 and C4 are low). In this patient, complement levels are normal, making these diseases less likely. Additionally, cryoglobulinemic vasculitis is associated with hepatitis C virus infection, which is not present in this patient.

KEY POINT

- IgA vasculitis is associated with abdominal pain, palpable purpura, arthralgia, and glomerulonephritis, with normal complement levels.

Bibliography

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Item 72 Answer: D

Educational Objective: Identify vomiting as a cause of hypokalemia.

Vomiting is the most likely cause of this patient's hypokalemia. She presents with hypokalemic metabolic alkalosis with extracellular volume depletion. Hypokalemia, defined as a serum potassium concentration <3.5 mEq/L (3.5 mmol/L), can be life-threatening when severe. Patients usually have minimal symptoms unless serum potassium levels are <3.0 mEq/L (3.0 mmol/L); symptoms correlate with the rapidity of the decrease, ranging from generalized weakness and malaise to paralysis, depending on the serum potassium level. This patient's history (generalized weakness and lightheadedness), physical examination findings (volume contraction and dental caries), and urine electrolyte levels are most consistent with vomiting from bulimia nervosa. Vomiting results in loss of hydrogen chloride and fluid from gastric secretions, and, if persistent, results in volume contraction. Hypovolemia activates the renin-angiotensin system with an increase in sodium-hydrogen exchange and increased bicarbonate reabsorption in the proximal tubule due to increased luminal hydrogen ion, and exacerbated by decreased chloride available for reabsorption with sodium. Increased aldosterone secretion stimulates sodium-potassium exchange in the distal tubule. The urine electrolytes in this patient reflect these physiologic changes. With volume depletion, the urine sodium concentration is generally low (<20 mEq/L [20 mmol/L]) due to the kidney's conservation of sodium. However, in this case, excess filtered bicarbonate associated with the alkalosis is excreted through the renal tubule, and sodium is lost in the urine as an obligatory cation with bicarbonate necessary to maintain electroneutrality; this results in increased urine sodium excretion. Because of this, the urine chloride is a more accurate determination of volume status than the urine sodium in metabolic alkalosis. The urine chloride concentration is low (<20 mEq/L [20 mmol/L]), reflecting gastrointestinal losses and prolonged volume contraction that leads to avid reabsorption of chloride with sodium. The urine potassium concentration in this patient is elevated (>40 mEq/L [40 mmol/L]) due to increased aldosterone production and distal nephron bicarbonate delivery that promote potassium loss through the kidney. Treatment of these abnormalities is to treat the vomiting and provide volume expansion with normal saline and potassium replacement, which will reverse these changes and correct the acid-base and electrolyte abnormalities.

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Bartter syndrome mimics the effect of a loop diuretic and is accompanied by increased urine sodium (>40 mEq/L [40 mmol/L]), urine potassium (>40 mEq/L [40 mmol/L]), and chloride excretion (>40 mEq/L [40 mmol/L]).

Hypokalemic periodic paralysis is due to a shift of potassium into cells and is not associated with a metabolic alkalosis; furthermore, urine potassium would be low (<20 mEq/L [20 mmol/L]) and not increased.

Hypokalemia from Sjögren syndrome occurs in the setting of renal tubular acidosis, and a hyperchloremic metabolic acidosis would occur, which is not seen in this patient.

KEY POINT

- Hypokalemia due to vomiting is associated with metabolic alkalosis, increased urine potassium excretion, and decreased urine chloride excretion.

Bibliography

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Item 73 Answer: C

Educational Objective: Diagnose thrombotic microangiopathy.

The next step in diagnosis is a peripheral blood smear. This patient has findings suggestive of Shiga toxin–associated hemolytic uremic syndrome (HUS). This is a diarrhea-associated syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and kidney failure caused by Shiga toxin–producing *Escherichia coli*, typically with serotypes O157:H7, O104:H4, and, less commonly, *Shigella dysenteriae*. Shiga toxin binds to endothelial cells, triggering thrombosis and resulting in a thrombotic microangiopathy. It also binds to renal mesangial cells, podocytes, and renal tubular cells, causing direct damage. These actions lead to acute kidney injury (AKI). Although this patient has a consistent clinical history, a peripheral blood smear is essential to determine whether the anemia is caused by a microangiopathic hemolytic process as indicated by the presence of schistocytes. Stool cultures may reveal the offending organism. Treatment is primarily supportive, and many patients require dialysis.

ADAMTS13 is a metalloprotease enzyme that cleaves von Willebrand factor; low activity levels are supportive of a diagnosis of thrombotic thrombocytopenic purpura (TTP). Although this would be a reasonable study in this patient if a likely diagnosis of Shiga toxin–associated HUS were less clear to assess for the possibility of TTP, confirmation of true thrombocytopenia and microangiopathic hemolytic anemia would be an initial diagnostic step before additional testing.

Kidney biopsy would show evidence of capillary thrombosis as well as glomerular and tubular damage, but it is not necessary to establish the diagnosis of Shiga toxin–associated HUS.

Urine protein electrophoresis may be useful in evaluating AKI due to monoclonal urine immunoglobulin light chains (Bence Jones proteins). Although a plasma cell disorder may cause anemia and AKI due to precipitation of light chains in the renal tubule (myeloma kidney), it is not a cause of microangiopathic hemolytic anemia or thrombocytopenia as seen in this patient.

KEY POINT

- Shiga toxin–associated hemolytic uremic syndrome is a diarrhea-associated syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and kidney failure caused by Shiga toxin–producing *Escherichia coli*.

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George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014 Aug 14;371(7):654-66. [PMID: 25119611]

Item 74 Answer: B

Educational Objective: Evaluate a pregnant patient for suspected nephrolithiasis using ultrasonography.

Bilateral kidney ultrasonography is the most appropriate diagnostic study for this pregnant patient with suspected nephrolithiasis. Although noncontrast helical CT has traditionally been the most commonly used imaging technique for suspected nephrolithiasis because it detects most stones, provides helpful anatomic information, visualizes the entire urinary tract, and may potentially provide alternative diagnoses if nephrolithiasis is not detected, it is associated with significant radiation exposure and is therefore contraindicated in pregnant women. Kidney ultrasonography is increasingly being used as an initial diagnostic study for nonpregnant patients with suspected nephrolithiasis, particularly younger patients, to avoid significant radiation exposure, and it is the study of choice for pregnant women with possible kidney stones. Although it is less sensitive than CT for kidney stones, particularly for small stones or those in the distal urinary tract, a positive study for nephrolithiasis can exclude complications such as hydronephrosis and remove the need for more extensive additional testing.

Abdominal MRI can be used during pregnancy, but it is not optimal for imaging kidney stones. Ultrasonography is preferred, although MRI may be a diagnostic option if additional imaging is required for diagnosis.

Low-dose CT is both sensitive and specific for detecting kidney stones but is also associated with significant radiation exposure, similar to conventional stone protocol CT. Low-dose CT is absolutely contraindicated in the first trimester of pregnancy and is used only in specific situations in pregnant women in the second or third trimesters. It is not an appropriate study for this patient.

Plain abdominal radiography has limited utility for suspected nephrolithiasis due to its inability to detect

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radiolucent stones and the limited anatomic information it provides. It also involves radiation exposure and is not an appropriate next test in this patient.

Transvaginal ultrasonography may be used to detect distal ureteral stones in pregnant women with suspected nephrolithiasis and an unrevealing kidney ultrasound. However, it is not an appropriate next test for this patient.

KEY POINT

- Ultrasonography is the preferred diagnostic imaging modality for pregnant patients with suspected nephrolithiasis because it does not expose patients to radiation.

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Item 75 Answer: A

Educational Objective: Treat calcium oxalate nephrolithiasis with bile salt binders in a patient with enteric hyperoxaluria.

Treatment with cholestyramine is an appropriate additional therapy for this patient with enteric hyperoxaluria. Hyperoxaluria predisposes to calcium oxalate stone formation. Excessive oxalate in the urine may result from excessive intake (from foods such as chocolate, spinach, rhubarb, or green and black tea) or in situations in which there is significant restriction in dietary calcium intake, which decreases binding of calcium to dietary oxalate in the gut and increases oxalate absorption. Enteric hyperoxaluria results from malabsorption when excessive free fatty acids in the gastrointestinal lumen bind calcium, increasing free oxalate absorption in the colon as may be seen in patients with small bowel disease or bowel resection. In addition to maintaining an adequate urine output of at least 2 L/d and ensuring adequate dietary calcium intake, patients with enteric hyperoxaluria may benefit from the bile salt binder cholestyramine, which also binds oxalate in the gut. This therapy is indicated in this patient with recurrent calcium oxalate nephrolithiasis following small bowel resection unresponsive to other treatments.

Thiazide diuretics, such as hydrochlorothiazide, are used in patients with idiopathic hypercalciuria to reduce calcium excretion in the urine by inducing mild hypovolemia that results in increased sodium reabsorption and passive calcium reabsorption in the proximal tubule. However, this patient does not have evidence of hypercalciuria, and thiazide therapy would not decrease the excessive oxalate in the urine.

Urine citrate inhibits stone formation by binding calcium in the tubular lumen, preventing it from precipitating with oxalate. Citrate excretion can be enhanced in patients with low urine citrate levels by alkalinizing the serum with potassium citrate, which decreases uptake of filtered citrate from the tubular lumen. However, this patient does not have evidence of hypocitraturia and would not be expected to benefit from additional urine citrate.

Pyridoxine is indicated in some patients with primary hyperoxaluria to improve glyoxylate metabolism and reduce overproduction of oxalate. However, this would not be effective in this patient with enteric hyperoxaluria.

KEY POINT

- Patients with enteric hyperoxaluria and calcium oxalate nephrolithiasis may benefit from treatment with bile salt binders to decrease intestinal oxalate absorption.

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Item 76 Answer: D

Educational Objective: Diagnose a complex mixed acid-base disorder.

The most likely diagnosis is a complex mixed acid-base disorder consisting of respiratory alkalosis, increased anion gap metabolic acidosis, and metabolic alkalosis. Analysis of acid-base disorders requires the identification of the likely dominant acid-base disorder, followed by an assessment of the secondary, compensatory response. When measured values fall outside the range of the predicted secondary response, a mixed acid-base disorder is present; multiple acid-base disturbances may coexist in a single patient. This patient's dominant acid-base disorder is alkalosis, as indicated by the blood pH of 7.56. The low P_{CO_2} indicates a respiratory component to the alkalosis. The expected compensation for chronic respiratory alkalosis is a decrease in the serum bicarbonate of 4 to 5 mEq/L (4-5 mmol/L) for each 10 mm Hg (1.3 kPa) decrease in the P_{CO_2}. The expected serum bicarbonate concentration in this patient is calculated to be 14 to 16 mEq/L (14-16 mmol/L), and the measured serum bicarbonate of 20 mEq/L (20 mmol/L) suggests coexistence of a metabolic alkalosis. This patient also has an elevated anion gap indicating the presence of an increased anion gap metabolic acidosis. The change of the anion gap from normal is 10 mEq/L (10 mmol/L). Calculating the ratio of the change in the anion gap (Δ anion gap) to the change in bicarbonate level (Δ bicarbonate), or the "Δ-Δ ratio," can help confirm if there is a coexisting acid-base disturbance. A ratio of <1 may reflect the presence of concurrent normal anion gap metabolic acidosis, whereas a ratio of >2 may indicate the presence of metabolic alkalosis. This patient's Δ-Δ ratio is 2.5, confirming the coexistence of a metabolic alkalosis. The clinical scenario most likely responsible for this complex acid-base disorder is salicylate toxicity with central hyperventilation from the salicylate, anion gap metabolic acidosis from the salicylate, and metabolic alkalosis from gastritis and vomiting.

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KEY POINT

- Analysis of acid-base disorders requires the identification of the likely dominant acid-base disorder, followed by an assessment of the secondary, compensatory response; when measured values fall outside the range of the predicted secondary response, a mixed acid-base disorder is present.

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Seifter JL. Integration of acid-base and electrolyte disorders. N Engl J Med. 2014 Nov 6;371(19):1821-31. [PMID: 25372090]

Item 77 Answer: D

Educational Objective: Diagnose drug-induced tubulointerstitial disease presenting as Fanconi syndrome.

This patient has tubulointerstitial disease, likely due to long-standing exposure to tenofovir. Evidence for a tubulointerstitial process includes a slowly progressive course without a clear inciting event, subnephrotic proteinuria, bland urine sediment, and a kidney ultrasound showing atrophic kidneys. History and physical examination should focus on conditions associated with tubulointerstitial disease and a careful review of medications, because numerous medications may induce tubulointerstitial disease. An associated characteristic that may be present with tubulointerstitial disease is abnormal tubular handling of glucose, amino acids, uric acid, phosphate, and bicarbonate (termed *Fanconi syndrome*); renal tubular acidosis is also common. Patients may also have concentrating defects and may present with nocturia and polyuria. With more advanced disease, anemia may be present due to the destruction of erythropoietin-producing cells in the kidney. This patient's findings are consistent with tubulointerstitial disease with Fanconi syndrome, indicated by glucosuria in the context of normoglycemia, trace proteinuria, and hypophosphatemia. Because tenofovir has been associated with tubulointerstitial disease, it is the likely cause in this patient.

Hypertensive nephropathy involves damage to the vascular structures, glomeruli, and tubulointerstitial regions of the kidney. It may cause progressive kidney failure, often with elevated protein excretion (less than 1000 mg/24 h). However, the rapid progression of kidney dysfunction and the presence of tubular dysfunction (Fanconi syndrome) characteristic of tubulointerstitial disease make hypertensive nephropathy less likely in this patient.

Membranoproliferative glomerulonephritis may also be associated with chronic hepatitis B infection and involves immune complex deposition in the glomeruli. It typically presents with hematuria (often with dysmorphic erythrocytes and/or erythrocyte casts), variable degrees of proteinuria, and a reduced glomerular filtration rate. This would not be a consistent finding in this patient with a bland urine sediment.

Membranous glomerulopathy is common in patients with chronic hepatitis B infection and appears to be related to subendothelial and mesangial immune deposits in the glomeruli. Because it primarily affects the glomeruli, it is associated with high levels of proteinuria, usually in the nephrotic range, and would not be expected to present with tubular dysfunction and Fanconi syndrome as seen in this patient.

KEY POINT

- Kidney disease with a tubulointerstitial process is characterized by a slowly progressive course without a clear inciting event, subnephrotic proteinuria, bland urine sediment, and a kidney ultrasound showing atrophic kidneys.

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Tourret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword? J Am Soc Nephrol. 2013 Oct;24(10):1519-27. [PMID: 24052632]

Item 78 Answer: E

Educational Objective: Diagnose hypophosphatemia due to refeeding syndrome.

The most likely cause of this patient's respiratory failure is hypophosphatemia, which occurs in patients with chronic alcohol use, malnutrition, or critical illness. Symptoms rarely occur unless the serum phosphate concentration is <2.0 mg/dL (0.65 mmol/L); severe symptoms occur with a serum phosphate concentration <1.0 mg/dL (0.32 mmol/L). Symptoms include weakness, myalgia, rhabdomyolysis, arrhythmias, heart failure, respiratory failure, seizures, coma, and hemolysis. This patient has chronic alcoholism with moderate hypophosphatemia on presentation. Factors that contribute to hypophosphatemia in the patient with chronic alcohol use include decreased dietary intake of phosphate and vitamin D, chronic diarrhea, and a direct toxic effect of alcohol on the proximal tubule. Intravenous dextrose-containing fluids can exacerbate the hypophosphatemia by causing a refeeding syndrome. Glucose stimulates insulin release, which promotes phosphate uptake by the cells and worsening hypophosphatemia. Severe hypophosphatemia can cause respiratory failure from impaired diaphragmatic contractility.

In general, total calcium declines by 0.8 mg/dL (0.2 mmol/L) for each 1.0 g/dL (10 g/L) decrement in serum albumin concentration. This patient's calcium correction for hypoalbuminemia is 8.8 mg/dL (2.2 mmol/L), which is not low and does not explain the respiratory failure.

This patient has mild hypokalemia. Although severe hypokalemia can cause profound muscle weakness, it is unlikely that his serum potassium would decrease to such critically low levels to cause paralysis based on his current treatment.

The patient's magnesium level is within the lower limits of normal range and unlikely to be the cause of his respiratory failure.

Although the patient does have hyponatremia, it is not severe and would not result in respiratory failure. Symptoms

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CONT. of acute hyponatremia are caused by cerebral edema and usually do not manifest until the sodium concentration is lower than 125 mEq/L (125 mmol/L).

KEY POINT

- Intravenous dextrose-containing fluids can exacerbate hypophosphatemia by stimulating insulin release, which promotes phosphate uptake by the cells and worsening hypophosphatemia.

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Item 79 Answer: C

Educational Objective: Identify NSAIDs as a cause of elevated blood pressure.

Discontinuing ibuprofen is an appropriate next step in managing this patient's blood pressure. She has elevated blood pressure not yet defined as hypertension, a diagnosis that requires a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg documented during three separate office visits over a period of 1 week or longer. In this case, a review of medications, including over-the-counter and herbal medications, is important because a number of these agents can contribute to elevated blood pressure. This patient is taking an NSAID, ibuprofen, for osteoarthritis. All NSAIDs contribute to hypertension by inhibition of cyclooxygenase-2 in the kidneys, promoting sodium retention and increased intravascular volume. Additional effects of NSAIDs include hyperkalemia, which is mild in this case. NSAIDs lower renal renin secretion and angiotensin II–induced aldosterone release, reducing urine potassium excretion. Therefore, discontinuing the ibuprofen is appropriate for this patient. Reassessing her blood pressure when not taking an NSAID will provide a more accurate measure of her baseline blood pressure status.

Beginning antihypertensive therapy at this point is not indicated; in particular, ACE inhibitor use would be contraindicated because further inhibition of the renin-angiotensin system could exacerbate this patient's hyperkalemia.

Similarly, hydrochlorothiazide is an effective antihypertensive agent, but initiating treatment is not indicated prior to establishing a diagnosis of hypertension.

A plasma aldosterone-plasma renin ratio is used to evaluate patients with hypertension and a high suspicion for hyperaldosteronism (for example, evidence of resistant hypertension and a low serum potassium level). Testing is therefore not indicated in this patient without a clear diagnosis of hypertension and who has hyperkalemia.

KEY POINT

- Identification of medications that contribute to blood pressure elevation is necessary in patients with elevated blood pressure not yet defined as hypertension.

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Item 80 Answer: A

Educational Objective: Diagnose D-lactic acidosis.

This patient has an increased anion gap metabolic acidosis, and the most likely cause is D-lactic acidosis. Accumulation of the D-isomer of lactate can occur in patients with short-bowel syndrome following jejunoileal bypass or small-bowel resection. In these patients, excess carbohydrates that reach the colon are metabolized to D-lactate. Symptoms include intermittent confusion, slurred speech, and ataxia. Laboratory studies show increased anion gap metabolic acidosis with normal plasma lactate levels, because the D-isomer is not measured by conventional laboratory assays for lactate. Diagnosis should be considered in patients with an unexplained increased anion gap metabolic acidosis in the appropriate clinical context; it is confirmed by specifically measuring D-lactate.

Ethylene glycol or methanol intoxication should be suspected in patients with an increased anion gap metabolic acidosis associated with a serum bicarbonate level <10 mEq/L (10 mmol/L) and a plasma osmolal gap >10 mOsm/kg H_2O. This patient's serum bicarbonate level is 20 mEq/L (20 mmol/L) and the calculated osmolal gap is 6 mOsm/kg H_2O, making alcohol poisoning a less likely diagnosis.

Propylene glycol is a solvent used as a vehicle for numerous intravenously administered medications. In propylene glycol toxicity, laboratory findings include increased anion gap metabolic acidosis and concomitant increased osmolal gap. The metabolic acidosis is principally due to L-lactic and D-lactic acidosis, the acid metabolites of propylene glycol. This patient's clinical history and osmolal gap are not consistent with propylene glycol toxicity.

Pyroglutamic acidosis is a cause of increased anion gap metabolic acidosis in patients receiving therapeutic doses of acetaminophen on a chronic basis. Clinical manifestations are limited to mental status changes and increased anion gap metabolic acidosis. The syndrome most commonly occurs in patients with critical illness, poor nutrition, liver disease, or chronic kidney disease as well as in persons on a vegetarian diet. Diagnosis can be confirmed by measuring urine levels of pyroglutamic acid. This patient's history is most compatible with D-lactic acidosis and does not support acetaminophen ingestion.

KEY POINT

- Manifestations of D-lactic acidosis include intermittent confusion, slurred speech, ataxia, and an increased anion gap metabolic acidosis with a normal plasma lactate level.

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Item 81 Answer: B

Educational Objective: Treat suspected catheter-related bacteremia in a patient with end-stage kidney disease.

The most appropriate next step in management is to begin broad-spectrum antibiotic coverage, such as vancomycin plus ceftazidime. This patient with end-stage kidney disease (ESKD) who is receiving dialysis via a catheter is at high risk for catheter-related bacteremia. Infection is the second most common cause of death in patients with ESKD (after cardiovascular disease), and catheter-related infections are an important cause of morbidity and mortality. It is therefore important to provide immediate empiric broad-spectrum antibiotics in patients dialyzing via a catheter who exhibit evidence of infection unless there is another obvious source of fever. Most dialysis-related bacteremias are caused by gram-positive bacteria, and empiric coverage must include therapy that takes into account the local resistance patterns of *Staphylococcus aureus*. Additionally, gram-negative organisms should also be covered until culture results are known and appropriate, focused antimicrobial therapy is prescribed.

If blood cultures remain negative, empiric antibiotics may be stopped if symptoms have resolved and no other potential source of infection has been identified. If blood cultures return positive, it is usually advisable to remove the catheter because success rates for catheter salvage are low for most organisms. If there is no evidence of infection of the catheter tunnel, dialysis catheters can be safely exchanged over a wire in patients who have been asymptomatic on appropriate antibiotic therapy for at least 48 hours. However, either removing or exchanging the dialysis catheter in the setting of possible infection without antibiotic therapy is not appropriate.

KEY POINT

- Immediate empiric broad-spectrum antibiotics must be initiated in patients with end-stage kidney disease who are on dialysis and have suspected catheter-related infection.

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Item 82 Answer: C

Educational Objective: Measure urine chloride levels to determine the cause of metabolic alkalosis.

Measurement of this patient's urine chloride level is the most appropriate next step in management. She has a metabolic alkalosis as evidenced by the elevated blood pH and elevated serum bicarbonate level. Metabolic alkalosis is caused by net loss of acid or retention of serum bicarbonate. Metabolic alkalosis can be classified as either occurring with normal extracellular fluid volume, hypovolemia, or decreased effective arterial blood volume and increased extracellular fluid volume (heart failure, cirrhosis, nephrosis), or occurring with increased extracellular fluid volume and hypertension. This patient's clinical volume status is equivocal; blood pressure is slightly low and pulse rate is slightly high, yet there is peripheral edema, which could be explained by either cardiac or noncardiac causes (for example, a side effect of amlodipine), and mild hypoxia, which could be cardiac or pulmonary in etiology, given her medical history. Urine chloride measurement can help determine the cause of metabolic alkalosis, particularly if it is difficult to clinically assess volume status. In such patients, a low (<15 mEq/L [15 mmol/L]) urine chloride suggests reduction in extracellular volume and the presence of saline-responsive metabolic alkalosis. Conditions that are associated with saline-responsive metabolic alkalosis include vomiting, remote use of diuretics, and post-hypercapnic metabolic alkalosis. If the urine chloride is high (>15 mEq/L [15 mmol/L]), the metabolic alkalosis is saline resistant and can be caused by active diuretic use, stimulant laxative abuse, and rare renal tubular disorders such as Gitelman and Bartter syndromes. In this case, the patient's metabolic alkalosis is due to vomiting, and a low urine chloride would direct appropriate management to saline infusion.

Saline infusion without first categorizing the nature of the metabolic alkalosis is inappropriate and potentially dangerous in patients with limited cardiac reserve or hypoxia.

There is no clear evidence of volume overload that requires administration of a loop diuretic such as furosemide. Loop diuretic therapy is likely to worsen metabolic alkalosis by increasing the secretion of aldosterone and distal delivery of sodium, resulting in urine potassium and hydrogen loss.

In patients with metabolic alkalosis, measurement of urine chloride rather than urine sodium is used to determine volume status and saline responsiveness because urine sodium can be artificially high during periods of appropriate compensatory urine bicarbonate excretion (sodium is the primary cation excreted in an obligatory fashion with bicarbonate).

KEY POINT

- Measurement of urine chloride levels can be useful to determine volume status and saline responsiveness in patients with metabolic alkalosis.

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Item 83 Answer: A

Educational Objective: Diagnose autosomal dominant polycystic kidney disease.

The most likely diagnosis is autosomal dominant polycystic kidney disease (ADPKD). The hallmark of ADPKD is

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CONT.

large kidneys with multiple kidney cysts, and patients may have resulting chronic, mild abdominal discomfort; in some cases, palpable abdominal masses occur, as in this patient. Patients with ADPKD may also present acutely with severe pain and hematuria resulting from bleeding of a cyst, as seen in this patient. ADPKD is the most common inherited kidney disorder, occurring in 1 of 400 to 1 of 1000 live births. Although transmitted in an autosomal dominant manner, a negative family history does not necessarily exclude ADPKD. Approximately 15% of patients with ADPKD have spontaneous mutations that result in the disease. Alternatively, one of the patient's parents may have a less severe phenotype without clinical manifestations.

Renal cell carcinoma does not occur with greater frequency in patients with ADPKD than in the general population and does not present with bilateral abdominal masses.

Renal vein thrombosis may present with acute-onset flank pain and macroscopic hematuria and may show enlargement of the involved kidney. However, renal vein thrombosis does not result in bilateral abdominal masses and is more commonly seen in hypercoagulable states, such as the nephrotic syndrome or the antiphospholipid antibody syndrome. This patient has no evidence of hypercoagulability.

Gross hematuria often occurs in patients with urinary tract infection. However, this patient has no accompanying urinary symptoms, and the leukocytes in her urine are likely the result of gross bleeding into the urinary tract. Additionally, urinary tract infection would not explain the abdominal masses seen in this patient.

KEY POINT

- A negative family history does not exclude autosomal dominant polycystic kidney disease (ADPKD)—approximately 15% of patients with ADPKD have spontaneous mutations that result in the disease.

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Grantham JJ. Clinical practice. Autosomal dominant polycystic kidney disease. N Engl J Med 2008 Oct 2;359(14):1477-85. [PMID: 18832246]

Item 84 Answer: D

Educational Objective: Treat tumor lysis syndrome.

Rasburicase is appropriate to treat hyperuricemia in this patient with tumor lysis syndrome (TLS). TLS is characterized by the massive release of uric acid, potassium, and phosphate into the blood from rapid lysis of malignant cells. It typically occurs after initiation of cytotoxic therapy for hematologic malignancies with large tumor burden (such as high-grade lymphomas) or high cell counts (such as acute lymphoblastic leukemia), but TLS can also occur spontaneously. Acute kidney injury (AKI) results from intratubular precipitation of urate and calcium phosphate crystals. Clinical features include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. General principles for the management of patients at high or intermediate risk or presenting with TLS are aggressive volume expansion, management of hyperkalemia, and preventive therapy for hyperuricemia. This patient has TLS with evidence of uric acid nephropathy and requires rasburicase to reduce serum urate levels. Rasburicase rapidly converts uric acid to allantoin, which is 5 to 10 times more soluble than uric acid and readily excreted through the kidney. Rasburicase has a much faster action than allopurinol and can decrease serum urate levels within 4 hours of administration.

Indications for dialysis include oliguria or anuria, persistent hyperkalemia, hyperphosphatemia-induced symptomatic hypocalcemia, and a calcium phosphate product $\geq 70\ mg^2/dL^2$ in the setting of AKI. This patient has none of these indications for dialysis.

Urine alkalinization increases the excretion of uric acid by increasing its solubility. However, in the setting of hyperphosphatemia, it can cause precipitation of calcium phosphate crystals in the kidney. Urine alkalinization is not necessary when rasburicase is used, and it role in TLS is controversial.

Allopurinol competitively inhibits xanthine oxidase, blocking the metabolism of hypoxanthine and xanthine to uric acid. Allopurinol effectively decreases the formation of new uric acid and therefore does not affect circulating uric acid. Increasing the dose of allopurinol is therefore not indicated.

KEY POINT

- Patients with tumor lysis syndrome and evidence of uric acid nephropathy require treatment with rasburicase to reduce serum urate levels.

Bibliography

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011 May;364(19):1844-54. [PMID: 21561350]

Item 85 Answer: D

Educational Objective: Manage IgA nephropathy.

Continued observation is the appropriate next step in management in this patient with likely IgA nephropathy (IgAN). IgAN is the most frequent cause of chronic glomerulonephritis, occurs more commonly in men, and most frequently occurs in the second to third decades of life. IgAN involves formation of autoantibodies against structurally abnormal IgA leading to immune complex formation; these immune complexes are deposited in the glomeruli in IgAN or in multiple extrarenal sites in IgA vasculitis (Henoch Schönlein purpura). This young patient has asymptomatic gross hematuria with a nephritic urine sediment without the full nephritic syndrome (hypertension and azotemia are absent). The presence of nephritis with normal or negative serologies (particularly normal complement levels) and improving kidney function and proteinuria suggests IgAN as the most likely diagnosis. IgAN tends to be a chronic condition with a good prognosis in most patients. Factors associated with

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a worse outcome include hypertension, kidney dysfunction, persistent proteinuria >1000 mg/g, and mesangial and endothelial proliferation with tubulointerstitial damage on kidney biopsy. However, continued observation with serial blood pressure measurements, serum creatinine levels, and urine studies is appropriate in this patient without high-risk features and an improving clinical course.

Treatment with inhibitors of the renin-angiotensin system (such as an ACE inhibitor) slow the rate of progression of most proteinuric chronic kidney diseases and are often used in patients with IgAN with significant proteinuria and high-risk features. However, low-risk patients with minimal proteinuria are usually not actively treated and are followed with continued observation.

Kidney biopsy is usually reserved for patients with high risk for poor outcome. It is not indicated in this patient with no high-risk features of progressive IgAN, such as a urine protein-creatinine ratio >1000 mg/g or a low glomerular filtration rate.

Glucocorticoids are used to treat patients with high-risk disease.

KEY POINT

- Observation with serial blood pressure measurements, urine studies, and serum creatinine levels is appropriate for patients with IgA nephropathy with low-risk features for progression.

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Item 86 Answer: C

Educational Objective: Manage preeclampsia.

The most appropriate next step in management is delivery of the baby in this woman with preeclampsia without features of severe disease. Preeclampsia is classically defined as new-onset hypertension after 20 weeks of pregnancy with proteinuria (≥300 mg/24 h or a urine protein-creatinine ratio ≥300 mg/g). Delivery of the baby is the definitive treatment for preeclampsia. In patients with preeclampsia and severe disease, generally defined as severe hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg), thrombocytopenia (platelet count <100,000/μL [100 × 10^9/L]), kidney dysfunction (serum creatinine concentration >1.1 mg/dL [97.2 μmol/L] or doubling of the serum creatinine concentration in the absence of other kidney disease), impaired liver function (elevated blood concentrations of liver aminotransferases to twice the normal concentration), pulmonary edema, or cerebral or visual symptoms, management decisions are usually made based on the balance of fetal and maternal risk with the implications of preterm delivery. In women with preeclampsia without severe features, delivery at 37 weeks has been shown to optimize both maternal and neonatal outcomes (such as fetal growth restriction, abruption placentae, hemorrhage due to thrombocytopenia, seizures, cerebral hemorrhage, pulmonary edema, and kidney injury) and is the most appropriate next step in managing this patient.

Treatment of mild hypertension in preeclampsia has not been shown to alter the course of disease or improve fetal outcomes. Therefore, antihypertensive treatment is generally reserved for patients with preeclampsia with severe hypertension, which is not present in this patient.

There is evidence that low-dose aspirin therapy may be beneficial in reducing the occurrence of preeclampsia in moderate- to high-risk women. However, it does not have a role in treating preeclampsia or eclampsia.

Glucocorticoids are used to accelerate fetal lung maturation if delivery is contemplated before the 34th week of pregnancy but do not directly affect outcomes in preeclampsia. Therefore, their use is not indicated in this patient.

Because of the benefit of delivery at 37 weeks' gestation in women with preeclampsia, continued monitoring beyond this time is not optimal.

KEY POINT

- Definitive therapy for preeclampsia is delivery of the baby.

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Item 87 Answer: D

Educational Objective: Manage secondary focal segmental glomerulosclerosis.

In addition to starting an ACE inhibitor, weight loss is indicated for this patient with likely secondary focal segmental glomerulosclerosis (FSGS). This patient with obesity, hypertension, and nephrotic-range proteinuria (with normal serum albumin) has FSGS on kidney biopsy. FSGS may be primary (idiopathic) or secondary, and the appropriate therapeutic approach is based on determining the likely cause of the disorder. Primary FSGS involves glomerular injury due to an unclear insult; features suggesting primary FSGS include a low serum albumin level and extensive foot process effacement on kidney biopsy. Patients usually present with hypertension, hypoalbuminemia, and some degree of kidney failure in addition to nephrotic-range proteinuria. Some patients with primary FSGS respond well to immunosuppressive therapy, and this is typically offered to patients with this diagnosis. Secondary FSGS is believed to result from an adaptive response to glomerular hypertrophy or hyperfiltration associated with a number of conditions (including obesity) in which the glomerular filtration rate may be markedly increased; glomeruli on biopsy are often enlarged, reflecting hyperfiltration with only mild foot process effacement. These patients have minimal edema and rarely have the full spectrum of the nephrotic syndrome. In obese patients with likely secondary FSGS, weight loss is

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sometimes associated with a drop in proteinuria, as is the use of ACE inhibitors or angiotensin receptor blockers, and is the preferred initial therapy.

Immunosuppressive therapy with glucocorticoids or other agents such as the calcineurin inhibitor tacrolimus is not indicated in secondary FSGS.

FSGS is not typically associated with syphilis, and testing for this entity using a rapid plasma reagin test is not indicated.

KEY POINT

- In obese patients with likely secondary focal segmental glomerulosclerosis, weight loss is sometimes associated with a drop in proteinuria, as is the use of ACE inhibitors or angiotensin receptor blockers, and is the preferred initial therapy.

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Item 88 Answer: B

Educational Objective: Diagnose atheroembolic kidney disease.

The most likely diagnosis is atheroembolism of cholesterol crystals. Disruption of an atheromatous plaque by instrumentation or anticoagulation during this patient's cardiac catheterization likely caused embolization of cholesterol crystals from the plaque through the arterial circulation distal to the point of disruption. These crystals lodge in capillary beds and cause vascular obstruction but also trigger an inflammatory response. Acute kidney injury (AKI) is a common result of cholesterol embolization, which causes peripheral eosinophilia and hypocomplementemia and shows evidence of inflammation on urinalysis, frequently with eosinophiluria present. Embolization may also lead to digital ischemia or infarction ("blue toe" syndrome) due to digital arterial occlusion or central scotoma due to central retinal artery occlusion. Although not specific for cholesterol atheroembolism, livedo reticularis (areas of lace-like mottled and purplish skin over the legs and thighs) is commonly associated with this disorder. Management is primarily supportive; anti-inflammatory agents (such as glucocorticoids) are not routinely given for treatment of cholesterol atheroembolism.

Acute interstitial nephritis (AIN) should be suspected following the initiation of new medications, although none of the agents this patient is taking has been reported as a cause of AIN. A diffuse rash, but not livedo reticularis, is characteristic of AIN. Eosinophiluria was previously believed to diagnose AIN, but urine eosinophil determination has been shown to be neither sensitive nor specific in the diagnostic evaluation of AIN.

Contrast-induced nephropathy (CIN) is a diagnostic consideration given the dye load associated with cardiac catheterization. However, CIN typically presents as acute tubular necrosis with granular casts, and AKI due to CIN typically peaks at 24 to 72 hours but improves within 5 to 7 days.

Polyarteritis nodosa (PAN) is a necrotizing vasculitis of medium-sized arteries, sometimes associated with hairy cell leukemia or infection with hepatitis B or C. PAN may present with livedo reticularis, as in this patient, but kidney manifestations usually include renal arterial aneurysms with perirenal hematomas and severe hypertension, which findings are missing here. This patient also lacks any of the other neurologic or gastrointestinal manifestations of PAN.

KEY POINT

- Acute kidney injury is a common result of cholesterol embolization, which causes peripheral eosinophilia and hypocomplementemia and shows evidence of inflammation on urinalysis, frequently with eosinophiluria present.

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Item 89 Answer: C

Educational Objective: Treat stage 1 hypertension in a black patient.

The thiazide diuretic hydrochlorothiazide is the most appropriate agent for treating hypertension in this 57-year-old patient who is black. He has stage 1 hypertension, defined as a systolic blood pressure of 140-159 mm Hg and/or a diastolic blood pressure of 90-99 mm Hg. Thiazide diuretics (such as hydrochlorothiazide) and calcium channel blockers (such as amlodipine or diltiazem) alone or in combination are effective hypertensive treatment options for black patients and are recommended by the eighth report of the Joint National Committee (JNC 8) as initial therapy in this patient group. However, this patient is already taking a moderate dose of a statin (simvastatin) that undergoes significant metabolism via the cytochrome P450 3A4 (CYP3A4) pathway; lovastatin and, to a lesser extent, amlodipine are also metabolized through this pathway. Several calcium channel blockers inhibit or are metabolized through the CYP3A4 pathway and can increase the risk of statin myopathy in patients taking one of these particular statins. The dihydropyridine agents verapamil and diltiazem and the non-dihydropyridine agent amlodipine have been associated with increased risk with concurrent therapy with these drugs. Thus, hydrochlorothiazide is the most appropriate choice for this patient. The JNC 8 recommends a blood pressure goal of <140/90 mm Hg for black patients (for age ≥60 years, the target is <150/90 mm Hg, regardless of race). Prior recommendations had suggested blood pressure goals of <135/85 mm Hg in black patients given the higher risk of stroke and kidney disease compared with white patients. However, the African American Study of Kidney Disease and Hypertension (AASK) trial

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(comprised of black patients with hypertension and chronic kidney disease) did not demonstrate any difference in more aggressive (achieved blood pressure of 128/78 mm Hg) or less aggressive (achieved blood pressure of 141/85 mm Hg) blood pressure goals in slowing the rate of glomerular filtration rate decline or other secondary end points. Given his age and race, this patient's blood pressure goal is <140/90 mm Hg, according to JNC 8.

In general, black persons have less blood pressure response to renin-angiotensin system agents than other agents, despite similar plasma renin activity. Therefore, the ACE inhibitor lisinopril is not indicated for this patient.

KEY POINT

- The eighth report of the Joint National Committee recommends a thiazide diuretic or a calcium channel blocker alone or in combination as initial therapy for black patients with hypertension.

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Item 90 Answer: C

Educational Objective: Treat acute ethylene glycol poisoning with intravenous sodium bicarbonate.

The most appropriate additional management intervention in this patient is intravenous sodium bicarbonate therapy. He has findings typical of ethylene glycol intoxication, with evidence of central nervous system depression presumably due to the alcohol, an increased anion gap metabolic acidosis of 28 mEq/L (28 mmol/L), an osmolal gap of 27 mOsm/kg H_2O, and kidney failure likely resulting from deposition of calcium oxalate crystals in the renal tubules. Because the laboratory confirmation of ethylene glycol intoxication may take days, empiric therapy for patients with likely ethylene glycol intoxication is recommended pending confirmation. Treatment usually consists of intravenous hydration, fomepizole (a competitive inhibitor of alcohol dehydrogenase), and hemodialysis to clear both the parent alcohol as well as the toxic metabolites. Intravenous sodium bicarbonate therapy is also recommended in suspected ethylene glycol or methanol ingestion when the blood pH is below 7.30. This is because the toxic metabolites of ethylene glycol (glycolate, glyoxylate, and oxalate) and methanol (formate) penetrate tissues more effectively when in the neutral state, which is increased by an acidic blood pH. Bicarbonate is given to normalize the blood pH and maximize formation of the ionized forms of the associated toxic metabolites.

Both ethylene glycol and methanol are completely absorbed from the gastrointestinal tract, with peak serum levels occurring within 1 to 2 hours of ingestion. Therefore, gastric decontamination, such as with activated charcoal, is not usually performed unless the timing of a large ingestion is known and decontamination can be performed within 1 hour.

Intravenous ethanol was traditionally used as a competitive inhibitor of alcohol dehydrogenase; it is effective because this enzyme has greater affinity for ethanol than for ethylene glycol or methanol. However, fomepizole has been found to be a superior therapy to ethanol, is easier to administer, and has fewer side effects. Although ethanol is a reasonable second-line therapy, there is no benefit to coadministration of fomepizole and ethanol.

Given the patient's possible ingestion of ethylene glycol with an associated low blood pH, not providing bicarbonate therapy would be inappropriate.

KEY POINT

- Empiric therapy with sodium bicarbonate, fomepizole, and hemodialysis is indicated for patients with suspected ethylene glycol intoxication.

Bibliography

Kruse JA. Methanol and ethylene glycol intoxication. Crit Care Clin. 2012 Oct;28(4):661-711. [PMID: 22998995]

Item 91 Answer: C

Educational Objective: Treat secondary hyperparathyroidism in a patient with chronic kidney disease.

The most appropriate next step in management is to begin oral calcitriol. This patient has secondary hyperparathyroidism due to severe chronic kidney disease (CKD). The first priority in treating these patients is to attempt to normalize calcium and phosphorus levels and treat vitamin D deficiency, if present. This patient has normal calcium, phosphorus, and 25-hydroxy vitamin D levels. If vitamin D levels are robust and the phosphorus level is normal, but the parathyroid hormone (PTH) level is elevated above target levels, active vitamin D analogues should be initiated. This is because 1-α hydroxylation of 25-hydroxy vitamin D is impaired in most patients with severe CKD, and these patients should begin oral calcitriol (1,25-dihydroxy vitamin D) or a calcitriol analogue (such as paricalcitol or doxercalciferol) to maintain bone health. Calcitriol directly suppresses PTH production by the parathyroid glands, thereby protecting bones from osteitis fibrosa cystica, which can occur as a result of chronic secondary hyperparathyroidism. Vitamin D analogues should be discontinued in the setting of hypercalcemia or hyperphosphatemia.

Bisphosphonates may be used in the treatment of osteoporosis. However, bisphosphonates may actually worsen some types of bone disease observed in the setting of CKD, especially adynamic bone disease.

Current Kidney Disease Improving Global Outcomes (KDIGO) guidelines do not recommend the routine use of dual-energy x-ray absorptiometry (DEXA) scans in patients with CKD because DEXA has poor predictive value for distinguishing histologic subtypes of bone disease in patients with CKD.

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This patient does not have primary hyperparathyroidism, which is typically characterized by inappropriately elevated PTH levels in the setting of hypercalcemia. She has secondary hyperparathyroidism, which is driven by multiple factors, including reduced renal production of calcitriol and factors that are often present in patients with CKD such as hyperphosphatemia and hypocalcemia. Parathyroidectomy is reserved for patients with secondary hyperparathyroidism that is refractory to medical therapy (often referred to as tertiary hyperparathyroidism).

KEY POINT

- Patients with chronic kidney disease and normal calcium and phosphorus levels should be treated with active vitamin D analogues to reduce elevated parathyroid hormone levels and prevent renal osteodystrophy.

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Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2009 Aug;(113):S1-130. [PMID: 19644521]

Item 92 Answer: B

Educational Objective: Diagnose pseudohyponatremia.

The most likely diagnosis is pseudohyponatremia. Plasma osmolality can be measured using the following equation:

$$\text{Plasma Osmolality (mOsm/kg } H_2O) = 2 \times \text{Serum Sodium (mEq/L)} + \text{Plasma Glucose (mg/dL)}/18 + \text{Blood Urea Nitrogen (mg/dL)}/2.8$$

Using this formula, this patient's calculated plasma osmolality is approximately 266 mOsm/kg H_2O. However, his measured plasma osmolality is in the normal range. In the absence of ingested osmoles such as methanol or ethylene glycol, a normal plasma osmolality in a patient with a low serum sodium level strongly suggests pseudohyponatremia, caused by a laboratory error in the measurement of serum sodium. In normal persons, 93% of plasma is water. Laboratory analysis of serum sodium measures the amount of sodium (and thus the concentration of sodium) dissolved in the plasma water. If a substance is present that decreases the proportion of plasma that is water, such as in laboratories using ion-selective electrodes and indirect potentiometry, the measured serum sodium and concentration will be falsely low, resulting in pseudohyponatremia. There are two usual causes of pseudohyponatremia: elevated serum lipid levels or the presence in the serum of abnormal paraproteins such as myeloma proteins. This patient has a medical history, symptoms, and signs suggestive of acute pancreatitis, which can be caused by significant hypertriglyceridemia and may result in pseudohyponatremia.

Patients with adrenal insufficiency may also have hyponatremia, caused by increased antidiuretic hormone (ADH) secretion in response to hypovolemia from urine salt wasting. However, these patients demonstrate a decrease in plasma osmolality rather than a normal plasma osmolality as seen in this patient.

Psychogenic polydipsia, in which patients ingest massive amounts of water, is characterized by hyponatremia with decreased plasma osmolality and decreased urine osmolality to less than the plasma osmolality, indicating maximum suppression of ADH with maximal urine dilution. These findings are not present in this patient.

Patients with the syndrome of inappropriate antidiuretic hormone secretion have hyponatremia with decreased plasma osmolality, which is not seen in this patient.

KEY POINT

- Pseudohyponatremia is caused by a laboratory error in the measurement of serum sodium due to the presence in the serum of elevated serum lipid levels or abnormal paraproteins such as myeloma proteins.

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Liamis G, Liberopoulos E, Barkas F, Elisaf M. Spurious electrolyte disorders: a diagnostic challenge for clinicians. Am J Nephrol. 2013;38(1):50-7. [PMID: 23817179]

Item 93 Answer: C

Educational Objective: Treat minimal change glomerulopathy with glucocorticoids.

Glucocorticoids are indicated for this patient who most likely has minimal change glomerulopathy (MCG). MCG is the most common cause of idiopathic nephrotic syndrome in children and accounts for approximately 10% of cases in adults. Although the mechanism of MCG is not well understood, it results in fusion and dysfunction of the epithelial foot processes of the glomerulus, causing significant loss of protein and other macromolecules into the urine. Patients with MCG typically present with acute onset of edema and weight gain due to fluid retention. Urine protein levels tend to be significantly elevated (urine protein-creatinine ratio typically 5000-10,000 mg/g). The abrupt onset of the full nephrotic syndrome, a history of kidney disease in childhood that remitted, negative serologic tests, and a kidney biopsy showing normal light microscopic findings and negative immunofluorescence are diagnostic of MCG. Electron microscopy is confirmatory and usually demonstrates the extensive effacement of the podocyte foot processes. Most patients with MCG are symptomatic, and the disease does not remit spontaneously in the weeks or months after presentation. Treatment with immunosuppressive medications is recommended to prevent complications of severe nephrotic syndrome, including severe symptomatic edema, thromboembolic events, and infections. Glucocorticoids such as prednisone are recommended

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as first-line therapy unless there are contraindications. More than 80% of patients respond within 16 weeks of treatment. Alternative first-line therapy for patients with contraindications to glucocorticoids (for example, obesity, impaired glucose tolerance or diabetes mellitus, or psychiatric conditions) includes calcineurin inhibitors such as cyclosporine.

Alkylating agents such as cyclophosphamide are reserved for frequently relapsing or glucocorticoid-dependent patients with MCG.

ACE inhibitors such as lisinopril or angiotensin receptor blockers (typically used to inhibit the progression of chronic kidney disease) are typically not indicated to treat MCG because the duration of disease is short with glucocorticoid therapy, and patients are not hypertensive.

Although MCG is not a common cause of end-stage kidney disease in adults, and untreated patients may slowly improve, the nephrotic-range proteinuria of MCG is associated with a significantly increased risk for thromboembolism and infection. Therefore, because most patients treated with glucocorticoid therapy recover with a favorable prognosis, not providing treatment is inappropriate.

KEY POINT

- Glucocorticoids are recommended as first-line therapy in the treatment of minimal change glomerulopathy unless there are contraindications.

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Hogan J, Radhakrishnan J. The treatment of minimal change disease in adults. J Am Soc Nephrol. 2013 Apr;24(5):702-11. [PMID: 23431071]

Item 94 Answer: B

Educational Objective: Diagnose thyrotoxic periodic paralysis.

This patient has features of acquired hypokalemic periodic paralysis occurring in association with hyperthyroidism (thyrotoxic periodic paralysis). Hypokalemic periodic paralysis is a rare familial or acquired disorder characterized by generalized flaccid muscle weakness from a sudden intracellular potassium shift precipitated by strenuous exercise or a high carbohydrate meal. Attacks may also occur spontaneously. The acquired form occurs with thyrotoxicosis and is found in men of Asian or Mexican descent. This patient's hyperthyroidism is suggested by the presence of hypertension, tachycardia, palpitations, tremor, heat intolerance, and weight loss. Hypokalemic periodic paralysis resolves with treatment of hyperthyroidism.

Bartter syndrome represents a group of autosomal recessive renal tubular disorders characterized by metabolic alkalosis, hypokalemia, and normal to low blood pressure with mild volume depletion. It is not associated with high blood pressure as seen in this patient.

Primary hyperaldosteronism is associated with hypertension and hypokalemia and is not associated with attacks of sudden weakness or paralysis.

Hypokalemia from Sjögren syndrome occurs in the setting of renal tubular acidosis; in this setting, a hyperchloremic metabolic acidosis with hypokalemia would occur, which is not present in this patient.

KEY POINT

- Hypokalemic periodic paralysis secondary to thyrotoxicosis is characterized by generalized flaccid muscle weakness from a sudden intracellular potassium shift precipitated by strenuous exercise or a high carbohydrate meal.

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Falhammar H, Thorén M, Calissendorff J. Thyrotoxic periodic paralysis: clinical and molecular aspects. Endocrine. 2013 Apr;43(2):274-84. [PMID: 22918841]

Item 95 Answer: C

Educational Objective: Manage hypertension during pregnancy.

The most appropriate next step in management is to stop the angiotensin receptor blocker (ARB) losartan and monitor the blood pressure in this patient with hypertension who is attempting to conceive. ARBs, ACE inhibitors, and direct renin inhibitors are all associated with adverse fetal and neonatal outcomes; these agents are absolutely contraindicated during pregnancy and should be stopped prior to conception. Physiologic changes associated with pregnancy cause the systemic blood pressure to fall during most of gestation, and there is evidence that neither the patient nor the fetus appears to be at risk from mildly elevated blood pressure during pregnancy. The 2013 American College of Obstetricians and Gynecologists (ACOG) guidelines recommend treating persistent blood pressure elevations of >160/105 mm Hg in pregnant women with chronic hypertension, with a goal blood pressure with medical therapy in these patients being 120-160/80-105 mm Hg. Because this patient's current blood pressure is well below the recommended goal of therapy and her blood pressure would be expected to decline once she conceives, monitoring her blood pressure once the losartan is stopped is a reasonable approach. If her blood pressure rises into the recommended treatment range, reinstitution of treatment with a medication likely to be safe in pregnancy may be warranted.

Labetalol, a β-blocker with some α-blocking effect, may help preserve placental blood flow and is considered to be relatively safe during pregnancy. However, all antihypertensive medications cross the placenta, and it would be preferable to avoid treatment with any medication during early pregnancy. Because this patient might be able to be managed without medication should she become pregnant, switching to another agent from her ARB is not preferable. However, if further medical therapy is required, labetalol would be an appropriate option.

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KEY POINT

- ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors are associated with adverse fetal and neonatal outcomes; these medications are absolutely contraindicated during pregnancy and should be stopped prior to conception.

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Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension. 2012 Aug;60(2):444-50. [PMID: 22753220]

Item 96 Answer: D

Educational Objective: Diagnose lithium-induced nephrogenic diabetes insipidus using a water restriction test.

The most appropriate diagnostic test to perform next is a water restriction test to evaluate for diabetes insipidus (DI). DI is caused by either an absence of antidiuretic hormone (ADH) secretion (central DI) or renal resistance to ADH (nephrogenic DI), which results in an inability to appropriately concentrate the urine in response to an increase in plasma osmolality. This patient's symptoms of polyuria and polydipsia, in association with long-standing lithium therapy, are suggestive of nephrogenic DI. Lithium is one of the most common causes of nephrogenic DI in adults. On laboratory testing, serum sodium and plasma osmolality are usually high normal or slightly elevated, whereas urine osmolality is lower than plasma osmolality. Like the patient described, most patients with DI do not usually have frank hypernatremia because increased thirst stimulates oral consumption of fluids, which maintains the serum sodium near the upper normal range as long as access to fluids is not impaired. In a water restriction (or deprivation) test, urine volume, urine osmolality, and plasma sodium concentration are measured hourly after complete water restriction. A normal urine osmolality response (usually defined as an increase in urine osmolality above 600 mOsm/kg H_2O) indicates that ADH release and corresponding renal response to ADH are intact. A failure of the urine osmolality to rise despite rising plasma osmolality suggests either central or nephrogenic DI. Desmopressin is then administered. Patients with central DI will respond with increased urine osmolality, whereas in patients with nephrogenic DI (as is likely in this patient), desmopressin will not result in increased urine osmolality after water restriction, confirming the diagnosis.

The cosyntropin stimulation test is used to diagnose adrenal insufficiency, which is manifested by hyponatremia, decreased plasma osmolality, and increased urine osmolality, none of which is seen in this patient.

Hypothyroidism, which is diagnosed by the finding of a high thyroid-stimulating hormone level, can be associated with hyponatremia. In contrast to this patient with DI, patients with hyponatremia secondary to hypothyroidism present with hyponatremia, decreased plasma osmolality, and increased urine osmolality.

A urine sodium measurement is useful in the evaluation of patients with suspected urinary salt wasting, such as those with adrenal insufficiency. Patients with DI have a deficit of free water rather than urinary salt wasting, and as such, urine sodium measurement is not useful in diagnosing DI.

KEY POINT

- An inadequate response to water restriction (urine osmolality does not rise despite rising plasma osmolality) suggests either central or nephrogenic diabetes insipidus.

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Devuyst O. Physiopathology and diagnosis of nephrogenic diabetes insipidus. Ann Endocrinol (Paris). 2012 Apr;73:128-9. [PMID: 22503803]

Item 97 Answer: A

Educational Objective: Treat hyperkalemia using intravenous glucose and insulin to rapidly shift potassium intracellularly.

The most appropriate treatment for lowering this patient's serum potassium level most quickly is intravenous glucose and insulin. He has end-stage kidney disease (ESKD) and presents with hyperkalemia and peaked T waves on electrocardiogram. Hyperkalemia is defined as a serum potassium level >5.0 mEq/L (5.0 mmol/L). Any level >6.0 mEq/L (6.0 mmol/L) can be life-threatening. Signs and symptoms are related to adverse effects of serum potassium on skeletal and cardiac muscle cell membranes, including muscle weakness and cardiac conduction and rhythm abnormalities. Intravenous calcium gluconate stabilizes the myocardium by lowering the threshold potential and is usually administered acutely to decrease the risk of arrhythmias; however, calcium does not have any effect on serum potassium levels. Major underlying causes of persistent hyperkalemia are disorders in which urine potassium excretion is impaired. The most common cause is chronic kidney disease with a glomerular filtration rate <20 mL/min/1.73 m^2 or acute kidney injury. The appropriate treatment for reducing serum potassium quickly in this patient with ESKD and hyperkalemia is both insulin and glucose given intravenously to rapidly shift potassium intracellularly. Insulin effectively drives potassium into cells by increasing activity of the Na-K-ATPase pump in skeletal muscle. Glucose is given to counteract potential hypoglycemia associated with insulin therapy.

High-dose loop and thiazide diuretics increase kidney potassium loss, particularly when combined with saline hydration, in patients with normal kidney function or mild to moderate kidney failure. However, this effect is not immediate, and bumetanide would be ineffective in this patient with ESKD.

Intravenous sodium bicarbonate raises the serum pH and leads to a shift of potassium into cells as part of the buffering process. However, it has not been shown to be an

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effective or predictable method for producing a hypokalemic response, especially in patients with ESKD.

Oral sodium polystyrene sulfonate in sorbitol binds potassium in the colon in exchange for sodium. It is not useful for acute control of hyperkalemia because its effect on potassium is delayed for at least 2 hours and peaks at 4 to 6 hours. In addition, its effect on hyperkalemia is modest.

KEY POINT

- To quickly lower serum potassium levels related to hyperkalemia, initial treatment involves intravenous glucose (to counteract hypoglycemia) and insulin to rapidly shift potassium intracellularly.

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PaPutcha N, Allon M. Management of hyperkalemia in dialysis patients. Semin Dial. 2007 Sep-Oct;20(5):431-9. [PMID: 17897250]

Item 98 Answer: A

Educational Objective: Manage stage 1 hypertension in an older patient.

Addition of the ACE inhibitor lisinopril is appropriate. This 60-year-old patient has stage 1 hypertension. The eighth report of the Joint National Committee (JNC 8) recommends a treatment goal of <150/90 mm Hg for patients with hypertension who are ≥60 years. Given her age and no evidence of cardiovascular or kidney disease and lack of frailty, this patient's treatment goal according to JNC 8 is <150/90 mm Hg. In her circumstance, given a longer expected lifetime than the general population for this age, cautious stepped care for lower blood pressure goals is reasonable. Increasing the dose of one agent is less effective in reducing blood pressure than the addition of a second agent at low dose, which also avoids the risk of side effects more commonly seen at higher doses. In this case, the minor pedal edema may be exacerbated by increasing the amlodipine.

In the absence of any indications for β-blocker therapy (tachycardia, history of angina, or a recent myocardial infarction), metoprolol is not indicated for the initial therapy of hypertension. It can be considered as add-on therapy typically in the setting of vasodilator-induced tachycardia, but given the low resting pulse rate in this patient, an alternative agent should be considered. The Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial demonstrated the benefit of combination therapy with a calcium channel blocker and an ACE inhibitor in reducing cardiovascular events compared with combination therapy using a thiazide diuretic and an ACE inhibitor.

KEY POINT

- The eighth report of the Joint National Committee recommends a blood pressure goal of <150/90 mm Hg for patients with hypertension who are ≥60 years.

Bibliography

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Item 99 Answer: A

Educational Objective: Diagnose masked hypertension using ambulatory blood pressure monitoring.

Ambulatory blood pressure monitoring (ABPM) is appropriate for this patient who likely has masked hypertension. He has evidence of end-organ manifestations (left ventricular hypertrophy) that is potentially related to hypertension, yet has not presented with blood pressure measurements consistent with hypertension (≥140/90 mm Hg). This raises the possibility of masked hypertension, which is defined as normal office blood pressure measurements but elevated blood pressure (>135/85 mm Hg) in the ambulatory setting. Prior to initiating medical therapy, a more detailed assessment of this patient's blood pressure should be pursued, with ABPM as an appropriate next step. Although ABPM does not carry a formal indication for the diagnosis of masked hypertension, it may be useful in establishing this blood pressure pattern. ABPM-ascertained hypertension is associated with a higher risk of cardiovascular death compared with office or home blood pressure–determined hypertension.

The left ventricular hypertrophy identified by electrocardiogram in this case may be secondary to hypertension but also may be due to other (such as genetic) causes and requires formal echocardiography to further evaluate and guide therapy. Initiating a blood pressure–lowering agent is not appropriate until both blood pressure and the electrocardiogram findings are clarified further with ABPM and echocardiography.

A plasma renin-plasma aldosterone ratio is used to evaluate for hyperaldosteronism as a secondary cause of hypertension and is typically indicated in patients with difficult-to-treat blood pressure elevations and hypokalemia. This patient has not been diagnosed with hypertension and has no electrolyte abnormalities.

Because this patient has evidence of end-organ damage possibly due to hypertension, follow-up assessment of his blood pressures in 6 months might further delay diagnosis and is not appropriate.

KEY POINT

- Ambulatory blood pressure monitoring may be helpful in diagnosing masked hypertension in patients with end-organ manifestations but normal office blood pressure measurements.

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Item 100 Answer: C

Educational Objective: Diagnose respiratory alkalosis.

The most likely acid-base disorder in this patient is respiratory alkalosis with acute metabolic compensation. This patient has primary acute respiratory alkalosis, likely resulting from a panic attack associated with her anxiety disorder. Acute respiratory alkalosis is evidenced by a low P_{CO_2} and an appropriately reduced serum bicarbonate occurring in response to the lowered P_{CO_2}. For each 10 mm Hg (1.3 kPa) decrease in P_{CO_2}, serum bicarbonate falls acutely by 2.0 mEq/L (2.0 mmol/L) due to intracellular-to-extracellular shift of hydrogen ions as an immediate buffering mechanism. If the respiratory alkalosis is persistent, renal compensation will eventually occur, leading to reduced proximal tubule reabsorption of bicarbonate, and, after 24 to 48 hours, a further decrease in serum bicarbonate totaling 3.0 to 4.0 mEq/L (3.0-4.0 mmol/L) for every 10 mm Hg (1.3 kPa) decrease of P_{CO_2}. The reduction in bicarbonate of 4.0 mEq/L (4.0 mmol/L) for the decrease in P_{CO_2} of 18 mm Hg (2.4 kPa) indicates that renal compensation has not yet occurred. The laboratory studies are not consistent with a primary metabolic alkalosis because the bicarbonate is not elevated.

KEY POINT

- Primary acute respiratory alkalosis is characterized by a low P_{CO_2} and an appropriately reduced serum bicarbonate.

Bibliography

Palmer BF. Evaluation and treatment of respiratory alkalosis. Am J Kidney Dis. 2012 Nov;60(5):834-8. [PMID: 22871240].

Item 101 Answer: C

Educational Objective: Treat metabolic acidosis with alkali therapy to slow progression of chronic kidney disease.

Treatment with oral sodium bicarbonate, 0.5 mEq/kg/d, is appropriate. This patient with chronic kidney disease (CKD) has a normal anion gap metabolic acidosis. Normal anion gap metabolic acidosis may be due to failure of the kidneys to excrete the daily fixed acid load, gastrointestinal loss of bicarbonate, diversion of urine through a gastrointestinal conduit, or retention of hydrogen ions derived from organic anions that are excreted in the urine as sodium salts. The cause is often apparent from the history. This patient's history of analgesic nephropathy, normal anion gap metabolic acidosis, and hyperkalemia suggests the presence of distal (type 4) renal tubular acidosis. Studies have demonstrated that administration of oral alkali to maintain serum bicarbonate levels between 23 and 29 mEq/L (23-29 mmol/L) reduces the risk of progression of CKD. Typical starting doses of alkali for metabolic acidosis due to CKD are 0.5 to 1.0 mEq/kg/d.

The patient has a relatively mild and asymptomatic decrease in serum bicarbonate, and there is no indication for acute administration of intravenous sodium bicarbonate.

Although citrate becomes metabolized to bicarbonate and is therefore considered to be a "bicarbonate equivalent," this patient has hyperkalemia, which is likely due to the decreased ability of the kidneys to excrete potassium in the setting of CKD. Potassium citrate could therefore exacerbate the existing hyperkalemia and should be avoided. Bicarbonate treatment will help correct this patient's hyperkalemia.

Current guidelines suggest treatment with alkali to keep serum bicarbonate levels between 23 and 29 mEq/L (23-29 mmol/L). Therefore, providing no alkali therapy to this patient with a serum bicarbonate level of 18 mEq/L (18 mmol/L) would be inappropriate.

KEY POINT

- Oral alkali therapy to maintain serum bicarbonate levels between 23 and 29 mEq/L (23-29 mmol/L) reduces the risk of progression of chronic kidney disease.

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Item 102 Answer: A

Educational Objective: Diagnose interstitial nephritis caused by mesalamine therapy.

The most likely diagnosis is interstitial nephritis caused by mesalamine therapy. Interstitial nephritis is characterized by an inflammatory infiltrate into the kidney interstitium that can lead to tubular dysfunction and kidney failure. Interstitial nephritis may be associated with autoimmune diseases and infections but is most commonly caused by drugs. Mesalamine-induced interstitial nephritis is a well-described complication that can be either acute or chronic and may occur months to years after exposure, even in patients who have safely tolerated the medication in the past. Sterile pyuria and leukocyte casts are hallmarks of interstitial nephritis, which can present acutely or may progress indolently and present as chronic kidney disease of unclear duration. Mild subnephrotic proteinuria also can be seen with interstitial nephritis.

Kidney disease in systemic lupus erythematosus is relatively common and may have a variable presentation, often with significant hematuria, proteinuria, and cellular casts. However, lupus nephritis is unlikely in this patient because of the absence of extrarenal lupus manifestations, his male gender, and lack of significant proteinuria or hematuria.

Membranous glomerulopathy primarily affects the glomerulus and is therefore associated with heavy proteinuria and the nephrotic syndrome, making this an unlikely diagnosis for this patient.

Rapidly progressive glomerulonephritis is associated with hematuria and erythrocyte casts and variable

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proteinuria, usually with other clinical manifestations such as hypertension. In some cases, other systemic symptoms or clinical findings associated with an underlying etiology may be present, such as pulmonary hemorrhage or upper and lower respiratory tract involvement. None of these findings is present in this patient, making this diagnosis unlikely.

KEY POINT

- In patients with interstitial nephritis, the hallmark findings on urinalysis are sterile pyuria and leukocyte casts.

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Item 103 Answer: D

Educational Objective: Diagnose preeclampsia.

The most likely diagnosis is preeclampsia, which is classically defined as new-onset hypertension after 20 weeks of pregnancy with proteinuria (≥300 mg/24 h or a urine protein-creatinine ratio ≥300 mg/g). According to new guidelines, preeclampsia can also be diagnosed in patients without proteinuria if the hypertension is accompanied by one of the following conditions: thrombocytopenia (platelet count <100,000/μL [100 × 10^9/L]), kidney dysfunction (serum creatinine concentration >1.1 mg/dL [97.2 μmol/L] or a doubling of the serum creatinine concentration in the absence of other kidney disease), impaired liver function (elevated blood concentrations of liver aminotransferases to twice the normal concentration), pulmonary edema, or cerebral or visual symptoms. Because this patient meets the criteria for blood pressure elevation and also has thrombocytopenia and possibly mild pulmonary edema, the diagnosis of preeclampsia may be made without the presence of proteinuria. She has several risk factors for preeclampsia, including advanced maternal age and first pregnancy. Other risk factors for preeclampsia include family history, diabetes mellitus, obesity, chronic kidney disease, and twin gestation.

Chronic hypertension is defined as systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg that existed before pregnancy, is present before the 20th week of gestation, or persists longer than 12 weeks postpartum. This patient had normal blood pressures prior to her most recent visit, making chronic hypertension unlikely.

The diagnosis of HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome requires evidence of hemolysis and abnormal liver chemistry tests in addition to thrombocytopenia.

Normal hemodynamic changes occurring during pregnancy include an increase in cardiac output and reduction in both systemic vascular resistance and systemic blood pressure. Therefore, the significant blood pressure elevation seen in this patient who was previously normotensive is not considered to be a normal change associated with pregnancy. Crackles, an S_3 gallop, and an elevated central venous pressure would not be expected findings during a normal pregnancy and reinforce the diagnosis of preeclampsia.

KEY POINT

- Preeclampsia is classically defined as new-onset hypertension after 20 weeks of pregnancy with proteinuria but can also be diagnosed in patients without proteinuria if the hypertension is accompanied by other end-organ damage.

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Item 104 Answer: D

Educational Objective: Treat hyperphosphatemia in a patient with chronic kidney disease.

In addition to dietary counseling regarding a low phosphate diet, this patient with stage G4/A1 chronic kidney disease (CKD) who now has hyperphosphatemia should begin taking a phosphate binder such as sevelamer. Elevated serum phosphorus levels, particularly exceeding 6.5 mg/dL (2.09 mmol/L), are closely associated with increased mortality. Most patients with severe CKD require oral phosphate binders to be administered with meals. This patient also has known cardiovascular disease and vascular calcification. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest avoiding the use of calcium-containing phosphate binders in patients with known vascular calcification due to the potential for an increase in calcium absorption and worsening calcification of vessel walls. Therefore, a non-calcium–containing phosphate binder such as sevelamer or lanthanum is the preferred agent for this patient. Ferric citrate, another non-calcium–containing phosphorus binder, was recently approved for use in patients receiving dialysis but is not yet approved for patients with non-dialysis CKD.

Although this patient has secondary hyperparathyroidism, administration of calcitriol will increase intestinal absorption of calcium and phosphorus, which will exacerbate the hyperphosphatemia and potentially worsen vascular calcification.

Although administration of oral calcium carbonate will lead to increased absorption of calcium that may treat this patient's mild hypocalcemia and reduce her parathyroid hormone (PTH) levels, it may exacerbate vascular calcium in the setting of severe hyperphosphatemia.

Administration of the calcimimetic cinacalcet will likely decrease this patient's PTH level toward the normal range; however, it will worsen her hypocalcemia and is not an effective treatment for the hyperphosphatemia.

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KEY POINT

- Patients with chronic kidney disease and hyperphosphatemia should be counseled regarding a low phosphate diet, and most patients require phosphate binders.

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Item 105 Answer: A

Educational Objective: Treat chronic kidney disease-related iron deficiency anemia with intravenous iron.

The most appropriate management of this patient with chronic kidney disease–related iron deficiency anemia is to administer intravenous iron. Iron deficiency is the most common cause of hyporesponsiveness to erythropoietin. It is therefore important to optimize iron stores to maximize the response to erythropoietin. Many patients who receive hemodialysis are unable to maintain adequate iron stores by oral supplementation. The Kidney Disease Improving Global Outcomes (KDIGO) recommendations suggest maintaining transferrin saturation levels of >30% and serum ferritin levels of >500 ng/mL (500 µg/L). In hemodialysis patients, parenteral iron therapy is preferred to oral iron therapy because it is more effective in increasing hemoglobin concentrations and iron stores. Patients treated with intravenous iron are more likely to reduce the dose of erythropoiesis-stimulating agents (ESAs) compared with those taking oral iron. KDIGO guidelines recommend intravenous rather than oral iron replacement among hemodialysis patients who require iron.

As the estimated glomerular filtration rate declines below 30 mL/min/1.73 m^2 (stages G4-G5), anemia can become symptomatic. ESAs are highly effective in raising hemoglobin concentrations and alleviating symptoms, although these medications are associated with risks and are expensive. Once iron stores are replaced, KDIGO guidelines suggest avoiding dosing erythropoietin to achieve a hemoglobin level >11.5 g/dL (115 g/L) unless there are compelling reasons to do so to improve quality of life and the patient agrees to the risks.

There is no role for the routine measurement of erythropoietin levels in the setting of chronic kidney disease because this expensive test does not aid in the diagnosis or guide treatment decisions.

KEY POINT

- Iron deficiency is the most common cause of hyporesponsiveness to erythropoietin, and guidelines recommend intravenous rather than oral iron replacement among hemodialysis patients who require iron.

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Item 106 Answer: A

Educational Objective: Evaluate a patient for secondary causes of membranous glomerulopathy.

Chest radiography is the most appropriate next diagnostic step. This middle-aged patient presented with the insidious onset of the nephrotic syndrome with membranous glomerulopathy (MG) demonstrated on kidney biopsy. MG may be primary (idiopathic) or secondary to other causes. Primary MG is associated with the antibody to the phospholipase A_2 receptor (PLA_2R) on the podocyte surface in up to 80% of patients, and the presence of the antibody supports this diagnosis. Testing for anti-PLA_2R antibodies may be performed on serum or by staining of kidney biopsy tissue. Secondary causes of MG include malignancies (solid organ cancers, especially lung, colon, and breast), autoimmune diseases (such as lupus or mixed connective tissue disease), infections (hepatitis B and C), and medications (penicillamine, gold, and NSAIDs). Evaluation for potential secondary causes should always be undertaken in patients with MG, especially those who are negative for PLA_2R antibodies. Serologic tests for lupus and hepatitis were negative in this patient, and he has not been exposed to potential offending medications. Although MG may be associated with malignancy, an extensive evaluation for cancer is not indicated in patients with a diagnosis of MG beyond age-appropriate cancer screening except for those with symptoms suggestive of a cancer diagnosis (such as weight loss or blood in the stool) or significant risk factors for specific malignancies. Because of this patient's significant smoking history and his associated increased risk for lung cancer, chest radiography should be obtained as part of his evaluation for secondary MG.

Both PET and PET coupled with CT are useful studies in evaluating selected patients with known malignancy, often for staging purposes. However, neither is indicated to initially evaluate for lung cancer. Similarly, whole body CT is of low yield in searching for malignancy.

Although an extensive evaluation for malignancy is usually not indicated in patients with MG beyond age-appropriate cancer screening, this patient's increased risk for lung cancer warrants further evaluation.

KEY POINT

- An extensive evaluation for cancer is not indicated in patients with membranous glomerulopathy beyond age-appropriate cancer screening except for those with symptoms suggestive of a cancer diagnosis or significant risk factors for specific malignancies.

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Item 107 Answer: C

Educational Objective: Protect sites of current or future vascular access in a patient with severe chronic kidney disease.

Placement of a single-lumen catheter in the right internal jugular vein to allow for 6 weeks of intravenous ceftriaxone is appropriate for this patient with severe chronic kidney disease (CKD). This strategy seeks to protect the integrity of peripheral veins. Protecting peripheral veins is an important consideration for all patients with severe CKD or end-stage kidney disease (ESKD) because adequate veins are a prerequisite for the creation of arteriovenous fistulas, which are associated with lower mortality than other forms of vascular access for hemodialysis. Because most patients will require multiple vascular accesses during the course of ESKD therapy, it is critical to protect peripheral veins even if patients already have a functional dialysis access. Small-bore single-lumen catheters placed into the internal jugular vein are less likely to impair venous drainage from the arm than subclavian catheters.

Peripherally inserted central catheter (PICC) lines have a high risk of causing permanent thrombosis or sclerosis to peripheral veins that might otherwise be useful for the creation of vascular access for hemodialysis. PICC lines should be avoided in patients with severe CKD or ESKD who are expected to require future hemodialysis.

Subclavian catheters have a high risk of causing stenosis of the subclavian veins, which can impede return of blood from the arm with arteriovenous dialysis access due to high blood flows. High venous pressure due to subclavian stenosis can lead to arm edema and failure of the arteriovenous access.

The patient's arteriovenous fistula should not be used to administer daily intravenous antibiotics. Inserting needles into a recently created fistula can damage it because the walls of the vein will not have had adequate time to "arterialize," which usually requires at least 2 to 3 months. Dialysis vascular access sites should only be accessed by trained dialysis personnel due to the need to protect against injury and/or infection to the access site. It is also important to avoid inflating blood pressure cuffs on the arm with vascular access to avoid injury or thrombosis.

KEY POINT

- Protection of the peripheral veins for future vascular access is essential in patients with chronic kidney disease.

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Item 108 Answer: B

Educational Objective: Identify normal physiologic changes of pregnancy as the cause of decreased serum sodium levels in a pregnant patient.

Normal physiologic changes of pregnancy are the most likely cause of this pregnant patient's decrease in her serum sodium level. While the plasma volume increases during pregnancy, water retention exceeds the concomitant sodium retention, resulting in mild hypo-osmolality and hyponatremia. The plasma osmolality typically decreases by 8 to 10 mOsm/kg H_2O, and the serum sodium decreases by 4.0 mEq/L (4.0 mmol/L). These hormonally mediated changes in plasma osmolality and serum sodium do not require therapy and resolve following delivery.

Cerebral salt wasting can be mistaken for the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and can occur in response to central nervous system disease (particularly subarachnoid hemorrhage) and closed head injury. It is associated with an increased loss of sodium by the kidney, resulting in hyponatremia. However, these changes occur over a longer timeframe than seen in this patient with recent head trauma.

Pituitary apoplexy is acute hemorrhage into the pituitary gland and would be a consideration in this patient. If severe, it may cause headache, vision changes due to ocular nerve compression, and hypopituitarism. All pituitary hormonal deficiencies can occur, including adrenocorticotropic hormone (ACTH) deficiency, which may lead to cortisol deficiency and hypotension if it occurs rapidly. Although the resulting cortisol deficiency may result in mild hyponatremia, this would not occur immediately after injury. Additionally, this patient has a normal blood pressure for pregnancy and no other symptoms or clinical findings suggesting this diagnosis.

Neurologic conditions such as a closed head injury from a motor vehicle accident can cause the SIADH, but hyponatremia would not develop acutely upon initial presentation as in this patient.

KEY POINT

- While the plasma volume increases during pregnancy, water retention exceeds the concomitant sodium retention, resulting in mild hypo-osmolality and hyponatremia; these hormonally mediated changes do not need direct therapy and resolve following delivery.

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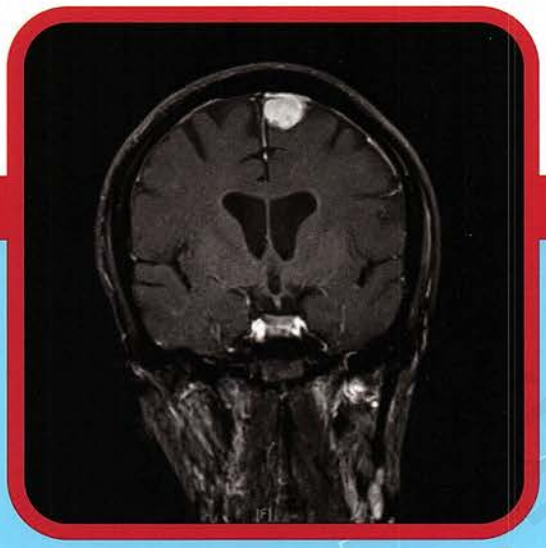

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Sincerely,



Philip A. Masters, MD, FACP
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- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
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For the convenience of subscribers who provide care in hospital settings, content that is specific to the hospital setting has been highlighted in blue. Hospital icons (H) highlight where the hospital-based content begins, continues over more than one page, and ends.

High Value Care Key Points

Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon (HVC).

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Errata

Errata for MKSAP 17 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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Neurology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 17 in several important ways. MKSAP 17 now includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Neurology section of MKSAP 17.

- Guidelines specifically recommend against neuroimaging studies in patients with stable headaches that meet criteria for migraine or uncomplicated headache (see Item 48).
- No evidence supports the superiority of anticoagulation over antiplatelet therapy in prevention of stroke after carotid and vertebral artery dissections, and most patients are initially managed with aspirin.
- Patients with unruptured intracranial aneurysms should be counseled to stop smoking because of the increased risk of aneurysmal rupture (see Item 72).
- Because of the documented significantly higher rates of medication overuse headache in patients exposed to butalbital compounds and opioid analgesics, these agents should be avoided in headache management.
- One way of remedying the high rate of misdiagnosis of migraine is to use the POUND mnemonic, which includes the following criteria: headache that is Pulsatile, is One-day in duration (with episodes lasting 4-72 hours if untreated), is Unilateral, is accompanied by Nausea/vomiting, and is Disabling; patients with greater than three of these criteria can be diagnosed with migraine without further evaluation.
- Evidence-based guidelines suggest that NSAIDs, triptans, and dihydroergotamine are effective treatments for acute migraine without aura and that NSAIDs are preferred as initial treatment because of their greater cost-effectiveness (see Item 69).
- No good evidence supports the superior efficacy of any oral NSAID or triptan choice; cost, formulary availability, and results of previous medication trials are all considerations in the selection of acute migraine medication.
- In order to improve health outcomes, such as attack frequency, intensity, disability, and cost, the use of preventive agents should be considered in patients with eight or more total days or four or more disabling days of migraine per month.
- In persons who sustain mild traumatic brain injury, neuroimaging is only recommended if symptoms of worsening headache, repeated vomiting, drowsiness, persistent confusion, dysarthria, or focal neurologic findings are present; head CT is preferable to brain MRI for initial neuroimaging because of its wider availability, lower cost, and greater sensitivity for identifying skull fractures.
- Contact sports should be prohibited in patients who are symptomatic after sustaining a mild traumatic brain injury (see Item 51).
- Because patients older than 75 years have the highest rates of morbidity, hospitalization, and mortality after traumatic brain injury, prevention is key; preventive measures include avoiding overmedication and encouraging regular physical activity and living area modifications.
- Single seizures that are provoked usually do not require treatment with an antiepileptic drug and instead should be addressed by correcting the underlying condition or removing the offending agent; further diagnostic evaluation, such as neuroimaging and electroencephalography, may not be needed if a clear reversible cause of the seizure is identified and the patient has normal findings on neurologic examination.
- In a patient with a single unprovoked seizure and a normal electroencephalogram and MRI, the 2-year recurrence risk is 30% to 40%; because seizure medications reduce this risk by only approximately 50%, antiepileptic drug therapy is not typically recommended.

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- Choosing an AED for an individual patient depends on several factors, including his or her epilepsy syndrome, age, sex, and comorbid medical conditions and the drug's adverse-effect profile and cost.
- The use of generic antiepileptic drugs (AEDs) is a way to control costs for patients with epilepsy, and the major consideration in using a generic AED is its bioavailability, which may differ by as much as 20% between manufacturers; because drug level maintenance is critical to maintaining seizure threshold, patients taking generic AEDs should try to use the same drug manufacturer from month to month.
- Most patients with asymptomatic extracranial internal carotid artery stenosis should be treated with aggressive risk factor control and not stenting or elective endarterectomy, which should only be considered in patients with a greater than 80% stenosis and low cardiovascular risk (as long as the operative complication rate is less than 3%).
- Using a statin to treat patients with asymptomatic internal carotid artery stenosis is associated with a stroke risk of less than 2% per year (see Item 35) and may prevent the need for endarterectomy.
- No reliable clinical markers or diagnostic tests can predict the likelihood that an individual patient with mild cognitive impairment will develop dementia, and no intervention has been shown to delay the onset of dementia in such a patient.
- For older patients with suspected cognitive impairment who are asymptomatic, insufficient evidence supports routine cognitive testing.
- Currently, the use of Alzheimer disease biomarkers in the clinical setting has no role because of the absence of disease-modifying therapies and the cost of advanced neuroimaging techniques and laboratory testing.
- Cholinesterase inhibitors have not been approved to treat frontotemporal dementia and vascular neurocognitive disorder or to delay progression from mild cognitive impairment to dementia.
- Nonpharmacologic interventions are often effective in treating the behavioral symptoms experienced by patients with dementia and should be the first-line treatment.
- No pharmacologic therapy is currently FDA approved for the prevention or treatment of delirium.
- Neurologic examination, particularly assessments of motor function and gait, is a low risk, high value means to distinguish the various movement disorders.
- The diagnosis of Parkinson disease can be made on the basis of clinical findings and requires the presence of bradykinesia and at least one of the other cardinal features of resting tremor, rigidity, or postural instability (see Item 73).
- Single photon emission CT of the brain should be reserved for differentiating Parkinson disease from drug-induced parkinsonism in patients with an atypical clinical picture.
- Recent studies have shown the beneficial role of rigorous daily exercise in improving motor fitness and gait in patients with Parkinson disease, and thus physical activity or physical therapy should be encouraged in all patients with the disease.
- Cerebrospinal fluid testing can be helpful when the diagnosis of MS is not clear but is not required for diagnosis if the full McDonald criteria have been met and other causes have been excluded.
- Maintenance of an active healthy lifestyle and strengthening, stretching, and aerobic exercise are recommended for all patients with multiple sclerosis to mitigate disability and preserve appropriate muscle tone.
- Routine vaccinations, such as an annual influenza vaccination, are recommended for patients with multiple sclerosis (MS) to prevent infections leading to a heightened immune state and potential MS relapse (see Item 68).
- Smoking cessation is strongly advised for all patients with multiple sclerosis because of the threefold increased risk of conversion to secondary progression associated with cigarette smoking.
- Treatment of a pseudorelapse of multiple sclerosis, which is worsening of baseline neurologic symptoms or recurrence of previous symptoms in the setting of physiologic stressors, should consist of observation and supportive therapy and not include increased immunosuppressive therapy (see Item 74).
- Although newer medications, such as pregabalin and duloxetine, have been used successfully to treat neuropathic pain in multiple sclerosis, less expensive generic alternatives, such as tricyclic antidepressants and gabapentin, are as effective and well tolerated.
- Low doses of tricyclic antidepressants, such as amitriptyline and nortriptyline, are a cost-effective, first-line treatment option for patients with painful peripheral neuropathy.
- Nerve biopsy is indicated only in a small subset of neuropathies when concern for vasculitic, infectious, or infiltrative neuropathy exists.
- Meralgia paresthetica, a compressive neuropathy of the lateral femoral cutaneous nerve that causes isolated anterolateral thigh numbness without weakness, can be clinically diagnosed and treated conservatively.
- Carpal tunnel syndrome can be diagnosed clinically by the presence of hypalgesia in the distribution of the median nerve; initial treatment involves wrist bracing, occupational therapy, and anti-inflammatory medications; electromyographic studies are not necessary.
- Bell palsy is idiopathic paralysis of the facial nerve that leads to complete unilateral facial paralysis; patients with a classic presentation and no other neurologic deficits can be diagnosed without brain imaging and laboratory testing.

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- Early treatment of Bell Palsy with oral prednisone (within 72 hours of symptom onset) improves outcomes; antiviral therapy does not affect prognosis.
- Diagnosis of diabetic peripheral neuropathy is clinical, and electromyographic studies are not necessary for patients with classic symptoms.
- Amyotrophic lateral sclerosis (ALS) is a fatal disease involving the motoneurons that is associated with progressive weakness and muscle wasting for which treatment is supportive; it is essential to discuss prognosis and establish goals of care with patients and families, thereby avoiding unnecessary diagnostic and therapeutic measures.
- Small asymptomatic meningiomas can be followed conservatively with an initial repeat MRI at 3 to 6 months.
- Prophylactic use of antiepileptic drugs is not recommended in most patients with brain tumors.

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Neurology

Headache and Facial Pain

Approach to the Patient with Headache

Headache is one of the most common reasons for presentation to an internist or emergency department. The diagnostic classification outlined in the third edition of the International Classification of Headache Disorders (ICHD-3) categorizes headache as primary, secondary, or related to a cranial neuralgia. Primary headaches are biologic disorders of the brain that are differentiated on the basis of clinical criteria (**Table 1**). Secondary headache disorders are defined by identifiable organic causation (**Table 2**) and typically display one of the following clinical "red flags."

- First or worst headache
- Abrupt-onset or thunderclap attack
- Progression or fundamental change in headache pattern
- Abnormal physical examination findings
- Neurologic symptoms lasting greater than 1 hour
- New headache in persons younger than 5 years or older than 50 years
- New headache in patients with cancer or immunosuppression or in pregnant women
- Association with alteration in or loss of consciousness
- Headache triggered by exertion, sexual activity, or Valsalva maneuver

The neurologic examination must involve thorough cranial nerve assessments, including funduscopic and visual field testing; additional examination of the cervical spine, carotid and temporal vessels, and temporomandibular joint may be helpful. Neuroimaging is indicated for suspected secondary headaches that exhibit one of the clinical red flags but is rarely appropriate in the evaluation of primary headache disorders; guidelines specifically recommend against neuroimaging studies in patients with stable headaches that meet criteria for migraine. When neuroimaging is necessary, MRI is preferred over CT (except in emergency settings, such as trauma-related headache or suspected acute intracerebral hemorrhage) because of its greater sensitivity and lack of radiation exposure. Suspected giant cell (temporal) arteritis should provoke measurement of erythrocyte sedimentation rate and C-reactive protein level. Lumbar puncture may be helpful in patients with suspected infectious or neoplastic meningitis or disorders of

TABLE 1. Primary Headache Syndromes

Migraine
Migraine without aura
Migraine with aura
Migraine with typical aura
Migraine with brainstem aura
Hemiplegic migraine
Retinal migraine
Chronic migraine
Complicated migraine
Probable migraine
Episodic syndromes possibly associated with migraine
Tension-Type Headache
Infrequent episodic tension-type headache
Frequent episodic tension-type headache
Chronic tension-type headache
Trigeminal Autonomic Cephalalgias
Cluster headache
Chronic paroxysmal hemicrania
Short-lasting unilateral neuralgiform headache attacks
With conjunctival injection and tearing (SUNCT)
With cranial autonomic symptoms (SUNA)
Hemicrania continua
Other Primary Headache Disorders
Primary cough headache
Primary exercise headache
Primary headache associated with sexual activity
Primary thunderclap headache
Cold-stimulus headache
External-pressure headache
Primary stabbing headache
Nummular headache
Hypnic headache
New daily persistent headache

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TABLE 2. Secondary Headache Syndromes

Posttraumatic headache
Head injury
Whiplash injury
Headache attributed to cranial or cervical vascular disorder
Ischemic stroke or transient ischemic attack
Parenchymal or subarachnoid hemorrhage
Unruptured vascular malformation or aneurysm
Intracranial or extracranial arteritis
Arterial dissection
Venous or sinus thrombosis
Headache attributed to nonvascular intracranial disorders
Intracranial hypotension or hypertension
Brain neoplasia
Noninfectious inflammatory disorders (sarcoidosis)
Chiari malformation
Headache attributed to substance use or withdrawal
Medication adverse event (nitrates)
Alcohol
Caffeine withdrawal
Medication overuse headache
Headache attributed to infection
Intracranial infection (meningitis, encephalitis, brain abscess)
Extracranial infection (systemic bacterial infection, viral syndrome)
Headache attributed to disorder of homeostasis
Hypertensive crisis, dialysis, hypoxia, hypercapnia, hypothyroidism
Headache attributed to disorder of the neck, eyes, ears, nose, sinuses, teeth, or mouth
Cranial neuralgias

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intracranial pressure. Electroencephalography has no role in the assessment of headache disorders.

After exclusion of secondary headache, primary headaches are best classified by evaluation of headache frequency, duration, and phenotypic expression, including pain descriptors and any associated neurologic, sensory, gastrointestinal, or autonomic components. The term episodic is used when headache-free days outnumber headache days over a defined period of time, and the term chronic when the number of days with headache is greater than the number of days without headache. Quantification of acute headache medication use is critical to identify those at risk for medication overuse headache. Greater than 90% of primary headaches involve a variant of migraine. Other primary disorders, such as tension-type and cluster headache, should be considered only after both secondary headache and migraine have been excluded. An algorithmic approach to headache assessment is provided in **Figure 1**.

KEY POINTS

- Primary headaches are biologic disorders of the brain, whereas secondary headaches have an identifiable organic causation and typically display a clinical red flag.
- Guidelines specifically recommend against neuroimaging studies in patients with stable headaches that meet criteria for migraine. HVC

Secondary Headache

Thunderclap Headache

The term thunderclap headache is applied to severe headaches that reach maximum intensity within 1 minute. The patient characteristically describes an attack as "the worst headache of my life." Although many benign primary headache syndromes can present with severe pain, the abrupt onset and rapid escalation of thunderclap headache signal the potential for serious intracranial disorders, most commonly subarachnoid hemorrhage (SAH). The headache can present as an isolated symptom and be global or localized. Associated features can vary depending on the underlying pathology and may include neck stiffness, nausea, vomiting, photophobia, phonophobia, or focal neurologic symptoms. Examination findings can be normal but can include nuchal rigidity, focal deficits, or alteration in consciousness.

Affected patients require emergent evaluation with head CT, and if CT scans are normal, lumbar puncture is mandatory. Neurovascular imaging with catheter magnetic resonance or CT angiography may be necessary to diagnose cerebral aneurysm, vascular malformation, arterial dissection, venous thrombosis, or reversible cerebral vasoconstriction syndrome (RCVS; also known as Call-Fleming syndrome).

Approximately 25% of thunderclap headaches result from SAH, with most of these (85%) involving rupture of previously unidentified saccular aneurysms. Risk of rupture is highest for cerebral aneurysms greater than 5 mm in diameter and those located in the posterior circulation. SAH-associated thunderclap headache can be spontaneous or associated with physical exertion. Many patients experience warning sentinel leaks, manifested as transient headaches, in the days or weeks before aneurysmal rupture. Head CT identifies 98% of SAHs within the first 12 hours, but sensitivity drops to 50% after 7 days. Lumbar puncture typically reveals an elevated opening pressure, high protein levels, and an erythrocyte count usually greater than 10,000/μL (10,000 × 10^6/L). Xanthochromia, or yellowing of the cerebrospinal fluid (CSF) due to breakdown of heme into bilirubin, is 100% sensitive for SAH between 12 hours and 7 days but may take 4 hours or more to develop. Because SAH has a 50% mortality rate and 25% serious morbidity rate, urgent neurosurgical evaluation is warranted.

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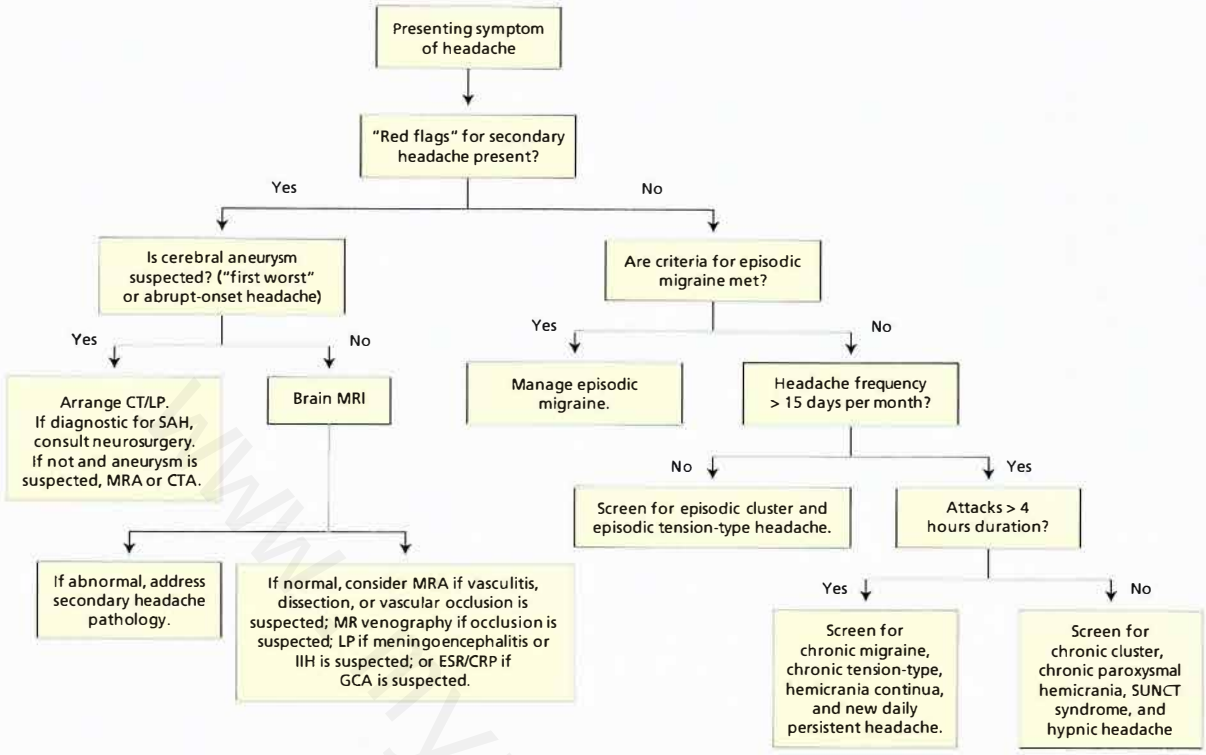

FIGURE 1. Algorithmic approach to a patient with headache. CRP = C-reactive protein level; CTA = CT angiography; ESR = erythrocyte sedimentation rate; GCA = giant cell (temporal) arteritis; IIH = idiopathic intracranial hypertension; LP = lumbar puncture; MRA = magnetic resonance angiography; SAH = subarachnoid hemorrhage; SUNCT = short-lasting unilateral neuralgiform headache with conjunctival injection and tearing syndrome.

Thunderclap headache occurs in two thirds of patients with cervical (carotid or vertebral) artery dissection but is rarely the only symptom. Dissections of the cranial vessels may occur spontaneously or as a result of either trivial or serious trauma. More than 90% of patients will have additional neck pain or associated neurologic features related to ischemic events within the territory of the affected artery. The headache may be diffuse but commonly is ipsilateral to the dissected vessel, with frontotemporal locations more common in carotid artery dissection and occipital locations more frequent in vertebral artery dissection. Visual amaurosis fugax, diplopia, or Horner syndrome can indicate carotid artery involvement, whereas dissections of the vertebral artery sometimes present with ataxia, vertigo, nausea and vomiting, and brainstem findings. Pulsatile tinnitus or audible bruits can be present with either type of dissection. No evidence supports the superiority of anticoagulation over antiplatelet therapy in prevention of stroke after carotid and vertebral artery dissections, and most patients are initially managed with aspirin.

Thrombosis of the cerebral veins or dural sinuses can present with abrupt-onset headache. Clinical symptoms may be related to the resulting increase in intracranial pressure and include pain exacerbation with the Valsalva maneuver, pulsatile tinnitus, and diplopia. Papilledema and focal findings, such as sixth nerve palsy, can be present, and some patients develop altered mentation and seizures. Suspicion of venous thrombosis should increase in the presence of hypercoagulable states, pregnancy and the puerperium, oral contraceptive use, infections of the ears or sinuses, or dehydration. Treatment with low-molecular-weight heparin results in lower hospital mortality than treatment with unfractionated heparin. Anticoagulation with warfarin is generally continued for 3 to 6 months.

Recurrent thunderclap headaches occur in patients with RCVS. This disorder is more common in women, particularly before menopause. RCVS appears to arise from transient failure of cerebrovascular autoregulation and is often triggered by exposure to adrenergic or serotonergic drugs. Headaches occur over the span of several days or weeks. Episodes can be triggered by exertion, the Valsalva maneuver, or abrupt head movements. Some patients have focal neurologic deficits, and neuroimaging may show evidence of parenchymal strokes, hemorrhages, or cerebral edema. A subset of patients have clinical and imaging features of posterior reversible encephalopathy syndrome, including seizures, confusion, visual loss, and cerebral edema, particularly of the parietal and occipital lobes. The CSF in RCVS is normal or near normal, and angiographic studies reveal multifocal areas of cerebral vasoconstriction. Management includes normalization of blood pressure and elimination of any triggering drug or substance. Nimodipine and verapamil have shown benefit

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in headache control. Although RCVS is sometimes complicated by stroke, seizures, or (rarely) death, most outcomes are benign.

C1 Posterior reversible encephalopathy syndrome (PRES) is a disorder of cerebrovascular regulation frequently showing clinical and neuroimaging overlap with RCVS. Headaches are common but not necessarily thunderclap in type. Nausea, vomiting alterations in mental status, seizures, and visual compromise are all frequently noted. Brain MRI reveals areas of white matter edema in posterior brain regions (occipital and parietal cortex), and vasoconstriction may not be present. Causes include malignant hypertension, eclampsia, and various drugs, such as sympathomimetic agents and immunosuppressive drugs. H

KEY POINTS

- Thunderclap headache requires emergent evaluation with head CT; if CT scans are normal, lumbar puncture is mandatory.
- Most (85%) thunderclap headaches resulting from subarachnoid hemorrhage involve rupture of previously unidentified saccular aneurysms.

H/C
- No evidence supports the superiority of anticoagulation over antiplatelet therapy in prevention of stroke after carotid and vertebral artery dissections, and most patients are initially managed with aspirin.

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Idiopathic intracranial hypertension (IIH), also called pseudotumor cerebri, is characterized by increased intracranial pressure without identifiable structural pathology. This disorder may arise from elevated venous pressure and secondarily increased resistance to CSF absorption. More than 90% of affected patients are female, obese, and of child-bearing age. Other risk factors include hypervitaminosis A, tetracycline antibiotics, isotretinoin, pregnancy, and glucocorticoid use or withdrawal. Headaches are typically diffuse, steady or throbbing, and worse in the mornings or with the Valsalva maneuvers. Brief episodes of bilateral dimming of vision lasting seconds ("visual obscurations") are classically reported, but blurring, scotomas, and diplopia also are noted. Pulsatile tinnitus, dizziness, and neck pain are common. Papilledema is almost always present on examination. Diagnosis is confirmed by a CSF opening pressure greater than 250 mm H_2O with normal fluid composition. Brain MRI may either be normal or show small ventricles, a partially empty sella turcica, widening of the optic nerve sleeves, or flattening of the optic globes. Visual field testing is crucial in the initial and follow-up evaluations of IIH. Enlargement of the blind spot and reduction in peripheral fields are commonly seen, and patients who do not improve with standard treatment may require surgical methods that reduce CSF pressure along the optic nerve to preserve vision.

The carbonic anhydrase inhibitor acetazolamide is considered the drug of choice to treat this disorder. Topiramate possesses a weak carbonic anhydrase effect but may provide the added benefit of weight loss. In patients with an elevated BMI, a weight-reduction program is necessary, with some requiring bariatric procedures. Repeated lumbar punctures may be helpful in the early stages of the disorder as medication takes effect and in the settings of pregnancy or poor surgical risk. CSF decompressive procedures (such as optic nerve fenestration) or lumboperitoneal shunting should be considered when medical options are ineffective.

KEY POINT

- Carbonic anhydrase inhibitors, such as acetazolamide or topiramate, are generally used to treat idiopathic intracranial hypertension.

Headaches from Intracranial Hypotension H

Headaches from intracranial hypotension are characteristically postural, worsening in the upright and improving in the supine position. Some affected patients may report dull interval head pain, neck pain or stiffness, diplopia, nausea, vertigo, tinnitus, or hyperacusis. Physical examination findings are usually normal, although sixth nerve palsy or other abnormalities are possible. CSF hypotension may arise as a result of lumbar puncture, surgery, or trauma or may occur spontaneously. Risk factors for postdural puncture headaches include young age, female sex, low BMI, and the use of larger gauge or conventional cutting (traumatic) needles. Contrary to previous reports, a migraine history does not appear to increase the risk.

Evaluation of patients with spontaneous intracranial hypotension is initiated with contrast-enhanced MRI scans of the brain and spinal cord. Brain MRI can be normal or reveal diffuse pachymeningeal thickening and enhancement, subdural fluid collections, or caudal cerebellar tonsillar descent suggestive of a Chiari malformation. If the spinal MRI does not reveal the site of leak, CT myelography should then be performed.

Conservative treatment measures for all forms of intracranial hypotension include bed rest, analgesia, and fluid resuscitation. In patients who do not respond to conservative measures, 10 to 15 mL of homologous blood can be injected into the epidural space. The resultant blood patch is associated with resolution of symptoms in 80% to 90% of patients. Alternative treatments include intravenous caffeine and epidural saline infusions, local injections of fibrin glue, and surgical correction of the dural tear or diverticula. H

KEY POINT

- Epidural blood patching is highly effective in resolving headaches from cerebrospinal fluid leaks that failed to respond to conservative management.

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Trigeminal Neuralgia

Trigeminal neuralgia involves paroxysms of severe facial pain isolated to the territory of the trigeminal nerve. More common in older patients, this disorder also can affect younger adults, particularly those with multiple sclerosis. Patients describe electric, lancinating pain that can be repetitive at short intervals and typically involves the second or third divisions of the trigeminal nerve on one side, occasionally occurring bilaterally. Patients with multiple sclerosis are more likely to have bilateral pain. Paroxysms typically last seconds but may build in duration over time. Episodes can be spontaneous or triggered by sensory stimulation to the face or teeth, seriously affecting nutrition and facial and oral hygiene. Interictal pain of lower intensity may be noted. Neurologic examination may be impaired by reluctance of the patient to allow examination of the face, but results of facial sensory and motor examinations are generally normal. Brain MRI with contrast should be used to identify potential compressive or demyelinating causes.

Carbamazepine is the drug of choice for initial management, with a greater than 50% response rate. Dizziness and drowsiness are common adverse effects. Serum carbamazepine drug levels, complete blood counts (to check for potential agranulocytosis), and serum electrolyte levels (to check for potential hyponatremia) should be intermittently monitored. Oxcarbazepine, a structural derivative of carbamazepine, is a more expensive choice that has fewer adverse effects and drug interactions. Second-line agents, such as gabapentin, baclofen, clonazepam, lamotrigine and other antiepileptic drugs, may be considered as adjunctive therapies. Approximately 30% of patients do not respond to drug treatment, even after two or three trials of single or multiple agents, at which point surgical procedures should be considered. Noninvasive options include percutaneous radiofrequency coagulation, glycerol injection, or focused stereotactic (gamma knife) radiation. These techniques are generally effective in greater than 50% of patients. Posterior fossa microvascular decompression of a vessel adjacent to the trigeminal nerve root is more invasive but typically more than 90% effective and is recommended in settings of low surgical risk.

KEY POINT

- Carbamazepine is the drug of choice for initial management of trigeminal neuralgia, with a greater than 50% response rate; for the 30% of patients not responding to drug therapy, surgical procedures should be considered.

Medication-Induced Headache

Medication may provoke headache directly or aggravate an underlying headache disorder. The most common drugs directly provoking headache include nitrates, phosphodiesterase inhibitors, and hormones. This type of headache can occur in patients without a history of previous headache. Medication overuse headache (or rebound headache) requires both a patient susceptible to headache (someone, for example, with repeated migraine or tension-type headaches) and exposure to an offending agent. These patients develop either a marked worsening of their underlying headache or a new milder nonspecific headache associated with the overuse of the acute headache medication. Medication overuse headache must be considered in all patients taking simple or combination analgesics, ergotamine products, or triptans for more than 10 days per month. In light of evidence documenting significantly higher rates of medication overuse headache in patients exposed to butalbital compounds and opioid analgesics, these agents should be avoided in headache management.

KEY POINTS

- Medication overuse headache must be considered in all patients taking simple or combination analgesics, ergotamine products, or triptans for more than 10 days per month.
- Because of the documented significantly higher rates of medication overuse headache in patients exposed to butalbital compounds and opioid analgesics, these agents should be avoided in headache management. HVC

Primary Headache

Migraine

Clinical Features and Diagnosis

The diagnosis of migraine is made if several specific clinical criteria are present, as outlined by the International Headache Society (**Table 3**). Because some symptoms overlap with those of secondary headache disorders, the criteria for migraine also include the stipulation that potentially causative conditions be excluded. Phenotypic expression of migraine attacks varies widely among patients and among attacks experienced by an individual patient. In addition to severe or disabling attacks, most patients experience milder episodes of headache that frequently represent milder migraine. This phenotypic variability, combined with the misperception that any single clinical feature (aura, nausea, throbbing discomfort) is a requirement for migraine, may be responsible for misdiagnosis in as many as 50% of affected patients. One way of remedying this high rate of misdiagnosis is to use the POUND mnemonic, which includes the following criteria: headache that is Pulsatile, is One-day in duration (with episodes lasting 4-72 hours if untreated), is Unilateral, is accompanied by Nausea/vomiting, and is Disabling. Patients with greater than three of these criteria can be diagnosed with migraine without further evaluation. Unidentified migraine is usually mislabeled as either a tension-type or sinus headache, even though the latter is now felt to be exceedingly uncommon outside the context of acute sinusitis.

The aura of migraine is present in as many as 30% of migraine episodes and may precede, occur concurrently with, or occur outside the context of a headache attack. Migraine auras without headache are often referred to as silent or

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TABLE 3. International Headache Society Criteria for Migraine Headache

Without Aura

A. At least five attacks fulfilling criteria B-D

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. Headache with at least two of the following four characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity that inhibits or prohibits daily activities
   4. Aggravation by walking up or down stairs or similar routine physical activity

D. During headache, occurrence of at least one of following symptoms:
   1. Nausea/vomiting
   2. Photophobia/phonophobia

E. Not better accounted for by another ICHD-3 diagnosis

With Aura

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:
   1. Visual
   2. Sensory
   3. Speech and/or language
   4. Motor
   5. Brainstem
   6. Retinal

C. At least two of the following four characteristics:
   1. At least one aura symptom spreads gradually over >5 minutes, and/or two or more symptoms occur in succession.
   2. Each individual aura symptom lasts 5-60 minutes.
   3. At least one aura symptom is unilateral.
   4. The aura is accompanied, or followed within 60 minutes, by headache.

D. Headache not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

ICHD-3 = International Classification of Headache Disorders, 3rd edition.

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acephalgic migraine. Aura symptoms generally develop gradually and last between 5 and 60 minutes. Both positive (visual lights, paresthesias) and negative (visual loss, numbness) symptoms are typically described. Aura that occurs for the first time after age 40 years usually involves solely negative symptoms or is either very short or prolonged; other causes, such as transient ischemic attack, should be excluded. Aura is considered typical if it involves any combination of homonymous visual, hemisensory, or language symptoms. Purely monocular aura falls into the retinal migraine category. Previously known as basilar migraine, migraine with brainstem aura is defined by the presence of vertigo, ataxia, dysarthria, diplopia, tinnitus, hyperacusis, or alteration in consciousness. Any aura complex that involves some degree of motor weakness is categorized as hemiplegic migraine. Both migraine with brainstem aura and hemiplegic migraine must be recognized because triptan therapy is contraindicated for both.

Migraine with aura is a strong contributor to stroke risk in women, comparable to systolic hypertension, obesity, and diabetes mellitus. Strokes usually occur outside the context of acute migraine, but when infarction is noted during the course of a typical migraine with aura attack, it is termed migrainous infarction. These strokes typically occur in the posterior circulation (occipital-parietal cortex, cerebellum) and in young women. Estrogen-containing oral contraceptives must be avoided in women experiencing migraine with aura because of the already increased risk of stroke. The risk of stroke also is slightly elevated in men who have migraine with aura. However, most studies have shown no association between stroke and migraine without aura. Management of stroke does not differ in those with migraine, although an adjustment in acute migraine therapy may be necessary because cerebrovascular disease is a contraindication for triptan use. Clinical stroke must be differentiated from MRI-identified subclinical deep white matter hyperintensities, which tend to be smaller than lesions associated with cerebrovascular or demyelinating disease and are clinically insignificant in most patients with migraine. In the absence of vascular risk factors, further investigation or management adjustments are unnecessary.

Episodic migraine occurs less than 15 days per month. Mean migraine frequency is nearly three episodes per month, with an average duration of less than 24 hours. Chronic migraine describes headache occurring on 15 or more days per month for more than 3 months, with headache possessing the features of migraine on at least 8 days per month. Chronic migraine affects 2% of the adult population and imposes substantial burdens on patients, their families, and their workplaces. Most cases arise from gradual transformation of episodic to chronic migraine, but the transition can occur abruptly, particularly with significant life events, trauma, or (in female patients) hormonal changes. Patients whose baseline frequency of headache or acute medication use is greater than 10 days per month are 20 times more likely to experience transformation. Additional factors, some potentially modifiable, also have been shown to increase the risk of transformation, such as older age, female sex, obesity, excessive intake of caffeine or nicotine, trauma, low socioeconomic status, and the presence of comorbid pain, sleep, or psychiatric conditions.

Acute Migraine Management

The goal of acute migraine management is to resolve the entire symptom complex of migraine and return the patient to

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normal function. Ideally, pain, nausea, and sensory sensitivities are resolved completely within 1 to 2 hours of treatment, and the patient remains free of symptoms for at least 24 hours. Evidence-based guidelines suggest the medications that are most effective as acute migraine therapy are NSAIDs, triptans, and dihydroergotamine (DHE) (**Table 4**). Trials of NSAIDs are preferred initially because of their cost-effectiveness. Guidelines recommend against the use of opioid- or butalbital-containing compounds as first-line treatments for headache. Because these drugs have been linked to lowered responsiveness to other acute and preventive migraine therapies, to increased rates of emergency department utilization, and to increased risk of transformation into chronic migraine, they should be reserved for those with medical conditions that preclude the use of NSAIDs or triptans.

Most patients manage the majority of migraine attacks with an oral medication. NSAIDs are often effective in the management of mild to moderate migraine. Triptans are used in patients not responding to one or more NSAID. No good evidence supports the superior efficacy of any oral NSAID or triptan choice. Cost, formulary availability, and results of previous medication trials are all considerations in the selection of acute migraine medication. Each drug is best evaluated after three episodes to assess efficacy and consistency, and it is reasonable to try several different drugs in any class. Evidence indicates that outcomes are more favorable when acute medication is administered within the first hour of the attack. Unless medication overuse headache is a concern, patients should be advised to treat at the first sign of pain. Because migraine intensity is highly variable, occasional attacks that are less responsive to medication are to be expected. Certain patients may benefit from coadministration of an antiemetic agent or from combination treatment with NSAIDs and triptans.

Nonoral routes of administration may be necessary in certain settings when early administration of an oral agent is impossible or ineffective. Migraine with severe nausea or vomiting, migraine that occurs on awakening, and migraine that escalates rapidly within minutes may be best treated by nasal triptans, subcutaneous sumatriptan, or nasal or subcutaneous DHE (see Table 4).

Refractory migraine may require management in emergency department or inpatient settings. Data also support the use of intravenous antidopaminergic agents, such as prochlorperazine, in the treatment of severe migraine. These are often combined with intravenous fluids and diphenhydramine, with the latter drug aimed at preventing potential dystonic reactions from the antidopaminergic drugs. Ketorolac is frequently administered for pain. Parenteral opioids should be avoided if possible. Status migrainosus, defined as an attack duration greater than 72 hours, is the most common complication of acute migraine. A short course of glucocorticoids may be helpful for outpatients, and repetitive intravenous DHE is effective in inpatient settings. The latter is typically delivered over 3 days and is combined with fluid resuscitation and parenteral antidopaminergic agents.

TABLE 4. Acute Migraine Therapies

Drug	Recommended Dose
NSAIDs[a]	
Aspirin	325-900 mg
Ibuprofen	400-800 mg
Naproxen	250-1000 mg
Combination of acetaminophen/aspirin/caffeine	2 tablets
Diclofenac (oral solution)	50 mg
Migraine-Specific Oral Agents[a]	
Almotriptan	6.25-12.5 mg
Eletriptan	20-40 mg
Frovatriptan	2.5 mg
Naratriptan	1-2.5 mg
Rizatriptan	5-10 mg
Sumatriptan	25-100 mg
Sumatriptan-naproxen	85-500 mg
Zolmitriptan	2.5-5 mg
Nonoral Therapies[a]	
Dihydroergotamine	1 mg nasally
Dihydroergotamine	1 mg subcutaneously
Prochlorperazine	10 mg intravenously
Sumatriptan	5-20 mg nasally
Sumatriptan	4-6 mg subcutaneously
Zolmitriptan	5 mg nasally

[a]Doses listed may be administered once or twice daily.

Migraine Prevention

Reduction in migraine frequency and intensity may be accomplished initially through lifestyle modification. Triggers should be identified and avoided when possible. The patient should be advised to sleep regular hours, eat small but frequent meals, hydrate appropriately, and exercise regularly. Although evidence supporting these recommendations is limited, hunger, dehydration, and changes in sleep schedule are common aggravating factors in migraine. Valuable stress management techniques include relaxation therapy, biofeedback, and cognitive behavioral therapy. Caffeine may be helpful in the acute management of migraine, but chronic excessive exposure may exacerbate the condition. Daily caffeine intake should be limited to less than 100 mg. Good evidence supports the use of *Petasites hybridus* (butterbur), magnesium, riboflavin, and feverfew for migraine prevention.

In order to improve health outcomes, such as attack frequency, intensity, disability, and cost, the use of preventive agents should be considered in patients with eight or more total

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days or four or more disabling days of migraine per month. However, research has shown that most patients with migraine who might benefit from preventive medications do not receive them. Additional indications for using preventive medications include the use of acute medications (over-the-counter or prescription) more frequently than 8 days per month and persistent disability despite aggressive management of migraine attacks. Evidence-based guidelines for selecting an effective agent for episodic migraine prevention are available (**Table 5**). Only topiramate and injectable onabotulinumtoxinA have good evidence in the setting of chronic migraine, but both are marginally effective. Given the potential for medication overuse headache, long-term opioids are not recommended for migraine prevention except in extremely limited circumstances. The selection of a preventive agent additionally should be guided by patient age, sex, and medical history; by the presence of comorbid conditions; and the results of previous treatments. The goal is to reduce headache frequency and intensity by 50%. A titration phase, which can take 2 to 3 months to achieve benefit, is followed by a maintenance phase of 6 to 12 months. Many patients then tolerate a slow taper of the drug, with future reinstitution possible if headache frequency escalates.

KEY POINTS

HVC
- One way of remedying the high rate of misdiagnosis of migraine is to use the POUND mnemonic, which includes the following criteria: headache that is Pulsatile, is One-day in duration (with episodes lasting 4-72 hours if untreated), is Unilateral, is accompanied by Nausea/vomiting, and is Disabling; patients with greater than three of these criteria can be diagnosed with migraine without further evaluation.

(Continued)

TABLE 5. Episodic Migraine Preventive Therapies

Drug	Recommended Daily Dose
Level A: Effective	
Divalproex sodium/ valproic acid	500-1000 mg
Metoprolol	50-200 mg
Propranolol	40-240 mg
Timolol	10-30 mg
Topiramate	50-200 mg
Level B: Probably Effective	
Amitriptyline	25-150 mg
Atenolol	50-100 mg
Fenoprofen	600-1800 mg
Ibuprofen	400 mg
Ketoprofen	150 mg
Naproxen	500-1100 mg
Venlafaxine	150 mg

KEY POINTS *(continued)*

HVC
- Evidence-based guidelines suggest that the most effective medications for acute migraine therapy are NSAIDs, triptans, and dihydroergotamine; trials of NSAIDs are preferred initially because of their cost-effectiveness.

HVC
- No good evidence supports the superior efficacy of any oral NSAID or triptan choice; cost, formulary availability, and results of previous medication trials are all considerations in the selection of acute migraine medication.

HVC
- In order to improve health outcomes, such as attack frequency, intensity, disability, and cost, the use of preventive agents should be considered in patients with eight or more total days or four or more disabling days of migraine per month.

Tension-Type Headache

Tension-type headache is the most prevalent primary headache disorder. Despite its common occurrence, tension-type headache is an uncommon reason for medical consultation. The clinical classification identifies tension-type headache largely by the absence of disabling features (**Table 6**). By definition, pain is never severe, nausea is absent (or possibly mild, with the chronic form), and photophobia and phonophobia are never present together. Neurologic and autonomic features are lacking. Basically, tension-type headache is defined by the absence of migraine. Subclassification based on attack frequency has been found to be clinically helpful.

TABLE 6. International Headache Society Criteria for Tension-Type Headache

A. At least 10 attacks fulfilling criteria B-D

B. Headache attacks (untreated or unsuccessfully treated) lasting from 30 minutes to 7 days

C. Headache with at least two of the following four characteristics:
   1. Bilateral location
   2. Pressing/tightening (nonpulsating) quality
   3. Mild or moderate intensity
   4. Not aggravated by walking or climbing stairs or similar routine physical activity

D. Headache characterized by both of the following:
   1. No nausea/vomiting
   2. No more than one episode of photophobia or phonophobia

E. Not better accounted for by another ICHD-3 diagnosis

ICHD-3 = International Classification of Headache Disorders, 3rd edition.

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Infrequent episodic tension-type headache (<1 day/month) is benign and requires no medical attention. Frequent episodic tension-type headache (1-14 days/month) may occasionally cause disability warranting the use of prescription medication. Chronic tension-type headache (>14 days/month) is a serious disorder with significant morbidity that requires acute and preventive medications. Brain MRI is also required to exclude organic pathology.

Acetaminophen, aspirin, and NSAIDs are often successful in the acute treatment of tension-type headache. Caffeine-containing compounds may help those not responding to simple analgesics. Preventive medication may be necessary for those with headache frequency greater than 8 days/month. Amitriptyline is considered the drug of choice for prevention of tension-type headache, and efficacy may be enhanced by the addition of stress management techniques. Venlafaxine and mirtazapine may be useful alternatives. Muscle relaxants, benzodiazepines, and onabotulinumtoxinA have no role in the acute or preventive treatment of tension-type headache.

KEY POINT

- Acetaminophen, aspirin, and NSAIDs are often successful in the acute treatment of tension-type headache; amitriptyline is considered the drug of choice for prevention of this type of headache.

Cluster Headache

Cluster headache is considered the most severe of the primary headache syndromes and is the most common of the headaches classified as trigeminal autonomic cephalgias. These disorders are characterized by severe unilateral pain, typically in the first division of the trigeminal nerve (periorbital, frontal, temporal), and are accompanied by ipsilateral cranial autonomic symptoms (**Table 7**). Although episodes of migraine and other primary headaches may occur repeatedly over the course of several days or weeks, the term "cluster" is derived from this disorder's characteristic short cycles of headache activity (weeks) interrupted by long periods of complete remission (month or years). Attacks of cluster headache can best be differentiated from migraine on the basis of their shorter duration. Whereas untreated migraine typically lasts between 4 and 72 hours, most cluster attacks have a duration of less than 3 hours. Male sex and cigarette smoking are risk factors for the development of cluster headache, and most affected patients are young or middle aged. Alcohol is a commonly reported trigger during an active cycle. Cluster periods can occur at specific times of year, most often in the spring or fall. Nocturnal attacks are the norm. Frequency may vary from attacks every other day to eight attacks per day. Approximately 10% of affected patients develop a chronic form notable for absent or brief remissions. Brain MRI should be performed initially to exclude structural lesions mimicking cluster headache. Oxygen inhalation and subcutaneous sumatriptan are first-line therapies for acute cluster headache. Transitional prophylaxis with 2 to 3 weeks of glucocorticoid administration may help reduce attacks at the onset of the cycle. Verapamil is the drug of choice for prevention of cluster headache. Refractory headaches may require trials of lithium carbonate, anticonvulsant agents, or pericranial nerve blockade.

TABLE 7. International Headache Society Criteria for Cluster Headache

A. At least five attacks fulfilling criteria B-D

B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 minutes (when untreated)

C. Either or both of the following:

1. At least one of the following symptoms or signs, ipsilateral to the headache:
   a) conjunctival injection and/or lacrimation
   b) nasal congestion and/or rhinorrhea
   c) eyelid edema
   d) forehead and facial sweating
   e) forehead and facial flushing
   f) sensation of fullness in the ear
   g) miosis and/or ptosis
2. A sense of restlessness or agitation

D. Attack frequency from 1 every other day to 8 per day when the disorder is active

E. Not better accounted for by another ICHD-3 diagnosis

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Chronic paroxysmal hemicrania (CPH) and short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing (SUNCT) have phenotypic features identical to cluster headache but differ in attack frequency and duration. CPH attacks occur at least five times daily and last between 3 and 20 minutes. Diagnosis of CPH is confirmed by absolute response to indomethacin, which is unhelpful in cluster headache. SUNCT typically recurs dozens or even hundreds of times per day, with durations of 1 second to 10 minutes. Although lamotrigine has been recommended, SUNCT is often refractory to treatment. The presence of ipsilateral autonomic features and the typical distribution of pain in the first division of the trigeminal nerve help distinguish these syndromes from trigeminal neuralgia.

KEY POINTS

- In patients with suspected cluster headache, brain MRI should be performed initially to exclude structural lesions mimicking cluster headache.
- Oxygen inhalation and subcutaneous sumatriptan are first-line therapies for acute cluster headache.

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Other Primary Headache Syndromes

Primary stabbing headaches ("ice-pick headaches") are characterized by brief episodes of stabbing head pain typically lasting a few seconds but occasionally extending to a few minutes. They have no associated autonomic features. Although the eye may be affected ("needle in the eye" sensation), the face is typically spared. The location of pain is fixed in one third of patients, and brain MRI may be justified in some of these patients. Primary stabbing headache may be seen in isolation or in those with migraine. Indomethacin can be helpful during cycles of more frequent attacks.

Primary cough headache develops abruptly after a cough, remains severe for seconds to minutes, and then fades. The pain is typically bilateral and described as an intense pressure. Mild headache may then linger for several hours. A significant correlation exists between cough frequency and headache intensity. Primary cough headache is most common in older adults, and response to indomethacin is typical. Secondary cough headaches have a structural cause, such as a Chiari malformation, and constitute up to half of cough headaches. If this diagnosis is suspected, brain MRI is mandatory.

KEY POINT

- Primary cough headache develops abruptly after a cough, remains severe for seconds to minutes, and then fades; response to indomethacin is typical.

Head Injury

Traumatic Brain Injury

Traumatic brain injury (TBI) arises from the exposure of the brain to external physical forces that cause either temporary dysfunction or permanent damage to brain tissue from blunt or penetrating trauma. **Table 8** outlines the classification of mild, moderate, and severe brain injury.

TABLE 8. Classification of Brain Injury Severity

	Mild	Moderate	Severe
Neuroimaging findings	Normal	Normal or abnormal	Normal or abnormal
Duration of loss of consciousness	0-30 minutes	>30 minutes and <24 hours	>24 hours
Duration of alteration in consciousness	Momentary-24 hours	>24 hours	>24 hours
Duration of posttraumatic amnesia	0-1 day	1-7 days	>7 days
Glasgow Coma Scale score	13-15	9-12	3-8

Skull fracture, intracranial (epidural, subdural) hematomas, parenchymal hemorrhages, and contusions may be complications of TBI.

Mild Traumatic Brain Injury

Mild TBI, also known as concussion, is the most common form of TBI. Initial manifestations include any loss of consciousness or alteration in awareness (such as feeling "dazed" after a head injury), amnesia near the time of the event, or focal neurologic deficit. Symptoms, which may persist, can be divided into physical, cognitive, psychological, and sleep-related domains (**Table 9**). A thorough neurologic examination is necessary, with findings of hemotympanum (blood in the middle ear), orbital ecchymoses ("raccoon eyes"), or mastoid ecchymoses (Battle sign) suggesting a basilar skull fracture. Neuroimaging and, possibly, hospital admission are recommended for persons with worsening headache, repeated vomiting, drowsiness, persistent confusion, dysarthria, or focal neurologic findings. In the emergent setting, head CT is preferable to brain MRI because of its wider availability, lower cost, and greater sensitivity for identifying skull fractures.

TABLE 9. Symptoms of Mild Traumatic Brain Injury

Physical
Headache
Nausea/vomiting
Dizziness/vertigo
Gait disturbance
Photophobia or phonophobia
Visual blurring
Dysarthria
Seizures
Cognitive
Poor concentration
Mental "fogginess" or confusion
Poor memory
Learning impairment
Slowed reaction times
Psychological
Irritability
Depression
Anxiety
Sleep
Fatigue
Insomnia
Hypersomnia
Drowsiness
Vivid dreams

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KEY POINT

HVC

- In persons who sustain mild traumatic brain injury, neuroimaging is only recommended if symptoms of worsening headache, repeated vomiting, drowsiness, persistent confusion, dysarthria, or focal neurologic findings are present; head CT is preferable to brain MRI for initial neuroimaging because of its wider availability, lower cost, and greater sensitivity for identifying skull fractures.

Head Injury in Special Populations

Athletes

Any athlete suspected of sustaining a mild TBI should be immediately removed from play and undergo sideline assessment through administration of standardized tools, such as the Graded Symptom Checklist and the Standardized Assessment of Concussion. Neuropsychological testing may be helpful in identifying and tracking those with cognitive dysfunction. Future participation in contact sports must be prohibited until the patient returns to cognitive baseline and is asymptomatic without taking any medication to treat trauma-related symptoms.

KEY POINT

- Any athlete suspected of sustaining mild traumatic brain injury should be immediately removed from play and prohibited from participating in contact sports until he or she returns to cognitive baseline and is asymptomatic without taking any medication to treat trauma-related symptoms.

Military Personnel

Blast injuries from weaponry, especially improvised explosive devices, now account for most TBIs in members of the armed services returning from combat. Guidelines recommend that these military personnel undergo mandatory screening for TBI if involved in a vehicular accident, exposed to an explosive blast, struck by a direct blow to the head, or instructed to by a superior officer. Specifically, a Military Acute Concussion Evaluation and a mandatory 24-hour rest period are required, with full recovery necessary before return to duty. Because the manifestations of TBI may vary widely, treatment programs should be individualized. Headaches and sleep dysfunction should be managed with appropriate medications. Emotional disorders, such as depression and posttraumatic stress disorder, must be identified early and managed with counseling and medication, when necessary. The addition of pain medicine or mental health providers to the health care team is highly recommended.

Older Patients

Adults older than 75 years have the highest rates of morbidity, hospitalization, and death from TBI. Falls, motor vehicle accidents, and accidental blows to the head are the leading causes of TBI in this population. Older age also is associated with less rapid and less complete recovery. Therefore, TBI prevention is key. Prevention involves decreasing the risk of falls by avoiding overmedication and encouraging regular physical activity and living area modifications, such as removal of trip hazards and installation of appropriate lighting, nonslip mats in the bathroom, and handrails in the bathroom and along stairways.

KEY POINT

- Because patients older than 75 years have the highest rates of morbidity, hospitalization, and mortality after traumatic brain injury, prevention is key; preventive measures include avoiding overmedication and encouraging regular physical activity and living area modifications. HVC

Postconcussion Syndrome

The term postconcussion syndrome (PCS) is applied to those persons who continue to report symptoms of mild TBI beyond a typical recovery period of several weeks. Risk factors predictive of PCS include female sex, low socioeconomic status, headaches, unsettled court cases, severe bodily injury from the TBI, or previous TBI. Management of PCS is largely supportive and rehabilitative, with medical treatments directed at specific symptoms. NSAIDs and triptans may be useful in treating posttraumatic headache. Opioids should be avoided. Tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors can be effective in managing posttraumatic headache, mood, and anxiety disorders. Although data are inconclusive, those with visual accommodation issues may benefit from visual therapy, and those with balance disorders from vestibular rehabilitation. Similarly, those with cognitive impairment may benefit from a rest period followed by gradual reintroduction of cognitive activities.

KEY POINT

- Management of postconcussion syndrome is largely supportive and rehabilitative, with medical treatments directed at specific symptoms.

Epidural and Subdural Hematomas H

Epidural hematomas involve the collection of blood from an arterial source between the inner table of the skull and the dura (Figure 2). Most of these hematomas result from blunt head injury causing fracture of the temporal bone and laceration of the middle meningeal artery, with blood accumulation under arterial pressure. Headache, mental status abnormalities, and rapid neurologic decline with ipsilateral pupillary dilatation and brain herniation can occur. Some patients exhibit a brief "lucid interval" before subsequent precipitous decline. Prognosis is often excellent with emergent evacuation

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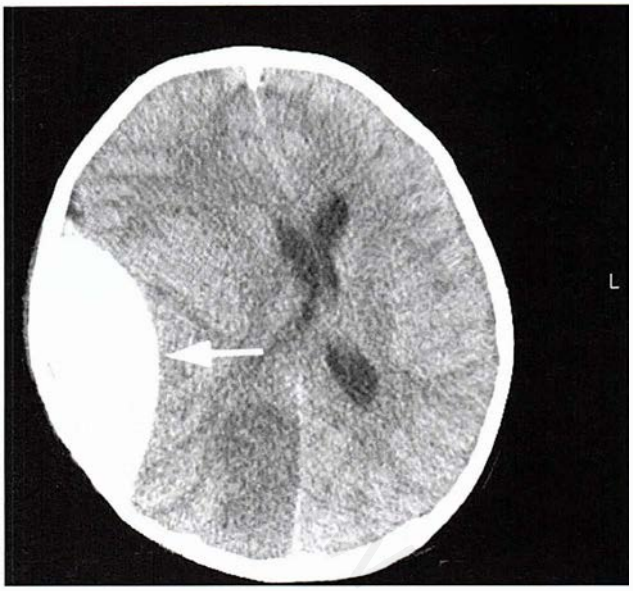

FIGURE 2. CT scan of an epidural hematoma. Note the biconvex lens appearance as blood under arterial pressure collects between the skull and outer margin of the dura (*arrow*).

CONT.

of the hematoma because the underlying brain tissue is frequently uninjured. Without immediate surgical evacuation, however, death can occur within a matter of hours.

Subdural hematomas (**Figure 3**) arise from injury to the small bridging veins between the cortex and the dura. Because the collection of blood is under venous pressure, the clinical course is often more indolent than with epidural hematomas. Acute subdural hematomas can develop over hours to days,



FIGURE 3. CT scan of a subdural hematoma. Note the crescent shape as blood under venous pressure separates the dura from the arachnoid membrane (*arrow*).

and chronic subdural hematomas over weeks to months. The latter can occur in the absence of significant trauma, particularly among older patients and those taking anticoagulant drugs. Patients may warrant either observation or surgical evacuation, depending on their specific presentation.

KEY POINTS

- The prognosis of epidural hematomas is often excellent after emergent surgical evacuation because the underlying brain tissue is frequently uninjured; without immediate evacuation, however, death can occur within a matter of hours.
- Subdural hematomas can occur in the absence of significant trauma, particularly among older persons and those taking anticoagulant drugs; observation or surgical evacuation is appropriate treatment, depending on the specific presentation.

Seizures and Epilepsy

Clinical Presentation of Seizures

Seizures are stereotyped paroxysmal events caused by hypersynchronization of neurons. Approximately 10% of the population will experience isolated seizures in their lifetimes. Epilepsy, which occurs in 1% to 3% of the population, is diagnosed after two unprovoked seizures have occurred. Tonic-clonic seizures (often referred to as convulsions) are the most commonly recognized seizures; they are characterized by loss of consciousness associated with tonic stiffening and clonic jerking of all extremities. However, seizures can have many different manifestations depending not only on where in the brain they begin, but also on the extent of their spread throughout the brain. Tonic-clonic seizures can be focal or generalized in onset. Properly labeling the seizure type helps identify the potential cause of a seizure, the associated epilepsy syndrome (if any), and the appropriate therapy.

Partial (Focal) Seizures

Most seizures occurring in adults are partial seizures, or seizures caused by abnormal electrical activity beginning in a single region of the brain. Determining whether an isolated tonic-clonic seizure was partial or generalized at onset can be difficult. Clinical clues to identifying a partial seizure that has progressed to a generalized tonic-clonic seizure (also known as a secondarily generalized seizure) include unilateral shaking, head turning to one side (versive head turning), or a subjective aura before the onset of convulsion. Focal weakness after a convulsion (Todd paralysis) may occur. The absence of one of these focal features does not exclude a partial onset. It is generally helpful to inquire if the patient has had other types of seizures in the past.

Simple partial seizures and complex partial seizures are two types of partial seizures; although more common than

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convulsions, they may be subtle and often are not recognized as seizures. Simple partial seizures do not impair consciousness. Their symptoms depend on the area of the brain involved. Whereas simple partial seizures in the motor cortex can cause rhythmic jerking in one body part, in other areas of the brain they may cause subjective phenomena known as auras. For example, the most common temporal lobe aura is a difficult-to-describe epigastric rising sensation; patients sometimes describe this sensation as nausea or simply motion towards their chest with an upward gesture. Temporal lobe auras also can cause paroxysmal feelings of fear or déjà vu. These temporal lobe seizures are often misdiagnosed as panic attacks, although the stereotyped features, paroxysmal onset, and short duration (usually less than 1 minute) are distinguishing features. Complex partial seizures are associated with a disturbance of awareness. During these seizures, patients may exhibit semipurposeful behaviors known as automatisms, such as lip smacking or fumbling of the fingers. Patients with complex partial seizures may recognize a typical aura before losing consciousness, but they often are unaware that they have become impaired and may have no recollection of the seizure. This makes interviewing family and friends imperative in patients with a suspected seizure disorder.

KEY POINTS

- Simple partial seizures are partial-onset seizures that do not impair consciousness, whereas complex partial seizures are partial seizures associated with a disturbance of awareness.
- During complex partial seizures, patients may exhibit semipurposeful behaviors (automatisms), such as lip smacking or fumbling of the fingers.

Generalized Seizures

Generalized seizures involve both hemispheres of the brain at onset. Primary generalized seizures are tonic-clonic seizures without a focal onset. Absence seizures, which typically develop in childhood or adolescence, are another type of generalized seizure characterized by a brief behavioral arrest and impairment of awareness. The term absence seizure is often incorrectly used to describe a complex partial seizure; as with complex partial seizures, patients may be unaware they have experienced absence seizures, noting at most "missed time," but absence seizures are usually much shorter (<5 seconds versus 30-90 seconds) and are not associated with postictal confusion. Myoclonic seizures are characterized by quick, nonrhythmic, shock-like muscular contractions that can occur in rapid succession and usually are not associated with impaired consciousness. These seizures are typical of juvenile myoclonic epilepsy.

KEY POINT

- Absence seizures are shorter than complex partial seizures (<5 seconds versus 30-90 seconds) and are not associated with postictal confusion.

Epilepsy Syndromes

Epilepsy syndromes also are classified as partial or generalized. The diagnosis of an epilepsy syndrome depends on the seizure type(s) a patient experiences and can be supported by electroencephalographic and MRI findings.

Focal (Partial) Epilepsy

Temporal lobe epilepsy is the most common type of focal epilepsy and the most common epilepsy syndrome presenting in adulthood. Patients with this type of epilepsy typically experience complex partial seizures, which often begin with auras (an epigastric rising sensation or a feeling of déjà vu). These patients also may have simple partial or secondarily generalized seizures. Mesial temporal sclerosis (neuronal loss and gliosis in the hippocampus) is a characteristic finding in patients with temporal lobe epilepsy (**Figure 4**). Frontal lobe epilepsy is the second most common type of focal epilepsy and is often characterized by nocturnal complex partial seizures that awaken patients from sleep because of chaotic movements. Structural causes of focal epilepsy syndromes include brain tumors, vascular malformations (**Figure 5**), malformations of cortical development (**Figure 6**), chronic strokes, and head trauma. An increasing number of genetic focal epilepsy syndromes are being recognized. Most of the time, however, the cause of focal epilepsy remains unknown.

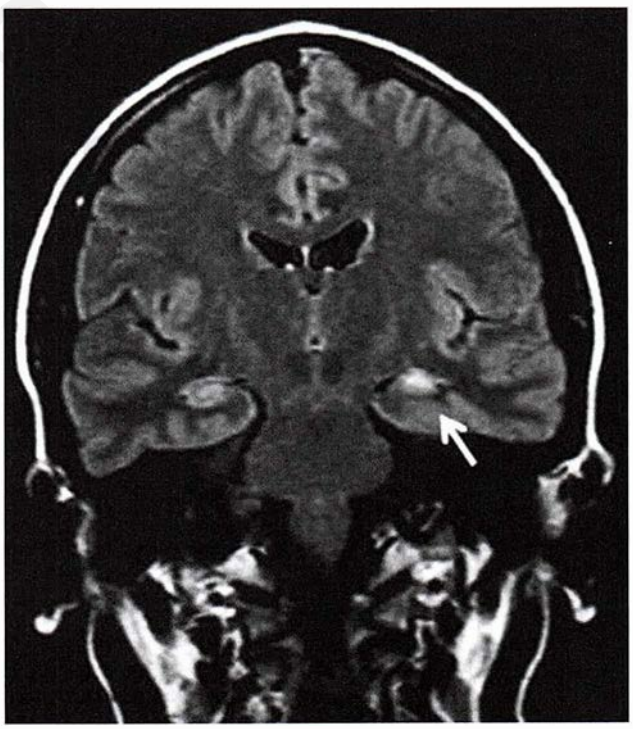

FIGURE 4. Mesial temporal sclerosis. Coronal flair MRI shows increased signal intensity and atrophy of the left mesial temporal lobe (*arrow*).

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FIGURE 5. Cavernous malformation. Coronal T1-weighted MRI shows an intra-axial mass (cavernous hemangioma) in the right temporal lobe with a surrounding hemosiderin ring.

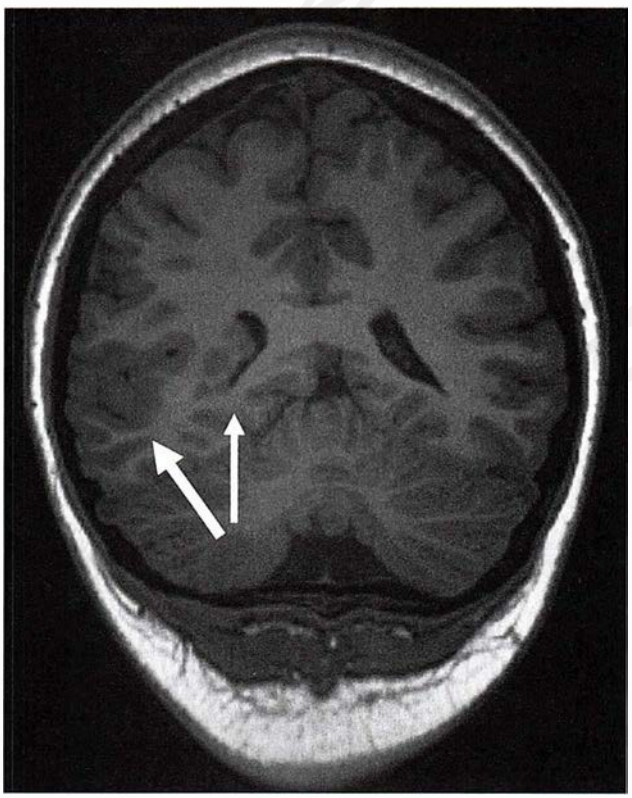

FIGURE 6. Focal cortical dysplasia with periventricular nodular heterotopia. Coronal MRI showing a focal area of thickened cortex in the right temporal region (*thick arrow*) and nodules of abnormal neuronal tissue along the ventricular surface (*thin arrow*).

KEY POINT

- Temporal lobe epilepsy is the most common type of focal epilepsy; in most patients, the cause of focal epilepsy remains unknown.

Idiopathic Generalized Epilepsy

Idiopathic generalized epilepsy (IGE) accounts for approximately one third of all epilepsy syndromes. IGE is typically diagnosed in patients before age 20 years and is presumed to be genetic in origin, although a close relative with the disorder often cannot be identified. Patients with IGE may have any combination of tonic-clonic seizures, absence seizures, and myoclonic seizures. Juvenile myoclonic epilepsy (JME) is one of the most common types of IGE. Typically beginning in adolescence, JME is characterized by morning myoclonus, which is often perceived as tremors or "jitteriness." Patients with JME often also have primary generalized seizures and may or may not have absence seizures. IGE syndromes are presumed to be genetic; a family history of epilepsy is common but not always present.

Although all patients with epilepsy are sensitive to the effects of alcohol and sleep deprivation, patients with IGE are particularly susceptible to these triggers. MRI findings are typically normal, and an EEG may show generalized spike-wave activity (**Figure 7**).

KEY POINTS

- Idiopathic generalized epilepsy is genetic, accounts for one third of all epilepsy syndromes, and may manifest as tonic-clonic seizures, absence seizures, or myoclonic seizures.
- Juvenile myoclonic epilepsy, one of the most common types of idiopathic generalized epilepsy, is characterized by morning myoclonus; affected patients often also have tonic-clonic seizures and sometimes absence seizures.

Initial Approach to the Patient with a First Seizure

General Comments

The appropriate immediate management of a seizure focuses on stabilization of the patient, with attention paid to the airway and vital signs, and on rapid identification of any reversible causes. If a serum glucose level cannot be obtained quickly, thiamine followed by glucose should be administered. Basic metabolic function and liver chemistry panels should be ordered, as should an electrocardiogram; if appropriate, urine toxicology and serum alcohol and antiepileptic drug (AED) levels also should be obtained.

The clinical history and evaluation of a potential seizure should focus on answering the following questions:

- Was the event a seizure?
- Was the seizure provoked?
- Was this a first seizure?
- Does the patient have risk factors for subsequent seizures?

There are several paroxysmal events that can mimic a seizure (**Table 10**). For example, syncope is associated with tonic-clonic activity in 5% to 15% of patients. The distinction between seizures and similar events relies heavily on a careful clinical history, which usually requires interviewing observers. The patient and his or her friends and family members also should be asked about more subtle events in the past that may

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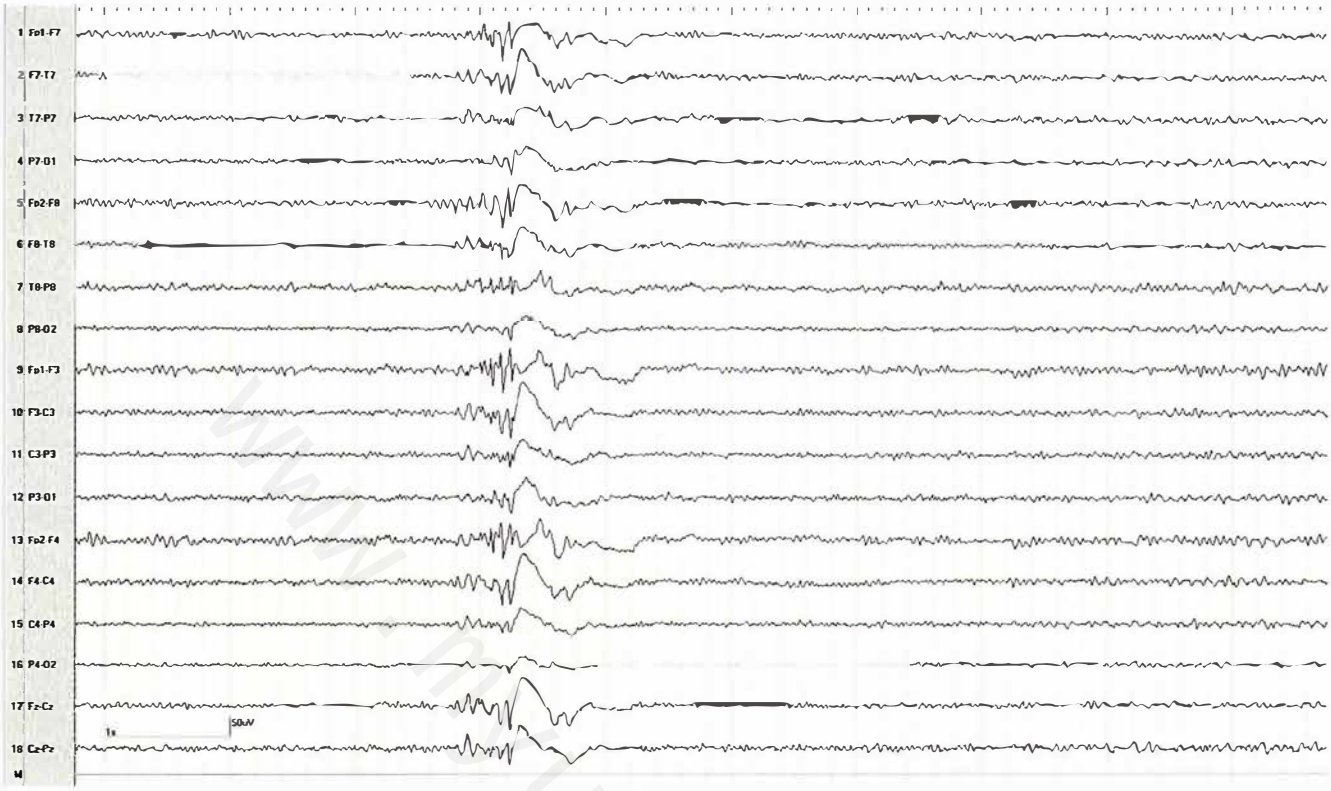

FIGURE 7. Characteristic electroencephalogram of a patient with idiopathic generalized epilepsy shows a generalized interictal epileptiform discharge during sleep.

TABLE 10. Characteristics of Seizures and Common Mimics in Adults

Characteristic	Epileptic Seizure	Psychogenic Nonepileptic Seizure	Syncope	TIA	Migraine	Vertigo
Warning/aura	Variable (<1 min)	Variable	Lightheaded feeling, sweating	None	Variable (15-30 min)	None
Duration	1-2 min	5-15 min	Seconds to minutes	5-30 min	Hours	Minutes to days
Position dependent	No	No	Typically, but not always	No	No	Often on standing or moving head, but not always
Symptoms during episode	Variable: automatisms, confusion, aphasia, tonic-clonic movements	Pelvic thrusting, jerking that waxes and wanes, forced eye closure	Loss of tone, brief tonic extension or clonic jerks	Hemiparesis, hemisensory loss, visual loss, aphasia	Visual disturbance, vertigo, paresthesias, aphasia, dysarthria	Nausea, ataxia
Altered consciousness	Common	Common	Common	Rare	Rare	No
Incontinence	Variable	Variable	Variable	None	None	None
Heart rate	Increased	Variable	Irregular and decreased	Variable	No effect	Variable
Symptoms after episode	Confusion, fatigue	Variable	Alert	Alert	Fatigue	Alert
EEG during event	Epileptiform pattern	Unaltered	Diffuse slowing	Focal slowing	Rare slowing	Unaltered

EEG = electroencephalogram; TIA = transient ischemic attack.

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CONT.

not have been recognized as seizures (such as auras and periods of inattention) and about precipitating factors (such as sleep deprivation and toxic exposures [alcohol, illicit drugs, and certain medications]) and the presence of epilepsy risk factors, including:

- Family history of epilepsy
- Childhood febrile convulsions
- History of head trauma with loss of consciousness
- History of central nervous system infection
- Central nervous system lesion (brain tumor, vascular malformation, stroke)
- Prenatal or birth injury

Neuroimaging is indicated in most patients with a first unprovoked seizure. An urgent noncontrast head CT is recommended to exclude hemorrhage in patients with focal neurologic deficits, impaired mental status, or head trauma. An MRI is preferred in otherwise clinically stable patients and should be performed at, or very soon after, presentation. EEG also is recommended for all patients with an unprovoked seizure. If the patient is not returning toward baseline mental status by 15 minutes after a first seizure, continuous EEG monitoring (to rule out nonconvulsive seizures) is indicated. Lumbar puncture should be considered in patients with a seizure in the setting of suspected meningitis or encephalitis or in the setting of immunosuppression. H

Because seizures are unpredictable, all patients who have had a seizure should be counseled to avoid situations in which a momentary loss of consciousness could be hazardous; avoiding heights, heavy lifting, and swimming or bathing alone are recommended. Additionally, it is the physician's obligation to counsel any patient who has had a seizure about the risks of driving. Driving restrictions apply in patients with an unexplained loss of consciousness even if the diagnosis is unclear. Some states require the reporting of a patient's seizures to the department of motor vehicles (state driving laws can be found at www.epilepsy.com/driving-laws). Although laws vary from state to state, most require that patients abstain from driving for a period of 3 to 12 months after any event causing an impairment of consciousness, including complex partial and absence seizures and convulsions. The laws apply to patients who have had a single seizure (provoked or unprovoked) and to patients with diagnosed epilepsy.

KEY POINTS

- The appropriate immediate management of a seizure focuses on stabilization of the patient with attention paid to the airways and vital signs and on rapid identification of any reversible causes.
- Brain imaging is recommended in any patient with an unprovoked seizure; an urgent noncontrast head CT is recommended to exclude hemorrhage in patients with focal neurologic deficits, impaired mental status, or head trauma.

Provoked Seizures

H

Several medical conditions and treatments can provoke seizures (**Table 11**). Single seizures that are provoked should be addressed by correcting the underlying condition or removing the causative agent; they usually do not require treatment with an AED. Further diagnostic evaluation, such as neuroimaging and EEG, may not be needed if a clear reversible cause of the seizure is identified and the patient has normal findings on neurologic examination. In patients with recurrent provoked seizures, AED treatment occasionally is needed on a short-term basis, but long-term therapy usually is not indicated. Similarly, patients with acute symptomatic seizures that occur within 1 week of head trauma or acute brain injury, such as intracerebral hemorrhage, may benefit from a short course of an AED but do not necessarily require long-term treatment. H

KEY POINT

- Single seizures that are provoked usually do not require treatment with an antiepileptic drug and instead should be addressed by correcting the underlying condition or removing the offending agent; further diagnostic evaluation, such as neuroimaging and electroencephalography, may not be needed if a clear reversible cause of the seizure is identified and the patient has normal findings on neurologic examination. HVC

Psychogenic Nonepileptic Seizures

At least 20% of patients evaluated at epilepsy referral centers receive a diagnosis of psychogenic nonepileptic seizures (PNES). Although some patients with PNES may be malingering, PNES typically is a type of conversion disorder, with affected patients remaining unaware of why they have these

TABLE 11. Medical Conditions and Treatments Provoking Seizures

Condition	Specific Cause
Metabolic disturbance	Hyponatremia, hypo- or hypercalcemia, hypo- or hyperglycemia, uremia
Drug intoxication	Cocaine, phencyclidine, methamphetamines
Drug withdrawal	Alcohol withdrawal, benzodiazepine withdrawal, barbiturate withdrawal, baclofen withdrawal
Medication-induced lowered seizure threshold[a]	Bupropion, cefepime, ciprofloxacin, clozapine, cyclosporine, imipenem, isoniazid, tacrolimus, theophylline, tricyclic antidepressants, tramadol
Infection	Encephalitis, meningitis
Vasculopathy	Eclampsia, hypertensive encephalopathy, posterior reversible leukoencephalopathy syndrome

[a]The medications listed are those most commonly associated with lowered seizure threshold, particularly at supratherapeutic levels or in association with chronic kidney disease. Note that both cyclosporine and tacrolimus have been associated with posterior reversible leukoencephalopathy syndrome; therefore, patients taking these medications should be evaluated with MRI.

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events. A history of trauma or abuse is common in patients with PNES but is not always present. Some of the characteristic features of PNES are summarized in Table 10 and include forced eye closure, long duration, and hypermotor activity that starts and stops.

Inpatient video EEG monitoring is required to make this diagnosis because of the difficulty in distinguishing between PNES and epileptic seizures, particularly frontal lobe seizures. A high index of suspicion is critical for making a diagnosis of nonepileptic events, particularly in patients who do not respond to AED therapy. Early diagnosis by video EEG and referral to appropriate psychological resources provide the best chance of a good outcome. Limiting or eliminating unnecessary AEDs is critical, particularly in women of childbearing age. Approximately 10% to 30% of patients with PNES also have epileptic seizures, which underscores the need for a careful and complete assessment.

KEY POINT

- Inpatient video electroencephalographic monitoring is required to make the diagnosis of psychogenic nonepileptic seizure.

Diagnostic Evaluation of Seizures and Epilepsy

Imaging Studies

All patients with unprovoked seizures should have brain MRI to identify structural lesions that increase the risk of recurrent seizure, such as tumors and small vascular lesions (see Figure 5), malformations of cortical development (see Figure 6), and mesial temporal sclerosis (see Figure 4). Most centers have seizure or epilepsy MRI protocols that include a coronal flair sequence (see Figures 4 and 5), which is critical in identifying lesions in the mesial temporal region (common in epilepsy). MRI results are normal in most patients with generalized epilepsy and in many patients with focal epilepsy. The older the patient, the more likely a structural cause will be detected.

Electroencephalography

A routine EEG is a 30- to 60-minute recording of brain activity. Under ideal circumstances, the recording captures both the awake and sleep states because sleep is more sensitive for revealing epileptiform abnormalities. Seizures are rarely recorded on routine EEG, but the presence of interictal epileptiform discharges is highly correlated with an increased risk of recurrent seizures. Interictal epileptiform abnormalities also can help characterize the epilepsy syndrome as focal (**Figure 8**) or generalized (see Figure 7). An EEG can help confirm the presence of epilepsy but cannot be used to exclude the diagnosis. The likelihood that a single 30-minute EEG will record interictal epileptiform discharges in a patient with epilepsy is approximately 25% to 50%, varying by the type of epilepsy. Performing a second EEG increases the sensitivity for detecting epileptiform abnormalities, as does performing an EEG shortly after a seizure.

Epilepsy Monitoring Units

Epilepsy monitoring units are inpatient units designed for continuous simultaneous video and EEG monitoring. Patients are admitted electively to the hospital for 2 to 7 days, during which time their AED(s) may be withdrawn. Inpatient



FIGURE 8. Characteristic electroencephalogram of a patient with temporal lobe epilepsy showing an interictal left temporal epileptiform discharge during sleep.

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epilepsy monitoring is recommended for most patients who have not responded to two or more AEDs to determine their candidacy for epilepsy surgery and to exclude PNES. It may be reasonable to admit patients sooner if their epilepsy diagnosis is uncertain or if they are women of childbearing age.

Continuous Electroencephalographic Monitoring

Continuous EEG monitoring, which typically includes video monitoring, has become increasingly more available outside of epilepsy monitoring units. This type of monitoring is useful in detecting nonconvulsive seizures and nonconvulsive status epilepticus (NCSE) in patients who are comatose or have an altered mental state. Approximately 8% to 37% of patients with coma will be found to have nonconvulsive seizures on continuous EEG. Risk factors for nonconvulsive seizures and NCSE include intracerebral hemorrhage, traumatic brain injury (TBI), and central nervous system infections. The greatest risk for nonconvulsive seizures and NCSE occurs in patients with persistent altered mental status after apparently successful treatment of convulsive status epilepticus (CSE), with 48% of these patients showing evidence of seizures on EEG. Notably, only 50% of nonconvulsive seizures and NCSE will be detected on a 1-hour EEG, but continuous EEG monitoring for 12 to 24 hours increases the sensitivity for nonconvulsive seizures to 80%, and sensitivity approaches 96% after 48 hours of monitoring.

Treatment of Epilepsy

Antiepileptic Drug Therapy

Treatment with an AED is recommended for all patients who have had two or more unprovoked seizures. In a patient with a single unprovoked seizure and a normal EEG and brain MRI, the 2-year recurrence risk is 30% to 40%. Because seizure medications reduce this risk by only approximately 50%, AED therapy is not typically recommended. The risk of seizure recurrence is higher in patients older than 65 years and in those with a history of significant head trauma or partial seizure, postictal Todd paralysis, and focal findings on an EEG or brain MRI. The presence of one or more of these risk factors argues for the institution of AED treatment after a single seizure.

Selection of Antiepileptic Drugs

No single AED is recommended for the initial treatment of epilepsy. Approximately 50% of patients with this disorder will respond to the first AED administered. Choosing an AED for an individual patient depends on several factors, including his or her epilepsy syndrome, age, sex, and comorbid medical conditions and the drug's adverse-effect profile and cost. Only a few AEDs (lamotrigine, levetiracetam, topiramate, valproic acid, and zonisamide) are considered broad-spectrum agents and can be used to treat both generalized and partial epilepsy syndromes. Other narrow-spectrum AEDs (carbamazepine, gabapentin, oxcarbazepine, phenobarbital, phenytoin, and pregabalin) have the potential to exacerbate seizures in patients with generalized epilepsy. Phenytoin may control the tonic-clonic seizures in generalized epilepsy and is indicated in the treatment of convulsive status epilepticus but also can worsen other seizure types when used for chronic treatment of generalized epilepsy.

Because only a few randomized placebo-controlled trials of various epilepsy treatments exist and little evidence suggests a significant difference in efficacy between different AED monotherapy regimens, most experts recommend choosing an AED based on tolerability and the adverse-effect profile that is most appropriate for a particular patient. Treatment options and considerations are summarized in **Table 12**. Levetiracetam is a common first-line drug because it can be used for both generalized and partial epilepsy and for patients in whom the specific epilepsy syndrome is not yet apparent (for example, a patient with two convulsive seizures and no history of other seizures or focal features). Levetiracetam also can be started quickly, has few drug-drug interactions, and is typically well tolerated; however, it has the common adverse effect of irritability and also has been associated in some patients with anxiety, depression, and psychosis. In a patient with a clear focal epilepsy syndrome at presentation, carbamazepine provides a relatively cost-effective option, although its common adverse effects of fatigue and dizziness make it not well tolerated by some (particularly older) patients.

Carbamazepine and other enzyme-inducing AEDs (such as felbamate, oxcarbazepine, phenobarbital, and phenytoin)

TABLE 12. Initial Treatment of Epilepsy and Considerations in Special Populations

Epilepsy Syndrome	Best Evidence	Commonly Used Drugs	Least Expensive Drugs	Women of Childbearing Age	Older Patients	Liver Failure	Chronic Kidney Disease	Mood Disorder
Partial epilepsy	Carbamazepine, levetiracetam, phenytoin, zonisamide	Lacosamide, lamotrigine, oxcarbazepine, topiramate, valproic acid	Carbamazepine, phenobarbital, phenytoin	Lamotrigine, levetiracetam (avoid valproic acid and topiramate)	Lamotrigine, levetiracetam, gabapentin	Levetiracetam, gabapentin (avoid valproic acid)	Lamotrigine, levetiracetam	Carbamazepine, lamotrigine, oxcarbazepine, valproic acid (avoid levetiracetam)
Generalized epilepsy	No high-quality evidence available	Lamotrigine, levetiracetam, topiramate, valproic acid, zonisamide	Valproic acid	Lamotrigine, levetiracetam (avoid valproic acid and topiramate)	Lamotrigine, levetiracetam	Levetiracetam (avoid valproic acid)	Lamotrigine, levetiracetam	Lamotrigine, valproic acid (avoid levetiracetam)

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H CONT. can have significant interactions with other hepatically metabolized drugs and also are associated with an increased risk for osteoporosis and hypercholesterolemia. Phenobarbital is another inexpensive option for treating partial epilepsy but is rarely used because of its significant adverse effects, including sedation and the risk of a severe withdrawal syndrome. Valproic acid has been shown in one trial to be superior to other AEDs for treating generalized epilepsy, but its associated adverse effects include sedation, weight gain, and hypercholesterolemia; in young women, it has the additional adverse effect of polycystic ovary syndrome. It should never be used as a first-line drug in women of childbearing age because of the significantly elevated risk of congenital and cognitive abnormalities in exposed offspring (see Epilepsy and Pregnancy section and Table 12). Lamotrigine is commonly prescribed in women of childbearing age and is also a good option for older patients or those who have depression or other mood disorders. Topiramate and zonisamide can be used for both generalized and partial epilepsy and are associated with weight loss; however, both drugs have been associated with an increased risk of kidney stones and should be avoided in patients with a history of nephrolithiasis.

Common adverse effects of AEDs and less common but more serious adverse reactions to AEDs are summarized in **Table 13**. The most common serious adverse reactions associated with AEDs are hypersensitivity syndromes, such as Stevens-Johnson syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (see MKSAP 17 Dermatology); systemic findings include facial edema, widespread erythema, fever, lymphadenopathy, skin necrosis, purpura, eosinophilia, hepatitis, and nephritis. Hypersensitivity reactions are most common in the weeks following initiation of the drug but can occur at any time during therapy. The AEDs most commonly associated with rashes and hypersensitivity reactions are carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, and phenytoin. Lamotrigine needs to be titrated

TABLE 13. Adverse Effects of Antiepileptic Drugs

Drug	Common Adverse Effects	Serious Adverse Reactions
Carbamazepine	Sedation, fatigue, dizziness, ataxia, mild leukopenia, hyponatremia	Aplastic anemia, agranulocytosis, acute liver failure, rash, severe hyponatremia, Stevens-Johnson syndrome, DRESS
Clobazam	Sedation, dizziness, constipation	Tolerance, pyrexia, Stevens-Johnson syndrome; abrupt or excessively rapid discontinuation of therapy associated with benzodiazepine withdrawal syndrome
Ezogabine	Sedation, dizziness	Blue skin discoloration and retinal pigment changes, QT prolongation, urinary retention, confusion, psychosis, hallucinations
Felbamate	Insomnia, weight loss, nausea, headache	Aplastic anemia, acute liver failure
Gabapentin	Sedation, lower extremity edema, weight gain	—
Lacosamide	Sedation, dizziness, ataxia, diplopia, nausea, prolonged PR interval	Cardiac conduction abnormalities (bradyarrhythmias, AV block), rash
Lamotrigine	Insomnia, headache, acne, dizziness, double vision	Rash, Stevens-Johnson syndrome, DRESS, acute liver failure, blood dyscrasias
Levetiracetam	Irritability, sedation	Depression, psychosis, blood dyscrasias
Oxcarbazepine	Sedation, dizziness, ataxia, mild leukopenia, hyponatremia	Rash, Stevens-Johnson syndrome, DRESS, severe hyponatremia
Phenobarbital	Sedation, nausea, ataxia	Rash, Stevens-Johnson syndrome, acute liver failure, blood dyscrasias, barbiturate withdrawal
Phenytoin	Sedation, dizziness, ataxia	Rash, Stevens-Johnson syndrome, DRESS, blood dyscrasias, gingival hyperplasia, acute liver failure, drug-induced lupus, cardiac conduction abnormalities
Pregabalin	Sedation, weight gain, lower extremity edema	—
Topiramate	Word-finding difficulty, anorexia	Kidney stones, acute angle-closure glaucoma, heatstroke, metabolic acidosis
Valproic acid	Weight gain, tremor, hirsutism, hair loss, hyperammonemia, menstrual irregularity	Acute liver failure, pancreatitis, aplastic anemia, thrombocytopenia, platelet dysfunction
Vigabatrin	Sedation, headache, dizziness	Peripheral vision loss (irreversible), peripheral neuropathy, rash
Zonisamide	Sedation, anorexia	Kidney stones, rash

[a]AV = atrioventricular; DRESS = drug reaction with eosinophilia and systemic symptoms.

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CONT. slowly because the risk of rash has been specifically related to rapid titration; this dose escalation needs to be even slower in patients also taking valproic acid because valproic acid inhibits lamotrigine metabolism and increases the risk of a hypersensitivity syndrome. Asian patients who have the HLA-B*1502 allele are at an increased risk for hypersensitivity reactions to the aromatic AEDs (carbamazepine, lamotrigine, oxcarbazepine, and phenytoin). Therefore, genotype testing is recommended before starting one of these drugs in patients of Asian heritage; alternatively, other AEDs can be used as first-line therapy. H

Monitoring and Discontinuing Medications

The target dose for an AED is the dose that controls a patient's seizures without significant adverse effects. Therapeutic drug ranges published by many laboratories are useful guides, but the patient's response defines his or her own therapeutic drug level. For example, if a patient requires a drug level above the recommended range for seizure control and has no adverse effects to this higher level, the dose does not need to be adjusted; a notable exception to this is phenytoin, for which supratherapeutic levels are associated with an increased risk of cardiac arrhythmias. In general, AED levels do not need to be monitored routinely in a patient who is doing well. A baseline level (ideally, a trough level) should be established once the target dose has been reached and the patient's seizures are well-controlled. Further AED monitoring is indicated in pregnancy, kidney or liver disease, menopause, change from a brand name to a generic medication, or around the time of initiating a new medication that may affect metabolism or protein binding. In these situations, doses should be adjusted to maintain the patient's personal therapeutic drug level.

The use of generic medications is a major way to control costs for patients with epilepsy. The major consideration in using a generic drug is its bioavailability, which may differ by as much as 20% between manufacturers. Because drug level maintenance is critical to maintaining seizure threshold, patients taking generic AEDs should try to use the same drug manufacturer from month to month.

Certain AEDs are associated with adverse effects that require additional monitoring. For example, both carbamazepine and oxcarbazepine can cause hyponatremia. Evaluation of the serum sodium level after initiating the drug and at 3 months is recommended. Because many AEDs are associated with liver abnormalities and/or blood dyscrasias, obtaining a complete blood count and comprehensive metabolic profile at 6 and 12 months in the first year of therapy is advisable; if no abnormalities are detected, yearly monitoring is reasonable.

Patients taking AEDs should be regularly screened for suicidal thoughts. All AEDs carry a black box warning indicating a potentially increased risk of suicidal ideation, which is based on a pooled analysis of clinical trials. Mood disorders also are prevalent in patients with epilepsy.

Epilepsy can go into remission, and many childhood epilepsy syndromes often resolve in adulthood. A major exception is JME, which typically is regarded as a life-long condition requiring continuous treatment. Many patients who have been seizure free for 2 to 4 years can choose to be weaned from AEDs; seizure recurrence after AED withdrawal in these patients is 30% to 40% over 5 years. Those with normal EEG and MRI results who have no other risks factors for epilepsy are more likely to remain seizure free after stopping their medications. Discontinuing medications is a difficult decision that requires careful counseling about the risks of recurrent seizures, including a discussion of sudden unexplained death in epilepsy (SUDEP; see later discussion) and the implications for driving.

KEY POINTS

- In a patient with a single unprovoked seizure and a normal electroencephalogram and MRI, the 2-year recurrence risk is 30% to 40%; because seizure medications reduce this risk by only approximately 50%, antiepileptic drug therapy is not typically recommended. **HVC**
- Choosing an AED for an individual patient depends on several factors, including his or her epilepsy syndrome, age, sex, and comorbid medical conditions and the drug's adverse-effect profile and cost. **HVC**
- The antiepileptic drugs (AEDs) lamotrigine, levetiracetam, topiramate, valproic acid, and zonisamide are considered broad-spectrum agents and can be used to treat both generalized and partial epilepsy syndromes; some narrow-spectrum AEDs (such as carbamazepine, gabapentin, oxcarbazepine, phenobarbital, phenytoin, and pregabalin) have the potential to exacerbate seizures in patients with generalized epilepsy.
- The use of generic antiepileptic drugs (AEDs) is a way to control costs for patients with epilepsy, and the major consideration in using a generic AED is its bioavailability, which may differ by as much as 20% between manufacturers; because drug level maintenance is critical to maintaining seizure threshold, patients taking generic AEDs should try to use the same drug manufacturer from month to month. **HVC**

Counseling and Lifestyle Adjustments

Alcohol, stress, and sleep deprivation can reduce a patient's seizure threshold. Therefore, counseling patients to minimize exposure to these triggers is an important part of epilepsy treatment. Likewise, use of interventions to optimize adherence to AED regimens (such as the use of pill boxes) should be encouraged. Several medications, including antibiotics, antihistamines, and psychiatric and pain medications, can lower seizure threshold and interact negatively with AEDs. Patients and their physicians should discuss any new medications, and alternatives should be used when appropriate. Testing for and treating sleep apnea when appropriate also may improve seizure control. All patients must be counseled about driving restrictions.

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KEY POINT

- Alcohol, stress, sleep deprivation, and certain drugs—including antibiotics, antihistamines, and psychiatric and pain medications—can lower a patient's seizure threshold; these agents also can interact negatively with antiepileptic drugs.

Comorbidities and Complications of Epilepsy

Common comorbidities of epilepsy include mood disorders, sleep disorders, metabolic bone disease, and hyperlipidemia. Screening for these conditions is a vital part of caring for a patient with epilepsy.

Sudden Unexplained Death in Epilepsy

Sudden unexplained death in epilepsy (SUDEP) is nonaccidental death in otherwise healthy patients with epilepsy. SUDEP is a significant cause of mortality in epilepsy, with approximately 1 in 1000 patients with epilepsy dying of it each year. The mechanism of SUDEP is poorly understood, but it is likely related to a disturbance in cardiac or respiratory autoregulation. Death often occurs during sleep. Risk factors include refractory epilepsy, cognitive impairment, generalized tonic-clonic seizures, and poor medication adherence.

Intractable Epilepsy

Epilepsy Surgery

Patients who do not respond to either their first or their second AED (in sequence or combination) have a less than 10% chance of experiencing seizure remission with pharmacotherapy. These patients are considered to have refractory epilepsy and should be referred to a comprehensive epilepsy center to confirm the diagnosis of epilepsy and determine their candidacy for epilepsy surgery.

KEY POINT

- Patients with epilepsy who do not respond to either their first or their second antiepileptic drug are considered to have refractory epilepsy and should be referred to a comprehensive epilepsy center to confirm the diagnosis and determine their candidacy for epilepsy surgery.

Seizures and Epilepsy in Specific Populations

Older Patients

Patients age 65 or greater who have a first unprovoked seizure at presentation are much more likely to have underlying brain disease (such as a tumor, previous stroke, or dementia) and a higher risk for recurrent seizures. Morbidity related to seizures in this population also is higher. For these reasons, it may be reasonable to start AED treatment after an initial seizure in older patients. Medication tolerability may be problematic in this age group. Lamotrigine, levetiracetam, and gabapentin are generally well-tolerated in older patients and have few drug-drug interactions. One study showed that lamotrigine was the most effective, followed by levetiracetam. Titration of the drug dosage may need to be slower, and the ultimate dosage should account for decreased glomerular filtration rate, when present.

KEY POINT

- Antiepileptic drugs (preferably lamotrigine, levetiracetam, and gabapentin) are sometimes given to older patients after a first seizure because their risks of recurrent seizure and seizure-related morbidity are higher.

Patients with Organ Failure

The management of AEDs in patients with liver failure or chronic kidney disease depends on the metabolism of the drug and the degree to which the drug is protein bound. **Table 14** summarizes dosing considerations for specific AEDs in organ failure. Levetiracetam is a good option in patients with either liver failure or chronic kidney disease, although dose adjustment is required in patients with chronic kidney disease.

Returning Combat Veterans

TBI, with or without evidence of intracranial abnormalities, is a risk factor for epilepsy. Therefore, it is reasonable to consider AED treatment in a combat veteran with a history of TBI and a single unprovoked seizure. Inpatient monitoring should be considered early in veterans whose seizures do not respond to AEDs because these patients are at risk not only for epileptic seizures, but also for nonepileptic seizures. The diagnosis of PNES is often delayed in veterans, most often because these patients often report a history of TBI. Early monitoring and diagnosis is critical, as are interventions to minimize disability. Posttraumatic stress disorder is strongly associated with PNES in veterans.

Women and Epilepsy

Women of childbearing age who have epilepsy require special consideration regarding AED treatment and management. Valproic acid in particular should be avoided in this population because the risk of teratogenesis is much higher with this drug than with other AEDs. Other adverse effects in a female population are weight gain, hair loss, and polycystic ovary syndrome. Contraception can be a particular challenge in women with epilepsy because AEDs have complex interactions with oral contraceptives and other forms of hormonal contraception.

Epilepsy and Pregnancy

Most women with epilepsy have healthy pregnancies and children. In most women with active epilepsy, AED therapy during pregnancy is required to control seizures, which can adversely affect the pregnancy. Early planning (well before a patient

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TABLE 14. Dose Adjustment of Antiepileptic Drugs in Organ Failure

Drug	Requires Dose Adjustment in Chronic Kidney Disease	Requires Supplemental Dose After Dialysis	Requires Dose Adjustment in Liver Failure
Carbamazepine	No	No	Avoid
Clobazam	No	No	Yes
Felbamate	Yes	Possibly[a]	Avoid
Gabapentin	Yes	Yes	No
Lacosamide	Only with a glomerular filtration rate < 30 mL/min/1.73 m^2	Yes	Yes; avoid drug in patients with severe impairment
Levetiracetam	Yes	Yes	Yes, in severe disease
Oxcarbazepine	Yes	Possibly[a]	No, but avoid in patients with severe liver failure
Phenobarbital	No	Possibly[a]	Yes
Phenytoin	No, but monitoring free phenytoin levels recommended	Possibly[a]	Yes
Pregabalin	Yes	Yes	No
Topiramate	Yes	Yes	Possibly
Valproic acid	No	Possibly[a]	Avoid if possible
Vigabatrin	Yes	Probably	No
Zonisamide	No[b]	Possibly[a]	Possibly

[a]Filtration of these drugs during dialysis depends on the pore size of the dialyzer. Supplementation is needed with many of the new high-efficiency dialyzers. Checking antiepileptic drug levels pre- and postdialysis can help determine the need for supplemental dosing.

[b]Insufficient evidence for dose adjustment even with a glomerular filtration rate < 30 mL/min/1.73 m^2.

attempts pregnancy) can optimize the outcome of any future pregnancy. The initial drug choice in young women with seizures should keep a potential pregnancy in mind. Supplemental folic acid (1-4 mg) is recommended for all women of childbearing age who are taking AEDs.

Valproic acid is associated not only with an increased risk (6%-17%) of major congenital malformations (MCMs) compared with other AEDs, but also with decreased intelligence quotients (IQs) and autism in exposed children. Other drugs that are associated with a high risk of MCMs are phenobarbital and phenytoin; topiramate has recently been categorized as a class D drug in pregnancy (evidence of human fetal risk) because of a specifically increased risk of cleft lip and cleft palate; this drug should be avoided (if possible) in patients who are pregnant or may become pregnant.

Lamotrigine is a good option for women with epilepsy and has been associated with a relatively low risk of MCM (2%-6%) compared with a baseline risk of 2% to 3% in the general population. Levetiracetam also appears to have a low risk of birth defects, although the number of published exposures is still small. Carbamazepine has been associated with an overall low risk of MCMs in several studies but may have a specific association with spina bifida, one of the more severe MCMs.

AED levels must be followed closely during pregnancy. Lamotrigine and oxcarbazepine are particularly sensitive to the effect of estrogen on glucuronidation, which leads to an increase in liver metabolism. The levels of these AEDs can decrease precipitously during pregnancy and result in increased seizure frequency. Increasing the dosage of these drugs during pregnancy is thus recommended.

KEY POINT

- In most women with active epilepsy, antiepileptic drug (AED) therapy during pregnancy is required to control seizures, which can adversely affect the pregnancy; because of its association with major congenital malformations, decreased intelligence, and autism in exposed children (compared with other AEDs), valproic acid should be avoided.

Contraception

Enzyme-inducing AEDs, including carbamazepine, phenytoin, and phenobarbital, decrease both estrogen and progestin levels and thus inactivate many forms of hormonal contraception. Topiramate, oxcarbazepine, clobazam, and felbamate can have a similar effect. Because lamotrigine is metabolized by glucuronidation, a process induced by estrogens, estrogen-containing contraceptive agents can reduce lamotrigine levels and lead to more seizures if a patient's dosage is not increased.

KEY POINT

- Estrogen-containing contraceptive agents can reduce lamotrigine levels in women with epilepsy and lead to more seizures if the lamotrigine dosage is not increased.

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Status Epilepticus

Convulsive Status Epilepticus

CSE is a medical emergency that can lead to significant morbidity and mortality. Prompt intervention is critical. CSE is defined as persistent tonic-clonic activity with impaired mental status that lasts longer than 5 minutes. Initial management of CSE requires rapidly assessing airways, breathing, and circulation; checking the blood glucose level; and administering thiamine with glucose, if needed. These steps should be performed simultaneously with initiating drug treatment. First-line pharmacologic treatment (**Figure 9**) is intravenous lorazepam followed by phenytoin. Intramuscular midazolam (or lorazepam) or rectal diazepam can be used as an alternative to lorazepam if intravenous access is not possible. If available, fosphenytoin, a prodrug of phenytoin, is preferable to phenytoin for initial treatment of CSE because it can be administered faster and does not carry the risk of thrombophlebitis or skin necrosis (purple glove syndrome) that is associated with phenytoin extravasation. Fosphenytoin can be given intramuscularly, if needed. Both fosphenytoin and phenytoin can cause hypotension and cardiac conduction abnormalities. Valproic acid is an alternative to phenytoin or

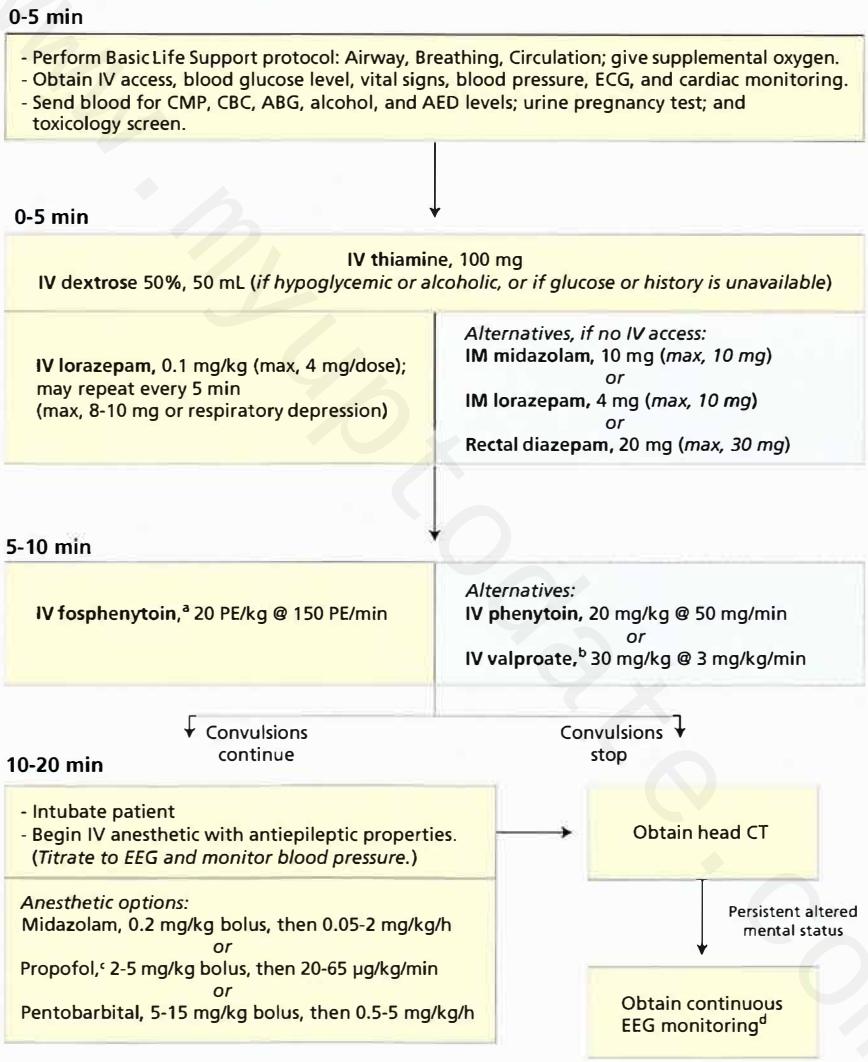

FIGURE 9. Management algorithm for generalized convulsive status epilepticus with ongoing convulsive activity lasting longer than 5 minutes *or* recurrent convulsive seizures without a regaining of consciousness. ABG = arterial blood gases; AED = antiepileptic drug; CBC = complete blood count; CMP = comprehensive metabolic panel; ECG = electrocardiogram; EEG = electroencephalogram; IM = intramuscular; IV = intravenous; max, maximum; PE = phenytoin equivalent.

[a]Monitor ECG and blood pressure with fosphenytoin and phenytoin use; monitor for drug extravasation with phenytoin use.

[b]Consider valproic acid (valproate) as first-line therapy in those with known idiopathic generalized epilepsy; avoid when possible in women of childbearing age.

[c]Note that propofol infusion is dosed in µg/kg/min unlike other infusions. Caution is advised with prolonged use and high doses of propofol because of an increased risk of propofol infusion syndrome, particularly with rates greater than 65 µg/kg/min.

[d]Should be obtained in all patients not recovering baseline mental status, including those receiving IV anesthesia.

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CONT.

fosphenytoin, particularly in patients with an allergy to phenytoin or with IGE. No other AED is recommended as first-line treatment of CSE.

If a patient continues to convulse after receiving lorazepam, is medically unstable, or has an unprotected airway, intubation and intravenous anesthesia are typically required. Consensus about which anesthetic agent should be used first is lacking. Propofol is effective in stopping seizures but needs to be monitored closely because prolonged infusions of high-dose propofol can lead to rhabdomyolysis and multiorgan failure. All options are listed in Figure 9.

Patients with CSE who have stopped having clinical seizures are at high risk for NCSE. Thus, all patients with CSE who do not return to baseline within 15 minutes of pharmacologic treatment should be monitored with continuous EEG monitoring.

KEY POINT

- First-line pharmacologic treatment for convulsive status epilepticus, defined as persistent convulsive activity with impaired mental status lasting longer than 5 minutes, is intravenous lorazepam followed by intravenous phenytoin (or, if available, fosphenytoin).

Nonconvulsive Status Epilepticus

NCSE is defined as persistent clinical or electrographic seizure activity without convulsive motor manifestations. The implications and treatment of NCSE depend greatly on the clinical context in which it occurs. Arguably, the most critical patients with NCSE are those in whom CSE is followed by NCSE. Although management of the electrographic pattern in these patients is controversial, it is usually aggressive and uses either additional AEDs or increasing amounts of anesthesia to control seizures or induce burst-suppression.

On the other end of the spectrum, NCSE can occur in ambulatory patients with complex partial status epilepticus or absence status epilepticus; these patients are sometimes referred to as "the walking confused." This situation most often involves patients with established epilepsy and sometimes can present de novo in older persons. Affected patients occasionally respond to treatment with a benzodiazepine or initiation of a new AED; an initial aggressive approach involving intubation can cause unnecessary morbidity and is not recommended.

NCSE also is increasingly diagnosed in critically ill comatose or stuporous patients with acute neurologic or medical conditions who have not had a convulsive seizure. Similar to NCSE following CSE, NCSE in these populations also is associated with increased morbidity and mortality and requires prompt attention and intervention. The definition of NCSE in these patients, however, is controversial, and scant evidenced-based data exist on treatment of this population.

In all patients with NCSE and CSE, the underlying cause determines outcome, and early attempts to identify and correct the underlying cause are critical.

KEY POINT

- Although management of the electrographic pattern in patients with nonconvulsive status epilepticus is controversial, it usually is directed at controlling seizures.

Stroke

Definition of Stroke

Stroke is characterized by the sudden onset a focal neurologic impairment that can be ascribed to a specific location in the brain, retina, or spinal cord. The fourth leading cause of death in the United States and the leading cause of significant disability, stroke can be further subdivided into ischemic and hemorrhagic stroke, with the relative proportion of each varying by age and geographic location. Hemorrhagic stroke has two further subtypes: subarachnoid hemorrhage (SAH), which is usually caused by rupture of an intracranial aneurysm, and nontraumatic intracerebral hemorrhage (ICH). Ischemic stroke can be further classified as lacunar (a small subcortical infarct), large artery atherosclerotic (either intra- or extracranial), cardioembolic, or cryptogenic. One of the principal goals of hospitalization for stroke is the determination of stroke subtype, which has important implications for acute treatment, secondary prevention strategies, and prognosis.

KEY POINT

- A principal goal of hospitalization in patients with stroke is to determine the stroke subtype, which has important implications for acute treatment, secondary prevention strategies, and prognosis.

Diagnosis of Stroke

A complete neurologic examination is warranted in all patients with suspected stroke to localize the deficit to the central nervous system and inform prognosis. In the acute stroke setting, when time is of the essence, validated scales for measuring neurologic impairment can be rapidly performed by any health care provider. The National Institutes of Health Stroke Scale (**Table 15**) is the most commonly used scale, and training is available online through several organizations for certification.

Because the predictive value of any specific finding from the history or physical examination is insufficient to distinguish ischemic from hemorrhagic stroke, prompt neuroimaging also is required. A noncontrast CT scan of the head will readily identify ICH and SAH (**Figure 10**) and is the initial test of choice. Any patient with suspected SAH

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TABLE 15. National Institutes of Health Stroke Scale

Parameter (Testing Method)	Scores[a]
1a. LOC	0 = normal 1 = not alert but arousable by minor stimulation 2 = not alert and requires constant verbal or painful stimuli to remain interactive 3 = unresponsive or responds with only reflexive movements
1b. LOC, questions (state month and age)	0 = answers both correctly 1 = answers one correctly 2 = answers neither correctly
1c. LOC, commands (close and open eyes; make fist or close one hand)	0 = performs both tasks correctly 1 = performs one task correctly 2 = performs neither task correctly
2. Gaze (track a finger in a horizontal plane)	0 = normal 1 = partial gaze palsy or isolated cranial nerve paresis 2 = forced gaze deviation or total gaze paresis
3. Visual fields (each eye tested individually)	0 = no visual loss 1 = partial hemianopia 2 = complete hemianopia 3 = bilateral hemianopia
4. Facial strength (show teeth, raise eyebrows, close eyes)	0 = normal 1 = minor paralysis (flattening of the nasolabial fold or asymmetry on smiling) 2 = partial paralysis (paralysis of the lower face only) 3 = complete paralysis (upper and lower face)
5. Arm strength (hold arm with palms down or lift arm for 10 s; each arm scored separately)	0 = no drift 1 = some drift but does not hit bed 2 = drifts down to bed 3 = no effort against gravity 4 = no movement
6. Leg strength (hold leg at 30 degrees for 5 s; each leg scored separately)	0 = no drift 1 = some drift but does not hit bed 2 = drifts down to bed 3 = no effort against gravity 4 = no movement
7. Limb ataxia (finger-nose-finger test, heel-knee-shin slide)	0 = absent 1 = present in one limb 2 = present in two limbs
8. Sensation (pinch/pinprick tested in face, arm, and leg)	0 = normal 1 = mild to moderate sensory loss or loss of sensation in only one limb 2 = complete sensory loss
9. Language (describe a picture, name six objects, and read five sentences)	0 = no aphasia 1 = mild to moderate aphasia (difficulty with fluency and comprehension; meaning can be identified) 2 = severe aphasia (fragmentary language; meaning cannot be clearly identified) 3 = global aphasia or mute
10. Dysarthria (repeat or read words)	0 = normal 1 = mild to moderate 2 = severe (speech not understandable)
11. Extinction/inattention (visual and tactile stimuli applied on right and left sides)	0 = normal 1 = visual or tactile extinction or mild hemispatial neglect 2 = profound hemi-inattention or extinction to more than one modality

LOC = level of consciousness.

[a]Score interpretation: 0 = no stoke; 1-4 = minor stroke; 5-15 = moderate stroke; 16-20 = moderate to severe stroke; 21-42 = severe stroke (maximum score, 42).

Adapted from www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf. Accessed February 9, 2015. Certification available at www.stroke.org/we-can-help/healthcare-professionals/improve-your-skills/tools-training-and-resources/training/nih?gclid=CJWx_IDO08MCFcnm7AodZloACA.

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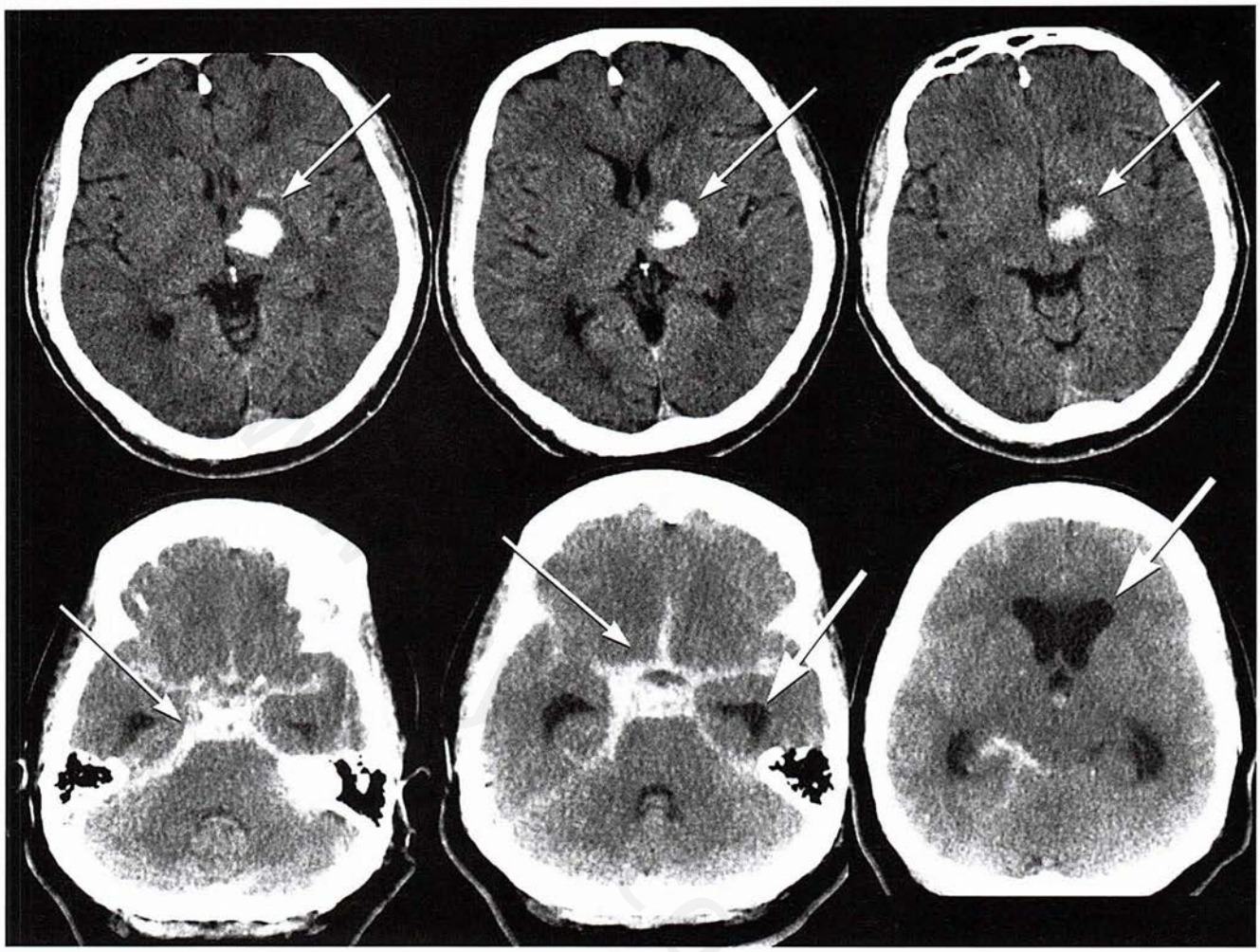

FIGURE 10. Noncontrast CT scans of the head. *Top panel*, an acute left thalamic intracerebral hemorrhage (*arrows*) without hydrocephalus or intraventricular extension is shown. *Bottom panel*, an acute subarachnoid hemorrhage is shown that involves the basal cisterns (*thinner arrows*) with associated enlargement of the lateral horn of the lateral ventricles, consistent with obstructive hydrocephalus and elevated intracranial pressure (*thicker arrows*).

CONT.

whose head CT scan is normal should have a lumbar puncture to evaluate for blood or xanthochromia in the cerebrospinal fluid to rule out aneurysmal bleeding. A noncontrast CT scan of the head also can identify the early changes seen in the acute setting in some patients with cerebral infarction (**Figure 11**). In many instances, the initial noncontrast CT will not show any appreciable changes for as long as 24 hours after ischemic stroke, and small infarcts, particularly in the thalamus and brainstem, may not be visible with CT beyond that time window. After an initial evaluation with noncontrast head CT, other neuroimaging studies may provide information regarding stroke location and allow for evaluation of the cerebral vasculature. MRI (**Figure 12**) can help determine the presence of cerebral infarction when the CT scan is not informative and provide additional information about previous strokes or other intracranial pathology. However, because of its greater cost, less widespread availability, and generally longer duration, MRI is rarely the initial imaging technique of choice to evaluate for hemorrhage or suitability for systemic thrombolysis. Similarly, CT of the head with contrast is rarely helpful in the evaluation of brain parenchyma in patients with stroke unless it is being used to exclude other intracranial pathology (such as metastasis) that may mimic stroke in a patient who cannot receive an MRI.

The neurologic examination provides useful information about the specific neuroanatomic localization of stroke, which in itself can suggest the stroke subtype. For example, the absence of cortical features, such as aphasia and visuospatial neglect, can point to a small subcortical infarct, whereas monocular visual loss and a carotid bruit can suggest extracranial large artery atherosclerotic disease. The examination, however, is not sufficiently sensitive or specific to further identify the subtype of ischemic stroke, and vessel imaging and cardiac evaluation are required in most patients with ischemic stroke.

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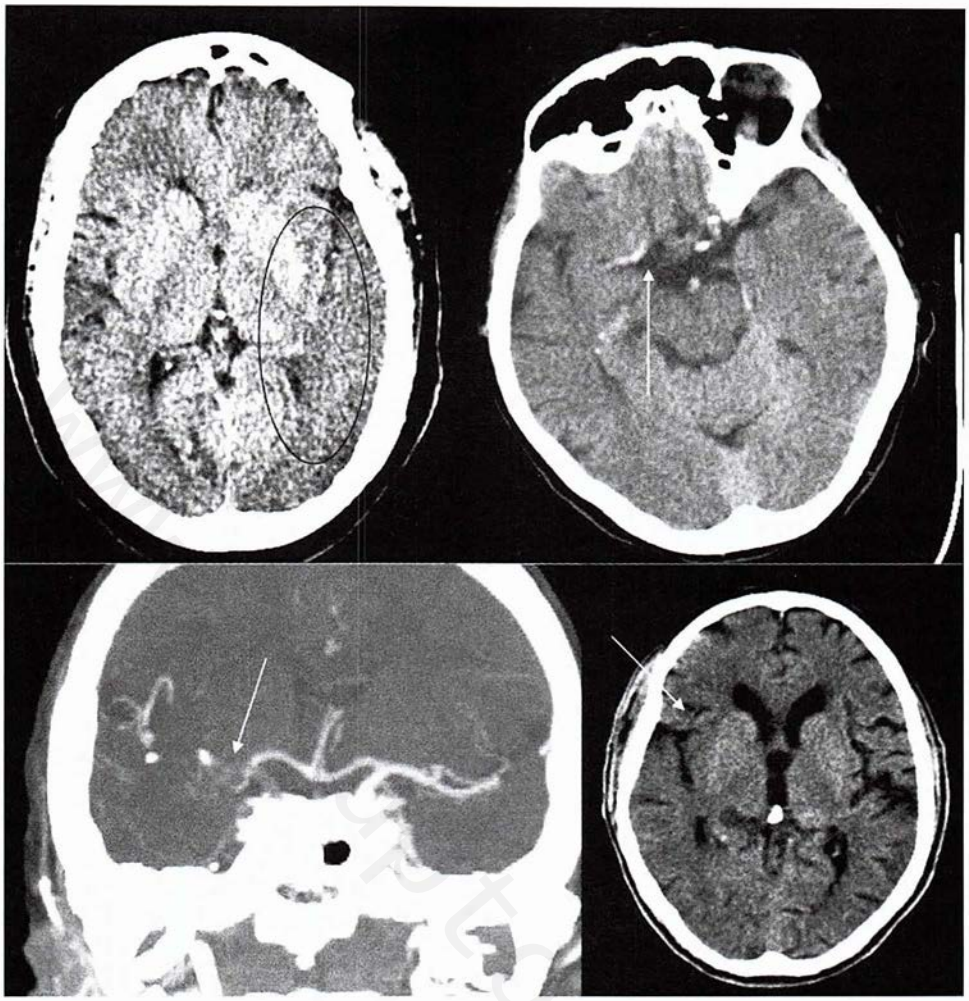

FIGURE 11. Head CT findings in acute ischemic stroke. *Top left*, sulcal effacement and loss of the gray-white differentiation (*oval circle*) in a patient 1.5 hours after the witnessed onset of global aphasia. *Top right*, hyperdensity (*arrow*) in the proximal right middle cerebral artery in a patient with left hemiparesis and left hemi-inattention 60 minutes after last being seen well. *Bottom left*, CT angiogram of the same patient that shows absent contrast in the right internal carotid and proximal middle cerebral arteries (*arrow*), consistent with a thrombus in the artery. *Bottom right*, loss of gray-white matter differentiation in the insula ("loss of the insular ribbon") on the right (*arrow*) compared with the left where the gray-white matter differentiation is clearly seen in a patient 2 hours after onset of left hemiparesis.

KEY POINT

- In patients with stroke, neuroimaging (usually a noncontrast CT scan of the head) is required to distinguish ischemic from hemorrhagic stroke; when subarachnoid hemorrhage is suspected but neuroimaging findings are normal, lumbar puncture is necessary to evaluate for blood or xanthochromia in the cerebrospinal fluid.

Stroke Subtypes

Transient Ischemic Attack

Transient ischemic attack (TIA) is defined by transient focal neurologic symptoms resulting from brain, retinal, or spinal cord ischemia and was initially defined as lasting less than 24 hours. A more recently adopted definition recognizes the high prevalence of acute infarcts on neuroimaging and emphasizes that TIA is defined by the absence of infarction on neuroimaging, independent of symptom duration. TIA symptoms typically are short lasting, usually 5 minutes to 1 hour, and include sudden-onset hemiparesis, hemisensory loss, change in speech function (either aphasia or dysarthria), loss of vision, or inability to walk. Patients with a suspected TIA should thus undergo neuroimaging with either noncontrast MRI or CT within 24 hours of the onset of neurologic deficits.

TIA is considered a neurologic emergency given the subsequent 48-hour and 90-day risk of ischemic stroke. Several clinical scales have been developed for risk stratification of patients with a TIA (or stroke); the most widely accepted is the ABCD^2 score, which is based on a patient's Age, Blood pressure, Clinical presentation, Duration of symptoms, and the presence of Diabetes mellitus (**Table 16**). The risk of stroke increases as the ABCD^2 score increases, and hospital admission is recommended for all patients with an ABCD^2 score of 3 or

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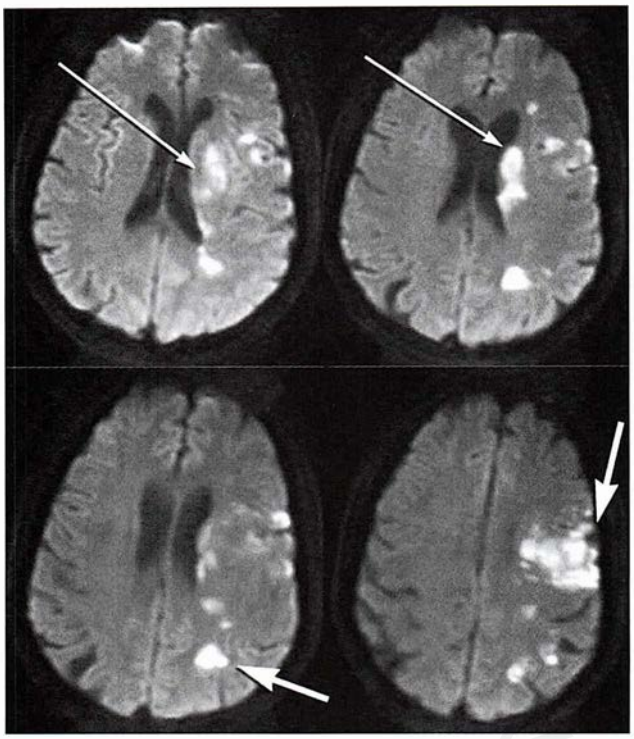

FIGURE 12. Diffusion-weighted MRIs from a patient with symptomatic left middle cerebral artery atherosclerosis reveal an acute infarction in deep (*thinner arrows*) and superficial (*thicker arrows*) structures in the left cerebral hemisphere.

TABLE 16. ABCD Scoring System[a]

Patient Characteristics	Score[b]
Age ≥60 y	1
Blood pressure ≥140/90 mm Hg	1
Clinical symptoms	
Focal weakness with the TIA	2
Speech impairment without weakness	1
Duration of TIA	
≥60 min	2
10-59 min	1
Diabetes mellitus present	1

TIA = transient ischemic attack.

[a]Based on Age, Blood pressure, Clinical presentation, Duration of symptoms, and the presence of Diabetes mellitus.

[b]The 48-hour stroke risk based on score: 0-1 = 0%; 2-3 = 1.3%; 4-5 = 4.1%; 6-7 = 8.1%.

CONT. greater so that rapid evaluation and treatment can occur. A noncontrast head CT is required to rule out hemorrhagic stroke. Hospital admission also can be considered in patients with a score of 0 to 2 if suspicion of infarction is high or if rapid outpatient evaluation cannot be completed within 48 hours. All patients with suspected TIA require an expedited evaluation within 48 hours with both cerebrovascular imaging and cardiac examination. Cerebrovascular imaging is necessary to exclude extracranial internal carotid artery disease, which is associated with a high risk of subsequent stroke, and can be performed with carotid ultrasonography; magnetic resonance and CT angiography are other options, but cost and risk from contrast and radiation should be considered. The cardiac examination is primarily focused on identifying patients who could be candidates for anticoagulation for stroke prevention; electrocardiography or cardiac event monitoring is performed to detect any atrial fibrillation, and echocardiography is needed to evaluate for ventricular thrombus or other high-risk embolic sources (for further discussion, see MKSAP 17 Cardiovascular Medicine).

KEY POINT

- In patients who have had a transient ischemic attack, the risk of stroke increases as the ABCD^2 score (based on a patient's Age, Blood pressure, Clinical presentation, Duration of symptoms, and the presence of Diabetes mellitus) increases; hospital admission is recommended for all patients with an ABCD^2 score of 3 or greater so that rapid evaluation and treatment can occur.

Ischemic Stroke

Cardioembolic Stroke

The most common cause of cardioembolic stroke is atrial fibrillation. Other potential cardioembolic sources can be identified during the diagnostic evaluation, including reduced left ventricular ejection fraction, severe calcific mitral stenosis, ventricular thrombus or apical aneurysm, or congenital abnormalities (such as a patent foramen ovale [PFO]). For further details on risk stratification with cardioembolic sources and anticoagulation criteria, see MKSAP 17 Cardiovascular Medicine.

Several findings on neuroimaging suggest a cardioembolic cause, such as involvement of the cortical surface in the absence of cerebral artery atherosclerosis; presence of more than one infarct, especially if bilateral or involving the territory of both the internal carotid and vertebrobasilar arteries; and involvement of the entire territory of a large intracranial artery. Cardiac rhythm evaluation is advisable for all patients with ischemic stroke, including electrocardiography and in-hospital telemetry, to evaluate for atrial fibrillation. Transthoracic echocardiography should be considered in patients with stroke who have a suspected embolic stroke or underlying heart disease without another identified cause to identify candidates for anticoagulation. Transesophageal echocardiography can be considered on a case-by-case basis to identify rare causes of stroke, such as valvular endocarditis or intracardiac tumors.

Large Artery Atherosclerosis

Stroke due to large artery atherosclerosis commonly occurs after local thrombus formation in the area of plaque rupture with subsequent distal embolization. Of the common causes of stroke, extracranial internal carotid artery atherosclerosis

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has the highest risk of recurrent stroke in the first 2 weeks. Suggestive clinical history and examination findings include recent monocular visual loss and the presence of a carotid bruit, both on the side of the affected hemisphere. The risk of recurrent stroke is highest when the stenosis is greater than 70%; stenosis in the 50% to 70% range has a more modest risk of recurrence. Prompt vascular imaging is therefore recommended for patients with a TIA or a carotid territory infarction seen on neuroimaging. Several imaging modalities are available for quantifying the degree of stenosis, including ultrasonography, magnetic resonance angiography (MRA), and CT or catheter digital subtraction angiography. Carotid ultrasonography is a useful initial, noninvasive test, particularly because of its high sensitivity for hemodynamically significant stenosis and its low risk. If the carotid ultrasound shows significant stenosis, the percentage of narrowing and the anatomic location should be confirmed with either CT angiography or MRA without contrast before recommending stenting procedures or other surgery (see **Figure 13** for a comparison of different imaging modalities). Unless carotid artery angioplasty with stenting is planned, catheter angiography is not routinely necessary.

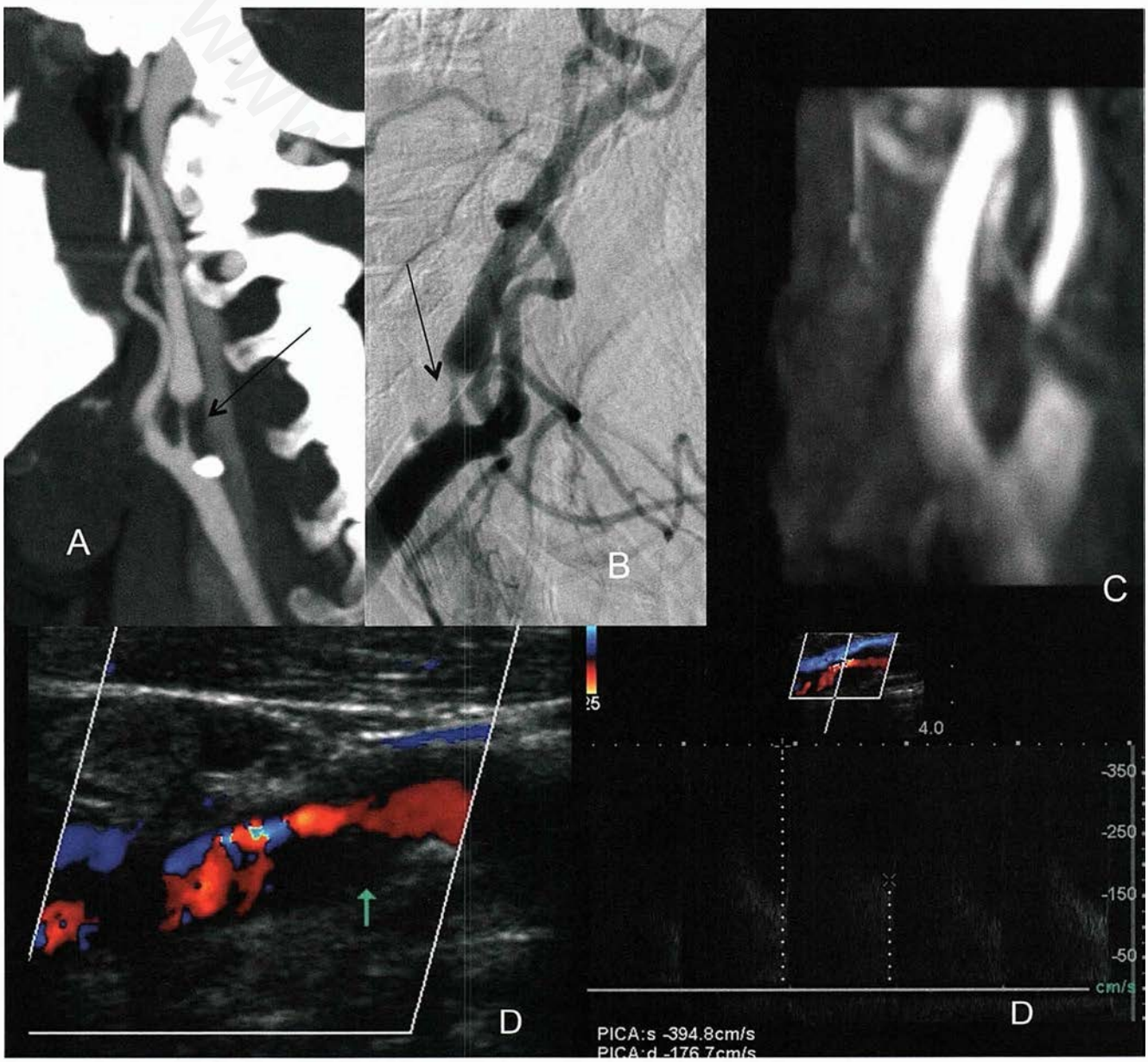

FIGURE 13. Diagnostic imaging modalities in a patient with a symptomatic extracranial internal carotid artery atherosclerotic plaque and associated 90% stenosis. *Top panels*: a CT angiogram (*A*), a digital subtraction angiogram (*B*), and a magnetic resonance angiogram (*C*) all show high-grade stenosis at the area of the origin of the internal carotid artery (*arrows*). *Bottom panel*: ultrasounds (*D*) of the extracranial proximal internal carotid artery show a large plaque at the origin (*arrow*) of the artery, with associated elevated systolic (−394.8 cm/s) and diastolic (−176.7 cm/s) velocities consistent with 80% to 99% stenosis. PICA = proximal internal carotid artery.

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Stroke arising from atherosclerosis of the intracranial arteries typically occurs with stenosis greater than 70% in the vertebrobasilar, intracranial internal carotid, and middle cerebral arteries. Intracranial atherosclerosis also is associated with a high long-term risk of recurrent stroke; its presence can be detected with either CT or MRA. Transcranial Doppler ultrasonography can detect accelerated velocities consistent with significant stenosis and can be used in patients unable to undergo CT or MRA; diagnostic cerebral angiography is rarely necessary in these patients.

Small Subcortical Infarcts (Lacunes)

Small subcortical infarcts (lacunes) are commonly less than 1.5 cm in size and arise from occlusion of small perforating arteries emanating from the large intracranial vessels. This stroke subtype typically presents with only motor or sensory findings on examination; cortical hemispheric symptoms, such as visual field cuts, aphasia, or hemispatial neglect, are lacking. The main risk factor for lacunar stroke is hypertension, leading to associated pathologic changes at the origin of the perforating arteries. Because these infarcts may still arise from atherothrombotic lesions in large cerebral arteries, vascular imaging is required in affected patients to initiate appropriate secondary stroke prevention.

Cryptogenic and Rare Causes of Stroke

A sizeable proportion of patients will have a cerebral infarction with no definitive cause identified on cardiac or vascular diagnostic testing. In these patients, prolonged cardiac rhythm monitoring or interrogation of a pacemaker, if present, may reveal undiagnosed paroxysmal atrial fibrillation that could change secondary prevention strategies. Other diagnostic testing can be considered on a case by case basis, depending on the specific circumstances. Headache preceding stroke in younger patients without cardiovascular disease risk factors, particularly those with recent head/neck trauma, suggests cervicocephalic arterial dissection and can be ruled out with head and neck vascular imaging. Testing for autoimmune and hypercoagulable disorders can be considered in young patients with otherwise unexplained stroke. Echocardiography may reveal a PFO, which is present in up to 25% of the general population. In younger patients, a PFO is likely to be causally related to the stroke, although these patients generally are at a low risk of subsequent stroke in the absence of a hypercoagulable disorder. Recently completed clinical trials, however, have failed to show the benefit of percutaneous closure compared with best medical therapy. For further details see MKSAP 17 Cardiovascular Medicine. H

KEY POINTS

- Cardiac rhythm evaluation, including electrocardiography and in-hospital telemetry, is advisable for all patients with ischemic stroke to evaluate for atrial fibrillation. *(Continued)*

KEY POINTS *(continued)*

- Stroke is commonly caused by large artery atherosclerosis, and the risk of stroke recurrence is highest when any associated stenosis is greater than 70%.

Hemorrhagic Stroke H

Subarachnoid Hemorrhage

Nontraumatic SAH presents with the sudden onset of a severe headache, described by patients as the worst headache of their life or "thunderclap" in origin (see Headache and Facial Pain). The most common examination finding in patients with SAH is impairment in consciousness due to elevated intracranial pressure that manifests as a spectrum ranging from mild somnolence to coma or brain death. The initial clinical examination is often summarized by using clinical scales that correlate well with mortality (**Table 17**). Other early localizing findings include subhyaloid hemorrhages on funduscopy (**Figure 14**) and oculomotor nerve palsies with pupillary dilation from direct compression. In patients with elevated intracranial pressure from either

TABLE 17. Clinical Grading Scale for Subarachnoid Hemorrhage

Hunt-Hess Grade	Clinical Description
1	Asymptomatic or mild headache
2	Moderate to severe headache, cranial nerve palsies
3	Somnolence, confusion, or minor focal neurologic deficits
4	Significant impairment in consciousness, significant focal neurologic deficits
5	Coma, posturing

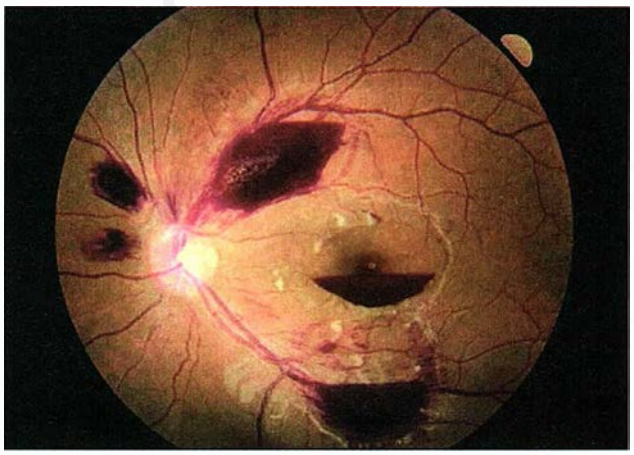

FIGURE 14. Subhyaloid hemorrhages on funduscopic examination suggesting an aneurysmal subarachnoid hemorrhage.

Adapted with permission from Laforest C, Selva D, Crompton J, Leibovitch I. Entopic phenomenon as initial presentation of acute myelogenous leukemia. Ann Intern Med. 2005 Dec 6;143(11):847. [PMID: 16330805]

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cerebral edema or obstructive hydrocephalus, loss of brainstem reflexes, posturing in response to painful stimuli, and impairments in consciousness can occur. Any patient with sudden unexplained coma requires neuroimaging to exclude SAH and hydrocephalus. The principal cause of SAH is a ruptured cerebral saccular aneurysm, which often can be identified by CT angiography. Catheter angiography still is required in all patients to confirm the presence of a symptomatic aneurysm and to detect other pathology that may be beyond the resolution of CT angiography, such as intracranial arterial dissection, intracranial vascular malformation, or small distal aneurysms. Catheter angiography has the additional benefit of being a treatment modality for ruptured intracranial aneurysms (**Figure 15**). Besides intracranial arterial dissections and intracranial vascular malformations, other conditions that can lead to SAH include reversible cerebral vasoconstriction syndrome and dural sinus thrombosis.

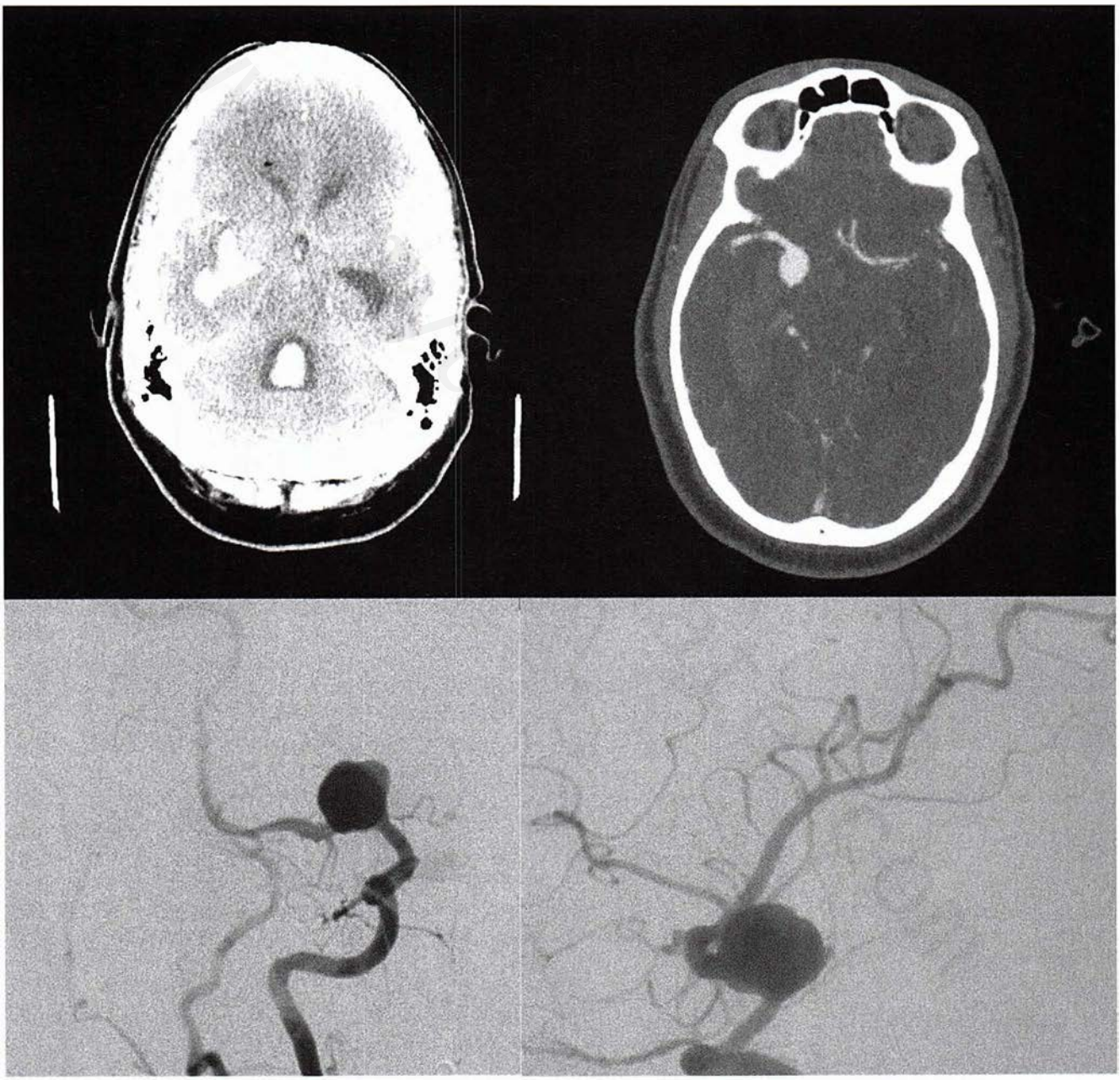

FIGURE 15. Angiograms showing an internal carotid artery aneurysm in a patient with a subarachnoid hemorrhage (SAH). *Top left*, noncontrast head CT scan showing an extensive SAH with intraventricular extension. *Top right*, CT angiogram showing a large right internal carotid artery aneurysm. *Bottom left*, anteroposterior view of a digital subtraction angiogram of the right intracranial internal carotid artery showing the same large aneurysm. *Bottom right*, lateral view of the digital subtraction angiogram showing the same large aneurysm.

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Intracerebral Hemorrhage

CONT.

ICH should be suspected in any patient with focal neurologic symptoms with associated headache, nausea, or impairment in consciousness. Other predictive features of ICH include hypertension at onset, use of oral anticoagulants, and sudden unexplained loss of consciousness. However, no reliable history or examination findings can reliably confirm or rule out hemorrhagic stroke, and the diagnosis of ICH requires a prompt CT scan of the head without contrast, which can readily identify the presence of blood. This procedure can be completed quickly and allows for the identification of associated pathology that can have a significant negative effect on prognosis, including cerebral edema and hydrocephalus. Repeat neuroimaging often is required in patients with ICH to detect hematoma expansion, worsening cerebral edema, or other causes of changes in neurologic status.

The location of the ICH correlates with different underlying pathologies, which can further dictate long-term prognosis and secondary prevention strategies. ICH originating from deep structures of the brain, such as the basal ganglia, pons, and cerebellum, is typically due to hypertension. With adequate control of the blood pressure, patients with deep hemorrhages may still be candidates for anticoagulation, if needed, in the future. Lobar hemorrhages in older patients without hypertension that originate near the cortical surface can be caused by amyloid angiopathy stemming from amyloid-β deposits in distal cerebral arterioles; this process is similar to what occurs in Alzheimer disease, in which amyloid-β deposits are found in the parenchyma. Amyloid angiopathy is associated with a high risk of recurrent lobar hemorrhage, and anticoagulation and statins should be avoided in these patients. Vascular imaging or MRI may be required in patients with atypical presentations or otherwise unexplained ICH. H

KEY POINTS

- The principal cause of subarachnoid hemorrhage is a ruptured cerebral saccular aneurysm, which can be identified by CT angiography; catheter angiography is required for confirmation of the diagnosis and potential treatment of the aneurysm.
- Repeat neuroimaging often is required in patients with intracerebral hemorrhages to detect hematoma expansion, worsening cerebral edema, or other causes of changes in neurologic status.

Acute Stroke Therapy

The initial therapy in acute stroke depends on whether the stroke is ischemic or hemorrhagic. Regardless of stroke etiology, a primary goal of hospitalizing all affected patients is the prevention and treatment of associated medical and neurologic complications.

Ischemic Stroke Treatment

Thrombolysis

The initial goal in the evaluation of a patient with acute ischemic stroke is to establish eligibility for intravenous thrombolysis. The primary determinant of eligibility is the time since stroke onset, which is determined by either self-report or the time when the patient was last witnessed at a prestroke baseline. Thrombolysis in stroke aims to restore cerebral blood flow to the ischemic penumbra where cerebral tissue has sustained ischemic injury but has not yet progressed to infarction. Intravenous thrombolysis in ischemic stroke is indicated within 3 hours of onset in patients with a measurable deficit who do not meet any of the exclusion criteria and is most effective the earlier it is administered. A focused history and physical examination and a fingerstick measurement of blood glucose level can determine any of the exclusion criteria; rapid imaging with noncontrast head CT is required to exclude ICH. Laboratory testing, including a complete blood count, coagulation profile, and basic metabolic profile, also should be obtained in all patients with acute ischemic stroke, although the results are not necessary to initiate thrombolysis unless a suspicion of coagulopathy or thrombocytopenia exists. The optimal time from hospital arrival to treatment with thrombolysis is 60 minutes or less, which is considered a marker of high-quality care. Additional testing is not indicated in most patients because it leads to unnecessary delays in treatment. Vascular imaging in the acute ischemic stroke setting also is not necessary and can lead to treatment time delays.

Treatment with intravenous thrombolysis between 3 to 4.5 hours from stroke onset can be considered in a select group of patients who meet strict inclusion/exclusion criteria, although this therapy lacks FDA approval. The efficacy of endovascular stroke therapy in lieu of, or after, intravenous thrombolysis has not been established by several recently completed clinical trials. Endovascular acute stroke therapy with intra-arterial thrombolytic or thrombectomy devices can be considered on a case by case basis for patients within 6 hours of stroke onset who are otherwise ineligible for intravenous thrombolysis. A proposed pathway for the evaluation and treatment of acute ischemic stroke is provided in **Figure 16**.

The main complication from intravenous thrombolysis is symptomatic ICH, defined as intracranial bleeding with an associated decline in neurologic function detected on neurologic examination that cannot be ascribed to other causes. It occurs in approximately 6% of treated patients and has an associated 50% mortality. Headache, nausea, or worsening of neurologic examination findings are signs of intracranial bleeding and should prompt stopping the infusion and repeating the head CT. The main risk factors for symptomatic ICH are protocol violations, notably treatment beyond the time window and blood pressure above recommended targets. Blood pressure should be less than 185/110 mm Hg before thrombolysis, which can be achieved with intravenous labetalol or nicardipine, according to American Heart Association guidelines.

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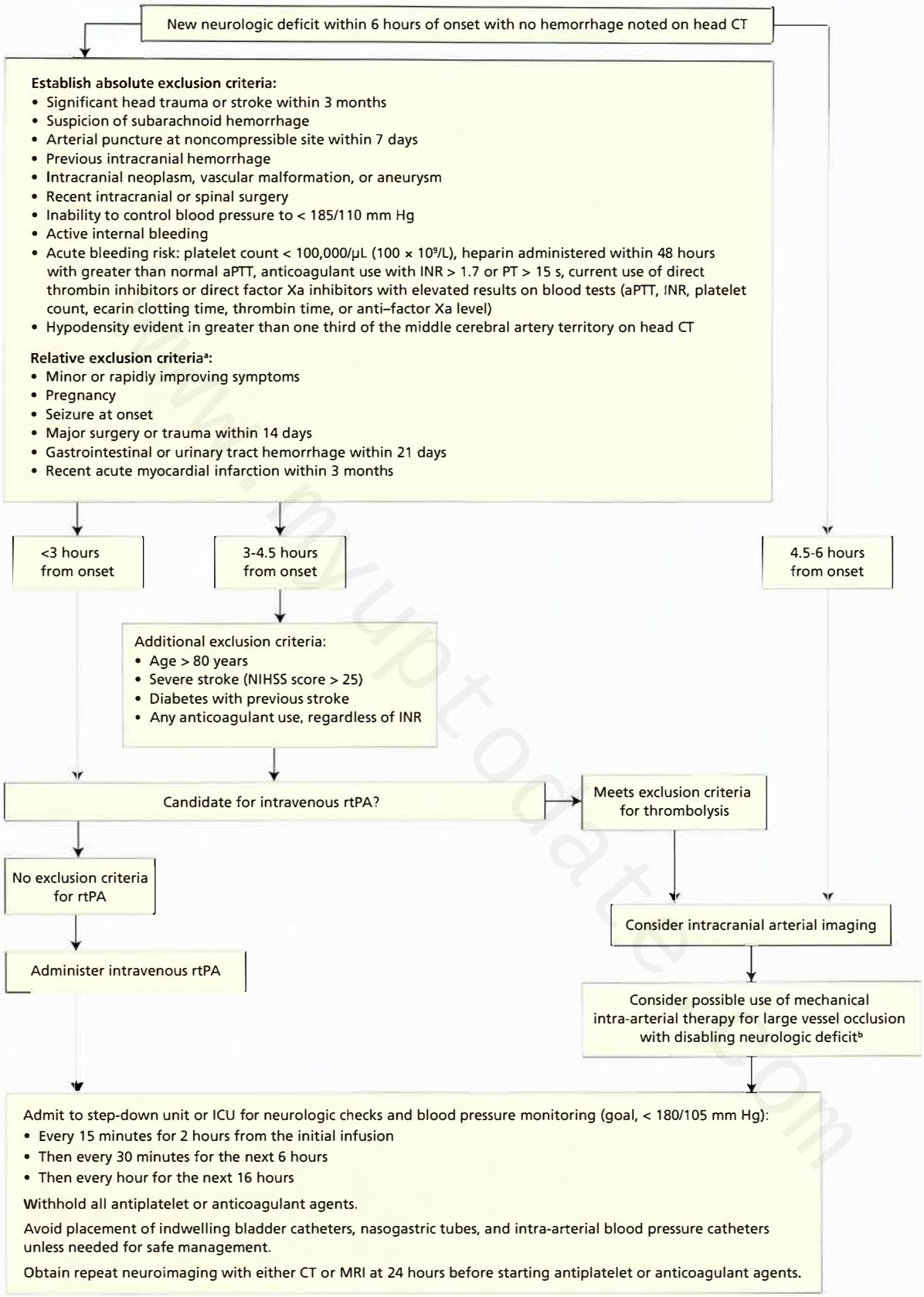

FIGURE 16. Proposed pathway for the evaluation and treatment of an acute stroke within 6 hours of onset. aPTT = partial thromboplastin time, activated; NIHSS = National Institutes of Health Stroke Scale; PT = prothrombin time; rtPA = recombinant tissue plasminogen activator.

[a]rtPA can be considered in patients with one or more relative exclusion criteria after consideration of neurologic deficits and risks versus benefits.

[b]Available evidence for the benefit of mechanical intra-arterial therapy is limited, and its appropriate use remains to be defined.

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After the initiation of intravenous thrombolysis using recombinant tissue plasminogen activator, adherence to strict monitoring protocols regarding vital signs and neurologic examination findings is required to achieve a target blood pressure less than 180/105 mm Hg and to detect signs of symptomatic ICH. Other precautions after intravenous thrombolysis include withholding all antithrombotic agents until a repeat head CT or MRI performed 24 hours after the procedure excludes ICH and monitoring for angioedema.

Antiplatelet, Anticoagulant, and Other Agents for Acute Ischemic Stroke Treatment

Most patients with ischemic stroke will arrive beyond the stated windows for intravenous thrombolysis. For most of these patients, aspirin is appropriate, but only after a dysphagia evaluation documenting the ability to safely swallow. In those unable to swallow, a rectal formulation of aspirin is available. Aspirin taken within 48 hours of ischemic stroke onset modestly reduces the risk of recurrent ischemic stroke at 2 weeks without significantly increasing the risk of intracerebral hemorrhage. No acute ischemic stroke trials have tested monotherapy with clopidogrel or the combination of aspirin and dipyridamole. However, in patients with a high-risk TIA ($ABCD^2$ score ≥ 4) or minor ischemic stroke (National Institute of Health Stroke Scale score ≤ 3), a 21-day course of combination aspirin and clopidogrel followed by clopidogrel monotherapy for a total of 90 days reduced the risk of subsequent stroke when administered within 24 hours of onset compared with aspirin monotherapy. No increase in the risk of ICH or differences in efficacy by subgroups was reported. Heparinoids do not reduce the risk of recurrent stroke in the acute setting for either cardioembolic or noncardioembolic stroke. Acute intravenous heparin occasionally is used in patients with rare causes of stroke, such as dissection or a hypercoagulable state, or in patients with mechanical cardiac valves if the risk of hemorrhage into the infarct is low.

Other medication classes have not been extensively studied in the acute setting. To date, no studies have been published about statins administered in the acute stroke setting. A recent trial of acute blood pressure lowering with candesartan within 36 hours showed no reduction in cardiac events or mortality but a trend toward worsening of neurologic deficits. Blood pressure lowering in patients who do not receive intravenous thrombolysis is only recommended if the blood pressure is greater than 220/120 mm Hg or if a high risk or evidence of other end-organ damage exists.

Antithrombotic Therapy After Ischemic Stroke

The management of antithrombotic agents after ischemic stroke and TIA differs from that in other ischemic atherosclerotic diseases because of the risk of hemorrhagic stroke. In patients with stroke and atrial fibrillation, anticoagulation can be started before hospital discharge if the risk of hemorrhage into the bed of the infarct is low, such as in patients with infarcts but no petechial hemorrhage, as determined by neuroimaging, or with involvement of less than one third of the middle cerebral artery distribution. For further discussion of anticoagulation in atrial fibrillation, see MKSAP 17 Cardiovascular Medicine. Warfarin is not recommended for patients with symptomatic intracranial atherosclerosis unless another high-risk condition also is identified because this drug is associated with increased mortality compared with antiplatelet agents. In all other noncardioembolic ischemic strokes, warfarin and antiplatelet agents are equivalent in terms of efficacy, although antiplatelet agents often are considered first-line agents because of ease of use.

In the nonacute setting, the combination of aspirin and clopidogrel for noncardioembolic stroke increases the risk of mortality and hemorrhagic stroke without significantly reducing the risk of ischemic stroke, compared with single-agent therapy. The combination of aspirin and dipyridamole twice daily modestly reduces the risk of recurrent ischemic stroke when compared with aspirin monotherapy, but in a large ischemic stroke secondary prevention trial, the combination of aspirin and dipyridamole was equivalent to clopidogrel monotherapy. The choice of antiplatelet agents for secondary stroke prevention is often driven by patient preference, including cost, and by risk for other medical comorbidities, given the small absolute risk differences between each agent. For noncardioembolic stroke, low-dose (81 mg/d) aspirin monotherapy is often first-line therapy for patients not previously taking antiplatelet agents. Clopidogrel or aspirin plus dipyridamole can be considered in patients who have a recurrent ischemic stroke, despite adequate control of other stroke risk factors, while taking aspirin monotherapy. The effectiveness of newer antiplatelet agents or platelet resistance assays has not been established for stroke. H

KEY POINTS

- Intravenous thrombolysis is indicated within 3 hours (and can be considered within 3 to 4.5 hours) of onset of ischemic stroke in patients with a measurable deficit who meet inclusion/exclusion criteria.
- After initiation of intravenous thrombolysis, adherence to strict monitoring protocols regarding vital signs and neurologic examination findings is required to achieve a target blood pressure less than 180/105 mm Hg and to detect signs of symptomatic intracranial hemorrhage.
- For most patients with ischemic stroke who arrive at the hospital beyond the treatment window for intravenous thrombolysis, oral or rectal aspirin is usually appropriate treatment; aspirin taken within 48 hours of ischemic stroke onset modestly reduces the risk of recurrent stroke at 2 weeks without significantly increasing the risk of hemorrhage.

Hemorrhagic Stroke Treatment

H

Intracerebral Hemorrhage Treatment

The mainstay of therapy for acute ICH is treatment of hematoma-associated neurologic complications. Antiplatelet and

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H CONT.

antithrombotic agents should be discontinued. Given the small risk of hemorrhage with selective serotonin reuptake inhibitors, discontinuation of these agents should also be considered. In patients with hydrocephalus, external shunting of cerebrospinal fluid may be required when clinical evidence of elevated intracranial pressure is detected; osmotherapy with mannitol or hypertonic saline can be considered in patients with elevated intracranial pressure as salvage therapy. Surgical evacuation of the hematoma should be considered in patients with a cerebellar ICH with a size greater than 3 cm, particularly if evidence of neurologic worsening or brainstem compression is present. Surgical decompression for other locations can be considered on a case-by-case basis.

An additional goal of therapy in patients with ICH has been to prevent expansion of the hematoma by lowering blood pressure or using hemostatic agents. Recombinant factor VIIa therapy, however, was not associated with improved clinical outcomes in a randomized clinical trial of spontaneous ICH. In patients with a vitamin K antagonist–associated ICH, fresh-frozen plasma or prothrombin complex concentrates are recommended, as is administration of intravenous vitamin K. The appropriate treatment of ICH related to direct thrombin inhibitors or factor Xa inhibitors and the effectiveness of using platelet transfusions in antiplatelet-associated ICH have not been well established. For further details see MKSAP 17 Hematology and Oncology. In patients without elevated intracranial pressure whose systolic blood pressure is greater than 180 mm Hg or mean arterial pressure is greater than 130 mm Hg at the time of their ICH, treatment with intravenous medications can be initiated, with a target blood pressure of 160/90 mm Hg or mean arterial pressure of 110 mm Hg. Further reductions in blood pressure also may be safe. A recent trial showed that acute lowering of systolic blood pressure to less than 140 mm Hg (compared with <180 mm Hg) within 6 hours was associated with a trend to reduction of disability, without any change in adverse events or mortality. Medications that can be titrated easily, such as nicardipine or labetalol, are preferred; nitrates should be avoided because of the potential for increasing intracranial pressure.

Subarachnoid Hemorrhage Treatment

Neurologic complications in aneurysmal SAH differ according to whether they occur early (within 48 hours) or later (typically, 5-10 days) in the clinical course of the hemorrhage. In the early phase, patients often have impairments in consciousness due to hydrocephalus and require external cerebrospinal fluid shunting to alleviate and subsequently monitor intracranial pressure. A significant cause of morbidity and mortality during this phase is aneurysmal rebleeding, and thus early vascular imaging is required in all patients with SAH to diagnose any ruptured cerebral artery aneurysm. Treatment with either endovascular coiling or clipping (performed during a craniotomy) should begin early; until the aneurysm is secured, the blood pressure should be less than 140/80 mm Hg to prevent rebleeding. Other sources of early neurologic complications include global cerebral edema and seizures; seizure prophylaxis is common in patients with SAH. Delayed cerebral ischemia due to arterial vasospasm is a significant source of later neurologic morbidity and can present with nonspecific examination findings. The patients at highest risk for developing vasospasm with subsequent delayed cerebral ischemia are those with the largest burden of blood in the basal cisterns on neuroimaging. These same patients generally have impairments in consciousness, which makes detection of subtle examination findings challenging. Although serial daily screening to identify vasospasm typically is performed with noninvasive transcranial ultrasonography during the first 2 weeks after SAH onset, CT angiography is more sensitive in detecting subtle vasospasms that may be treated with either the initiation of vasopressors to augment the blood pressure or ultimately endovascular treatment in more refractory disease. CT angiography has the additional benefit of imaging the ventricles, which will allow for detecting a change in ventricular size. Oral nimodipine improves neurologic outcomes in patients with aneurysmal SAH and is recommended in all patients with SAH for the first 21 days or until hospital discharge, whichever comes first. Cerebral vasospasm is often managed initially by inducing hypertension to prevent progression to cerebral ischemia, but only after the aneurysm has first been treated. However, clinical trial data supporting a particular target blood pressure are scant, and the American Heart Association has made no specific recommendation. In patients with clinically significant cerebral vasospasm, angiography may be necessary to confirm its severity and allow for potential therapeutic intervention.

Associated medical complications are a significant source of morbidity and mortality in SAH. Acute myocardial infarction due to contractile band necrosis in the setting of a significant sympathetic surge can occur early in the course of high-grade SAH (see Table 17) and can lead to significant reductions in systolic function, hypotension, and pulmonary edema. Respiratory failure requiring mechanical ventilation because of impaired consciousness or hypoxemia from either pneumonia or pulmonary edema is also common. Other medical complications include cerebral salt wasting syndrome, the syndrome of inappropriate antidiuretic hormone secretion, cardiac arrhythmias, and infections from pulmonary, urinary, and central venous catheters or from cerebrospinal fluid shunting sources. Given the associated level of monitoring and supportive care required for neurologic and medical complications of SAH, affected patients should be cared for in a neurologic ICU, if available. H

KEY POINTS

- Surgical evacuation of the hematoma should be considered in patients with a cerebellar intracerebral hemorrhage whose size is greater than 3 cm, particularly if evidence of neurologic worsening or brainstem compression is present.

(Continued)

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KEY POINTS *(continued)*

- Early vascular imaging is required in all patients with subarachnoid hemorrhage to evaluate for any ruptured cerebral artery aneurysm; treatment of the aneurysm with either endovascular coiling or clipping should begin early, with the blood pressure maintained at less than 140/80 mm Hg to prevent rebleeding.

Stroke Prevention

Table 18 lists the risk factors for stroke.

Primary Stroke Prevention

For a discussion of management of vascular disease risk factors and antiplatelet agents used in primary prevention of stroke, see MKSAP 17 Cardiovascular Medicine.

The approach to asymptomatic extracranial internal carotid artery stenosis has changed because of improvements in optimal medical therapy that have resulted in stroke rates close to 1% per year (compared with the previous rate of 2% per year). This lower rate seems driven by lipid-lowering therapy with statins. Aggressive risk factor control, with optimal medical therapy and comprehensive lifestyle modifications in diet, exercise habits, and tobacco use (among others), is required for all patients. Revascularization with either stenting or endarterectomy can be considered in patients with a greater than 80% stenosis and low cardiovascular risk, as long as the operative complication rate is less than 3%.

Unruptured cerebral artery aneurysms are commonly found in asymptomatic patients. A fraction of these patients have symptoms from compression of adjacent structures, such as pupillary enlargement from compression of the oculomotor nerve by a posterior communicating artery aneurysm or visual loss from compression of the optic nerve by a cavernous carotid artery aneurysm. Size, location, and a history of ruptured cerebral artery aneurysms in other locations are the principal determinants of treatment. Rupture rates from asymptomatic aneurysms without a prior history of SAH are outlined in **Table 19**. Surgical treatment with clipping or endovascular coiling can be considered in patients with aneurysms of 7 mm or greater in the posterior circulation (posterior communicating and basilar arteries) or 12 mm or greater in the anterior circulation. Regardless of aneurysmal size and location, all patients with unruptured cerebral artery aneurysms benefit from tobacco cessation and blood pressure control.

KEY POINTS

- Most patients with asymptomatic extracranial internal carotid artery stenosis should be treated with aggressive risk factor control and not stenting or elective endarterectomy, which should only be considered in patients with a greater than 80% stenosis and low cardiovascular risk (as long as the operative complication rate is less than 3%). **HVC**
- In primary stroke prevention, all patients with unruptured cerebral artery aneurysms benefit from tobacco cessation and blood pressure control.

Secondary Stroke Prevention

Lifestyle and Medical Management

The treatment of modifiable vascular disease risk factors can lead to a significant decrease in the risk of recurrent

TABLE 18. Common Risk Factors for Ischemic and Hemorrhagic Stroke

	Ischemic Stroke/TIA	Intracerebral Hemorrhage	Subarachnoid Hemorrhage
Shared Risk Factors			
	Hypertension	Hypertension	Hypertension
	Cocaine abuse	Cocaine abuse	Cocaine abuse
	Tobacco use	Tobacco use	Tobacco use
		Arteriovenous malformation	Arteriovenous malformation
Other Risk Factors			
	Diabetes mellitus	Amyloid angiopathy	Intracranial artery dissection
	Atrial fibrillation	Decreased LDL cholesterol level	Polycystic kidney disease
	Low left ventricular ejection fraction and intracardiac thrombus	Elevated HDL cholesterol level	
	Cervicocephalic arterial dissection	Anticoagulant agent use	
	Aortic arch atheromatous disease	Antiplatelet agent use	
	Cardiac valve vegetations	Selective serotonin reuptake inhibitor use	
	Patent foramen ovale		

TIA = transient ischemic attack.

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TABLE 19. Rupture Rates Over 5 Years of Unruptured Intracranial Artery Aneurysms

Position	Size (mm)	Rupture Rate (%)
Anterior circulation aneurysm (internal carotid, anterior communicating, middle cerebral arteries)	<7	0
	7-12	2.6
	13-24	14.5
	>25	40
Posterior circulation aneurysm (posterior communicating, basilar arteries)	<7	2.5
	7-12	14.5
	13-24	18.4
	>25	50

stroke. Hypertension is a common risk factor for recurrence of all stroke subtypes, and lowering of blood pressure in patients with stroke is associated with a significant reduction in the risk for recurrence. However, the optimal goal for secondary prevention of stroke is less clear. The Eighth Joint National Committee (JNC 8) recommendations and treatment guidelines for the prevention of secondary stroke recommend antihypertensive therapy for stable patients with a sustained blood pressure of 140/90 mm Hg or greater, including those older than 60 years with preexisting cardiovascular disease. However, the benefit of initiating antihypertensive therapy in patients with stroke who have a blood pressure less than 140/90 mm Hg is uncertain. There is evidence, however, that patients with a recent lacunar infarct may benefit from a systolic blood pressure goal of less than 130 mm Hg. No specific recommendations exist regarding preferred pharmacologic agents for secondary stroke prevention. Therefore, the choice of the most appropriate antihypertensive agent is often driven by a consideration of comorbid medical conditions.

All patients with stroke require comprehensive lifestyle changes, including improving physical activity and diet and stopping tobacco use. See MKSAP 17 Nephrology for further discussion of management of hypertension, MKSAP 17 Endocrinology and Metabolism for management of type 2 diabetes mellitus, and MKSAP 17 General Internal Medicine for management of dyslipidemia. For secondary stroke prevention, statins are recommended for patients with a plasma LDL cholesterol level of 100 mg/dL (2.59 mmol/L) or higher once the ability to safely swallow has been established. Statins have been associated with an increased risk of hemorrhagic stroke and may be contraindicated in patients with a lobar ICH due to amyloid angiopathy. However, they most likely are safe in those with a deep ICH. Regardless of ICH subtype, statins are indicated for patients at high risk for ischemic events.

Surgery for Secondary Ischemic Stroke Prevention

The stroke cause with the highest risk of recurrence is symptomatic extracranial internal carotid artery stenosis, with a 26% risk of recurrent stroke at 2 years and a close to 1% per day increased risk of recurrent stroke in the first 2 weeks. Carotid revascularization, preferably within 14 days from the index event, is indicated for nondisabling strokes or TIAs in patients with symptomatic extracranial internal carotid artery stenosis in the range of 70% to 99% and can be performed with endarterectomy or angioplasty-stenting. The choice of one surgical approach is often dictated by the risk of perioperative complications or anatomic considerations. Angioplasty-stenting is often performed in patients at high risk for periprocedural cardiopulmonary complications and in those with restenosis and previous radiation therapy. In clinical trials, periprocedural stroke is reported to be higher with angioplasty-stenting than with endarterectomy, but myocardial infarction is more likely with endarterectomy. In patients with complete occlusion, none of the surgical options (carotid stenting, endarterectomy, or external carotid to internal carotid bypass) reduces the risk of recurrent stroke, and best medical therapy (including antiplatelet agents and statins) is advised. Using angioplasty-stenting also is not recommended for patients with symptomatic intracranial artery stenosis because of the high risk of periprocedural stroke and the high efficacy of optimal medical therapy.

Using surgical approaches to treat causes of cardioembolic stroke is an evolving field. For further discussion of surgical approaches to cardiac disease for stroke prevention, see MKSAP 17 Cardiovascular Medicine.

KEY POINTS

- For secondary stroke prevention, statins are recommended for patients with a plasma LDL cholesterol level of 100 mg/dL (2.59 mmol/L) or higher once the ability to safely swallow has been established.
- In patients with nondisabling strokes or transient ischemic attacks who have symptomatic extracranial internal carotid artery stenosis, carotid revascularization, preferably within 14 days from the index event, is indicated for secondary stroke prevention.

Prognosis and Recovery

Neurologic Complications

Neurologic worsening can occur in patients with ischemic stroke during hospitalization as a result of stroke recurrence, hemorrhage into the area of infarction, seizures, or cerebral edema. Medical complications, particularly infections, can cause worsening of the neurologic deficit. Any patient with a change noted during neurologic examination requires repeat neuroimaging to establish any new structural lesions. Patients with a middle cerebral artery infarction involving greater than 50% of the arterial territory are at high risk for malignant cerebral infarction with associated edema and cerebral herniation. Hemicraniectomy is associated with a significant reduction in mortality and severe disability (from 76% to 25% in pooled data from three clinical trials) compared with best medical therapy

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CONT and also should be considered early in patients with malignant cerebral infarction if they exhibit impaired alertness or have at least one pupil reactive to light.

KEY POINT

- Patients with a middle cerebral artery infarction involving greater than 50% of the arterial territory are at high risk for malignant cerebral infarction with associated edema and cerebral herniation; hemicraniectomy, which is associated with a significant reduction in mortality and severe disability compared with best medical therapy, can be considered in these patients.

Medical Complications and Stroke Units

Early mobilization and rehabilitation to a level the patient can tolerate are indicated for all survivors of stroke to improve recovery and mitigate medical complications. These patients are prone to urinary tract infections from indwelling catheters, aspiration pneumonia from dysphagia, and deep venous thrombosis (DVT). The principal cause of stroke-related mortality, these complications can be ameliorated by admission to a stroke unit, defined as (ideally) a discrete ward where a multidisciplinary team with expertise in stroke cares for these patients. Early mobilization appears to be a significant determinant of the success of stroke units, although adherence to clinical care protocols for dysphagia, DVT, and indwelling urinary catheters also are instrumental. Several bedside dysphagia screening protocols are available and should be performed before any oral intake; a formal evaluation with a speech therapist is often required. Aspiration pneumonia can be further prevented by maintaining the head of the bed at 30 degrees and instituting oral hygiene protocols. DVT prevention is required for all hospitalized stroke patients unless they are fully ambulatory. Subcutaneous unfractionated or low-molecular-weight heparin should be started in all patients with impaired mobility by hospital day 1 for ischemic stroke and by hospital day 4 (if no active bleeding is documented) in hemorrhagic stroke. For those patients at high risk for hemorrhagic complications from pharmacologic therapy, pneumatic compression stockings should be used. For further details, see MKSAP 17 Hematology and Oncology. Unless required for other reasons, indwelling urinary catheters should be removed. H

KEY POINT

- Early mobilization is a significant determinant of the success of stroke units, although adherence to clinical care protocols for dysphagia, deep venous thrombosis, and indwelling urinary catheters also is instrumental.

Long-Term Prognosis and Recovery

The main predictor of stroke recovery is the severity of the neurologic deficit. Long-term follow-up evaluation shows that patients with stroke are at high risk for additional complications, including fatigue, depression, and recurrent cardiovascular disease. Survivors of stroke also are at high risk for having or developing undiagnosed obstructive sleep apnea, which can further complicate hypertension management and is a common cause of fatigue; polysomnography is helpful in diagnosis. Depression is highly prevalent in the acute and chronic setting after stroke and is one of the strongest modifiable predictors of stroke recovery.

Cognitive Impairment

Definitions, Description, and Evaluation

Cognitive impairment in older patients spans a continuum, from normal aging to dementia. Neurocognitive disorders are defined as conditions in which an acquired impairment of cognitive function occurs, with coexistent decline in function involving at least one of the following neuropsychological domains: memory/learning, complex attention, executive function, perceptual or motor abilities, language, or social cognition. Dementia is a syndrome characterized by a gradual and progressive decline in previously acquired cognitive function that results in impaired social or occupational functioning and ultimately leads to loss of independence. The diagnosis of dementia requires impairment of at least two of the previously listed neuropsychological domains. Although the incidence of dementia increases with age, this disorder is not an inevitable consequence of normal aging. Subtle cognitive decline with normal aging is common, but not universal, and should not affect independence in daily functioning. Age-associated cognitive decline is most notable for some slowing of processing speed and reaction time. Cognitive flexibility and multitasking abilities may decline with aging. Learning, or the acquisition of new information, decreases with age, but delayed recall remains relatively intact. Language comprehension and vocabulary (semantic memory) are preserved in normal aging.

Mild Cognitive Impairment

The available research suggests that a phase of cognitive impairment precedes the development of dementia. This intermediate stage between normal aging and dementia has been labeled mild cognitive impairment (MCI). In clinical practice, overlap exists between the stages, and the revised criteria for MCI further blur the line between MCI and early or mild dementia. The diagnosis of MCI is made on the basis of clinical judgment and requires the following four features: (1) subjective reports (from the patient or a reliable informant) of problems with memory, such as forgetfulness, or other cognitive difficulties; (2) objective impairment on cognitive testing in one or more cognitive domains; (3) diminished independence in daily function, with no or minimal problems with complex functional tasks, such as shopping or paying bills; and (4) no significant impairment in occupational or social functioning. The presence of significant functional deficit is what distinguishes dementia from MCI. MCI can be further

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subtyped as amnestic MCI or nonamnestic MCI, depending on the presence or absence of memory deficits and the number of cognitive domains that are affected (that is, a single domain versus multiple domains).

Patients with MCI have a significantly increased likelihood of conversion to dementia at a rate of 10% to 15% per year, in contrast to cognitively normal age-matched controls, who develop dementia at a rate of 1% to 2% per year. Within 6 years from the time of MCI diagnosis, approximately 80% of patients will progress to dementia. Although numerous factors have been studied, and some even have been associated with a higher risk of progression to dementia—such as baseline functional impairment, results of fluorodeoxyglucose-PET brain imaging, and the apolipoprotein E (*APOE ε4*) genotype—no reliable clinical markers exist that can predict the clinical likelihood that an individual patient with MCI will develop dementia. Similarly, no treatments or interventions have been shown to delay the onset of Alzheimer disease or other types of dementia in patients with MCI.

Neuropathologic studies have shown that most patients with amnestic MCI have pathologic findings of Alzheimer disease. The prognostic significance of nonamnestic MCI is less known. Other degenerative pathologies (such as Lewy body disease) and nondegenerative pathologies (such as vascular disease) may be the cause of MCI in a subset of patients. MCI associated with underlying Lewy body disease usually is characterized by diminished executive functioning, impairment of visuospatial abilities, or both. MCI due to vascular disease most often has a cognitive profile of impaired executive function or processing speed, with spared verbal memory. Other nondegenerative, and potentially reversible, diseases also may cause MCI, including metabolic disorders (such as hypothyroidism), vitamin B_{12} deficiency, and depression. Large-scale neuropathologic studies of MCI are not yet available to completely comprehend the full pathologic heterogeneity of the disease.

KEY POINTS

- Patients with mild cognitive impairment have a significantly increased likelihood of conversion to dementia at a rate of 10% to 15% per year.

HVC

- No reliable clinical markers or diagnostic tests can predict the likelihood that an individual patient with mild cognitive impairment will develop dementia, and no intervention has been shown to delay the onset of dementia in such a patient.

Dementia

In contrast to MCI, dementia is a progressive deterioration of cognitive function severe enough to impair occupational or social functioning. An estimated 35 million persons live with dementia worldwide, and that number is expected to triple by 2050 as life expectancy increases. Alzheimer disease is the most common type of dementia (60%-80%).

Advancing age is the major risk factor for dementia. For every 5 years after age 65 years, the prevalence of Alzheimer disease doubles. Vascular risk factors for MCI and dementia include cardiac disease, diabetes mellitus, hypertension, obesity, and tobacco use. The presence of the *APOE ε4* allele, a history of head injury, and mid- and late-life depression are additional risk factors for Alzheimer disease. Higher educational and occupational advancement are associated with a reduced risk or delayed onset of dementia.

Onset of dementia reduces one's life span. Median survival time from age of onset of dementia ranges from 3 to 12 years, with longer durations associated with earlier age of onset. Although significant interindividual variability in survival after the onset of dementia exists, disease duration tends to vary according to the underlying pathology. Persons with Alzheimer disease and dementia with Lewy bodies survive an average of 8 years after diagnosis, whereas persons with frontotemporal dementia survive an average of 6 years and persons with dementia associated with underlying vascular disease survive an average of 4 years.

Evaluation of the Patient with Suspected Cognitive Impairment

For older patients with no obvious cognitive symptoms, insufficient evidence supports routine cognitive testing. However, the following situations should prompt testing for dementia or cognitive impairment in persons age 65 years and older:

- Patients with cognitive symptoms, with or without functional impairment
- Patients who routinely miss scheduled appointments or arrive on the wrong date or at the wrong time
- Patients with inability to accurately follow instructions
- Patients with unexplained weight loss or failure to thrive
- Patients with new onset or worsening depression or anxiety, with or without cognitive symptoms
- Report from a witness, confirmed or unconfirmed by the patient, of a change in cognition, poor or decreased judgment, loss of initiative, or changes in behavior
- Patients with known risk factors for cognitive impairment (such as HIV infection or a personal history of alcohol abuse)

A careful history should focus on the evolution of symptoms, rate of progression, and functional impact on activities of daily living and work performance, if applicable. Patients with even mild restrictions in the ability to use a telephone, handle finances, use public or personal transportation, or take medications appropriately have a higher risk of progressing to dementia. Vascular risk factors, which increase the risk of cerebrovascular events, should be identified. Information on medication use and substance abuse should be elicited, and screening for depression is imperative. Multiple relationships between depression and cognitive impairment have been reported in the literature: (1) late-life depression may lead to

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prodromal Alzheimer disease; (2) depression may be a risk factor for future development of cognitive impairment, dementia, and Alzheimer disease (odds ratio of 1.85 for all-cause dementia); (3) cerebrovascular disease can precipitate late-life depression; and (4) cognitive impairment itself can lead to depression. More than half of patients with late-life major depression exhibit clinically significant cognitive impairment, most frequently affecting processing speed, executive function, and visuospatial ability. A history should be obtained from the patient and someone well acquainted with the patient who can provide information on current daily functioning relative to premorbid functioning. A general physical examination and a thorough neurologic examination should be performed, with motor and gait portions of the examination that evaluate for signs of parkinsonism emphasized. A detailed family history should be obtained, including any history of cognitive impairment or dementia, significant psychiatric illness in later life, motoneuron disease, or parkinsonism, because the presence of these disorders may suggest a familial neurodegenerative disease.

Although routine cognitive screening has not been recommended by the U.S. Preventive Services Task Force, the annual wellness visit covered by Medicare requires an assessment to detect cognitive impairment. Screening tests also are useful to detect cognitive impairment in patients who report cognitive difficulties. Performance on these tests can serve as a baseline and be used to monitor disease progression. Many instruments have been developed to quickly screen patients for cognitive impairment; common limitations are their low sensitivity to diagnose mild impairment, lack of validation in the primary care setting, cultural or education bias, and low reliability in distinguishing between different underlying causes. Although the Mini-Mental State Examination, on which a score less than 22 indicates dementia, has been the most extensively studied screening instrument, it is now proprietary with a cost per use. Additionally, this instrument has several weaknesses, such as a lack of sensitivity in identifying early signs of dementia and the absence of tasks that test executive function. Among the free tools that are available for clinical use, the Montreal Cognitive Assessment and "Mini-Cog" test have been validated in primary care populations; these instruments screen for impairments of executive function. Self-administered instruments, such as the Self-Administered Gerocognitive Examination and Test Your Memory examination, have been validated in memory-clinic populations to detect mild cognitive impairment and early dementia. In patients with a high intelligence quotient and normal performance on screening tests, further evaluation should be considered. Formal neuropsychological testing provides a more thorough assessment of cognitive function but is more time consuming and costly. It can provide meaningful information about the pattern and extent of cognitive impairment but should not be used in isolation to make a clinical diagnosis. Detailed neuropsychological testing is especially useful for the following patients:

1. Those with milder cognitive symptoms to determine if the cognitive difficulties are within the realm of normal age-associated cognitive decline versus MCI
2. Those with definite dementia, diagnosed on the basis of clinical impression and results of screening cognitive tests, who have clinical features overlapping two or more underlying pathologic processes
3. Those with cognitive symptoms whose clinical picture is confounded by significant depression.

Impaired performance on neuropsychological testing is determined by a patient's performance compared with healthy age- and education-matched controls. However, without premorbid results, this testing can only estimate the patient's premorbid baseline to determine cognitive areas of presumed decline; it can serve as a baseline with which to compare future test results. For patients with milder cognitive symptoms in whom the initial evaluation does not clearly indicate an early dementing process, longitudinal testing can be of value.

To identify reversible causes of cognitive decline, laboratory tests, such as a complete blood count, liver chemistry studies, thyroid function tests, and measurement of serum electrolyte, blood urea nitrogen, creatinine, and vitamin B_{12} levels, should be performed. A syphilis screening test should be performed in high-risk populations. Additional testing, such as evaluating for autoimmune disease, can be considered if relevant symptoms are present. In at-risk populations, HIV serologies should be performed. Once the presence of dementia has been confirmed, a structural neuroimaging study (MRI or CT scan) should be obtained to evaluate for nondegenerative causes that would alter management, such as cerebrovascular disease, neoplasm, subdural hematoma, or hydrocephalus. MRI and CT imaging provide similar information; however, MRI is more sensitive for detecting inflammation, infection, acute stroke, tumor, posterior fossa lesion, and characteristic imaging findings of Creutzfeldt-Jakob disease. The clinical presentation, examination findings, and differential considerations should determine the imaging study performed. Cerebrospinal fluid analysis is not part of the routine evaluation of cognitive impairment but should be considered in the following clinical situations:

- Rapidly progressive dementia
- Age of onset less than 60 years
- Malignancy or paraneoplastic disorders
- Suspicion of acute or subacute infection or of an immunosuppressed or immunodeficient state
- Positive syphilis or Lyme serology
- Systemic autoimmune disease or suspected CNS inflammatory disorder

Early-onset or rapidly progressive cognitive decline requires a more comprehensive and expedited evaluation. Brain MRI and cerebrospinal fluid (CSF) analysis should be

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performed promptly, and additional serologic tests and electroencephalography can be considered. The prion disorder Creutzfeldt-Jakob disease is the most common cause of rapidly progressive dementia, with a disease duration of less than 1 year until death. MRI can be diagnostic when diffusion-weighted or fluid-attenuated inversion recovery hyperintensities involving the cortex, caudate and putamen, or thalamus are seen. CSF analysis can establish the presence of a 14-3-3 protein, and electroencephalography may reveal characteristics triphasic spikes. Brain biopsy is sometimes necessary to confirm the diagnosis.

KEY POINTS

HVC
- For older patients with suspected cognitive impairment who are asymptomatic, insufficient evidence supports routine cognitive testing.
- Screening for depression is imperative in the evaluation of cognitive decline.
- Once the presence of dementia has been confirmed, a structural neuroimaging study, such as an MRI or CT scan, should be obtained to evaluate for cerebrovascular disease, neoplasm, subdural hematoma, or hydrocephalus.

Neurodegenerative Disorders

Alzheimer Disease

Alzheimer disease can be divided into three phases along a single continuum: an asymptomatic preclinical phase, a predementia phase (MCI due to Alzheimer disease), and a dementia phase.

Clinical Features

Classically, Alzheimer disease presents with the insidious development of recent memory loss. Forgetfulness of the details of recent events predominates early in the disease course. Problems with learning and retaining new information without benefit from cueing are the hallmark cognitive deficits. Aphasia is frequently seen early and is initially characterized by word-finding difficulties. Visuospatial dysfunction also is common and often presents as episodes of becoming lost in familiar environments (geographic disorientation) or problems in assembling objects (constructional apraxia). Executive dysfunction may manifest as impairment of problem-solving abilities, judgment, and multitasking. Atypical presentations of Alzheimer disease include early visuospatial or executive dysfunction, with relatively preserved memory.

Neurochemistry, Pathology, and Biomarkers

The pathogenesis of Alzheimer disease begins decades before the onset of clinical symptoms. Loss of choline acetyltransferase, the enzyme that synthesizes acetylcholine, results in an acetylcholine deficit, which has been shown to correlate with the degree of cognitive impairment. Alzheimer disease has the following pathologic hallmarks:

1. The accumulation of neuritic plaques composed of amyloid β protein
2. The accumulation of abnormally phosphorylated tau proteins (proteins normally present in neurons that stabilize intracellular microtubules) as neurofibrillary tangles
3. Prominent neuronal loss resulting in atrophy

Biomarkers reflecting the pathophysiology of Alzheimer disease have been incorporated into recently revised diagnostic criteria because they are assumed to be present many years before the onset of symptoms. The best validated and clinically available biomarkers are markers of neuronal degeneration or neuronal injury and markers of amyloid β deposition. However, the use of these biomarkers in the clinical setting currently has no role because of the absence of disease-modifying therapies and the cost of the advanced neuroimaging and laboratory testing.

For information on the treatment of the cognitive symptoms of Alzheimer disease, see "Pharmacologic Therapies for Cognitive Symptoms" later in this chapter.

KEY POINTS

- Alzheimer disease can be divided into three phases along a single continuum: an asymptomatic preclinical phase, a predementia phase (mild cognitive impairment due to Alzheimer disease), and a dementia phase.
- Currently, the use of Alzheimer disease biomarkers in the clinical setting has no role because of the absence of disease-modifying therapies and the cost of advanced neuroimaging techniques and laboratory testing. HVC

Lewy Body Disease

Lewy bodies are abnormal aggregates of proteins within neurons that occur in several neurodegenerative diseases. Lewy body disease is an umbrella term encompassing both dementia with Lewy bodies and Parkinson disease dementia. Dementia with Lewy bodies is the second most common cause of dementia (after Alzheimer disease) due to a neurodegenerative disease in older patients, accounting for 20% of patients with dementia in pathologic studies. Core features are fluctuating cognition, recurrent visual hallucinations, and parkinsonism. Cognitive fluctuations include variations in both attention and level of arousal and can vary hour to hour, day to day, or week to week. The parkinsonism is typically characterized by facial immobility and more axial than appendicular symptoms manifesting as postural instability and gait difficulty. Rapid eye movement sleep behavior disorder and severe sensitivity to neuroleptic medications are significantly more common in dementia with Lewy bodies than in other dementing illnesses. Recurrent falls, depression, delusions, hallucinations, severe autonomic dysfunction,

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syncope, and transient unexplained loss of consciousness also commonly are present but have low specificity for dementia with Lewy bodies. Cognitive testing shows the most pronounced impairment in attention, executive function, and visuospatial function.

The distinction between dementia with Lewy bodies and Parkinson disease dementia depends on the onset of cognitive impairment relative to motor impairment. If dementia precedes, occurs concurrently with, or develops within 1 year of onset of parkinsonian motor symptoms, the diagnosis is dementia with Lewy bodies. In contrast, Parkinson disease dementia describes dementia occurring at least 1 year after a diagnosis of Parkinson disease has been well established. The parkinsonism of dementia with Lewy bodies is less responsive to levodopa than is Parkinson disease.

KEY POINTS

- Core features of dementia with Lewy bodies are fluctuating cognition, recurrent visual hallucinations, and parkinsonism with pronounced postural instability and gait difficulty.
- Dementia with Lewy bodies rather than Parkinson disease dementia is the most likely diagnosis when the dementia precedes, occurs concurrently with, or develops within 1 year of onset of parkinsonian motor symptoms.

Frontotemporal Dementia

Frontotemporal dementia (FTD) is the third most common type of neurodegenerative disorder but the second most common cause of dementia in persons younger than 65 years. The average age of onset is 50 to 60 years, but patients can develop FTD as early as their 30s; only 10% of patients with this diagnosis are age 70 years or older. FTD comprises two distinct clinical syndromes. The first, behavioral variant FTD, is associated with prominent changes in behavior, personality, or executive function. The second, primary progressive aphasia, is associated with prominent and early changes in language function and is further subclassified according to the pattern of language impairment.

The changes in social behavior and personality that occur are variable and develop insidiously, but the unifying characteristic is that there is a change. Apathy, diminished interest, loss of empathy, lack of initiative, increased emotionality, disinhibition, euphoria, impulsivity, changes in eating behaviors (such as craving more sweets and binge eating), hyperorality, and compulsiveness are the most common symptoms reported by families. Other changes include irritability, aggression, verbal abuse, hypomania, and restlessness. Similar changes in personality and behavior can be seen in the other types of dementia during the disease course, but the prominence of these symptoms early in the course of FTD helps to establish the diagnosis. Psychosis is sometimes present but is not as common.

Executive function and decision making are typically affected early in the disease. Loss of insight is typically apparent, as is poor judgment. Memory and visuospatial function are relatively spared early in the disease course, which helps to distinguish patients with FTD from those with Alzheimer disease. Atypical parkinsonism or motoneuron disease can develop in some patients with the disease.

Motoneuron disease, including amyotrophic lateral sclerosis, is seen in approximately 15% of patients preceding, simultaneous with, or after the diagnosis of FTD. Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are two related syndromes that may present with dementia and are pathologically related to FTD. PSP is characterized by early postural instability and falls, axial parkinsonism that is poorly responsive to levodopa, vertical gaze palsy on examination, and slurred speech. Cognitive deficits include apathy, slow processing speed, and impaired executive function. CBD is a rare disorder characterized by rigidity, akinesia, apraxia, myoclonus, dystonia, and alien-limb phenomenon (initially affecting only one limb). Cognitive deficits can be prominent and include slowed processing speed, impaired working memory, executive dysfunction, and—occasionally—aphasia. Neuroimaging in CBD may show asymmetric cortical atrophy mostly involving the parietal and posterior frontal lobes.

FTD is associated with atrophy and neuronal loss involving the frontal or temporal lobes, which are sometimes visible on neuroimaging. The underlying pathologic changes are heterogeneous and characterized by abnormal proteins that accumulate in the brain: tau, transactivating-response region DNA binding protein 43 (TDP-43), or fused-in sarcoma (*FUS* gene) protein. Nearly all cases of PSP and CBD are due to underling tau pathology. FTD that is associated with motoneuron disease is always due to underlying TDP-43 pathology.

The genetics of FTD also are heterogeneous. As many as 40% of patients with FTD have at least one family member with a neurodegenerative disorder. Because many associated genetic mutations have been identified, genetic testing is appropriate in patients with one or more first-degree relatives with a clinical syndrome consistent with FTD, especially those with children in whom a positive result might affect family planning. However, this testing should be performed only after genetic counseling.

KEY POINTS

- The behavioral variant of frontotemporal dementia is associated with prominent changes in behavior, personality, or executive function, and the primary progressive aphasia variant is associated with prominent and early changes in language function.
- Genetic counseling and testing are appropriate in patients with frontotemporal dementia (FTD) who have one or more first-degree relatives with a clinical syndrome consistent with FTD.

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Nondegenerative Causes of Dementia

Idiopathic Normal Pressure Hydrocephalus

Idiopathic normal pressure hydrocephalus (NPH) is very rare, with an estimated incidence rate of 15 per 100,000 persons older than 50 years; an even smaller percentage of patients with NPH show sustained improvement with treatment. NPH is characterized by gait abnormalities, urinary symptoms, and cognitive decline. Accompanying neuroimaging findings include ventriculomegaly that is disproportionate to cortical atrophy in a patient without any known secondary causes of hydrocephalus, such as a history of meningitis, subarachnoid hemorrhage, or trauma. Because subcortical vascular ischemic disease can mimic the clinical symptoms and signs of NPH, MRI and a careful history that excludes hypertension, ischemic heart disease, diabetes mellitus, and dyslipidemia are essential. CSF opening pressure in patients with NPH is typically normal. Symptoms present insidiously, with peak prevalence in the seventh and eighth decades of life.

Abnormal gait is usually the first and principal symptom of NPH. This gait is characterized by a wide base, with slow, small steps and reduced foot-to-floor clearance, and can be accompanied by freezing of gait and postural instability. Urinary frequency and urgency typically precede incontinence and cognitive dysfunction. The cognitive dysfunction follows a pattern of impaired attention, psychomotor slowing, executive dysfunction, and impaired recall.

Ventriculoperitoneal shunt placement is the standard of care for NPH. Large-volume lumbar puncture or a lumbar drainage trial with cognitive and motor testing and symptom assessment before and after testing can be used to evaluate potential response to shunting. No currently available test, however, can reliably determine a positive response.

Although NPH traditionally has been considered a reversible disease if shunting is performed early in the clinical course, response to shunting is variable and infrequently sustained. Moreover, NPH is overdiagnosed, which results in a high frequency of unsuccessful procedures.

KEY POINTS

- Idiopathic normal pressure hydrocephalus is characterized by an abnormal gait that is often accompanied by urinary symptoms, cognitive decline, and ventriculomegaly on neuroimaging.
- Large-volume lumbar puncture or a lumbar drainage trial with cognitive and motor testing and symptom assessment before and after testing can be used to evaluate potential response to shunting in normal pressure hydrocephalus.

Vascular Neurocognitive Disorder

Vascular neurocognitive disorder (VND), the term now used to describe cognitive impairment of any degree (from mild cognitive impairment to vascular dementia) due to cerebrovascular disease, is the second most common cause of cognitive impairment in older persons (after Alzheimer disease). The associated clinical syndromes and underlying causes are heterogeneous. Cerebrovascular syndromes associated with cognitive decline are listed below:

- Multiple cortical infarcts, multiple subcortical infarcts, silent infarcts, or some combination of these
- Single infarcts in regions of the brain that control speech, motor functions, and senses (eloquent regions), such as lacunar infarcts involving the thalamus and basal ganglia that have vital interconnections with multiple cortical regions
- Subcortical ischemic small-vessel disease with white matter lesions that interrupt subcortical-frontal circuits or connections to distal cortical regions
- Hemorrhage, including intraparenchymal hemorrhage, subarachnoid hemorrhage, and subdural hematoma
- Hypotensive episodes that cause border-zone infarcts
- Cerebral vasculitis

Making the diagnosis of VND can be challenging because of its clinical heterogeneity. Current clinical criteria have not been validated and do not distinguish mixed causes from pure vascular causes. In contrast to the degenerative dementias, a neuropsychological profile specific to VND does not exist, and the cognitive symptoms are highly variable, depending on whether the deficits are due to microvascular or macrovascular disease. The diagnosis is made when neuroimaging or clinical history reveals evidence of a stroke or subclinical cerebrovascular disease that is responsible for impairment of at least one cognitive domain. Onset can be acute or insidious, and progression can be stepwise or gradual. Noncognitive symptoms in patients with VND are common and include focal neurologic findings, depression, pseudobulbar palsy (most commonly associated with multiple bilateral lacunar infarcts), gait abnormalities, and urinary difficulties (with the latter two symptoms explaining this disorder's confusion with NPH). Impairments of attention, executive function, and processing speed are commonly seen on neuropsychological testing, especially in patients with a subcortical vascular syndrome. Memory impairment is typically less prominent.

Treatment is aimed at identifying and treating cerebrovascular risk factors, such as smoking, diabetes mellitus, hyperlipidemia, hypertension, ischemic heart disease, atrial fibrillation, and hypercoagulable states, and at lowering stroke risk with antiplatelet or anticoagulant therapy, if indicated.

KEY POINTS

- The diagnosis of vascular neurocognitive disorder is made when neuroimaging or clinical history reveals evidence of a stroke or subclinical cerebrovascular disease that can be linked to impairment of at least one cognitive domain.
- Treatment of vascular neurocognitive disorder involves identifying and treating cerebrovascular risk factors and lowering stroke risk.

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Dementia Associated with Traumatic Brain Injury

Experiencing a head injury in early or mid-life is thought to be associated with an increased risk of dementia in late life, although the association is subject to recall bias. Current evidence suggests that the severity and frequency of head injuries correlate with the risk of dementia and severity of disease.

Chronic traumatic encephalopathy, formerly known as dementia pugilistica, is a distinct progressive neurodegenerative disorder triggered by repetitive mild head injury. This disorder has most often been described in military veterans who have sustained blast or conconcussive injuries and athletes with a history of multiple concussions and subconcussions (such as boxers, football players). Chronic traumatic encephalopathy is pathologically characterized by the presence of tau-positive neurofibrillary tangles with a different distribution than is seen in Alzheimer disease. Pathologic accumulation of amyloid β protein, TDP-43, and α-synuclein protein also has been reported in a subset of patients. Symptoms develop insidiously, typically 8 to 10 years after the repeated head injuries, and are progressive. The cognitive impairment is characterized by impaired concentration, poor short-term memory, executive dysfunction, and poor judgment. Behavioral symptoms include depression, irritability, aggression, violent behaviors, emotional lability, impulsivity, and suicidality. Motor symptoms are common and include parkinsonism, unsteady gait, shuffling gait, slurred speech, and motoneuron disease.

KEY POINT

- Chronic traumatic encephalopathy is a distinct progressive neurodegenerative disorder triggered by repetitive mild head injury that typically presents with cognitive impairment and behavioral and motor symptoms.

Mixed Dementias

The combination of more than one pathology contributing to a dementia syndrome is not uncommon. Because the diagnosis of mixed dementia requires pathologic confirmation, the prevalence of this type of dementia is not entirely known. Mixed dementia is the term classically used to describe coexisting Alzheimer disease and vascular dementia. However, coexisting Alzheimer disease and dementia with Lewy bodies also is seen in 20% of patients with dementia, and Alzheimer disease is sometimes seen in patients with NPH.

Pharmacologic Therapies for Cognitive Symptoms

Although no pharmacologic disease-modifying therapy that reverses or halts neurodegeneration in any neurodegenerative dementia yet exists, two drug classes have been shown to have a positive effect in slowing the symptomatic decline: cholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonists. Typical benefits of these drugs in patients with dementia are mild improvements in measured cognition and performance of some activities of daily living. However, their effectiveness in improving clinically significant outcomes, such as the ability to maintain independence and reduce the need for higher levels of care, has not been established. **Table 20** lists the FDA-approved medications for treating dementia. The cholinesterase inhibitors exert their effect by inhibiting the enzymes responsible for breaking down acetylcholine, thereby increasing the levels of acetylcholine in the neuronal synapse. No clinically significant difference in effectiveness has been shown between the cholinesterase inhibitors. Relative contraindications for their use include (but are not limited to) sick sinus syndrome, left bundle branch block, uncontrolled asthma, angle-closure glaucoma, and ulcer disease. Memantine, a second-line therapeutic option, is an *N*-methyl-D-aspartate receptor antagonist believed to reduce glutamate-mediated neurotoxicity in the central nervous system. Memantine is often used in conjunction with a cholinesterase inhibitor and is FDA approved for moderate to severe Alzheimer disease; however, a recent trial showed that the two medications in combination were not significantly more beneficial than the cholinesterase inhibitor donepezil alone in moderate to severe Alzheimer disease.

Although no cholinesterase inhibitor is FDA approved for treating dementia with Lewy bodies and rivastigmine is the only cholinesterase inhibitor approved for Parkinson disease dementia, recent data have suggested that patients with both types of dementia benefit from treatment with cholinesterase inhibitors in terms of cognition, behaviors, and hallucinations. No drug has been shown to be beneficial for the treatment of FTD. In VND, therapy is directed at identifying and controlling vascular risk factors to minimize progression of cerebrovascular disease; evidence supporting the use of any other medication is currently insufficient. Data are similarly insufficient to support using cholinesterase inhibitors to delay progression from MCI to dementia, so their routine use for this purpose is not recommended.

KEY POINTS

- Cholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonists may provide mild improvements in measured cognition and performance of some activities of daily living in patients with dementia but have not demonstrated effectiveness in improving clinically significant outcomes, such as the ability to live independently.
- Cholinesterase inhibitors have not been approved to treat frontotemporal dementia and vascular neurocognitive disorder or to delay progression from mild cognitive impairment to dementia. HVC

Neuropsychiatric Symptoms in Cognitive Impairment

Clinical Characteristics

Changes in behavior and mood are more common in patients with MCI and dementia than in age-matched controls. Depression, anxiety, apathy, irritability, and agitation are the

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TABLE 20. FDA-Approved Medications for the Symptomatic Treatment of Dementia

Medication (route)	Mechanism of Action	Available Doses	FDA-Approved Indications: Dementia Severity	FDA-Approved Indications: Dementia Subtype	Proven Efficacy	Adverse Effects	Practical Points
Donepezil (oral)	Acetylcholinesterase inhibitor	5 or 10 mg/d[a]	Mild, moderate, and severe	Alzheimer disease	Cognition, global function, ADLs, behavior	Nausea, vomiting, anorexia, diarrhea, dizziness, sleep disturbances, muscle cramps, symptomatic bradycardia	Dosages of 5 mg and 10 mg available as orally disintegrating tablet; dose in the AM to minimize risk of insomnia and vivid dreams.
Rivastigmine (oral)	Acetylcholinesterase inhibitor, butylcholinesterase inhibitor	1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg BID	Mild, moderate	Alzheimer disease, Parkinson disease	Cognition, global function, ADLs, behavior	Nausea, vomiting, anorexia, diarrhea, headache	Also available in an oral solution 2 mg/mL.
Rivastigmine (transdermal)	Acetylcholinesterase inhibitor, butylcholinesterase inhibitor	4.6 mg/d, 9.6 mg/d, 13.3 mg/d	Mild, moderate	Alzheimer disease, Parkinson disease	Cognition, global function, ADLs, behavior		Typically better tolerated in terms of gastrointestinal side effects.
Galantamine (oral)	Acetylcholinesterase inhibitor, modulates nicotinic acetylcholine receptors to increase acetylcholine	Immediate release: 4 mg, 8 mg, 12 mg BID Extended release: 8 mg/d, 16 mg/d, 24 mg/d	Mild, moderate	Alzheimer disease	Cognition, global function, behavior	Nausea, vomiting, anorexia, diarrhea, weight loss	Also available in an oral solution 4 mg/mL.
Memantine (oral)	*N*-methyl-D-aspartate receptor antagonist, dopamine antagonist	Immediate release: 5 mg, 10 mg BID Extended release: 7 mg/d, 14 mg/d, 21 mg/d, 28 mg/d	Moderate, severe	Alzheimer disease	Cognition, global function, ADLs, behavior	Confusion, drowsiness, dizziness, headache, change in behavior	Also available in an oral solution 10 mg/5 mL. Interactions with trimethoprim may exist; risk of myoclonus and delirium is increased.

ADLs = activities of daily living; BID = twice daily.

[a]Although donepezil, 23 mg/d, is approved for the treatment of moderate to severe Alzheimer disease on the basis of a small improvement in scores on a neuropsychological test, no significant difference in functional outcome was observed when compared with the 10-mg dose. In addition, gastrointestinal side effects were significantly greater and the cost substantially greater. Therefore, this medication is not frequently prescribed.

most common neuropsychiatric symptoms experienced by patients with MCI. With progression of cognitive impairment, the frequency and severity of neuropsychiatric symptoms increase. Behavioral symptoms vary according to the underlying cause but are prevalent in all subtypes of dementia. Depression is common in Alzheimer disease, dementia with Lewy bodies, and vascular dementia. Apathy is most prominent in FTD and PSP but also occurs in the other dementias. A lack of motivation and indifference are often misinterpreted by family members as depression. Irritability, aggressive behaviors, and anxiety are common in Alzheimer disease and vascular dementia, whereas aberrant motor behaviors (pacing, wandering, repetitive movements, excessive fidgeting), disinhibition, and eating disturbances are more commonly seen in FTD. Delusions are more frequent in Alzheimer disease and dementia with Lewy bodies than in FTD. Hallucinations are most common in dementia with Lewy bodies but can occur in all degenerative dementias.

Treatment of Neuropsychiatric Symptoms

Nonpharmacologic interventions can be very effective in treating the behavioral symptoms experienced by patients with dementia and should be the first-line treatment. Changes to the environment, including new caregivers, should be minimized. Structured activities should be provided and daily routines followed. Orienting tools, such as

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CONT.

easily visualized clocks and calendars, should be used. Triggers provoking agitation or frustration should be identified and minimized. Disputing delusions or false beliefs is often ineffective, especially because patients with dementia frequently are unable to reason, rationalize, or understand logic. Therefore, validating the patient's thinking and then distracting and redirecting him or her to something more pleasant usually is more successful in dealing with behavioral problems.

When nonpharmacologic interventions alone are not effective in managing behavioral symptoms sufficiently, pharmacologic therapies may improve them. Atypical antipsychotic agents can be effective in treating agitation, aggression, delusions, and hallucinations. However, these drugs are not FDA approved for this clinical indication and have an associated black box warning due to increased cerebrovascular events and mortality rates in patients with dementia. Nevertheless, behavioral problems can jeopardize the safety of the patient or caregiver and substantially impair quality of life. The benefits versus risks of instituting medication for behaviors must be considered in each patient and discussed with the patient and his or her caregivers; the risk of death is increased by 60% in the first 10 weeks after starting antipsychotic drugs. Antiepileptic drugs, such as valproic acid, also are used off-label for the behavioral symptoms associated with dementia. Antidepressants with the fewest anticholinergic side effects can be used for depression and anxiety. Apathy is notoriously difficult to treat, but off-label medications that sometime improve this symptom include cholinesterase inhibitors and neurostimulants. Benzodiazepines are not recommended for the treatment of behavioral symptoms in patients with dementia.

KEY POINTS

HVC

- Nonpharmacologic interventions are often effective in treating the behavioral symptoms experienced by patients with dementia and should be the first-line treatment.
- Atypical antipsychotic agents are effective in treating agitation, aggression, delusions, and hallucinations but have an associated black box warning due to increased cerebrovascular events and mortality rates in patients with dementia.
- Antidepressants with the fewest anticholinergic side effects can be used for depression and anxiety.

Delirium

Delirium is a potentially preventable syndrome associated with other medical disorders, the adverse effects of medication, or drug withdrawal. This disorder is characterized by an acute change in cognitive functioning occurring over hours to days, with fluctuations during the course of the day. Features of delirium include inattention, disorganized thinking, executive dysfunction, altered level of consciousness (lethargy or hypervigilance), perceptual disturbances (such as hallucinations or delusions), altered psychomotor activity (hyperactivity, hypoactivity, or alternating periods of hyperactivity and hypoactivity), sleep-wake disturbances, and labile mood.

Preexisting cognitive impairment is the major predisposing factor for delirium. Additional risk factors include older age, preexisting neurologic disease (such as Parkinson disease), visual or hearing impairment, immobilization, sleep deprivation, presence of multiple medical comorbidities, alcohol abuse, and terminal illness.

Delirium complicates hospitalization for as many as 30% of patients age 65 years and older, with prevalence significantly increasing (60%-90%) for patients with Alzheimer disease. In critically ill patients, delirium is seen in as many as 80% of patients receiving mechanical ventilation. In the year following a hospitalization complicated by delirium, patients with baseline dementia experience cognitive decline at twice the rate of those without a history of delirium. The rate of incident dementia after an episode of delirium in older patients without preexisting cognitive impairment is 1.4 to 2 times that of those without a history of delirium. In addition, delirium is associated with increased length of hospital stay, increased institutionalization, and increased mortality rates both at discharge and at 1 year. The 1-year mortality rate after an episode of delirium in older patients is approximately 35%.

Delirium is underdiagnosed. Administering a delirium screening test can enhance detection of the disorder. Although many screening tools have been developed, the best validated and most reliable clinical instrument for making the diagnosis of delirium is the Confusion Assessment Method (**Table 21**) and for assessing its severity is the Delirium Rating Scale. Serial measurements can be used to monitor improvement in symptoms.

The cause of delirium in an individual patient may be one or multiple coexisting conditions (**Table 22**). Two or more underlying causes are present in as many as 50% of older patients, so a complete medical evaluation is necessary. The quest for the cause of delirium begins with a thorough medication review, a history of any illicit drug use, and testing for concurrent medical illnesses.

Treatment involves identification and correction of the underlying cause, maintaining adequate nutrition and hydration, and preventing complications. With treatment, delirium typically resolves within days; in some patients, however, more subtle cognitive dysfunction can persist for weeks to months. Environmental interventions include orienting strategies (reliance on calendars, clocks, and familiar objects in the room), promoting a normal sleep-wake cycle (having no or limited interruptions during nocturnal sleeping hours, minimizing light and noise at night, and opening curtains and encouraging activity during the daytime), identifying and correcting sensory impairments (use of dentures, glasses, and hearing aids), avoiding physical restraints, and early discontinuation of catheters and intravenous lines. No medications

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TABLE 21. The Confusion Assessment Method Diagnostic Instrument[a]

Feature 1.	**Acute Onset and Fluctuating Course**
	This feature is usually obtained from a family member or nurse and is shown by a positive response to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?
Feature 2.	**Inattention**
	This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
Feature 3.	**Disorganized Thinking**
	This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Feature 4.	**Altered Level of Consciousness**
	This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or comatose [unarousable])

[a]The diagnosis of delirium by the Confusion Assessment Method requires the presence of features 1 and 2 and either 3 or 4.

Adapted with permission from Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113(12):947. [PMID: 2240918]

TABLE 22. Causes of Delirium

Drugs
Prescription medications (such as psychotropic medications, opioids, sedative hypnotics, anticonvulsants, antiparkinsonian agents, glucocorticoids, immunosuppressants, antiarrhythmics, antihypertensive agents, skeletal muscle relaxants, antibiotics)
Nonprescription medications (such as NSAIDs, antihistamines)
General anesthesia
Alcohol or drug withdrawal
Central Nervous System Diseases
Seizure, including nonconvulsive status epilepticus
Acute ischemic infarction
Intracranial hemorrhage (such as intraparenchymal hemorrhage, subdural hematoma, epidural hematoma, subarachnoid hemorrhage)
Head injury
Metabolic Disorders
Electrolyte disturbance
Hyperglycemia or hypoglycemia
Hypoxemia
Hypercarbia
Organ failure (such as cardiac failure, kidney impairment, liver failure)
Endocrine (such as hypothyroidism, hyperthyroidism, hyperparathyroidism, Cushing syndrome, adrenal insufficiency)
Nutritional (such as malnourishment, vitamin B_{12} deficiency, thiamine deficiency, niacin deficiency)
Cardiovascular Disease
Myocardial infarction
Hypertensive emergency
Dysrhythmias
Infections[a]
Surgery
Trauma
Environment
Post-acute care setting
ICU
Other
Acute blood loss
Uncontrolled pain
Fecal impaction
Urinary retention

[a]Such as urinary tract infections, respiratory infections, cellulitis, meningitis or encephalitis, and sepsis.

H CONT. are FDA approved for the treatment of delirium. Although atypical and typical antipsychotic agents are commonly used to treat the behavioral symptoms associated with hyperactive delirium when the patient's safety is at risk, evidence of their effectiveness in this setting is limited, and these drugs have black box safety warnings when used in patients with underlying dementia. Additionally, data are insufficient to support the prophylactic use of pharmacologic agents in the prevention of delirium. Benzodiazepines can worsen delirium and are not recommended, except in the management of alcohol withdrawal. H

KEY POINTS

- Treatment of delirium involves identification and correction of the underlying cause, maintaining adequate nutrition and hydration, and preventing complications.
- HVC No pharmacologic therapy is currently FDA approved for the prevention or treatment of delirium.

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Movement Disorders

Overview of Movement Disorders

Movement disorders are characterized by abnormal patterns of motor output and are broadly classified into conditions characterized by paucity and slowness of movements (hypokinetic disorders) and those marked by excessive involuntary movements (hyperkinetic disorders). Hypokinetic disorders include Parkinson disease and related disorders. Hyperkinetic movement disorders are classified according to their characteristic abnormal movements, such as tremor, tic, chorea, dystonia, and myoclonus.

Neurologic examination, particularly assessments of motor function and gait, helps distinguish the various movement disorders. Spontaneous and voluntary movements should be assessed, with attention paid to speed, amplitude consistency, and fatigability. Muscle tone should be evaluated by determining the resistance of extremities to passive movements, with special attention paid to effects of velocity and direction of movements. Hypokinetic movement disorders commonly display consistently increased tone (lead-pipe rigidity) throughout the movement of the joint, in contrast to the "give-way" hypertonia (clasp-knife phenomenon) seen with upper motoneuron lesions in which a cogwheeling component may also be present. The phenomenology of abnormal movements—especially their rhythmicity, suppressibility, randomness, directionality, and speed—can help in their classification (**Table 23**).

An examination of gait should consider the base of standing, pace of ambulation, stride length, foot clearance off the ground, postural stability, and arm swings. In Parkinson disease and other hypokinetic disorders, gait is slow, narrow based, shuffling, and associated with shortened stride length, reduced arm swings, and stooped posture. Turns may take several steps and appear stiff and unsteady. Ataxic gait is characterized by a wide base, frequent truncal swaying and veering, and impaired tandem walking on a straight line. This gait also can be accompanied by additional signs of cerebellar dysfunction, such as nystagmus, scanning and dysrhythmic speech, truncal titubation (to and fro movement), and dysmetria on finger-nose or heel-knee-shin tests.

Postural stability can best be checked by the pull test, in which the examiner throws the patient off base by pulling backward on the shoulders after a warning and the instruction to maintain balance. A positive test, characterized by toppling into examiner's arms or taking more than one corrective step, is the most reliable predictor of a risk of backward falls.

KEY POINT

H\/C
- Neurologic examination, particularly assessments of motor function and gait, helps distinguish the various movement disorders.

Hypokinetic Movement Disorders

Parkinson disease is the most common type of hypokinetic movement disorder. Parkinson-plus conditions combine parkinsonism with other clinical features, such as early falling, prominent dysautonomia, or early cognitive deficits. Vascular parkinsonism results from large or small vessel ischemic or hemorrhagic lesions and is characterized by a predominant abnormality of gait disproportionate to upper extremity involvement, a history of sudden or stepwise deterioration, and absence of typical neurodegenerative progression. Medication-induced parkinsonism should be considered in patients with a history of exposure to predisposing medications, such as neuroleptic agents.

Parkinson Disease

Parkinson disease is a slowly progressive neurodegenerative disorder associated with gradual loss of dopamine-producing neurons in the substantia nigra. The pathophysiologic process in Parkinson disease involves aggregation of α-synuclein protein and formation of Lewy body inclusions in the substantia nigra and other brain regions. Several genes, including the autosomal dominant gene *LRRK2* and the autosomal recessive gene *PARK2*, have been associated with Parkinson disease in a minority of patients. In addition, exposure to certain environmental factors, including pesticides (rotenone), herbicides, well water, and excessive manganese, can increase the risk for Parkinson disease. The prevalence of this condition increases with age and is expected to significantly increase as the U.S. population ages.

Clinical Features of Parkinson Disease

The four cardinal signs of Parkinson disease are resting tremor, bradykinesia, cogwheel rigidity, and gait/postural impairment. Resting tremor is characteristically unilateral at onset and remains asymmetric. This type of tremor emerges after a few seconds of outstretched posturing of the arms and during ambulation. Bradykinesia, the core feature in Parkinson disease, consists of slowness and gradual decreasing of the amplitude of repetitive movements. A relative paucity of movement on the more affected side may be noted, including reduced facial expression, reduction in arm swing, and small handwriting (micrographia). Patients may report difficulty with both fine and gross movements. Rigidity is associated with a cogwheeling quality in the presence of tremor. In early Parkinson disease, gait and postural impairment are mild and limited to shuffling, dragging of one leg, and mild disturbance of postural reflexes at turns. A prominent impairment of gait and balance may develop at later stages, with hesitation at onset of gait and turns, freezing of gait, and severe loss of postural reflexes. Early prominent postural instability with frequent falls should raise concern for a Parkinson-plus condition. Although the initial presentation of Parkinson disease is commonly tremor predominant, a minority of affected patients may first experience an akinetic rigidity without tremor.

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TABLE 23. Classification of Movement Disorders

Movement Type	Clinical Features	Causes
Hypokinetic		
Parkinsonism	Cardinal features: bradykinesia/akinesia, rigidity, resting tremor, postural instability Additional features: freezing gait, stooped posture, masked face, hypophonia	Parkinson disease, Parkinson-plus syndromes, Lewy body dementia, vascular, hydrocephalus, medications, Wilson disease, juvenile Huntington disease
Hyperkinetic		
Tremor	Rhythmic oscillations of a body part, can occur at rest or with action (postural or kinetic), intention tremor amplitude increased near target	At rest: parkinsonism (see above) Postural and kinetic: enhanced physiologic tremor, essential tremor Intention tremor: cerebellar For more information, see Table 29
Dystonia	Sustained, stereotyped, and directional twisting and posturing movements of various body parts; can be focal, segmental, or generalized; transient improvement possible with a sensory trick ("geste antagoniste")	Idiopathic or primary dystonia Generalized: positive for *DYT1* Segmental: Meige syndrome (facial and oromandibular dystonia) Focal: torticollis, blepharospasm, writer's cramp Dopa-responsive Damage to the basal ganglia: anoxic injury, postencephalitic, dystonic cerebral palsy Medication-induced Acute dystonic reaction, tardive dystonia
Chorea	Random, nonrepetitive, quick, unsustained, purposeless movements with a flowing dance-like pattern	Huntington disease, postinfectious (Sydenham chorea), chorea gravidarum, autoimmune (systemic lupus erythematosus, antiphospholipid syndrome), hyperglycemia, vascular, drug-induced, neuroacanthocytosis
Hemiballismus	Unilateral high-amplitude proximal flailing, choreiform movements of limbs	Lesions of contralateral subthalamic or other parts of basal ganglia (usually stroke)
Athetosis	Slow convoluted writhing movements of fingers and toes Pseudoathetosis similar but elicited by eye closure	Early life damage to basal ganglia (hypoxic, kernicterus, vascular) Pseudoathetosis caused by proprioceptive pathway lesions
Tic	Stereotyped, brief, purposeless, rapid movements that break the flow of normal movements; common premonitory urges; can be simple or complex, motor or vocal	Tourette syndrome, autism, developmental delay syndromes, Huntington disease
Myoclonus	Rapid, shock-like, jerky movements of isolated body parts	Metabolic (uremia, hepatic failure, electrolyte imbalance), serotonin syndrome, postanoxic, Creutzfeldt-Jakob disease, corticobasal degeneration Sleep-related (hypnic jerks, nocturnal myoclonus), myoclonic epilepsies
Akathisia	Inner restlessness associated with repetitive movements	Drug-induced, restless legs syndrome
Psychogenic	Highly variable, inconsistent, distractible, acute onset, episodic, tremor frequency suggestive of different frequencies, most fixed dystonias	Conversion disorder, malingering, factitious illness, somatoform disorder

In addition to symptoms affecting motor systems, Parkinson disease also is associated with a wide variety of nonmotor symptoms, ranging from autonomic dysfunction to problems with sleep, mood, and cognition (**Table 24**). Some nonmotor symptoms, including hyposmia (diminished sense of smell), constipation, and rapid eye movement (REM) sleep behavior disorder (acting out of dreams secondary to loss of normal muscle paralysis during the dream phase of sleep), may precede onset of motor symptoms by years.

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TABLE 24. Nonmotor Symptoms of Parkinson Disease

Type of Complication	Symptoms
Cognitive	Bradyphrenia (slow processing), mild subcortical cognitive impairment, and dementia possible at advanced stages
Affective and behavioral	Depression, anxiety, apathy, psychosis, drug-related impulse control disorder, dopamine dysregulation syndrome (craving for dopaminergic medications)
Sleep related	Sleep fragmentation, rapid eye movement sleep behavior disorder, restless legs syndrome, excessive daytime sleepiness, sleep-wake reversal, drug-related sleep attacks
Autonomic	Constipation, postural hypotension, bladder and sexual dysfunction, sialorrhea, seborrhea, excessive sweating, hyposmia
Musculoskeletal	Truncal and cervical flexion posturing, camptocormia (truncal flexion during standing and walking), frozen shoulder, striatal hand deformities (dystonic joint deformities, including flexion of metacarpophalangeal joints and extension of proximal interphalangeal joints), fall-related injuries
Pain related	Painful dystonia, painful rigidity, mechanical pain, central and visceral pain

Cognitive impairments in Parkinson disease are subcortical, which implies that they primarily involve slow processing speed, impaired short-term memory, and attention deficits with relative sparing of cortical functions, such as language and declarative memory. These impairments are typically mild in the early stages of the disease but can progress to dementia in the later stages. Early dementia within the first year of the appearance of motor parkinsonism is a hallmark of dementia with Lewy bodies (see Lewy Body Disease in Cognitive Impairment).

Diagnosis of Parkinson Disease

The diagnosis of Parkinson disease is made on the basis of history and clinical examination. Diagnostic criteria require the presence of bradykinesia with at least one other cardinal feature (resting tremor, rigidity, or postural instability) and the absence of red flags for atypical forms of parkinsonism (**Table 25**). An MRI of the brain is recommended to rule out vascular lesions and hydrocephalus. Single photon emission CT (SPECT) of the brain using ioflupane-123, a ligand for a dopamine transporter, may reveal reduced ligand uptake in the basal ganglia as a result of degeneration of dopamine terminals. However, the sensitivity of this test is not superior to that of an expert clinical assessment, and it should be reserved only for patients in whom the differentiation between Parkinson disease and essential tremor or drug-induced parkinsonism is not feasible on clinical grounds. The test cannot distinguish between Parkinson disease and Parkinson-plus conditions.

TABLE 25. Red Flags for Atypical Forms of Parkinsonism

Red Flags	Features
Dysautonomia	Prominent orthostatic hypotension, urinary incontinence, impotence, sweating dysfunction (mild autonomic deficits potentially seen in early Parkinson disease)
Abnormal eye movements	Supranuclear vertical gaze palsy (which can be overcome by the oculocephalic maneuver), slowness of vertical saccades
Prominent early cognitive impairment	Dementia within first year of onset (mild cognitive impairment common in Parkinson disease and dementia, may develop in a notable subgroup of patients in advanced stages)
Visual hallucinations	Early and not provoked by medications (levodopa-induced hallucinations seen in Parkinson disease, especially in later stages)
Early prominent postural instability and falls	Within first year of onset
Prominent gait ataxia	With or without additional cerebellar deficits (dysmetria, nystagmus)
Symmetric or markedly asymmetric involvement	Parkinson disease characteristically asymmetric at onset and throughout its course
	Lack of asymmetry indicative of atypical parkinsonism
	Very severe asymmetric involvement; possibly suggestive of corticobasal degeneration and usually associated with severe fixed dystonic posturing, myoclonus, apraxia, and sensory cortical deficits
Rapid onset and stepwise deterioration	More suggestive of vascular parkinsonism (Parkinson disease associated with slow onset and gradual course)
Lack of response to levodopa[a]	Most important red flag of atypical parkinsonism

[a]Must not be secondary to adverse effects or insufficient dosing of medication.

Treatment of Parkinson Disease

Currently, no medication with proven efficacy is available to slow the progression of Parkinson disease. Recent studies have shown the beneficial role of rigorous daily exercise in improving motor fitness and gait, and thus physical activity or physical therapy should be encouraged in all patients with the disease. Research is under way to determine whether specific exercise regimens, such as resistance or aerobic exercises, provide a neuroprotective effect.

Pharmacologic therapy should be tailored to optimize each patient's motor, social, and intellectual functioning and to minimize any adverse effects (**Table 26**). Early symptoms may not need treatment, but a bothersome tremor, decreased dexterity, increased rigidity, and slowness are reasons to consider treatment. In patients with mild symptoms, monotherapy with monoamine oxidase type B inhibitors can be considered as

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TABLE 26. Medications for Parkinson Disease

Medication Class	Clinical Indication
Dopamine substrate (levodopa)	Most effective treatment for motor deficits Initial therapy in older patients (>70 years) and in those with severe motor symptoms, gait freezing, or falls Second-line treatment in younger patients who have not benefitted from dopamine agonists
Decarboxylase inhibitors Carbidopa Benserazide[a]	Suppression of peripheral adverse effects of levodopa
Dopamine agonists Pramipexole Ropinirole Rotigotine (patch) Bromocriptine Pergolide Apomorphine (injection) Cabergoline[a] Lisuride[a] Piribedil[a]	First-line treatment in younger patients; adjuvant therapy to limit total dose of levodopa
Catechol-*O*-methyltransferase inhibitors Entacapone Tolcapone	Counteracting of wearing-off phenomenon, prolongation of levodopa effect
Monoamine oxidase type B inhibitors Selegiline Rasagiline	Initial therapy in mild cases, potentiation of levodopa effect, tremor
Glutamate antagonist Amantadine	Dyskinesia, tremor, fatigue
Anticholinergic agents Trihexyphenidyl Benztropine Biperiden	Tremor, mild benefit against parkinsonism but avoid use in old age and dementia

[a]Available in Europe.

initial therapy, but the benefit of these agents is usually modest. Dopaminergic medications, including levodopa (the precursor molecule converted to dopamine) and dopamine agonists (agents that activate dopamine D_2 receptors in the absence of dopamine), are the most effective drugs to control the key motor deficits in Parkinson disease. Levodopa generally is used in combination with the decarboxylase inhibitor carbidopa to block levodopa's peripheral adverse effects outside the central nervous system. Eventually, all patients with Parkinson disease will require the benefit of levodopa. The initial use of dopamine agonists instead of levodopa in younger patients (age <65-70 years) is encouraged by many experts in an effort to delay levodopa-related complications, such as motor fluctuations (caused by the wearing off of the beneficial effects of the medication before the next dose is administered) and medication-induced dyskinesia (involuntary choreic movements). These complications emerge in as many as 50% of patients treated for more than 5 years with levodopa and may reflect disease progression rather than duration of exposure to levodopa.

Dopamine agonists are associated with higher risk of specific adverse effects, including impulse control disorder, punding, sleep attacks, ankle edema, hallucinations, and confusion, that may limit their use, especially in older patients. Impulse control disorder is the increased tendency for compulsive behaviors, such as excessive gambling, shopping, or hypersexuality, and all patients taking dopamine agonists should be monitored for this complication. Punding is a complex prolonged, purposeless, and stereotyped behavior (such as collecting, sorting, cataloguing, or assembling and disassembling common objects) that can become disruptive. Sleep attacks involve falling asleep without warning and can cause motor vehicle collisions. Dopamine agonists all have similar efficacy and can be used interchangeably, but no rationale supports their use in combination.

Levodopa should be started as initial therapy in older patients and as replacement or additional therapy in younger patients who did not benefit or had adverse effects from dopamine agonists. Also, gait impairment and freezing that can increase the risk of falls mandate initiation of levodopa therapy. The immediate-release formulations of levodopa provide a higher peak dose effect than similar doses of sustained-release formulations. Therefore, immediate-release formulations commonly are used during the wake cycle and sustained-release formulations, if needed, at nighttime. However, sustained-release levodopa or dopamine agonists can be added to immediate-release levodopa to provide more sustained levels of dopamine receptor activation, thereby delaying the development of levodopa-related motor complications. A typical initial dose of levodopa is 300 mg/d divided into three doses, with most patients benefitting from a slow titration to minimize adverse effects; further dose adjustment should be made on an individual basis.

As Parkinson disease progresses, the medication regimen should be adjusted to address progressive motor deficits and minimize evolving medication-related complications. For patients in whom the motor benefits of medication wear off quickly, strategies include either using a greater frequency of immediate-release levodopa dosing or using sustained-release levodopa. Other options include adding a dopamine agonist, a catechol-*O*-methyltransferase inhibitor, or a monoamine oxidase type B inhibitor. In patients with dyskinesia, adding amantadine may help a subset of patients. In patients with prominent tremor, anticholinergic medications may provide some additional benefit, but their high adverse effect profiles limit their use, especially in patients with cognitive impairment and in older patients.

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Medication-induced psychosis, especially visual hallucinations, is another adverse effect of dopaminergic medications. Treatment strategies include monitoring for infection and metabolic derangement and discontinuing anticholinergic drugs, amantadine, or dopamine agonists. Discontinuing catechol-O-methyltransferase and monoamine oxidase type B inhibitors also can be considered but may worsen the wearing-off phenomenon. A reduction in levodopa dosing may be required. When necessary, the preferred antipsychotic agents are clozapine and quetiapine.

Deep brain stimulation (DBS) surgery is a treatment based on the delivery of electrical stimulation to targeted brain regions. The stimulation delivered can modulate abnormal activity within target regions. For example, subthalamic nucleus DBS can disrupt abnormal rhythmic activity within that region and should be considered in patients with Parkinson disease who have sustained motor benefit from levodopa but are limited by disabling medication-related adverse effects that are refractory to medical management. In this select group, DBS can be highly effective in reducing motor complications, such as wearing off and dyskinesia, while providing motor benefits comparable to those of levodopa. Patients with atypical parkinsonism, major cognitive deficits, and unstable mood disorder should not receive DBS. Patients who meet the criteria for DBS should be referred to a movement disorder neurologist for an "on/off" medication evaluation (**Figure 17**). Also, patients

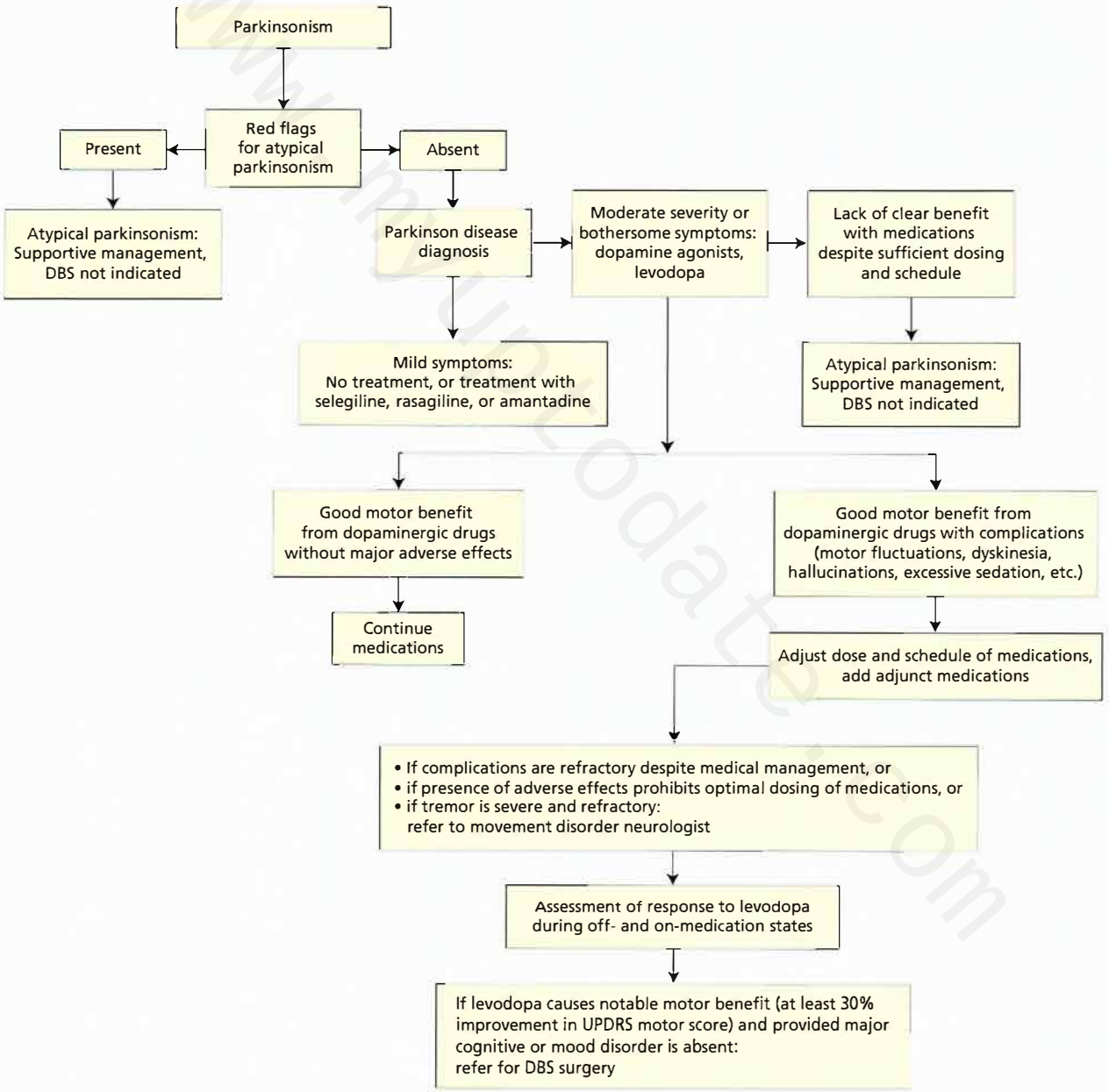

FIGURE 17. Algorithm for evaluation of candidacy for deep brain stimulation in Parkinson disease. DBS = deep brain stimulation; UPDRS = Unified Parkinson Disease Rating Scale.

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should be advised that levodopa-refractory symptoms, including speech deficits and postural instability, typically do not improve with DBS, with the potential exception of a refractory tremor. DBS targets in Parkinson disease include the subthalamic nucleus and globus pallidus interna, with the former being more amendable to a reduction in medication dose.

KEY POINTS

- Parkinson disease, the most common type of hypokinetic movement disorder, is characterized by four cardinal signs: resting tremor, bradykinesia, cogwheel rigidity, and gait or postural impairment.
- HVC The diagnosis of Parkinson disease is made on the basis of history and clinical examination and requires the presence of bradykinesia with at least one other cardinal feature (resting tremor, rigidity, or postural instability) and the absence of red flags.
- HVC Single photon emission CT of the brain should be reserved for differentiating Parkinson disease from drug-induced parkinsonism in patients with an atypical clinical picture.
- HVC Recent studies have shown the beneficial role of rigorous daily exercise in improving motor fitness and gait in patients with Parkinson disease, and thus physical activity or physical therapy should be encouraged in all patients with the disease.
- Dopaminergic medications, including levodopa and dopamine agonists, are the most effective drugs to control the key motor deficits in Parkinson disease.
- Deep brain stimulation surgery is highly effective for patients who have had a sustained motor benefit from levodopa but are limited by adverse effects of the medication.

Parkinson-Plus Syndromes

Parkinson-plus syndromes account for nearly 10% of patients with clinical parkinsonism. The diagnosis usually is suggested by the presence of defining features, a faster progression, and the absence of levodopa responsiveness. The primary syndromes involved are progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD). PSP is defined by parkinsonism with oculomotor abnormalities, including impairment of vertical saccades and supranuclear vertical gaze palsy, the latter of which can be overcome by passive head movements (such as the oculocephalic maneuver). Patients with PSP also exhibit facial dystonia (with a characteristic surprised appearance), axial rigidity, and prominent postural instability with early falls. MSA comprises three subtypes that are characterized by a combination of parkinsonism and prominent dysautonomia (Shy-Drager syndrome), cerebellar ataxia (MSA-C), or dystonia (MSA with predominant parkinsonism [formerly known as striatonigral degeneration], or MSA-P). CBD may present with markedly asymmetric parkinsonism and often is associated with dystonia, myoclonus, cortical sensory deficits, and cognitive deficits, including impairment in motor planning (apraxia), calculation, and left-right distinction. A brain MRI in a patient with CBD may reveal asymmetric cortical, particularly parietal, atrophy, although this finding may be absent at earlier stages.

KEY POINT

- Parkinson-plus syndromes include progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration.

Drug-Induced Parkinsonism

A number of drugs, especially dopamine receptor–blocking antipsychotic agents, can cause parkinsonism (**Table 27**). This complication is usually reversible but may not resolve for as long as 6 months after drug cessation. Drug-induced parkinsonism may be distinguishable from idiopathic Parkinson disease on the basis of the symmetry of symptoms and the absence of typical nonmotor features. For drug-induced extrapyramidal complications of dopamine blockers (**Table 28**), see later discussion of Other Drug-Induced Movement Disorders in Hyperkinetic Movement Disorders.

KEY POINT

- Drug-induced parkinsonism may be distinguished from idiopathic Parkinson disease on the basis of the symmetry of symptoms and the absence of typical nonmotor features.

Hyperkinetic Movement Disorders

Major hyperkinetic movement disorders are discussed in the following paragraphs. For additional hyperkinetic disorders, see Table 23.

Essential Tremor

Tremor is characterized by rhythmic and oscillatory movement and classified on the basis of its association with rest or

TABLE 27. Medications Causing Drug-Induced Parkinsonism

Medication Class	Examples
Common	
Antipsychotic agents	Typical: haloperidol, chlorpromazine
	Atypical: risperidone, olanzapine, ziprasidone, aripiprazole
Antiemetic agents	Metoclopramide, prochlorperazine
Dopamine depleters	Tetrabenazine, reserpine
Uncommon	
Mood stabilizers, antiepileptic drugs	Lithium, valproic acid
Other	Amiodarone, flunarazine, SSRIs including fluoxetine

SSRIs = selective serotonin reuptake inhibitors.

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TABLE 28. Extrapyramidal Complications of Dopamine D_2 Receptor Blockers

Type of Movement Disorder	Symptoms
Acute Reactions (Reversible)	
Acute dystonia	Immediate dystonic spasms; often involves the neck, face, larynx, and eyes (oculogyric crisis); rapid reversal with intravenous diphenhydramine
Acute akathisia	Immediate sensation of restlessness with urge to constantly move and pace
Subacute or Chronic Syndrome (Reversible)	
Parkinsonism	Similar to Parkinson disease, dose dependent, resolves within months after removal of the causative agent, symmetry and absence of nonmotor features, which favors a drug-induced over idiopathic cause
Tardive Syndromes (Late Onset, May Be Irreversible)	
Tardive dyskinesia	Repetitive stereotyped choreiform movements, oral-facial-lingual predominance, also can affect the extremities and trunk
Tardive dystonia	Sustained dystonic posturing commonly affecting the face, neck, trunk, and arms; extensor axial dystonia common
Tardive akathisia	Chronic sensation of restlessness with urge to constantly move and pace
Other Disorders	
Withdrawal emergent syndrome (reversible)	Dyskinesia starting after withdrawal from neuroleptic agents, stops within a few months, differential diagnosis of tardive dyskinesia masked by antipsychotic agents and only appearing after their removal (dyskinesia may become persistent)
Neuroleptic malignant syndrome (treatable emergency)	Idiosyncratic, rapid onset and progression, rigidity, dystonia, hyperthermia, rhabdomyolysis, and altered mental status

action (**Table 29**). Essential tremor is a common movement disorder that typically presents with a bilateral upper extremity postural and action tremor. Common features include a reduction of tremor amplitude with alcohol, an age of onset in late adolescence or middle age, a slow progression, and the possible development of neck and vocal tremors. Family history is positive for tremor in 50% of affected patients. Although the tremor remains stable or exhibits minor progression over time in most affected patients, a subset may experience progressive worsening of the tremor that can markedly disrupt feeding, handwriting, and fine manual tasks. A fraction (4%) of patients with a long-standing history of essential tremor may develop parkinsonism over time; some, but not all, of these patients may have Lewy body pathology on autopsy (which also is characteristic of patients with Parkinson disease).

Essential (or action) tremor should be distinguished from enhanced physiologic tremor (see Table 29). This latter type of tremor is present but unnoticeable in most persons; when enhanced by triggers, such as medications, caffeine, toxins, thyroid disease, exertion, or anxiety, it can appear similar to essential tremor. Evaluation of patients with action tremor should include identification and removal of any potential causative medications (**Table 30**) and assessment of thyroid function. Patients younger than 40 years should undergo testing for Wilson disease with serum ceruloplasmin and 24-hour urine copper measurements and with slit lamp examination for Kayser-Fleischer rings (**Figure 18**). Atypical causes of action tremor include dystonic tremor, rubral tremor, and fragile X tremor ataxia syndrome (see Table 29).

The treatment of essential tremor is symptomatic. Mild low-amplitude tremor may not require treatment unless it causes unacceptable social embarrassment. For more disabling tremors, the two most effective medications are propranolol and primidone. If these first-line therapies are not effective, adding other agents, including clonazepam, topiramate, gabapentin, and nimodipine, may provide additional tremor control in some patients. Injection with botulinum toxin can benefit some patients with refractory tremor, especially those with prominent neck or voice tremor. Use of this drug for limb tremor is limited by its adverse effect of weakness. DBS of the thalamus (specifically, the ventral intermediate nucleus) should be considered in patients with refractory disease and can provide significant benefit.

KEY POINTS

- Essential tremor is common and presents with bilateral upper extremity action tremor in late adolescence or middle age, progresses slowly, and typically has reduced amplitude with alcohol ingestion.
- Mild essential tremors may not need treatment; more disabling tremors may be treated symptomatically with propranolol and primidone.

Dystonia

Dystonia involves sustained, stereotyped, and directional twisting and posturing movements of various body parts. Generalized dystonias involve multiple body parts, including the lower extremities, whereas focal and segmental dystonias have a restricted distribution and usually spare the lower extremities. The onset of generalized dystonias commonly occurs at a young age (<25 years) and may have various causes, including metabolic and genetic disorders and ischemic and infectious damage to the basal ganglia. All patients with primary generalized dystonia should be challenged by a short trial with low-dose levodopa to screen for dopa-responsive dystonia, a rare but treatable cause of generalized dystonia. Young adults with progressive dystonia should be screened for Wilson disease, especially in the presence of

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TABLE 29. Classification of Tremors

Tremor Type	Disease Association	Features
Resting Tremor[a]		
Parkinsonian resting tremor	Parkinson disease	Re-emergence of tremor after a short delay with outstretched posturing and during ambulation, associated with other parkinsonian signs (rigidity, bradykinesia, gait impairment)
	Atypical, drug-induced, and vascular parkinsonism	Similar to Parkinson disease; tremor sometimes symmetric; red flags for atypical parkinsonism sometimes present
Dystonic tremor	Dystonia	Associated with dystonic posturing; seen both at rest and with action; position dependent with a null point at which tremor stops
Action Tremor		
Postural and kinetic tremors[b]	Essential tremor	Present in the outstretched arm position and with various actions; commonly (but not universally) associated with a positive family history and an improvement in symptoms with alcohol
	Enhanced physiologic tremor	Normal low-amplitude, high-frequency tremor seen in association with triggers, such as stress, drugs, and thyroid disease; similar to essential tremor but resolves with resolution of underlying physiologic stressor
Intention tremor[c]	Cerebellar disease	Tremor during movements that increases in amplitude as hand approaches target (also known as terminal tremor); possible association with other cerebellar symptoms, including dysmetria
	Severe essential tremor	
	Fragile X tremor ataxia syndrome	Neurodegenerative disease seen in older men with a family history of mental retardation in young males and premature ovarian failure in females; symptoms of (intention) tremor, ataxia, parkinsonism, neuropathy, and dementia
Rubral tremor	Cerebellar outflow disorders (multiple sclerosis, stroke, traumatic brain injury)	Coarse proximal tremor present at rest, worse with posturing (especially large-amplitude and proximal tremors in the "wing-beating" position with elbows flexed), and most severe during movements.
Task-specific tremor	Primary writing tremor	Only present with specific task
Orthostatic tremor	Orthostatic tremor	High-frequency tremor emerging in the legs only during standing (orthostatic position); resolving with sitting or action

[a]Tremor present with the affected extremity resting unsupported.

[b]Postural tremor is present with the arm in an outstretched position, and kinetic tremor is present during reaching, writing, and other movements.

[c]Intention tremor is a specific subtype of kinetic tremor that becomes very prominent near target, exhibiting a crescendo of increased severity at the terminal section of the movement path.

TABLE 30. Medications Causing Drug-Induced Action Tremor

Medication Class	Examples
β-Adrenergic agonists	Albuterol, terbutaline, theophylline
Stimulants	Amphetamines, methylphenidate, nicotine, caffeine
Mood stabilizers/ antiepileptic drugs	Lithium, valproic acid, carbamazepine
Neuroleptic agents	Haloperidol, olanzapine (postural and at rest)
Tricyclic antidepressants	Amitriptyline
Selective serotonin reuptake inhibitors	Fluoxetine
Immunosuppressant agents	Cyclosporine, tacrolimus
Other agents	Amiodarone, procainamide, mexiletine, levothyroxine, verapamil, atorvastatin, glucocorticoids

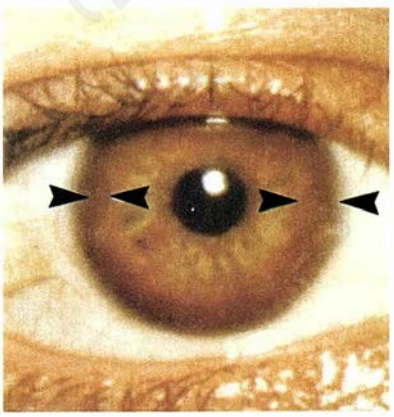

FIGURE 18. Kayser-Fleischer ring (bracketed by arrowheads) in the cornea of a patient with Wilson disease indicating copper deposition in the Descemet membrane of the iris.

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other associated findings, such as tremor, parkinsonism, and elevated levels of liver enzymes. The most common type of generalized dystonia is associated with mutation in the dystonia 1 gene (*DYT1*).

The most common focal dystonias include cervical dystonia (spasmodic torticollis), eyelid dystonia (blepharospasm), vocal cord spasmodic dysphonia, and task-specific hand dystonia (writer's cramp and musician's dystonia). Transient improvement of dystonic movement by a sensory trick ("geste antagoniste"), such as specific sensory stimuli (gently touching the involved area with the hand), provides further diagnostic clues.

Medications used for treatment of dystonia include anticholinergic agents, benzodiazepines, and baclofen. The benefit of pharmacotherapy in dystonia, however, is limited. In focal dystonias, including torticollis, injection with botulinum toxin is an effective treatment and is potentially superior to other medications. In primary generalized dystonia, DBS of the globus pallidus interna can markedly improve dystonia. Among patients with generalized dystonias, those with a positive *DYT1* mutation show the best response to DBS.

KEY POINTS

- Dystonia involves sustained, stereotyped, and directional twisting and posturing movements of various body parts.
- In focal dystonias, including torticollis, injection with botulinum toxin is an effective treatment and is potentially superior to use of other medications.

Choreiform Disorders and Huntington Disease

Chorea consists of random, nonrepetitive, flowing dance-like movements and can be caused by medications (such as antipsychotic agents and estrogen-containing drugs), endocrine derangement (as in thyrotoxicosis and acute hyperglycemia), pregnancy (chorea gravidarum), streptococcal infection (Sydenham chorea), autoimmune disease (systemic lupus erythematosus and antiphospholipid syndrome), and neurodegenerative disorders involving the basal ganglia. Huntington disease is the most common neurodegenerative cause of generalized chorea and is associated with progressive parkinsonism, gait impairment, impulsiveness, psychiatric disorders, and dementia. This condition, which is confirmed by genetic testing, is transmitted in an autosomal dominant manner, and its expression derives from the length of a repeat section (trinucleotide repeat) on chromosome 4 known as the *huntingtin* gene. The disease is caused when the repeat length exceeds a certain threshold; generational transmission often is associated with the phenomenon of "anticipation," in which the disease starts at an earlier age in a child because of increased repeat length compared with that of the parent. Because no disease-modifying treatment is available, Huntington disease is treated symptomatically.

KEY POINT

- Chorea consists of random, nonrepetitive, flowing dance-like movements and can be caused by medications, endocrine derangement, pregnancy, streptococcal infection, autoimmune disease, and neurodegenerative disorders involving the basal ganglia

Tic Disorders and Tourette Syndrome

Tics are stereotyped, brief, rapid movements that break the flow of normal movements. Partially suppressible, tics may be generated to achieve transient relief from preceding uncomfortable focal sensations (premonitory urges). Tics usually start during childhood and range from simple to complex motor movements. Most patients achieve full remission or significant reduction of tics by adulthood.

Tourette syndrome is characterized by childhood onset, persistence of multiple complex motor tics for at least 1 year, and presence of vocal tics. Echolalia (repetition of others' words) and coprolalia (utterance of obscenities) are rare but classic forms of complex vocal tics. The specific cause of the syndrome remains unclear but may involve genetic influences causing disruption of the basal ganglia–frontal cortex network. Common comorbidities include attention-deficit hyperactivity disorder, obsessive compulsive disorder, and mood disorders. Treatment options include reassurance (often appropriate in mild disease), cognitive behavioral therapy, and treatment of psychiatric comorbidities. Anti-tic medications are indicated when tics cause educational, occupational, or social dysfunction.

Although only the antipsychotic agents pimozide and haloperidol have been approved by the FDA to treat severe Tourette syndrome, other commonly used agents for this condition include the α_2-adrenergic agonists clonidine and guanfacine; benzodiazepines; the dopamine-depleting agent tetrabenazine; topiramate; and—in patients with refractory disease—the antipsychotic agents aripiprazole, ziprasidone, and risperidone. The risk of tardive dyskinesia is a concern when antipsychotic agents are used in adulthood. Botulinum toxin may provide an additional option for certain simple (blinking) or potentially dangerous (cervical whiplashing) tics.

KEY POINTS

- Tourette syndrome is characterized by childhood onset, persistence of multiple complex motor tics for at least 1 year, and presence of vocal tics.
- Treatment of Tourette syndrome includes reassurance (often appropriate in mild disease), cognitive behavioral therapy, and treatment of psychiatric comorbidities

Restless Legs Syndrome and Sleep-Related Movement Disorders

Restless legs syndrome (RLS) is a common movement disorder characterized by discomforting sensations in the legs at rest or when falling asleep, an urge to move the legs, and

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immediate relief after moving the legs or walking. Patients with RLS should be screened for iron deficiency and receive iron supplements in the presence of deficiency or even low-normal serum ferritin levels (<45 ng/mL [45 µg/L]). Certain drugs, such as selective serotonin reuptake inhibitors and dopamine-blocking agents, can worsen RLS. Stimulants should be avoided late in the day. The most effective treatments are dopamine agonists, specifically pramipexole, ropinirole, and the rotigotine patch. Adverse effects of these medications, such as impulse control disorder, may limit their use. Other dopamine agonist complications include the development of augmentation (that is, symptoms begin to appear earlier in the day) and rebound (that is, symptoms return with greater intensity as the dose wears off). Use of long-acting formulations can lessen both of these complications. Other pharmacologic options include levodopa, gabapentin, opioids, benzodiazepines, and carbamazepine.

Periodic limb movements of sleep are brief triple flexion movements of the lower legs that repeat several times in 20-second cycles during early sleep. This disorder is very common and can occur independently or be associated with RLS, sleep-disordered breathing, or narcolepsy. The diagnosis is made by polysomnography. Treatment is not required unless severe sleep fragmentation occurs.

In REM sleep behavior disorder, patients do not experience normal muscle paralysis during the REM phase of sleep and, as a result, tend to physically act out their dreams; this tendency leads to shouting, kicking, punching, and similar behaviors during sleep. The diagnosis is based on the report of a bed partner or results of polysomnography. The main disorder in the differential diagnosis is nocturnal epilepsy. Highly effective treatment options include clonazepam and melatonin. In recent years, REM sleep behavior disorder has been identified as a strong predictor of future development of Parkinson disease and other α-synuclein–related disorders, such as multiple system atrophy and dementia with Lewy bodies.

KEY POINTS

- Patients with restless legs syndrome should be screened for iron deficiency and receive iron supplements in the presence of deficiency or even low-normal serum ferritin levels.
- The most effective treatments of restless legs syndrome are dopamine agonists, specifically pramipexole, ropinirole, and the rotigotine patch

Other Drug-Induced Movement Disorders

Tardive Dyskinesia

Medications that block dopamine D_2 receptors can cause various extrapyramidal adverse effects, ranging from acute dystonic reaction to parkinsonism and tardive dyskinesia (see Table 28). Tardive dyskinesia is associated with characteristic choreiform and dystonic craniofacial movements, but involvement of other body parts, including the neck and trunk, also is possible. Removal of the causative medication is key to treatment, but symptoms of tardive dyskinesia can take months to resolve or may become permanent. A longer duration and higher dose of the causative medication, older age, and female sex carry a higher risk of permanent dyskinesia. Although typical antipsychotic agents (such as haloperidol) pose the highest risk of developing tardive dyskinesia, this disorder also can occur with the chronic use of many atypical antipsychotic drugs, the antiemetic agent metoclopramide, and the tricyclic antidepressant amoxapine. All patients taking any of these agents must first be warned of this potential complication. Pharmacologic treatment of tardive dyskinesia is often unsatisfactory, but options include clonazepam, tetrabenazine, anticholinergic agents, and clozapine.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening disorder caused by an idiosyncratic exposure to therapeutic doses of dopamine-blocking agents. NMS pathophysiology involves a sudden decrease in dopamine D_2 receptor activity, but the mechanism underlying this decrease is unclear. This condition has rapid onset and progression and is characterized by hyperthermia, rhabdomyolysis, altered mental status, and extrapyramidal symptoms, including rigidity and dystonia. Treatment of NMS involves the removal of the causative agent and supportive management; medical options include the muscle relaxant dantrolene (to relieve muscle breakdown) and dopamine agonists, such as bromocriptine

A similar syndrome can occur in the setting of rapid withdrawal from chronic dopaminergic treatment, as in hospitalized patients with Parkinson disease. H

KEY POINTS

- Medications that block dopamine D_2 receptors can cause various extrapyramidal adverse effects, ranging from acute dystonic reaction to parkinsonism and tardive dyskinesia.
- Removal of the causative medication is key to treating tardive dyskinesia, but symptoms can take months to resolve or may become permanent.
- Neuroleptic malignant syndrome is a life threatening disorder caused by an idiosyncratic reaction to dopamine-blocking agents that presents with hyperthermia, rhabdomyolysis, altered mental status, and extrapyramidal symptoms, including rigidity and dystonia.

Multiple Sclerosis

Spectrum, Pathophysiology, and Epidemiology

Multiple sclerosis (MS) is an autoimmune condition that results in immune-mediated damage to structures in the central nervous system (CNS). Autopsy studies have shown the

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widespread effects of MS on the brain, spinal cord, and optic nerve. The pathologic hallmarks of MS are focal areas of inflammation and demyelination in white matter tracts, sometimes associated with damage to glial structures and axonal transection. The neurologic symptoms and disability experienced by patients with MS are consequences of these pathologic processes.

MS generally has a younger age of onset than most chronic neurologic conditions, with most patients experiencing their first symptoms between the ages of 20 and 40 years. However, pediatric and older age–onset MS can occur. Patients with MS are mostly female, with a female to male ratio of approximately 3:1, according to most epidemiologic studies.

Multiple genetic and environmental factors contribute to the risk of MS. Genome-wide assays have identified risk alleles in genes for the major histocompatibility complex, interleukin-2 receptor, and interleukin-7 receptor, among many others. Despite the large number of genes involved, however, no specific genetic markers are diagnostic of MS. Twin studies show a concordance of 25% in monozygotic twins and 2.4% in dizygotic twins. Geographic location before adolescence is a clearly established environmental factor, with the highest risk of MS found in northern latitudes.

KEY POINT

- Multiple sclerosis is an autoimmune condition resulting in immune-mediated damage to structures in the central nervous system that is characterized by young age of onset (20-40 years) and a 3:1 female predominance.

Presenting Signs and Symptoms

The symptoms of MS are thought to occur as a result of the functional interruption by inflammatory lesions of critical axonal tracts. In most patients, focal lesions occur intermittently and acutely and lead to the rapid onset of clinical symptoms, often termed a relapse or "flare." Relapses tend to evolve over the course of a few days and often last for weeks to months before improving. Improvement in symptoms may represent remyelination of demyelinated areas and increased recruitment of other brain regions to substitute for areas of more extensive injury.

Because MS can affect nearly any part of the CNS, myriad symptoms can occur. The most common clinical manifestations of an MS relapse are optic neuritis, myelitis, and brainstem/cerebellar symptoms. Optic neuritis, or inflammation of the optic nerve, often presents as a subacute visual deficit in one eye along with pain with eye movement. An ophthalmologic examination will reveal a reduction in visual acuity, a scotoma or visual field deficit, and color desaturation (resulting in a decreased ability to discriminate colors). Pupillary examination will reveal an afferent pupillary defect, which results in paradoxical dilation of the pupil when light is rapidly shifted from the unaffected to the affected eye. If the anterior portion of the optic nerve is involved, funduscopic examination may also reveal papillitis (inflammatory changes in the retina causing a flared appearance of the optic disc).

Myelitis, or focal inflammation within the spinal cord, usually manifests as sensory or motor symptoms below the affected spinal level. Some patients also may experience a tight, band-like sensation around the chest or abdomen during the acute inflammatory process; Lhermitte sign, a shock-like sensation radiating down the spine or limbs induced by neck movements; and urinary frequency, urgency, or retention. Unlike other spinal cord processes, MS generally causes a partial myelitis, and thus symptoms of a full-cord transection are exceedingly rare. Physical examination often reveals focal weakness and possibly reduced sensation below a specific spinal level (sensory level). Muscle tone can be flaccid in the acute setting, but often spasticity is noted subsequently on muscular examination.

Disruption of vestibular or cerebellar pathways can lead to ataxia and vertigo; appendicular or truncal ataxia also can be seen, with dysmetria on finger-to-nose testing and difficulties with tandem gait. Brainstem involvement also can result in eye movement abnormalities and cause symptoms of diplopia or oscillopsia (a sensation of jerking of the visual field). Dysconjugate eye movements, nystagmus, and internuclear ophthalmoplegia (inability to adduct one eye and nystagmus in the abducting eye) sometimes are seen on oculomotor examination.

In addition to the development of acute and subacute focal symptoms, MS can also result in subtle chronic symptoms because of widespread cortical demyelination and atrophy, commonly manifested as cognitive dysfunction and mental and physical fatigue. In contrast to cerebrovascular disease, MS generally is not associated with cortical syndromes, such as aphasia and neglect.

Many patients with MS also experience the Uhthoff phenomenon, which is transient worsening of baseline neurologic symptoms with elevations of body temperature. Similar to electrical conductance, neuronal conductance is reduced at elevated temperatures, which allows a magnification of symptoms from previously demyelinated lesions. Uhthoff phenomenon events should be differentiated from relapses because they do not represent new inflammatory events and do not require direct treatment. Any patient with suspected relapse should be screened for intercurrent infection.

KEY POINT

- The most common clinical manifestations of a multiple sclerosis relapse are optic neuritis, myelitis, and brainstem/cerebellar symptoms; subtle chronic symptoms also can develop because of widespread cortical demyelination and atrophy, often manifested as cognitive dysfunction and mental and physical fatigue.

Diagnosis of Multiple Sclerosis

Diagnostic Criteria and Testing

No MS-specific diagnostic biomarkers are available; therefore, confirming the diagnosis of MS requires a full assessment of

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clinical symptoms, ancillary testing, and exclusion of other conditions in the differential diagnosis. The official diagnostic criteria for MS, known as the McDonald criteria, provide guidelines about the proper integration of clinical and diagnostic evidence. The McDonald criteria require evidence of CNS demyelination disseminated in both space and time. These criteria can be satisfied by a combination of documented clinical relapses, signs on physical examination, and the distribution of lesions on an MRI. Because MRI is the main diagnostic tool in MS, the McDonald criteria also provide guidance about which abnormalities are specific to MS, which is critical because many other disorders also cause brain lesions on MRI. **Figure 19** shows examples of each of the five lesion types that meet these criteria: periventricular, juxtacortical, infratentorial (brainstem and cerebellum), spinal cord, and contrast enhancing. Knowledge of the location and type of lesions that are specific to MS is critical because other common conditions, such as migraine, microvascular ischemic disease, and head trauma, can also cause white matter lesions on MRI. However, these conditions do not cause lesions that meet the McDonald criteria requirements in terms of location and conformation. Proper application of the diagnostic criteria as they apply to MRI findings can prevent unnecessary neurologic testing, referrals, and misdiagnoses.

In addition to MRI, ancillary testing can be used to show objective evidence of demyelinating lesions. Reduced evoked potential conduction velocity on electrophysiologic testing—such as visual evoked potentials, brainstem auditory evoked potentials, and somatosensory evoked potentials—can be used as surrogate markers for demyelinating lesions in CNS white matter pathways. Optic coherence tomography is being increasingly used to confirm optic nerve damage; this testing uses near-infrared light to quantify the thickness of the retinal nerve fiber layer in the optic disc and the thickness of the macula. Reduced thickness in these regions is seen in patients with MS, most severely in patients with previous optic neuritis, but also in those who have not had this syndrome.

Cerebrospinal fluid (CSF) testing can be helpful when the diagnosis of MS is not clear but is not required for diagnosis if the full McDonald criteria have been met and other causes have been excluded. The CSF of approximately 85% to 90% of persons with MS contains oligoclonal bands not present in their serum and also an elevated IgG index and synthesis rate. Additionally, mild elevations in the CSF leukocyte count or protein level are sometimes present.

KEY POINTS

- The diagnosis of multiple sclerosis (MS) requires evidence of central nervous system demyelination disseminated in both space and time; MRI is the main diagnostic tool in MS.
- Cerebrospinal fluid testing can be helpful when the diagnosis of MS is not clear but is not required for diagnosis if the full McDonald criteria have been met and other causes have been excluded. HVC

Differential Diagnosis of Multiple Sclerosis

Whenever the diagnosis of MS is being considered, conditions that mimic the disorder should be part of the differential diagnosis (**Table 31**). Various rheumatologic, inflammatory, infectious, and metabolic disorders can cause neurologic symptoms and MRI changes that sometimes are incorrectly diagnosed as MS. Knowledge of the other potential diagnoses in the differential and their distinguishing features can help reduce misdiagnoses and inappropriate referrals.

Clinical Course of Multiple Sclerosis

The potential clinical phenotypes of MS are shown in **Figure 20**. Most patients with MS (approximately 85%) initially experience a relapsing-remitting course. Those who do not meet the full diagnostic criteria for MS after a first event are said to have had a clinically isolated syndrome (CIS). Because disease-modifying therapies for MS have been shown to be useful in CIS for reducing the risk of

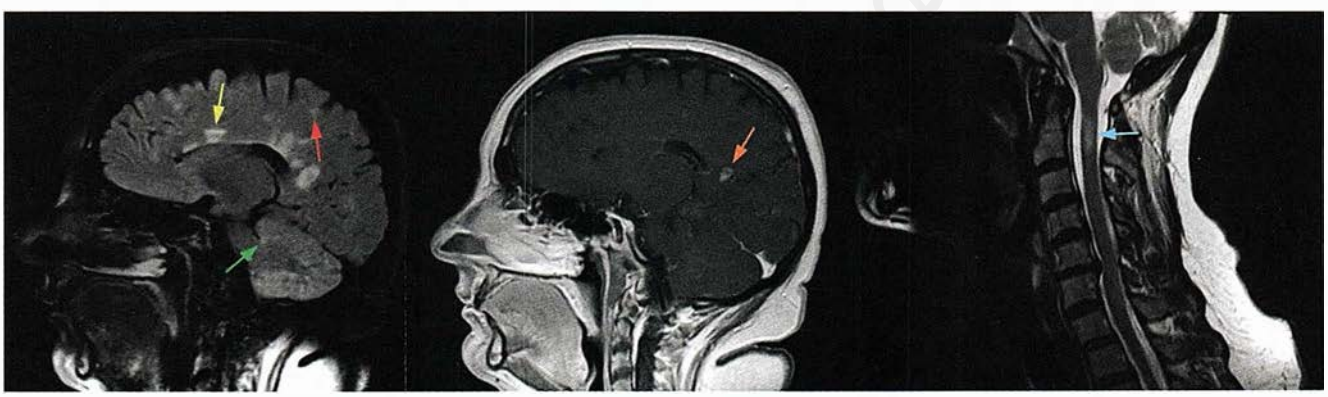

FIGURE 19. Characteristic lesions seen on MRI in multiple sclerosis. *Left*, sagittal fluid attenuated inversion recovery (FLAIR) brain sequence revealing periventricular (*yellow arrow*), juxtacortical (*red arrow*), and infratentorial (*green arrow*) lesions. *Center*, sagittal T1 brain image after administration of intravenous contrast; MS lesions are typically either silent or dark on T1 imaging, but those lesions that enhance with contrast (*orange arrow*) do so because of active inflammation within that lesion. *Right*, sagittal T2 scan of the cervical spine showing a lesion at approximately the C2 level (*blue arrow*).

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TABLE 31. Differential Diagnosis of Multiple Sclerosis

Disorder	Notes
Other demyelinating diseases	
ADEM	Monophasic, often postinfectious syndrome causing large, diffuse areas of inflammatory CNS demyelination
	Characterized by fevers and encephalopathy, typically with focal neurologic symptoms, that help differentiate this entity from MS
	More common in children (rare in adults)
Neuromyelitis optica (Devic disease)	Antibody-mediated inflammation directed at aquaporin-4 antibody channels in the CNS that results in inflammatory demyelination in the optic nerve and spinal cord
	Can be differentiated from MS by NMO IgG antibody testing and by its lack of significant brain involvement, large and longitudinally extensive spinal cord lesions, and profound CSF leukocytosis
Idiopathic transverse myelitis[a]	Monophasic, often postinfectious syndrome causing spinal cord inflammation
	Differentiated from MS by the presence of symptoms and findings unique to the underlying systemic disorder in addition to any neurologic symptoms
Systemic inflammatory diseases	
SLE	Can cause encephalopathy and white matter changes on MRI, often follows a relapsing-remitting course
Sjögren syndrome	Can cause an NMO-like disorder (with optic neuritis and myelitis), multiple cranial neuropathies, and a small-fiber neuropathy
Sarcoidosis	Causes granulomatous inflammation in the parenchyma and meninges of the brain and spinal cord
	Occasionally associated with myelopathy
Metabolic Disorders	
Adult-onset leukodystrophies	Rare
	Include adrenoleukodystrophy and metachromatic leukodystrophy
	May cause white matter changes and progressive neurologic symptoms
	Family history typically present
Vitamin B_{12} deficiency	Can cause optic neuropathy, cognitive changes, and subacute combined degeneration of the spinal cord (spasticity, weakness, and vibratory and proprioceptive sensory loss)
Copper deficiency	Can cause a myelopathy identical to that of vitamin B_{12} deficiency
Infections	
HIV infection, Lyme disease, and syphilis	Can cause encephalopathy and myelopathy
	Can be diagnosed with appropriate serologic and CSF analysis
HTLV	Causes a slowly progressive myelopathy with thoracic spinal cord atrophy
	Sometimes termed tropical spastic paraparesis because more common in patients in equatorial latitudes
Vascular disorders	
Sporadic and genetic stroke syndromes (hypercoagulability disorders)	Microvascular ischemic diseases potentially causing nonspecific white matter changes on MRI that are often confused with MS
	Distinguished from MS by age, other vascular risk factors, and findings on neurologic examination
CNS vasculitis	Primary type diagnosed by catheter angiography or tissue biopsy
	Can present with both stroke-like changes and meningeal contrast enhancement on MRI
Susac syndrome	Causes a small-vessel arteriopathy that causes dysfunction of the retina and cochlea and corpus callosum lesions seen on MRI
	Subacute clinical progression, without remission or relapse
Migraine	Subcortical white matter lesions sometimes present and often confused with MS lesions
	CADASIL a possible diagnosis in patients with a familial syndrome of migraine, subcortical strokes, mood disorders, and early dementia

(Continued on the next page)

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TABLE 31. Differential Diagnosis of Multiple Sclerosis *(Continued)*

Disorder	Notes
Neoplasia (primary CNS neoplasm [gliomas or lymphomas] or metastatic disease)	Neoplasms with progressively worsening symptoms and neuroimaging findings
	Brain biopsy indicated when imaging cannot differentiate neoplasms from demyelinating disease
Paraneoplastic syndromes	May cause progressive cerebellar ataxia or myeloneuropathy (neuropathy affecting the spinal cord and peripheral nerves)
	Personality and mental status changes in addition to seizures and movement disorders possible with paraneoplastic limbic encephalitis
	Diagnosis often made on the basis of antibody testing and evaluation for metastases
Somatoform disorders	Psychiatric disorders presenting with neurologic-like symptoms that are due to somatization, conversion, and similar conditions
	Neurologic evaluation findings normal

ADEM = acute disseminated encephalomyelitis; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS = central nervous system; CSF = cerebrospinal fluid; HTLV = human T-lymphotropic virus; MS = multiple sclerosis; NMO = neuromyelitis optica; SLE = systemic lupus erythematosus.

*For more information on idiopathic transverse myelitis, see Spinal Cord Disorders.

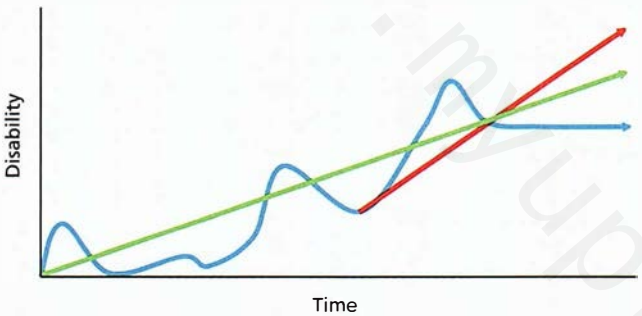

FIGURE 20. Visual representation of the three clinical phenotypes of multiple sclerosis. Most patients with MS will experience a relapsing-remitting course (*blue line*) at disease onset. Relapses initially do not result in significant permanent disability; however, as time goes on, residual disability accrues. Some patients with a relapsing-remitting course will continue in this manner and eventually plateau at a consistent level of disability. However, some will transition to a secondary progressive course (*red line*), in which disability accrues over time without clear relapsing or remitting events. Patients with primary progressive MS (*green line*) never experience any relapsing-remitting events, instead undergoing progressive disability accumulation from the start.

conversion to clinically definite MS by approximately 50%, stratification of the risk of conversion is helpful in making treatment decisions. Patients with brain lesions on MRI at the time of their CIS have a 10-year risk of conversion to clinically definite MS of approximately 90%, whereas the risk of those without brain lesions is only 10% to 20%.

Symptoms of an MS relapse tend to peak after a few days to weeks and are followed by a period of recovery that may take weeks to months. In the first few years of MS, significant or complete recovery is common. Eventually, however, recovery diminishes and permanent disability can accumulate. In approximately 50% to 60% of patients with an initial relapsing-remitting course, relapses become infrequent or cease completely after a median of 10 to 15 years, but neurologic disability continues to accrue in a slowly progressive manner. This latter disease stage is termed secondary progressive MS.

Approximately 15% of patients with MS never experience a relapse but instead have progressive disability accumulation from the time of disease onset. This clinical phenotype is termed primary progressive MS. Although this subtype often presents later in life (fifth or sixth decade), rapid disability accumulation can occur. Although early studies of the natural history of the disease type had implicated sex and age at onset as predictors of rapid progression, recent studies have only supported early disability accrual as a predictor of long-term progression rates.

In addition to the classic MS subtypes, the recent increased availability of MRI has led to the identification of radiologically isolated syndrome; this term describes the disease in patients without demyelinating symptoms but with incidental MRI changes that satisfy the radiologic requirements of the McDonald diagnostic criteria for MS. Although the official diagnosis of MS cannot be made in the absence of demyelinating symptoms, patients with these incidental MRI changes are thought to be at high risk for later conversion to clinically definite MS. The diagnosis, prognosis, and treatment of radiologically isolated syndrome are controversial and the subjects of ongoing research.

KEY POINT

- Patients who do not meet the full diagnostic criteria for multiple sclerosis (MS) after a first event (clinically isolated syndrome) but have brain lesions on MRI have a 10-year risk of conversion to clinically definite MS of approximately 90%.

Treatment of Multiple Sclerosis

Lifestyle Modifications and General Health Care

Although some patients with MS avoid physical activity because of disability and fatigue, strengthening, stretching, and aerobic exercise is recommended. Maintenance of an

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active healthy lifestyle and muscular fitness can mitigate disability to some extent and preserve appropriate muscle tone. Physical therapy and home exercise programs are useful in this regard, especially after a clinical relapse. Although symptoms can appear worse with exertion-related body temperature increases (Uhthoff phenomenon), patients with MS should be assured that neurologic injury will not result. In patients with significant Uhthoff phenomenon, minimization of discomforting symptoms can be achieved with strategies aimed at avoiding heat exposure or cooling the body.

Exercise also can help preserve bone health, which is vital given the increased risk of osteoporosis in patients with MS. The threefold to sixfold increased rate of reduction of bone mineral density seen in patients with MS is likely due to various factors, such as reduced physical activity, increased rates of vitamin D deficiency, and the effects of repeated glucocorticoid use. Vitamin D and calcium supplementation can help minimize this effect.

The use of vitamin D has additional benefits for patients with MS. The links between vitamin D deficiency and MS pathophysiology have been clearly established, with reduced serum vitamin D levels predicting future accumulation of new lesions on MRI. A recent randomized trial of the addition of vitamin D supplements to interferon-beta treatment showed that this supplementation reduced the accumulation of MRI lesions compared with placebo. Because of these data, vitamin D supplementation is now suggested for all patients with MS, although the ideal dosing regimen and serum 25-hydroxyvitamin D level are still unknown.

Because the risk of an MS relapse is increased at the time of systemic infections and because of the immunosuppressive nature of some of the newer MS medications, steps to prevent infection also are recommended. Current MS treatment guidelines suggest vaccination against influenza and maintenance of standard immunizations. Patients with MS with bladder dysfunction should be provided strategies to reduce the risk of urinary tract infection, such as intermittent catheterization or prophylactic antibiotics.

Smoking cessation is strongly advised for all patients with MS because of the threefold increased risk of conversion to secondary progression associated with cigarette smoking.

Because of the age and female sex of many patients with MS, issues related to pregnancy and lactation often must be addressed. Fortunately, the estrogenic state of pregnancy actually has an immunomodulatory effect that tends to reduce autoimmunity and result in the reduced MS relapse rates seen during pregnancy. However, the risk of relapse in the first three months after delivery is significantly increased. Despite this fact, repeated studies have shown that not only does pregnancy not cause additional permanent disability, but multiparous women seem to have better long-term MS outcomes than nulliparous or uniparous women. The impact of breastfeeding on MS relapse risk remains controversial, with various studies providing conflicting evidence.

KEY POINTS

- Maintenance of an active healthy lifestyle and strengthening, stretching, and aerobic exercise are recommended for all patients with multiple sclerosis to mitigate disability and preserve appropriate muscle tone. **HVC**
- Vitamin D supplementation, annual influenza vaccination, and maintaining a routine immunization schedule are recommended for all patients with multiple sclerosis. **HVC**
- Smoking cessation is strongly advised for all patients with multiple sclerosis because of the threefold increased risk of conversion to secondary progression associated with cigarette smoking. **HVC**

Treatment of Acute Exacerbations

A true MS relapse is likely when patients with the disease experience new or worsening neurologic symptoms lasting greater than 24 hours. Transient symptoms lasting minutes to hours, however, should not be considered a true relapse. Before initiation of treatment for an MS relapse, the possibility of a pseudorelapse (transient worsening of underlying neurologic symptoms in the setting of infection or systemic illness) should be considered. If a pseudorelapse is suspected, tests should be performed to discover and treat any occult infections or metabolic disturbances, which often results in resolution of neurologic symptoms.

Confirmed relapses typically are treated with high-dose glucocorticoids. Treatment is traditionally administered intravenously with methylprednisolone, 1 g/d for 3 to 5 days. However, recent studies have shown equivalency between this dose of intravenous glucocorticoids and oral prednisone, 1250 mg/d, and thus this alternative strategy is gaining wider use, especially given its reduced cost and ease of administration. The typical adverse effects of short-term, high-dose glucocorticoids are insomnia, hyperglycemia, a metallic taste, gastritis, fluid retention, irritability, and, on rare occasions, psychosis. Frequent glucocorticoid treatment should be avoided because it places patients at risk for the long-term adverse effects of these drugs, such as osteopenia and early cataracts. Relapses that are refractory to glucocorticoid treatment may respond to rescue therapy with plasmapheresis. H

KEY POINT

- Confirmed relapses of multiple sclerosis typically are treated with high-dose glucocorticoids.

Disease-Modifying Therapies

Definitive treatment of MS relies less on addressing relapses as they occur than on preventing relapse occurrence (and the associated accrual of disability) in the first place. This prevention is achieved with MS disease-modifying therapies, a series of immunomodulatory or immunosuppressive medications that have been shown to reduce the risk of relapse, disability progression, and new MRI lesion formation. Twelve disease-modifying therapies have been approved by the FDA for use in

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relapsing-remitting MS (**Table 32**), each differing in their route of administration, mechanism of action, and potential adverse effects. Additionally, the interferon beta preparations and glatiramer acetate have been shown to delay conversion to clinically definite MS in those with CIS. Unfortunately, the options are far more limited for those with progressive forms of MS; mitoxantrone is the only FDA-approved therapy for those with secondary progressive MS, and no therapies have proven benefit in primary progressive MS.

Choosing an appropriate therapy from these options depends on patient tolerability, risk stratification, and disease activity. Treatment decisions in MS often are made in discussion between an experienced specialist (a general neurologist or MS specialist) and the patient. No clear consensus exists about how to select the appropriate therapy, what defines treatment failure, or how to decide the order in which medications should be introduced. Generally, most physicians recommend self-injection medications (one of the interferon beta preparations or glatiramer acetate) as first-line agents, given their favorable risk profiles. Patients who are unable to tolerate these medications or in whom the medications are ineffective are often then switched to agents with better efficacy profiles (such as the oral or intravenous options outlined in Table 32), although this greater efficacy comes with greater potential risks.

The interferon beta preparations (beta-1a and beta-1b) use an immunomodulatory cytokine that shifts immune responses away from autoimmunity and increases the integrity of the blood-brain barrier. Interferon beta-1a is typically administered either once weekly by intramuscular injection or

TABLE 32. Disease-Modifying Therapies for Multiple Sclerosis

Medication	Route of Administration	Potential Adverse Effects	Recommended Monitoring	Pregnancy Category[a]
Interferon beta-1a (three formulations) and interferon beta-1b (two formulations)	Intramuscular or subcutaneous injection	Flu-like symptoms, fatigue, depression, increased spasticity, transaminitis, rare autoimmune hepatitis, and injection site reactions	CBC and liver chemistry testing every 3-6 months	C
Glatiramer acetate	Subcutaneous injection	Injection site reactions, lipoatrophy of skin at injection sites, and rare systemic panic attack-like syndrome	None	B
Natalizumab	Intravenous	Black-box warning of increased risk of PML, common adverse effects of headache and chest discomfort, and rare hepatotoxicity, infusion reactions and anaphylactic reactions	Rigorous, regimented, industry-sponsored monitoring (TOUCH™ program) and JC virus antibody testing	C
Alemtuzumab	Intravenous	Infusion reactions, including headache and rash; upper respiratory, urinary tract, and herpes virus infections; autoimmune thrombocytopenic purpura and autoimmune thyroid disease.	Pretreatment screening for varicella vaccination, thyroid function monitoring every 3 months, and monthly urinalysis and CBC and serum creatinine measurement	C
Fingolimod	Oral	Transaminitis, lymphopenia, increased risk of serious herpesvirus infection, hypertension, bradycardia (usually only with the first dose), and macular edema	Cardiac monitoring after administration of first dose, ophthalmologic screening, liver chemistry testing, and CBC	C
Dimethyl fumarate	Oral	Diarrhea, nausea, abdominal cramping, flushing, and lymphopenia	Frequent monitoring of CBC in first 6 months after administration and every 6 months thereafter	C
Teriflunomide	Oral	Alopecia, respiratory infections (including TB), pancreatitis, transaminitis, lymphopenia, hypertension, and peripheral neuropathy	Frequent CBC monitoring, hepatic panel, serum amylase and lipase measurements, and blood pressure determination in the first 6 months, every 6 months thereafter.	X
Mitoxantrone	Intravenous	Black-box warnings for cardiotoxicity and acute myeloid leukemia; other adverse effects of infection, nausea, oral sores, alopecia, menstrual irregularities, and blue discoloration of urine	Required monitoring of cardiac function by echocardiography or multigated radionucleotide angiography before each infusion and regular CBC	D

CBC = complete blood count; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis.

[a]Pregnancy categories: B, animal studies suggest fetal risk; C, animal studies suggest adverse fetal effects; D, evidence of human fetal risk; X = documented fetal abnormalities.

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three times weekly by subcutaneous injection, whereas interferon beta-1b is administered every other day by subcutaneous injection. A pegylated formulation of interferon beta-1a (peginterferon beta-1a) administered by twice-monthly subcutaneous injection also has recently been approved by the FDA. The interferons have been shown to reduce the relapse rate by approximately one third over 2 years compared with placebo and to have positive effects on disability progression and MRI findings. Head-to-head studies have shown general equivalence for most of the interferons, although more frequent administration resulted in slightly increased efficacy of one or the other in some studies.

Glatiramer acetate, a copolymer of four amino acids, is administered daily by subcutaneous injection. This medication likely has multiple mechanisms of action that result in immunomodulation. Glatiramer acetate and high-dose interferon betas exhibit similar reductions in relapse rates compared with placebo and are equivalent in head-to-head studies. Combining glatiramer acetate with an interferon-beta provides no added benefit to what either drug achieves alone.

Natalizumab is a monoclonal antibody that is administered by once-monthly intravenous infusion. Natalizumab binds to a cellular adhesion molecule on activated T-cells that is required for transmigration into the CNS. Natalizumab is a highly effective medication, reducing relapse rates by approximately two thirds compared with placebo over 2 years and slowing 2-year disability progression by approximately 40%. Despite its efficacy, natalizumab is typically limited to use as a second-line agent because of the risk of development of progressive multifocal leukoencephalopathy, a CNS demyelinating infection caused by reactivation of the JC virus. The overall risk is approximately 1:1000 but is significantly higher in patients who have previous exposure to immunosuppressant agents or chemotherapy and those who have elevated serum titers of antibodies against the JC virus. Stratification of risk by treatment history and JC virus antibody testing is thus an important step before initiating natalizumab.

Alemtuzumab is an anti-CD52 monoclonal antibody that causes complement-mediated lysis of circulating lymphocytes. It is administered as an infrequent intravenous infusion (once per day for 5 consecutive days and then again for 3 consecutive days 1 year later). Alemtuzumab reduces relapse rates and the risk of disability progression by approximately half and also significantly reduces the accumulation of new lesions and brain atrophy on MRI, compared with the interferon beta preparations. Because of significant safety concerns (see Table 32), alemtuzumab administration requires intensive safety monitoring and risk modification. Its increased risk of herpetic viral infections can be reduced with use of prophylactic antiviral agents.

Fingolimod is a once daily pill that results in sequestration of activated lymphocytes in lymph nodes. Fingolimod reduces relapse rates by approximately half over 2 years compared with placebo and also reduces the risk of disability progression and accumulation of new MRI lesions. Fingolimod requires first-dose monitoring because of the first-dose bradycardia that occurs in most patients and should not be used in patients with heart block.

Teriflunomide is a once daily pill that exerts an immunosuppressive effect by inhibiting a mitochondrial enzyme involved in pyrimidine synthesis in rapidly dividing cells. Compared with placebo, teriflunomide reduces relapse rates by one third and also reduces the risk of disability progression and the accumulation of new MRI lesions over 2 years.

Oral dimethyl fumarate exerts its immunomodulatory effects by modulating the nuclear factor–like 2 transcriptional pathway. Twice daily dosing is approved for use in relapsing-remitting MS and has been shown to reduce relapse rates by slightly less than one half and to reduce the risk of disability progression and new MRI lesion development over 2 years.

Mitoxantrone is an anthracenedione chemotherapeutic agent that exerts an immunosuppressive effect by reducing lymphocyte proliferation. Although this medication has been shown to reduce relapse rates and is the only drug ever to have had any success in reducing the rate of disability accumulation in those with secondary progressive MS, the risks of cardiac toxicity and secondary leukemia have significantly limited its use.

KEY POINTS

- Interferon beta preparations and glatiramer acetate are immunomodulatory, disease-modifying medications used to treat multiple sclerosis that reduce the risk of relapse, disability progression, and new MRI lesion formation.
- Natalizumab is a highly effective medication that reduces relapse rates in multiple sclerosis by approximately two thirds compared with placebo and slows disability progression by approximately 40% but is used only as a second-line agent because it can cause progressive multifocal leukoencephalopathy.

Symptomatic Management

Adequate management of MS requires the treatment of symptoms that remain chronic after previous relapses or progression. Symptomatic pharmacologic and nonpharmacologic interventions (**Table 33**) can increase the quality of life of patients with MS.

Spasticity is a frequent consequence of damage to the corticospinal tract in MS. This symptom manifests clinically as increased muscle tone, painful muscle cramps, spasms, and contractures. Spasticity can be reduced by using muscle relaxants, such as baclofen, tizanidine, or cyclobenzaprine. Gabapentin also has been used successfully to reduce spasms in MS. For severe spasticity, botulinum toxin or implantable intrathecal baclofen pumps also can be used.

Treatment of neuropathic pain frequently involves the use of many of the same medications used to treat painful diabetic neuropathy. Although newer medications, such as pregabalin and duloxetine, have been used successfully for this type of

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TABLE 33. Symptomatic Management in Multiple Sclerosis

Symptom	Nonpharmacologic Management	Pharmacologic Management
Spasticity	Physical therapy, stretching, massage therapy	Baclofen (oral or intrathecal pump), tizanidine, cyclobenzaprine, gabapentin, benzodiazepines, carisoprodol, botulinum toxin
Neuropathic pain	N/A	Gabapentin, pregabalin, duloxetine, tricyclic antidepressants, tramadol, carbamazepine, topiramate, capsaicin patch
Fatigue	Proper sleep hygiene, regular exercise	Modafinil, armodafinil, amantadine, amphetamine stimulants
Depression	Individual or group counseling	Antidepressants (such as SSRIs, SNRIs, tricyclic antidepressants, antipsychotic agents)
Cognitive dysfunction	Cognitive rehabilitation and accommodation strategies	No proven therapy
Impaired mobility	Physical and occupational therapy; use of braces, canes, rolling walkers, or electrostimulatory walk-assist devices	Dalfampridine
Urinary urgency/ frequency	Timed voids, avoidance of caffeine	Oxybutynin, tolterodine
Urinary retention	Manual pelvic pressure, intermittent catheterization	None
Pseudobulbar affect	None	Dextromethorphan-quinidine
Limb tremor	Occupational therapy	Botulinum toxin

N/A = not applicable; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

CONT.

pain, less expensive generic alternatives, such as tricyclic antidepressants and gabapentin, are equally effective and well tolerated. Treatment of trigeminal neuralgia, a common neuropathic pain syndrome in MS, is discussed in more detail in Headache and Facial Pain.

Chronic fatigue is a very common symptom in MS. The fatigue associated with MS can have various causes, such as depression, insomnia, or other comorbid conditions. However, patients with MS without these conditions also can experience significant fatigue, which is often described as a sensation of mental exhaustion, frequently occurring in the midafternoon. Lifestyle adjustments, such as improving sleep hygiene, getting regular exercise, and treating depression, can sometimes resolve this symptom. For those with refractory fatigue, stimulant medications can be used. The most common medications of this type used in MS are modafinil, armodafinil, and amantadine. For fatigue that is refractory to these medications, amphetamine stimulants, such as methylphenidate, also can be considered.

Depression also is a common symptom in patients with MS, and the suicide rate is elevated in those with MS compared with those with depression for other reasons. The depression that occurs in MS is likely multifactorial, involving the emotional response to dealing with a chronic disease, the consequences of demyelinating lesions and inflammatory cytokines, and the adverse effects of treatments (such as the interferon betas). Clinicians should be vigilant for signs of depression and have a low threshold for initiating antidepressants and offering referrals to psychiatry and individual or group therapy programs.

Cognitive dysfunction occurs in at least 50% of patients with MS. The most common deficits involve short-term memory, processing speed, and executive function. Cognitive disability has a significant effect on the employability of patients with MS and can reduce their overall quality of life. Unfortunately, no trials of pharmacologic therapy to reduce or prevent cognitive dysfunction in MS have yet been successful, including trials of memantine and donepezil. Formal neuropsychological testing and cognitive rehabilitation and accommodative strategies (such as creating checklists to overcome memory deficits) sometimes can be of benefit.

Maintenance of mobility in patients with MS is essential in maintaining overall quality of life, and maintenance of an active, healthy lifestyle can help stave off future disability. Physical and occupational therapy is useful to ensure gait safety and improve walking ability and endurance. Assistive aids, such as braces, canes, walkers, and electrostimulatory walk-assist devices, can be useful for many patients. Pharmacologic therapy with dalfampridine, a voltage-gated potassium channel antagonist, has been shown to improve walking speed, leg strength, and gait in approximately 40% of patients with baseline gait impairment. This medication likely functions by accentuating and amplifying action potentials, which allows for signal transmission through demyelinating lesions in the corticospinal tract. As a consequence of this method of action, however, dalfampridine has the rare adverse effect of seizures and should not be used in patients with kidney impairment, given the reduced clearance of the drug and resultant potentially higher rate of seizures.

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CONT.

Bladder dysfunction occurs in many patients with MS. Urinary frequency and urgency are more readily managed than other patterns of bladder dysfunction and are often amenable to abstinence from caffeine, timed voids, and anticholinergic medications, such as oxybutynin or tolterodine. Patients with urinary hesitancy or retention can be more difficult to treat, however, because anticholinergic agents can worsen retention and lead to predisposition to urinary tract infections. Those with mixed bladder symptoms should be evaluated by a urologist, and intermittent catheterization should be considered.

Pseudobulbar affect, a less common symptomatic manifestation of MS, can act as a significant impediment to social interaction in patients with MS. This symptom manifests as uncontrolled fits of laughter or crying that occur without distinct or appropriate triggers. A successful trial of the combination agent dextromethorphan-quinidine has led to FDA approval of the use of this pharmacotherapy for pseudobulbar affect in MS.

KEY POINTS

- Spasticity can be reduced in multiple sclerosis by using muscle relaxants, such as baclofen, tizanidine, or cyclobenzaprine; severe spasticity may respond to botulinum toxin or implantable intrathecal baclofen pumps.
- HVC Although newer medications, such as pregabalin and duloxetine, have been used successfully to treat neuropathic pain in multiple sclerosis, less expensive generic alternatives, such as tricyclic antidepressants and gabapentin, are as effective and well tolerated.
- Depression is a common symptom of multiple sclerosis (MS), and the suicide rate is elevated in patients with depression from MS compared with depression from other causes.

Disorders of the Spinal Cord

Presenting Symptoms and Signs of Myelopathies

The vital anatomy of the spinal cord and its susceptibility to injury because of its small diameter make recognizing and resolving spinal injury in a timely manner crucial. Spinal cord disorders, or myelopathy, can occur as a result of extrinsic (external compression) or intrinsic (intramedullary) pathology.

The presenting signs and symptoms of spinal cord injury often occur at or below the site of the lesion. When injury to the corticospinal tracts occurs, spastic paresis or paralysis is possible, manifesting as weakness, hyperreflexia, muscle spasms, and extensor plantar responses. Involvement of the distal spinal cord and lower roots (cauda equina syndrome) can involve weakness of the lower motoneuron type, with decreased muscle tone and areflexia. A detailed sensory examination in suspected spinal cord injury is critical, including ascending pinprick testing throughout the entire torso and neck, because myelopathies often result in a distinct sensory level below which sensation can be altered or lost. This typically correlates anatomically with the level of injury and thus helps with localization and directed spinal imaging. Loss of perianal sensation in particular is a key finding that suggests cauda equina syndrome. Gait is abnormal in most patients with myelopathy and sometimes can be an isolated presenting sign in mild progressive myelopathy. Findings can range from a subtle spastic gait or sensory ataxia to complete paralysis.

Many patients with myelopathy will report pain at the level of the compressive disease, and focal tenderness to percussion over the spinal column may be elicited. Some also describe squeezing or banding sensations around the chest or abdomen near the level of compression that sometimes lead to unnecessary cardiac, pulmonary, or gastrointestinal evaluations and delay in appropriate diagnosis. Patients also can experience disruptions in bowel and bladder function and loss of sphincter tone.

KEY POINTS

- When injury to the corticospinal tracts occurs, spastic paresis or paralysis is possible, manifesting as weakness, hyperreflexia, muscle spasms, and extensor plantar responses.
- Involvement of the distal spinal cord and lower roots (cauda equina syndrome) can involve weakness of the lower motoneuron type, with decreased muscle tone and areflexia.
- Myelopathies often result in a distinct sensory level below which sensation can be altered or lost, and this finding typically correlates anatomically with the level of injury and helps with localization and directed spinal imaging.

Compressive Myelopathies

Clinical Presentation

Spinal cord compression can result from acute or chronic causes. Prompt evaluation and confirmation of suspected acute spinal cord compression with appropriate neuroimaging studies should occur in an urgent manner. Immediate treatment may be necessary to prevent severe and irreversible neurologic injury.

The most common clinical presentation is neck or back pain, followed by weakness, sensory changes, and bowel and bladder dysfunction. Examination often reveals upper motoneuron signs (weakness, spasticity, hyperreflexia, and extensor plantar responses), but lower motoneuron signs (atrophy, hyporeflexia) also can occur at or below the level

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of compression. Specific signs and symptoms can provide clues about the cause of the compression. Patients with fevers and focal tenderness, especially those who have had recent instrumentation surgery to the back, may have an epidural abscess. Patients with a history of neoplasm and focal back pain should arouse concern for metastatic disease (**Figure 21**) or pathologic vertebral fracture. Patients receiving anticoagulation may have myelopathic symptoms from an epidural hematoma.

Patients with chronic spinal stenosis due to osteoarthritic degenerative spinal disease frequently have chronic myelopathic symptoms, most often involving the cervical and lumbar spines; thoracic spine symptoms are quite uncommon. Most patients with chronic compressive myelopathy will report progressive leg weakness, spasticity, distal numbness, and bladder impairment at presentation. Some with lumbar stenosis may describe symptoms resembling vascular claudication (pseudoclaudication) with exertional groin, thigh, or buttock pain and possibly weakness or numbness. Compressive myelopathy thus should be considered in older patients with gait dysfunction or weakness.

KEY POINT

- Prompt evaluation and confirmation of suspected acute spinal cord compression with appropriate neuroimaging studies should occur in an urgent manner because immediate treatment may be necessary to prevent severe and irreversible neurologic injury.

Diagnosis

MRI of the spinal cord in the suspected location of injury is the preferred means of diagnosing compressive myelopathy and can sometime reveal its cause. CT myelography is useful when MRI is not feasible (as in patients with implantable devices) but is difficult to obtain on an emergent basis, cannot be used in patients with contrast dye allergies or impaired kidney function, and may not directly establish the cause of the compression.

KEY POINT

- MRI of the spinal cord is the preferred method to diagnose compressive myelopathy.

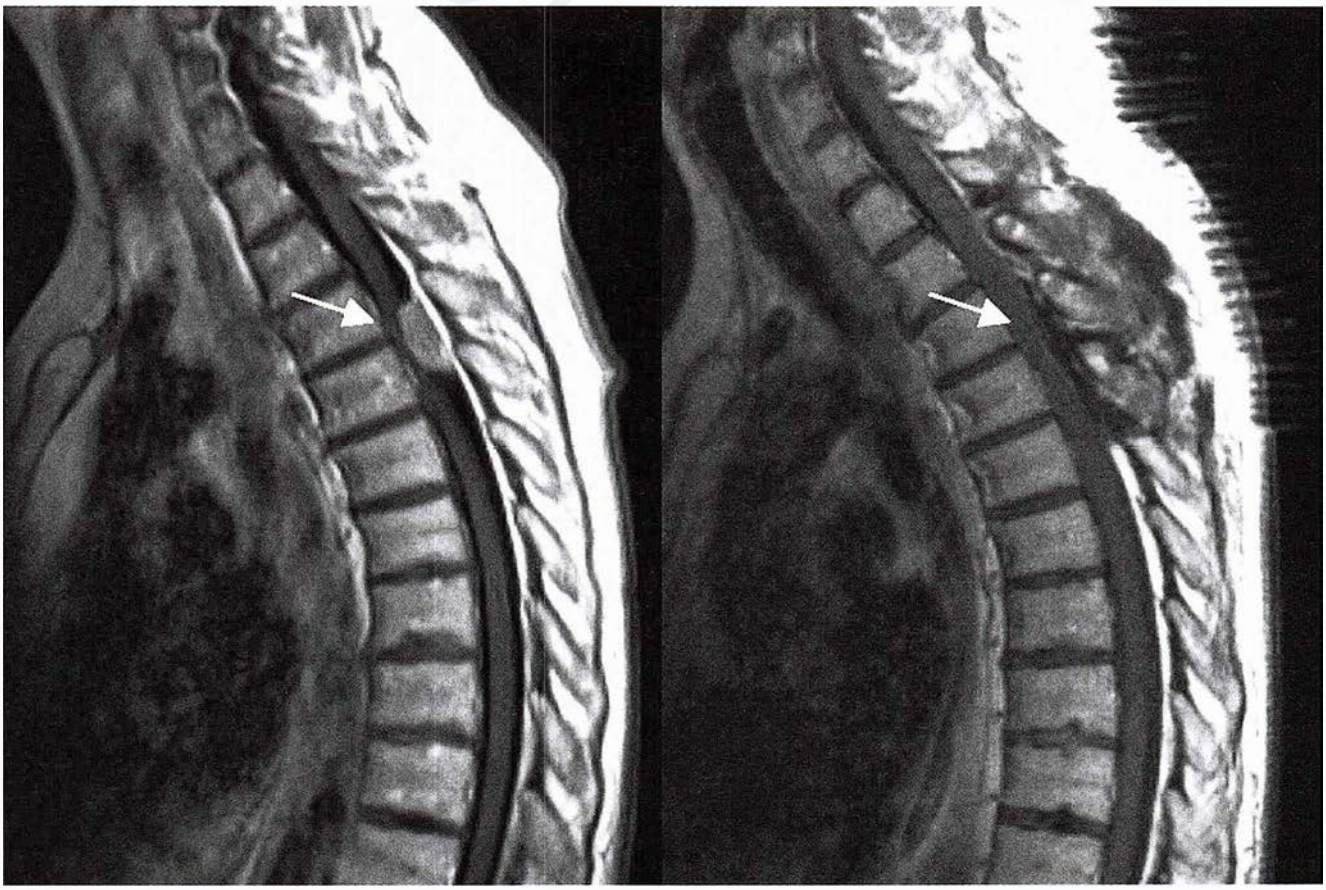

FIGURE 21. Spinal cord compression due to a tumor. MRI of the thoracic spine of a 60-year-old woman with progressive lower extremity weakness. A postcontrast T1 image (*left*) shows spinal cord compression by a mass lesion (*arrow*). *Right*, compression was relieved (*arrow*) after surgical resection. Pathologic analysis of the lesion suggested meningioma.

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Treatment

Surgical decompression is typically required to treat spinal cord compression. Medical therapies can complement surgical treatment, depending on the underlying cause. For example, epidural hematoma or abscess may require management of the bleeding diathesis or antibiotics. These complementary treatments, however, should not replace necessary neurosurgical intervention. Glucocorticoids have no role in treating spinal cord compression caused by infection or hematoma. However, several trials have shown the benefits of high-dose intravenous glucocorticoids administered within the first 8 hours of traumatic spinal cord injury.

Spinal cord compression from metastatic disease requires emergent use of high-dose glucocorticoids and subsequent treatment with surgical decompression followed by radiation for most tumor types. Clinical trials have shown the superiority of surgical decompression in optimizing ambulation. However, certain radiosensitive tumor types, such as leukemia, lymphoma, myeloma, and germ cell tumors, may not require initial surgical decompression and may be treated urgently with radiation therapy. Surgical intervention is also sometimes deferred in patients with a poor prognosis for long-term survival or with a low functional status and in those without a distinct neurologic deficit.

For chronic cervical or lumbar stenosis or acute disk herniations, physical therapy and symptomatic management of spasticity and pain (with oral or injected medications) can control symptoms in most patients. However, surgical decompression may also be required for those refractory to medical management. See MKSAP 17 General Internal Medicine for more information.

KEY POINTS

- High-dose intravenous administration of glucocorticoids within the first 8 hours of traumatic spinal cord injury improves outcomes.
- Urgent surgical decompression followed by glucocorticoids and radiation therapy is typically required to treat spinal cord compression due to metastatic disease.
- Radiosensitive tumor types, such as leukemia, lymphoma, myeloma, and germ cell tumors, often may be treated urgently with radiation therapy alone.

Noncompressive Myelopathies

Noncompressive myelopathy can be caused by many inflammatory, infectious, metabolic, vascular, and genetic disorders. The most common cause is multiple sclerosis (see Multiple Sclerosis) and associated inflammatory and demyelinating disorders (such as neuromyelitis optica and sarcoidosis).

Idiopathic Transverse Myelitis

Idiopathic transverse myelitis (TM) (**Figure 22**) is a monophasic inflammatory and demyelinating myelopathy affecting a portion of the spinal cord. Idiopathic TM usually is considered a para- or postinfectious inflammatory response.

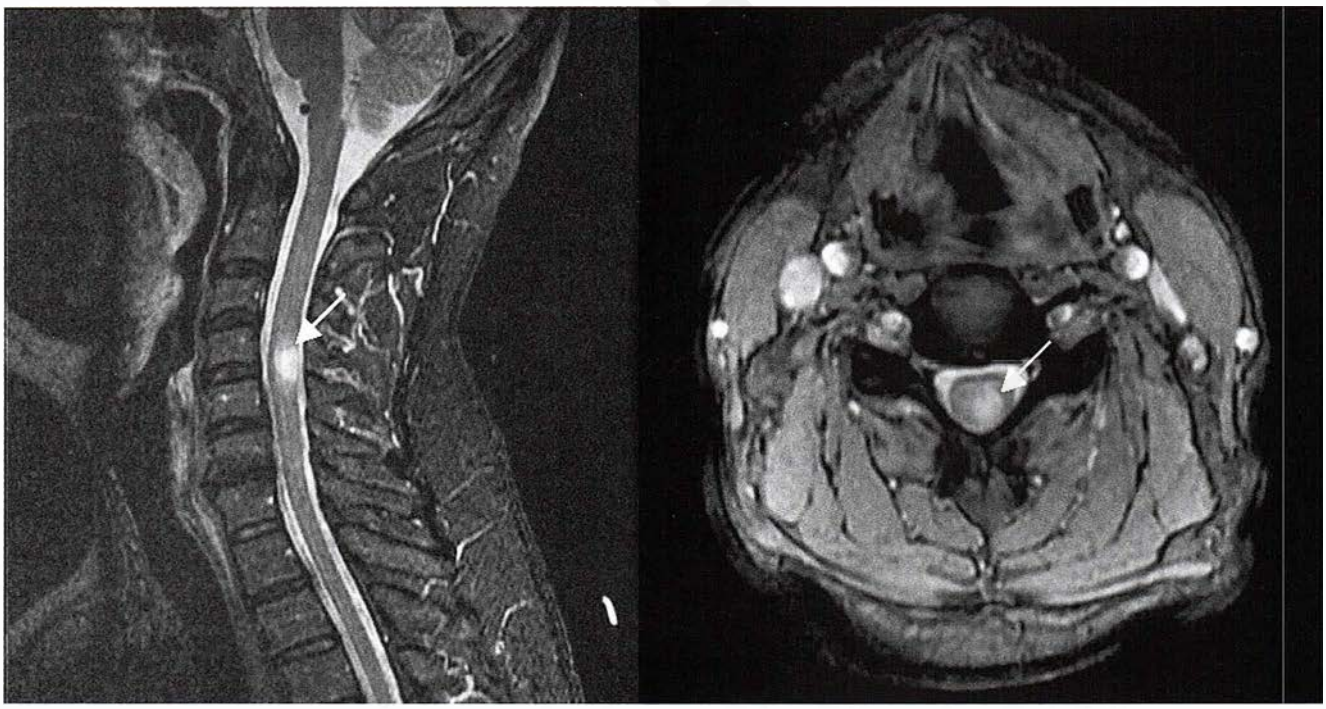

FIGURE 22. MRIs of a 53-year-old man with transverse myelitis. Sagittal (*left*) and axial (*right*) T2 sequences show an area of signal hyperintensity in the cervical spinal cord (*arrows*), mostly posterior with lateral extension to the left hemicord. This pattern could be consistent with disorders that have a predilection for the posterior columns, such as vitamin B_{12} and copper deficiencies and neurosyphilis, although inflammatory transverse myelitis and multiple sclerosis can also affect this region.

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Affected patients frequently experience a subacute onset of weakness, sensory changes, and bowel or bladder dysfunction, which is sometimes preceded by back pain or a thoracic banding sensation.

Diagnostic criteria for idiopathic TM require the presence of clinical features of the syndrome, evidence of inflammation (either leukocytosis in the cerebrospinal fluid or contrast enhancement on MRI), and exclusion of other potential causes. A recent consensus statement outlined the characteristics distinguishing true idiopathic TM from TM due to other causes (such as multiple sclerosis or neuromyelitis optica). The predictive signs of idiopathic TM were listed as complete myelitis (symptoms related to complete rather than partial transection of the cord), a lack of either oligoclonal bands or elevated IgG index in the cerebrospinal fluid, and the absence of lesions on brain MRI. Distinguishing idiopathic TM from TM due to multiple sclerosis or neuromyelitis optica is imperative because idiopathic TM does not relapse after approximately 30 days from symptom onset and does not require long-term immunomodulatory therapy. The standard of care for acute interventions for idiopathic TM is derived from experience in other demyelinating and inflammatory disorders and multiple small, open-label trials. The consensus-based treatment of idiopathic TM is acute infusion of intravenous methylprednisolone, 1 g/d for 3 to 7 days. This therapy is intended to result in cessation of the inflammatory damage to the spinal cord and allow for recovery of neurologic function. Patients whose disease is refractory to glucocorticoids may benefit from plasmapheresis or cyclophosphamide.

Potential infectious causes of nonidiopathic TM are herpes simplex virus, varicella zoster, West Nile virus, human T-lymphotropic virus, Lyme disease, and neurosyphilis. HIV infection also can cause a TM-like syndrome at the time of seroconversion or a chronic degenerative vacuolar myelopathy in patients with chronic low CD4 counts. Additionally, mycobacterium tuberculosis can infect the meninges and spinal cord and cause myelopathic symptoms. These infectious causes should be considered when evaluating patients with TM and excluded, as appropriate. Treatment should be directed against the particular infection present. The addition of glucocorticoids to treat these disorders is controversial but may be indicated when infections are associated with significant concomitant spinal cord edema (as is sometimes true in tuberculosis).

KEY POINT

- The consensus-based treatment of idiopathic transverse myelitis is acute infusion of intravenous methylprednisolone, 1 g/d for 3 to 7 days; patients whose disease is refractory to glucocorticoids may benefit from plasmapheresis or cyclophosphamide.

Subacute Combined Degeneration

Severe vitamin B_{12} deficiency (see MKSAP 17 Hematology and Oncology) can cause subacute combined degeneration, which is dysfunction of the corticospinal tracts and dorsal columns of the spinal cord. This entity manifests as a spastic paresis with reduced vibration and position sense and ataxia. MRIs may show increased signal in the affected white matter pathways, which usually is restricted to specific white matter tracts without signs of inflammatory change. Besides a low serum vitamin B_{12} level, laboratory study results usually show an elevated serum methylmalonic acid level, an elevated serum homocysteine level, and (potentially) a macrocytic anemia. Because clinical symptoms of vitamin B_{12} deficiency sometimes occur with low-normal serum levels of vitamin B_{12}, these other supportive laboratory values also should be obtained when a high index of suspicion for subacute combined degeneration exists. Abnormal findings should provoke an evaluation for their cause. Replacement of vitamin B_{12} usually halts progression of the disease but generally does not reverse existing symptoms. Copper deficiency, whether due to nutritional deficiency, malabsorption, or zinc toxicity, also can cause subacute combined degeneration and, thus, should be considered in patients with suggestive symptoms.

KEY POINT

- In patients with subacute combined degeneration, results of laboratory studies usually show a low serum vitamin B_{12} level, an elevated serum methylmalonic acid level, an elevated serum homocysteine level, and macrocytic anemia.

Vascular Disorders

Vascular disorders also can lead to noncompressive myelopathy. Infarcts in the territory of the anterior spinal artery may occur as a result of atherosclerosis or embolism and typically present as sudden-onset flaccid paralysis, with preservation of vibration and position sense (because the posterior columns are not supplied by this artery). Prolonged hypotension during cardiovascular or aortic surgery also sometimes cause watershed infarcts in the area where the anterior spinal artery meets with the most prominent radicular artery (artery of Adamkiewicz), which is part of the vascular supply of the thoracic spinal cord.

Dural arteriovenous fistulas of the spinal vascular supply can either result in a chronic myelopathy due to venous congestion or cause spinal infarcts due to altered vascular dynamics or thrombosis. These fistulas are most common in men older than 50 years, especially those with previous spinal surgery. Catheter-based angiography is still considered the gold-standard diagnostic tool for dural arteriovenous fistulas. Abnormal vascular flow voids also are sometimes noted on spinal MRI. These malformations can be treated with endovascular procedures or surgical ligation.

KEY POINT

- Dural arteriovenous fistulas causing noncompressive myelopathy of the spinal cord can be treated with endovascular procedures or surgical ligation.

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Genetic Testing

Genetic testing should be considered in those with a family history of myelopathy. Hereditary spastic paraplegia comprises a group of rare hereditary disorders that cause chronic, progressive, ascending weakness and spasticity, often beginning in childhood or adolescence. Genetic screening is available, but no treatment currently exists. Female carriers of X-linked adrenoleukodystrophy can develop adrenomyeloneuropathy, a degenerative condition of the spinal cord and peripheral nerves. In clinical situations in which one of these disorders is being considered, involvement of a genetic counselor is indicated.

Neuromuscular Disorders

Peripheral Neuropathies

Overview

Peripheral nervous system disorders can be distinguished from central nervous system disorders on the basis of clinical features and confirmed with specific diagnostic studies (**Table 34**). Neuromuscular disorders include peripheral neuropathy, myopathy, neuromuscular junction disease, plexopathy, radiculopathy, and motoneuron disease. See **Table 35** for further information.

Classification, Findings, and Diagnosis

Peripheral neuropathies are disorders of sensory, motor, and autonomic nerves. At presentation, patients may have negative (loss of sensation) or positive (paresthesia, dysesthesia, and pain) sensory symptoms, weakness, or dysautonomia (orthostatic symptoms, altered sweating, urinary symptoms, impotence, and gastroparesis). Physical examination may reveal deficits in various sensory modalities, flaccid weakness, hyporeflexia, and ataxia.

Peripheral neuropathies can be classified on the basis of distribution of sensorimotor deficits (symmetric versus asymmetric, distal versus proximal, focal versus generalized), pathology (demyelinating versus axonal), size of nerve fibers involved (large versus small fibers), family history, and autonomic involvement (**Figure 23**). Small-fiber neuropathies involve small, unmyelinated nerve fibers and affect pain and temperature sensation and autonomic function; large-fiber neuropathies are associated with the loss of joint position and vibration sense and sensory ataxia.

TABLE 34. Features Distinguishing Peripheral from Central Nervous System Disorders

Features	PNS Disorder	CNS Disorder
Onset	Subacute or insidious	Sudden (stroke) or gradual (mass lesions)
Pattern of weakness	Focal or multifocal (in the territory of the affected nerve, plexus, or root) or generalized	Entire limb, unilateral, or with a pyramidal pattern of weakness[a]
Atrophy	Yes (at times prominent)	No (or mild, if related to disuse)
Fasciculations	Yes	No
Tone	Decreased or normal	Increased (spastic) or normal
Pattern of sensory symptoms	Focal or multifocal (in the territory of the affected nerve, plexus, or root) or stocking-glove in distribution	Entire limb or unilateral
Type of sensory symptoms	Positive symptoms (paresthesia, dysesthesia, or allodynia[b]) more frequent, but negative symptoms (numbness) possible	Negative symptoms more frequent, but positive symptoms possible
Dissociated sensory loss	Pain/temperature and vibration/proprioception deficits travel together	Dissociation of pain/temperature and vibration/proprioception deficits possible with spinal and brainstem lesions
Deep tendon reflexes	Diminished or normal	Increased
Pathologic reflexes	Absent	Present, including extensor plantar response, Hoffmann sign,[c] knee cross adduction, jaw jerk, snout, and clonus
Additional localizing symptoms	Cramps	Headache, seizures, and visual and language-related symptoms
EMG	Abnormal	Normal

CNS = central nervous system; EMG = electromyography; PNS = peripheral nervous system.

[a]Pyramidal weakness is caused by upper motoneuron lesions and affects extensors more than flexors in the upper limbs and flexors more than extensors in the lower limbs.

[b]Paresthesia is an abnormal spontaneous sensation, such as tingling, burning, or electrical sensation. Dysesthesia is an unpleasant sensation provoked by neutral stimuli, such as light touch or contact of clothes. Allodynia is pain provoked by nonnoxious stimuli.

[c]Hoffmann sign is positive if thumb is flexed in response to flicking or snapping of the distal phalanx of the middle finger.

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TABLE 35. Common Symptoms and Signs of Neuromuscular Disorders

Symptoms and Signs	Differential Diagnosis
Weakness	
Distal extremities	Dying-back polyneuropathy (as in diabetes mellitus)
Proximal extremities	Myopathy, polyradiculopathy
Multifocal with pain (mononeuropathy multiplex)	Vasculitis, rheumatoid arthritis, diabetes
Focal asymmetric	ALS, inclusion body myositis, radiculopathy, multifocal motor neuropathy
Fluctuating	Myasthenia gravis
Ocular	Myasthenia gravis, mitochondrial myopathy
Bulbar (tongue, palate, lips)	ALS, myasthenia gravis, inclusion body myositis
Cranial nerves (especially III and VII)	Diabetes, Lyme disease, sarcoidosis, HIV infection
Neck extensors	ALS, myasthenia gravis (including with anti-MuSK antibody)
Fasciculations	ALS, GBS, radiculopathy
Sensory	
Stocking-glove gradient	Generalized polyneuropathies
Dermatomal pattern	Radiculopathy, peripheral nerve lesion
Distal pain without hyporeflexia or weakness	Small fiber neuropathy
Marked proprioceptive loss in single limb	Dorsal root ganglionopathy (cancer, Sjögren syndrome, HIV infection)
Autonomic	
Decreased sweating, early satiety, constipation, impotence, erectile dysfunction, orthostatic hypotension, resting tachycardia	Diabetes, amyloidosis, autoimmune dysautonomia (antiganglionic acetylcholine receptor antibody), paraneoplastic

ALS = amyotrophic lateral sclerosis; GBS = Guillain-Barré syndrome; MuSK = muscle-specific kinase.

Laboratory tests in all patients with a suspected peripheral neuropathy should include a complete blood count, erythrocyte sedimentation rate determination, serum protein electrophoresis with immune fixation, thyroid function tests, and measurement of hemoglobin A_{1C}, fasting plasma glucose, and serum vitamin B_{12} levels. Analysis of cerebrospinal fluid (CSF) is helpful if Guillain-Barré syndrome, demyelinating neuropathy, or mononeuropathy multiplex is suspected. Genetic testing can identify hereditary neuropathies in patients with a positive family history. Special laboratory testing can be considered in specific settings (**Table 36**).

Electromyography (EMG), which for the purpose of this discussion includes both nerve conduction studies (assessing electrical conduction through the nerves) and needle electrode examination (assessing the electrical activity pattern within muscles), can confirm the presence of neuropathy and distinguish between axonal and demyelinating forms. EMG also can differentiate neuropathy from myopathy and radiculopathy from plexopathy (see later discussions). Nerve biopsy is indicated only in a small subset of neuropathies when concern for vasculitic, infectious, or infiltrative neuropathy exists. Small-fiber neuropathies, which typically have normal EMG and nerve biopsy findings, can be diagnosed with autonomic testing, including a quantitative sudomotor axon reflex test and skin biopsy, to assess intraepidermal nerve fiber density. The cause of peripheral neuropathy remains unknown in nearly one third of patients (cryptogenic neuropathy).

KEY POINTS

- Electromyography, including both nerve conduction studies and needle electrode examination, can confirm the presence of neuropathy, differentiate between axonal and demyelinating forms, and distinguish neuropathy from myopathy and radiculopathy from plexopathy.
- Nerve biopsy is indicated only in a small subset of neuropathies when concern for vasculitic, infectious, or infiltrative neuropathy exists HVC

Mononeuropathies

Mononeuropathies generally involve a single nerve. A common type is meralgia paresthetica, a compressive neuropathy of the lateral femoral cutaneous nerve that causes isolated anterolateral thigh numbness without weakness. Diagnosis is clinical and treatment is conservative. Mononeuropathy multiplex involves multiple nerves at different sites and can indicate vasculitis, especially when pain is prominent. Plexopathies involve multiple sensory and motor nerves simultaneously at the brachial or lumbosacral plexus. Diagnosis is based on clinical pattern, EMG findings, and additional laboratory testing (see Table 36). Treatment is based on the specific cause.

Carpal Tunnel Syndrome

Carpal tunnel syndrome is caused by focal compression of the median nerve at the wrist. Initial presentation typically includes sensory symptoms in the thumb and second and third digits, with possible radiation to the whole hand. With progression, weakness of thumb abduction and opposition and thenar atrophy may be noted. Symptoms are exacerbated by prolonged wrist flexion or extension. The physical examination finding with the greatest likelihood ratio is the presence of hypalgesia in the distribution of the median nerve (LR, 3.1). The likelihood ratios for Tinel and Phalen signs are only 1.4 and 1.3, respectively. Treatment is supportive and usually involves wrist bracing, occupational therapy, anti-inflammatory medications, and—in patients with severe pain—glucocorticoid injections.

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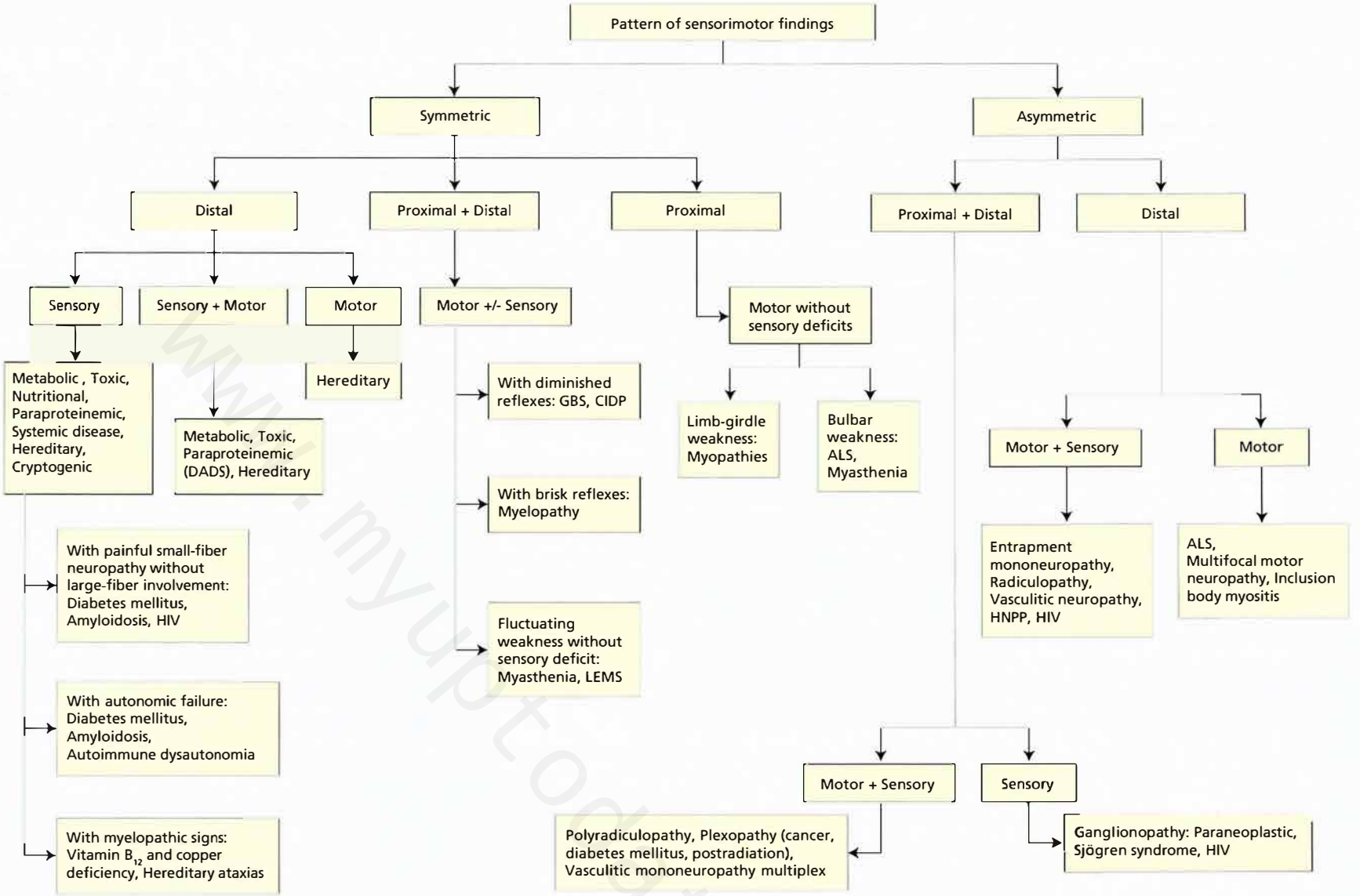

FIGURE 23. Algorithmic approach to peripheral neuropathies. ALS = amyotrophic lateral sclerosis; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; DADS = distal acquired demyelinating symmetric neuropathy; GBS = Guillain-Barré syndrome; HNPP = hereditary neuropathy with predisposition to pressure palsy; LEMS = Lambert-Eaton myasthenic syndrome.

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TABLE 36. Additional Laboratory Testing in Peripheral Neuropathy

Cause	Clinical Presentation	Laboratory Testing
Diabetes mellitus, impaired glucose tolerance	Distal symmetric polyneuropathy, mononeuropathy, lumbosacral radiculoneuropathy	Glucose tolerance test; hemoglobin A_{1c} measurement
Uremia, thyroid disease, anemia	Distal symmetric polyneuropathy	Hematocrit; serum creatinine, TSH, and free thyroxine (T_4) measurements
Collagen vascular disease, polyarteritis nodosa, vasculitis, Sjögren syndrome	Vasculitic mononeuropathy multiplex, ganglionopathy (in Sjögren syndrome)	ESR; rheumatoid factor; serum antinuclear antibody, ANCA, anti-Ro/SSA, and anti-La/SSB antibody measurements
Syphilis	Posterior column disease resembling large-fiber neuropathy	RPR; CSF VDRL
Paraproteinemia associated with MGUS, amyloidosis, lymphoproliferative disease	Symmetric sensory demyelinating neuropathy; other variants also possible, including symmetric axonal sensory neuropathy, multifocal motor neuropathy, cranial neuropathy	SPEP; UPEP; IFE; serum free light chain measurement
Vitamin B_{12} or copper deficiency	Myeloneuropathy with brisk reflexes	Serum copper, vitamin B_{12}, and methylmalonic acid measurements
CIDP, GBS	Progressive polyradiculoneuropathies	Serum antiganglioside antibody and CSF cell and protein measurements
Miller Fisher variant of GBS	Ophthalmoplegia, ataxia, areflexia	Serum anti-GQ1b antibody measurement
Multifocal motor neuropathy	Asymmetric, pure motor weakness	Serum anti-GM1 antibody measurement
Distal acquired demyelinating symmetric neuropathy	Distal sensory loss, tremor, sensory ataxia	SPEP; IFE; serum anti-MAG antibody measurement
Amyloidosis	Autonomic and small-fiber neuropathy	Abdominal fat pad biopsy; transthyretin gene testing (in familial disease)
Infectious neuropathy	Variable, cranial nerve palsy, myelopathy, flaccid paralysis (in West Nile virus)	Serum HIV antibody and Lyme antibody and CSF West Nile virus antibody measurements
Toxic neuropathy	Symmetric sensory or sensorimotor neuropathy, acute motor neuropathy (in lead poisoning)	Serum lead, arsenic, mercury, and thallium measurements; 24-hour urine excretion of heavy metals
Celiac disease	Sensory neuropathy and ataxia	Anti-tissue transglutaminase antibody and anti-endomysial antibody measurements
Porphyria	Acute painful polyradiculopathy	Urine porphobilinogen and δ-aminolevulinic acid measurements
Fabry disease	Painful small-fiber neuropathy	α-Galactosidase measurement
Paraneoplastic disease	Subacute progressive sensory neuropathy, ganglionopathy	Serum anti-Hu and anti-CRMP5 measurement; testing for CSF oligoclonal bands

ANCA = anti-neutrophil cytoplasmic antibody; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CRMP5 = collapsin response mediator protein 5; CSF = cerebrospinal fluid; ESR = erythrocyte sedimentation rate; GBS = Guillain-Barré syndrome; IFE = immune fixation electrophoresis; MAG = myelin-associated glycoprotein; MGUS = monoclonal gammopathy of unknown significance; RPR = rapid plasma reagin; SPEP = serum protein electrophoresis; TSH = thyroid-stimulating hormone; UPEP = urine protein electrophoresis.

If the diagnosis is uncertain or symptoms are persistent, EMG can differentiate the cause from radiculopathy, confirm median nerve compression, and quantify the severity of nerve injury. In the presence of refractory pain, weakness, or EMG evidence of active denervation, decompression surgery is recommended.

Bell Palsy

Bell palsy is idiopathic paralysis of the facial nerve that leads to complete unilateral facial paralysis. This disorder is distinct from a central weakness, such as stroke, in which forehead and periorbital muscles are spared because of bilateral innervation of the upper face. Hyperacusis and impaired taste may occur in Bell palsy. When the presentation is classic and without any additional neurologic deficits, brain imaging and routine laboratory testing are not necessary. However, Bell palsy can have a secondary cause, such as diabetes mellitus, vasculitis, Lyme disease, sarcoidosis, HIV infection, and compressive or infiltrative malignancies. In the presence of suggestive clinical features, therefore, determination of the hemoglobin A_{1c} value, erythrocyte sedimentation rate, and—in endemic areas—Lyme antibody titer should be considered. If symptoms

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worsen or do not improve by 2 months after symptom onset or if any new deficit develops, further assessment with brain MRI and additional testing for secondary causes is required.

Treatment with oral prednisone within the first 72 hours expedites both the speed and the rate of full recovery. In contrast, treatment with antiviral therapy alone has no benefit. Artificial tears should be used and a nighttime eye patch applied for corneal protection. A treatment course of several weeks is common, with complete recovery in 70% to 90% of affected patients. Older age and diabetes mellitus have a negative effect on prognosis. A few patients develop synkinesis (concomitant movement of perioral and periorbital muscles) as a result of aberrant reinnervation.

Brachial and Lumbosacral Plexopathies

Common causes of brachial and lumbosacral plexopathies include diabetes, cancer, radiation, and trauma. Imaging is mandatory to rule out structural lesions and malignancy. Idiopathic brachial plexitis is subacute severe pain and weakness that peak within 2 weeks. This type of plexopathy is associated with marked atrophy; a triggering event, such as infection or surgery, usually precedes its presentation. Spontaneous recovery over an extended period of time (as long as 2 years) is common.

KEY POINTS

H\C • Meralgia paresthetica, a compressive neuropathy of the lateral femoral cutaneous nerve that causes isolated anterolateral thigh numbness without weakness, can be clinically diagnosed and treated conservatively.

H\C • Carpal tunnel syndrome can be diagnosed clinically by the presence of hypalgesia in the distribution of the median nerve; initial treatment involves wrist bracing, occupational therapy, and anti-inflammatory medications.

H\C • Bell palsy is idiopathic paralysis of the facial nerve that leads to complete unilateral facial paralysis; patients with a classic presentation and no other neurologic deficits can be diagnosed without brain imaging and laboratory testing.

H\C • Early treatment of Bell Palsy with oral prednisone (within 72 hours of symptom onset) improves outcomes; antiviral therapy does not affect prognosis.

Polyneuropathies

Polyneuropathies preferentially affect distal parts of the longest nerves, a result of increased metabolic vulnerability of distal axons that gives rise to the dying-back phenomenon (axonal degeneration at the most distal point of the axon). Symptom onset typically is in the feet, and a stocking-glove gradient of sensory deficits is usually present. Polyneuropathies affecting large nerve fibers can be associated with loss of proprioception, weakness, and diminished reflexes. In contrast, polyneuropathies affecting small nerve fibers are associated with pain, dysesthesia, and autonomic deficits but no weakness or proprioceptive deficit.

Neuropathies of Diabetes Mellitus and Impaired Glucose Tolerance

Diabetes can cause various types of neuropathy (**Table 37**). The most common pattern is symmetric distal sensory or sensorimotor. Either small or large fibers can be affected. Autonomic neuropathy can be prominent in diabetes and lead to profound orthostatic hypotension, impotence, gastroparesis, and potentially dangerous unawareness of hypoglycemic symptoms. Diabetic mononeuropathy can involve cranial nerves or predispose patients to entrapment neuropathies, such as carpal tunnel syndrome. Diabetic amyotrophy, also known as proximal lumbosacral radiculoneuropathy, is associated with subacute painful involvement of the lumbosacral plexus. Prominent proximal lower extremity weakness and muscle wasting with weight loss are typical. Unlike polyneuropathy, diabetic amyotrophy is not related to glycemic control or diabetes duration. Recovery is slow, usually taking between 3 and 36 months.

Diagnosis of diabetic peripheral neuropathy is clinical. EMG can reveal a distal and symmetric axonal sensorimotor polyneuropathy. Dysautonomia can be confirmed by autonomic testing. Other forms of diabetic neuropathy can be diagnosed on the basis of clinical findings, EMG results, and exclusion of alternative causes. Although the prevalence and severity of neuropathy correlate with the duration of diabetes,

TABLE 37. Peripheral Nerve Dysfunction in Diabetes Mellitus

Classification	Signs and Symptoms
Autonomic neuropathy	Orthostatic hypotension, early satiety, nausea and vomiting (gastroparesis), constipation (colonic dysmotility), erectile dysfunction, hyperhidrosis, or hypohidrosis
Proximal lumbosacral radiculoneuropathy (diabetic amyotrophy)	Severe pain followed by weakness and muscle wasting in proximal lower extremities, weight loss, possible occurrence with or without proximal sensory loss
Mononeuropathy	Sensory loss, paresthesia or pain in the distribution of a single nerve followed by weakness (median or peroneal nerve), cranial nerve palsy (especially cranial nerves III, VI, or VII)
Radiculopathy	Sensory loss, pain and weakness in the distribution of nerve roots, thoracic radiculopathy causing patchy truncal numbness is common
Sensorimotor peripheral neuropathy	Asymptomatic (sometimes), distal length-dependent sensory loss and weakness, often painful, possible loss of ankle reflex
Small-fiber neuropathy	Burning distal extremity pain without weakness, may be non-length dependent, spares ankle reflex

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the association between glucose intolerance and neuropathy (especially involving the small fibers) has become increasingly recognized. A sizeable number of patients with glucose intolerance (11%-25%) show evidence of small-fiber neuropathy on specialized testing, but most of these patients are clinically asymptomatic; some (5%-10%) are symptomatic, experiencing symmetric distal pain and paresthesia. Therefore, screening for glucose intolerance should be performed in patients without diabetes who have distal sensory neuropathy on presentation.

Tight glycemic control and minimizing cardiovascular risk factors can slow the progression and improve the symptoms of diabetic neuropathy. Treatment of painful neuropathies resulting from diabetes or other causes is symptomatic. Tricyclic antidepressants (amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), antiepileptic drugs (pregabalin, gabapentin, valproic acid), opioids (tapentadol), and topical capsaicin are commonly used. Only pregabalin, duloxetine, and tapentadol (extended release) have FDA approval for painful diabetic neuropathy, but these agents are all costly, and other less expensive options, such as tricyclic antidepressants, should be tried first. Although opioids can be used for severe acute pain, their long-term use should be limited to truly refractory pain.

Hereditary Neuropathies

Hereditary neuropathies commonly present as slowly progressive distal weakness, numbness without pain or paresthesia, areflexia, and ataxia. Foot deformities, such as hammertoes, high arches, and distal leg atrophy ("stork legs") are common (**Figure 24**). The most common inherited neuropathy, Charcot-Marie-Tooth disease type 1, is demyelinating and associated with palpable peripheral nerves and uniform slowing of motor nerve conduction velocities on EMG; type 2 is axonal. Both types can be confirmed with genetic testing. Hereditary neuropathy with predisposition to pressure palsy is a form of hereditary neuropathy that presents with recurrent acute and reversible mononeuropathies caused by nerve compression at susceptible pressure sites (such as the elbows, wrists, and knees). Affected patients should be instructed to avoid compressive positions.

Inflammatory Polyradiculoneuropathies

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an autoimmune, primarily demyelinating polyradiculoneuropathy that presents with acute generalized weakness and rapid progression over several days or weeks. GBS is thought to be caused by an infection-induced (most commonly, *Campylobacter jejuni*) aberrant autoimmune response targeting peripheral nerves and spinal



FIGURE 24. High arches, hammertoes, and distal leg atrophy in a patient with inherited neuropathy.

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CONT.

roots. Half of patients with GBS have serum antibodies against gangliosides, which are components of peripheral nerves. Weakness is ascending, starting in the lower extremities and spreading to the upper limbs and bulbar and respiratory muscles. Diffuse areflexia is a key diagnostic clue. Paresthesia is common, but true sensory deficits are rare. Low back pain, a result of nerve root inflammation, can be prominent initially. Dysautonomia is common and may cause life-threatening labile blood pressure and arrhythmias. Because of the risk of dysautonomia and the possibility of respiratory failure, all patients with GBS should be hospitalized for respiratory and cardiovascular monitoring. Variants of GBS include a paraplegic variant, with weakness limited to the legs; a pharyngeal-cervical-brachial variant, with relative sparing of the legs; and the Miller Fisher variant, with multiple cranial neuropathies and ataxia.

The differential diagnosis of GBS includes myasthenic crisis, acute myelopathies, Lyme disease, West Nile virus, carcinomatous and sarcoid meningitis, acute lead neuropathy, botulism, and tick paralysis. The diagnosis is made on the basis of clinical features and results of CSF analysis, which reveal a classic pattern of a highly elevated protein level with a normal or mildly elevated leukocyte count (albuminocytologic dissociation) in 90% of patients. Although EMG confirms the diagnosis when it shows a predominantly demyelinating pattern, results may initially be normal. MRI of the lumbar spine is not mandatory but may reveal evidence of spinal root enhancement.

Therapy includes supportive management and, in most patients who experience severe progressive symptoms, treatment with either plasmapheresis or intravenous immune globulin (IVIG). Both therapies are equally effective and shorten the time to recovery by as much as 50%. Compared with IVIG, plasmapheresis has a faster mode of action but is less convenient and potentially requires longer hospitalization. Retreatment with IVIG is indicated if symptoms deteriorate after initial improvement or stabilization. Glucocorticoids are not beneficial in GBS and may even slow the recovery. Prognosis is favorable in 80% of patients, but relapse occurs in 6% and requires repeated treatment.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic and treatable autoimmune neuropathy. The classic presentation involves generalized areflexia and progressive or relapsing symmetric sensory and motor neuropathy. CIDP initially can present similarly to GBS, but symptoms do not stabilize after 4 weeks and continue to evolve over more than 2 months. Sensory symptoms and proximal weakness are more common in CIDP than in GBS. CIDP may be isolated or occur in the setting of a number of systemic conditions, including diabetes, lymphoma, and HIV infection. CSF and EMG findings are comparable to those in GBS. In the setting of diagnostic uncertainty, nerve biopsy can differentiate CIDP from vasculitis or amyloidosis. Treatment options include prednisone, immunosuppressive therapies, and periodic IVIG or plasmapheresis.

Critical Illness Neuropathy

Critical illness neuropathy is common in patients with prolonged stays in the ICU because of sepsis or multiorgan failure. Besides a lengthy stay in the ICU, risk factors include prolonged mechanical ventilation and prolonged use of neuromuscular blocking agents; sepsis is not a risk factor. Typical features of critical illness neuropathy include failure to wean from the ventilator and generalized or distal lower extremity weakness.

This condition is differentiated from critical illness myopathy by the absence of myopathic changes on EMG and a normal serum creatine kinase (CK) level. However, the two conditions can occur simultaneously. A normal CSF protein level also distinguishes this disorder from GBS.

Treatment is supportive. Tight glycemic control and early physical therapy can be protective and reduce morbidity. Most patients fully recover, but a sizable percentage (30%) experience significant residual weakness. H

Systemic Neuropathy

Certain metabolic, nutritional, toxic, infectious, and paraneoplastic disorders can provoke neuropathy (**Table 38**). Copper and vitamin B_{12} (cobalamin) deficiencies, most often caused by bariatric surgery, intrinsic factor antibodies, and a restrictive (usually vegetarian) diet, can damage peripheral nerve and spinal cord structures (see Disorders of the Spinal Cord). Vitamin B_1 deficiency can lead to an axonal sensorimotor neuropathy and should be treated with aggressive thiamine supplementation. Alcohol abuse can cause a distal axonal neuropathy that is often painful and sometimes complicated by superimposed nutritional deficiencies.

Paraproteinemic Neuropathy

Paraproteinemic neuropathy often presents as a symmetric distal sensory neuropathy and occurs in the setting of monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, amyloidosis, cryoglobulinemia, and other hematologic malignancies (see MKSAP 17 Hematology and Oncology). Paraproteinemic neuropathy is identified by the presence of monoclonal immunoglobulins (M-band paraproteins) and is treated by managing the underlying condition. Paraproteinemia also can be associated with other forms of neuropathy, including sensorimotor, cranial, or multifocal motor neuropathy. Therefore, patients with various forms of peripheral neuropathy should be screened for paraproteinemia.

Amyloid Neuropathy

Amyloidosis is characterized by extracellular deposition of amyloid protein in various tissues, including the peripheral nerves. This disorder is characterized by marked autonomic

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TABLE 38. Neuropathies Related to Systemic Disease
Metabolic
Uremia
Liver disease
Hypothyroidism
Acromegaly
Critical illness (multifactorial)
Nutritional
Vitamin B_{12} deficiency
Vitamin B_1 deficiency
Vitamin B_3 deficiency
Vitamin B_6 excess
Vitamin E deficiency
Copper deficiency
Infectious
HIV
Lyme disease
Leprosy
Sarcoidosis (granulomatous)
Rheumatologic and Vasculitic
Systemic lupus erythematosus
Rheumatoid arthritis
Polyarteritis nodosa
Sjögren syndrome
Mixed connective tissue disease
Paraproteinemic and Paraneoplastic
Monoclonal gammopathy of undetermined significance (MGUS)
Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin lesions (POEMS)
Amyloidosis
Multiple myeloma
Lymphoma
Paraneoplastic neuropathy and ganglionopathy

dysfunction and small-fiber neuropathy. Common symptoms include distal pain and paresthesia, orthostatic symptoms, gastroparesis, urinary incontinence, and impotence.

Primary amyloidosis is associated with monoclonal proteins, whereas familial amyloidosis is secondary to a genetic mutation.

Monoclonal Gammopathy of Undetermined Significance

Both isolated MGUS and MGUS related to hematologic malignancies (10%) are associated with neuropathy. MGUS with IgM gammopathy is linked to an immune-mediated neuropathy characterized by distal sensory loss, ataxia, and tremor (distal acquired demyelinating symmetric [DADS] neuropathy). Half of patients with DADS neuropathy have antibodies against myelin-associated glycoprotein, and these patients respond poorly to therapy. The other half respond favorably to glucocorticoids, IVIG, plasmapheresis, or rituximab. Additionally, paraproteinemic neuropathy with IgG or IgA has a favorable response to plasmapheresis.

KEY POINTS

- Diagnosis of diabetic peripheral neuropathy is clinical. **HVC**
- Low doses of tricyclic antidepressants, such as amitriptyline and nortriptyline, are a cost-effective, first-line treatment option for patients with painful peripheral neuropathy. **HVC**
- In 90% of patients with Guillain-Barré syndrome, cerebrospinal fluid analysis reveals a classic pattern of a highly elevated protein level with a normal or a mildly elevated leukocyte count (albuminocytologic dissociation); therapy includes supportive management plus intravenous immune globulin or plasmapheresis.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal disease involving motoneurons and is associated with progressive weakness and muscle wasting. ALS often presents with focal weakness, muscle twitches or cramping, or difficulties with speech or swallowing. The disease progresses relentlessly, eventually culminating in death from respiratory failure within several years. ALS is characterized by upper motoneuron signs (such as hyperreflexia, spasticity, and an extensor plantar response) coexistent with lower motoneuron findings (such as atrophy and fasciculation). Sensory deficits are characteristically absent. Frontotemporal dementia sometimes is present.

Diagnosis is based on clinical findings, EMG results, and exclusion of alternative causes. MRI of the brain and spinal cord can help exclude stroke and cervical cord compression and will occasionally reveal a T2 bright signal in bilateral corticospinal pathways suggestive of ALS. The differential diagnosis includes Lyme disease, hyperparathyroidism, thyrotoxicosis, and multifocal motor neuropathy. Benign fasciculation syndrome, which is associated with widespread fasciculations and (sometimes) cramping but not with weakness or upper motoneuron signs, should not be confused with ALS.

Treatment is supportive. Riluzole, a glutamate release inhibitor, may slow the progression of ALS by a modest 3 months. Monitoring of liver function is recommended during riluzole therapy. Percutaneous endoscopic gastrostomy can improve quality of nutrition and prolong survival and should be considered before patients reach the advanced stage of the disease. Respiratory support includes noninvasive methods, such as biphasic positive airway pressure, and should be started in the presence of respiratory symptoms or hypercarbia. It also is essential to discuss prognosis and establish goals

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of care with patients and families, thereby avoiding unnecessary diagnostic and therapeutic measures.

KEY POINTS

- Amyotrophic lateral sclerosis (ALS) is a fatal disease involving the motoneurons that is associated with progressive weakness and muscle wasting for which treatment is supportive; it is essential to discuss prognosis and establish goals of care with patients and families, thereby avoiding unnecessary diagnostic and therapeutic measures.
- Riluzole, a glutamate release inhibitor, may slow the progression of amyotrophic lateral sclerosis by a modest 3 months.

Neuromuscular Junction Disorders

Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disease directed against the postsynaptic neuromuscular junction. Onset is most common in the third decade of life in women and after age 50 years in men. Fluctuating, painless, and fatigable weakness involving the cranial, cervical, respiratory, and limb muscles is typical. Ocular involvement is sometimes the initial presentation of MG, but half of patients with only ocular symptoms at first will develop generalized weakness within 2 years; the other half will have limited disease. Bulbar weakness is common, either as the initial presentation or with progression of the disease. Physical examination can reveal ptosis, diplopia on sustained gaze, bilateral facial paresis, flaccid dysarthria, cervical weakness, and fatigable extremity weakness. The presence of respiratory symptoms should prompt close monitoring of respiratory parameters (vital capacity and negative inspiratory force) because of the risk of rapid respiratory failure (myasthenic crisis). Myasthenic crisis can occur as part of the natural history of extraocular MG or be triggered by external factors, including infection, surgery, and medications (aminoglycosides, fluoroquinolones, magnesium, β-blockers, or calcium channel blockers).

Diagnosis of MG is based on clinical findings, detection of disease-specific antibodies (acetylcholine receptor antibodies in 90% of patients with MG and anti–muscle-specific kinase [MuSK] antibodies in another 5% [with 5% of patients remaining antibody negative]), and EMG findings (such as a characteristic decremental response to repetitive stimulation). CT of the chest should be obtained in patients with MG to screen for thymoma, a tumor associated with the disease.

First-line treatment options in stable patients include the cholinesterase inhibitor pyridostigmine, glucocorticoids, and immunosuppressant agents. Pyridostigmine monotherapy may be sufficient in patients with mild disease but should be avoided in those with acute respiratory failure because the drug increases respiratory secretions. Glucocorticoids can transiently worsen any weakness and should be started at a lower dosage with slow upward titration in the presence of moderate weakness. In patients with severe weakness, initiation of acute treatment with IVIG or plasmapheresis must precede any glucocorticoid treatment. Glucocorticoid-sparing disease-modifying medications, such as azathioprine, mycophenolate mofetil, and cyclosporine, are mainstays of long-term maintenance therapy in patients with advanced disease. Myasthenic crisis and refractory disease should be treated with plasmapheresis or IVIG. MG associated with anti-MuSK-positive antibodies is typically refractory to pyridostigmine and requires more aggressive immunosuppressive therapy; patients with anti-MuSK-positive antibodies also respond well to plasmapheresis or IVIG.

Thymectomy should be performed in all patients with thymoma. Benefits of thymectomy in other patients are not firmly established, but some experts recommend it for patients with generalized MG who are younger than 65 years and within 3 years of diagnosis.

KEY POINTS

- Myasthenic crisis and refractory myasthenia gravis should be treated with plasmapheresis or intravenous immune globulin.
- Thymectomy should be performed in all patients with myasthenia gravis who have a thymoma.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome is an autoimmune disorder caused by autoantibodies against voltage-gated calcium channels located at the presynaptic neuromuscular junction. This condition has a presentation similar to MG except that weakness improves with exercise, and hyporeflexia and dysautonomia are present. Diagnosis is confirmed by detection of serum anti–voltage-gated calcium channel antibodies and the EMG finding of facilitation of motor response to rapid repetitive stimulation. Malignancy, especially small cell lung cancer, is found in as many as 60% of patients with Lambert-Eaton myasthenic syndrome. Therapy consists of treating any underlying malignancy or, in nonparaneoplastic disease, immunosuppression.

KEY POINT

- Malignancy, especially small cell lung cancer, is found in as many as 60% of patients with Lambert-Eaton myasthenic syndrome.

Myopathies

Overview

Myopathies are disorders of the skeletal muscles. Diagnosis requires a systematic approach involving clinical history, measurement of muscle-related serum marker (CK and aldolase) levels, EMG, muscle biopsy, and, in certain patients, genetic and imaging tests.

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Most myopathies involve symmetric weakness of the proximal limb muscles. An atypical distribution of weakness in ocular, bulbar, and distal limb muscles may point to a specific cause. Normal sensory and reflex examination can differentiate myopathy from neuropathy. Many myopathies are painless; the presence of pain should prompt investigation of metabolic, toxic, and infectious causes. Rapid progression is suggestive of inflammatory, toxic, or endocrine myopathies, whereas most hereditary myopathies have a stable or slowly progressive course. Mitochondrial myopathies may present with fluctuating weakness and ocular and bulbar involvement.

The serum CK level is elevated in many forms of myopathy and can be followed to monitor disease activity and response to treatment. Mild elevation of the serum CK level (<5 times normal) is not specific to myopathies and can be seen in ALS, CIDP, muscle trauma (falls, post-EMG), and persistent elevation of the serum CK level ("benign hyperCKemia"). Aldolase is a less specific marker of myopathy and can also indicate hematologic or hepatic disease. EMG can help confirm the presence of myopathic changes (such as low amplitude, short duration, and polyphasic motor unit potentials) and determine distribution of involved muscles. Muscle biopsy is the most helpful test to confirm the diagnosis, but in some hereditary myopathies, genetic testing can provide the confirmation without the need for biopsy. The serum CK level should be checked before EMG to prevent procedure-related false-positive results.

KEY POINTS

- Painful myopathies should prompt investigation of metabolic, toxic, and infectious causes.
- The serum creatine kinase level is elevated in many forms of myopathy and can be followed to monitor disease activity and response to treatment.

Inflammatory Myopathy

Idiopathic inflammatory myopathies include polymyositis, dermatomyositis, and inclusion body myositis. Polymyositis and dermatomyositis present with acute or subacute proximal muscle weakness. Involvement of cervical extensor and respiratory muscles can occur in later stages. Muscle pain and tenderness may be present in half of affected patients. Diagnosis is based on a highly elevated serum CK level, myopathic changes on EMG, and inflammatory findings on a muscle biopsy. Biopsy reveals endomysial inflammation in polymyositis and perimysial and perivascular inflammation in dermatomyositis. Dermatomyositis can further be distinguished by its distinct cutaneous manifestations, such as periorbital heliotrope rash and Gottron papules on the hands. Autoantibodies are found in 90% of patients with polymyositis and dermatomyositis.

Inclusion body myositis has a slowly progressive course and has a predilection to affect distal upper extremity flexor, quadriceps, and bulbar muscles. Presentation can be asymmetric and mimic ALS, but upper motoneuron signs are absent. Muscle biopsy reveals inflammation and characteristic inclusion bodies. This condition has a poor response to treatment.

For more information on inflammatory myopathy, see MKSAP 17 Rheumatology.

Endocrine-Related Myopathy

Hypothyroid myopathy can cause diffuse myalgia, proximal muscle weakness, and elevation of the serum CK level. Myoedema, the transient development of an edematous lump in a muscle in response to external percussion, may be seen on examination, as can depressed and delayed reflexes. In contrast, hyperthyroidism can lead to myopathy associated with brisk reflexes, fasciculations, and ophthalmoplegia. Hyperparathyroidism, Addison disease, Cushing disease, and acromegaly also can cause myopathy. Vitamin D deficiency can cause reversible proximal muscle weakness, myalgia, fatigue, and osteomalacia-related bone pain.

Glucocorticoid-Induced Myopathy

Glucocorticoid-induced myopathy usually is seen in patients receiving chronic high-dose treatment. Proximal weakness and myalgia are present. Testing reveals normal serum CK levels and normal EMG findings. In patients treated with glucocorticoids for inflammatory myopathies, persistence of weakness after normalization of the serum CK level may indicate glucocorticoid-induced myopathy. Glucocorticoid-free drug holidays may help decrease the risk of myopathy.

Critical illness myopathy is most often associated with use of intravenous glucocorticoids during prolonged stays in the ICU. However, this condition also may be triggered by prolonged inactivity and exposure to neuromuscular blockade. Patients have profound painless generalized weakness that may impede being weaned off a ventilator. The serum CK level is elevated, which helps to distinguish critical illness myopathy from its less common counterpart critical illness neuropathy. Treatment is supportive and should include weaning off glucocorticoids. H

KEY POINT

- Treatment of critical illness myopathy is supportive and should include weaning off any glucocorticoids.

Toxic Myopathy

Toxic myopathy often presents with painful proximal weakness that progresses rapidly. Statins can cause subacute toxic myopathy associated with rhabdomyolysis. The lipophilic statins, including simvastatin, atorvastatin, and lovastatin, have a higher propensity to cause this problem than the hydrophilic agents pravastatin, rosuvastatin, and fluvastatin. The risk of myopathy increases with higher dosage, the addition of fenofibrate or gemfibrozil, and the addition of cytochrome P3A4 inhibitors (including macrolides, cyclosporine, and itraconazole). Serum CK levels can be mildly or highly elevated. Coenzyme Q_{10} supplementation has been used to protect

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against statin myopathy, but its benefit remains uncertain. Ethanol, interferon, antiretroviral agents, and antimalarial drugs also cause toxic myopathy.

Inherited Myopathies

Inherited myopathies include muscular dystrophies, channelopathies, and metabolic, congenital, and mitochondrial myopathies. Many of these conditions start early in life, but some present in adulthood. Milder forms of muscular dystrophy, such as Becker and Emery-Dreifuss muscular dystrophy, survive into adulthood and should be closely monitored for cardiac complications. Myotonic dystrophies are associated with myotonia, an impairment of muscle relaxation causing stiffness and a delayed hand-grip release. Myotonic dystrophy type 1 causes distal weakness and is associated with cataracts, frontal balding, and cognitive impairment. Myotonic dystrophy type 2 is milder and causes proximal weakness. Mitochondrial myopathy can present with significant variability and may cause fatigue, myalgia, ophthalmoplegia, and various extramuscular manifestations. The estimated prevalence of mitochondrial myopathies is between 6 and 16 per 100,000 persons, and their presence should be suspected in the presence of multiorgan involvement and maternal transmission. Isolated mild myopathy is less common. Other adult-onset metabolic myopathies can present with isolated exercise-induced weakness, cramps, and myoglobinuria; they include many deficiencies of key metabolic pathways, such as glycogen storage and fatty acid oxidation.

Neuro-oncology

Intracranial Tumors

Intracranial tumors commonly present with new-onset seizures or headache. Rapidly progressing tumors also can present with focal neurologic deficits, including hemiparesis, hemineglect, or a visual field cut. Some tumors, particularly those affecting the frontal lobes and primary central nervous system (CNS) lymphomas (which affect the brain diffusely), can present with sometimes subtle changes in personality, behavior, or cognition. Symptoms of headache, lethargy, nausea, vomiting, and visual changes should prompt concern for a mass lesion causing increased intracranial pressure.

The neurologic examination of a patient with a suspected brain tumor should include an assessment of attention, language, and neglect and also visual field testing. A funduscopic examination should be performed to detect papilledema resulting from increased intracranial pressure. On cranial nerve examination, partial oculomotor nerve palsy (suggested by a dilated, nonreactive pupil) may indicate pressure on the brainstem or early herniation. Unilateral or bilateral abducens nerve palsy can be a sign of increased intracranial pressure. Other cranial nerve findings suggest the direct involvement of the brainstem. Multiple cranial nerve palsies can occur in leptomeningeal disease. Strength, sensation, and coordination should be carefully assessed; deficits may or may not be present, depending on the location of the lesion. Tone and deep tendon reflexes will be decreased acutely with a rapidly progressive lesion affecting the contralateral corticospinal tracts and will be increased with chronic lesions. The plantar response may be extensor contralateral to the lesion. Normal findings on neurologic examination do not exclude the presence of a brain tumor in patients with a concerning history, but focal findings and, particularly, findings of increased intracranial pressure necessitate a more urgent evaluation.

The differential diagnosis of an intracranial tumor includes any space-occupying lesion (such as an abscess, toxoplasmosis, or tuberculoma), sarcoidosis, a demyelinating disease, a vascular malformation, and radiation necrosis. The most useful diagnostic test in a patient with a suspected brain tumor is a contrast-enhanced MRI of the brain. In many instances, specific signal characteristics on the MRI suggest the diagnosis of a primary CNS tumor and even the specific pathology (**Table 39**). CT scans, which more effectively image blood and calcium, are indicated when intracranial bleeding or tumor-related calcification or bone erosion are suspected. PET and MRI spectroscopy can help predict tumor grade or distinguish a tumor from another mass lesion, but these tests are not definitive, are expensive, and are rarely necessary.

Lumbar puncture usually is not necessary in patients in whom the clinical history and MRI findings suggest a primary brain tumor. A lumbar puncture is indicated if the differential diagnosis includes a CNS mass lesion thought to be the result of infection, inflammatory or demyelinating disease, or primary CNS lymphoma. Lumbar puncture is contraindicated if clinical or imaging signs of herniation are present.

Ultimately, a tissue sample often is needed to make a definitive tissue diagnosis of a primary brain tumor. The decision to biopsy a lesion is based on the entire clinical picture. In suspected low-grade or benign tumors, serial MRI scanning is sometimes favored over a biopsy or resection. When an infectious source (such as an abscess or a tuberculoma) is strongly suspected, antibiotic treatment may be attempted before biopsy. In patients with a systemic malignancy and multiple brain lesions suggestive of brain metastases, biopsy usually is not needed for diagnosis.

Glucocorticoids are often used for symptomatic treatment of cerebral edema related to CNS mass lesions. This treatment can be life-saving in patients with impending herniation. However, glucocorticoids also can impede the diagnostic evaluation. For example, they can alter contrast enhancement on an MRI and significantly decrease the sensitivity of brain biopsy results in primary CNS lymphoma. Whenever possible, glucocorticoids should be deferred until after biopsy in patients with suspected CNS lymphoma.

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TABLE 39. Clinical and Radiographic Features of Intracranial Tumors

Tumor Type	Typical Age at Onset	Imaging Findings	Treatment	Median Survival
Metastatic tumor	60+ y	Multifocal lesions at gray-white matter junction; ring enhancement with contrast	Radiation, with or without surgery	10-16 mo
Glioma				
Astrocytoma		Infiltrating white matter lesion	Surgery	
Low-grade (fibrillary)	30-50 y	No enhancement	Surgery, with or without radiation	7-8 y
Anaplastic	35-55 y	Contrast enhancement	Surgery and radiation, with or without temozolomide	3-4 y
Glioblastoma multiforme	45-65 y	Possible hemorrhage, possible multifocal or "butterfly" lesions (bihemispheric)	Surgery and radiation and temozolomide (in older patients, sometimes only one modality is used)	12-15 mo
Oligodendroglioma	30-50 y	Infiltrating white matter lesion; vague contrast enhancement with a "honeycomb" pattern and calcifications that are best seen on CT scan	Surgery and chemotherapy (carmustine or temozolomide), with or without radiation	
Low grade				6-10 y
Anaplastic				3-4 y
Meningioma	50-65 y	Extra-axial (that is, not in the brain parenchyma); calcified, with diffusely enhancing "lightbulb" sign	Possible surgery, possible artery embolization, possible radiation (rare)	
Benign				Rarely limits life expectancy
Atypical				13 y
Anaplastic				3-4 y
Schwannoma	40-50 y	Cerebropontine angle; contrast enhancement	Possible surgery	Rarely limits life expectancy
Dysembryoplastic neuroepithelial tumor	<20 y	Temporal lobe; intracortical location often with small cysts. Contrast enhancement is rare. May be confused with low-grade glioma.	Surgery if intractable seizures, mass effect, or changes on serial MRIs are present	Rarely limits life expectancy
Ganglioglioma	<30y	Temporal lobe; homogeneous or nodular contrast enhancement	Surgery	Rarely limits life expectancy if complete resection possible
Ependymoma	30-40 y[a]	Posterior fossa or spinal cord lesion; contrast enhancement and calcifications, with or without hydrocephalus	Possible surgery, possible radiation	15-20 y
Medulloblastoma	20-30 y[a]	Posterior fossa (cerebellum); contrast enhancement and hydrocephalus	Surgery and radiation, with or without chemotherapy	17-18 y
Primary central nervous system lymphoma		Homogeneous white matter lesion; diffusely enhancing, periventricular, and often multifocal	Chemotherapy (methotrexate), with or without radiation	
Immunocompetent	45-70 y			1-4 y
AIDS-related	30-40 y		Antiretroviral therapy	1-2 y

[a]Age range given is for adult presentation; tumor is most common in children.

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KEY POINTS

- The most useful diagnostic test in a patient with a suspected brain tumor is a contrast-enhanced MRI of the brain.
- Glucocorticoids can be life-saving in patients with a mass lesion and impending herniation but can also alter contrast enhancement on an MRI and significantly decrease the sensitivity of brain biopsy results in primary CNS lymphoma.

Metastatic Brain Tumors

Brain metastases are the most common type of intracranial tumor in adults. The tumors most likely to metastasize to the brain are lung cancer, breast cancer, and melanoma. Metastatic brain tumors are often multiple but can be solitary. Typically located at the gray-white matter junction, these tumors exhibit ring enhancement with contrast. The suspicion of a metastatic brain lesion should prompt evaluation for a primary tumor and appropriate cancer staging.

Primary Central Nervous System Tumors

Primary Central Nervous System Gliomas

After metastatic tumors, the second most common intracranial tumors are glial tumors that arise from the supporting tissues that surround neurons. These tumors include astrocytomas, oligodendrogliomas, and ependymomas. Glioblastoma multiforme (World Health Organization grade IV astrocytoma) is the most common and the most aggressive primary CNS tumor.

KEY POINT

- Glioblastoma multiforme is the most common and most aggressive primary CNS tumor.

Primary Central Nervous System Lymphoma

Primary CNS lymphoma (PCNSL) is a non-Hodgkin lymphoma that can affect any part of the CNS but commonly presents as a focal supratentorial lesion. Visual symptoms are common because of frequent tumor involvement of the optic radiations. PCNSL most commonly affects immunocompromised patients but can occur in patients with intact immune systems. An association with the Epstein-Barr virus has been noted. Pathologic analysis, usually of a brain biopsy specimen, is required to make a diagnosis of PCNSL. Diffuse large B cell lymphoma is typical. Cerebrospinal fluid (CSF) cytology can be diagnostic in 10% of patients, although repeated samples often are necessary. Ocular involvement in the vitreous or retina may be seen in 10% to 20% of patients and can be detected with a slit lamp examination and confirmed by vitreal biopsy.

KEY POINT

- Pathologic analysis, usually of a brain biopsy specimen, is required for diagnosis of primary central nervous system lymphoma.

Meningioma

Meningiomas are benign tumors that arise from the meningeal coverings of the brain. They are the most common extra-axial (that is, not in the brain parenchyma) intracranial lesion in adults; other extraparenchymal tumors include schwannomas. Meningiomas are typically slow-growing tumors that often are discovered incidentally; clinical signs generally are subtle. These tumors have characteristic imaging features, including intense homogeneous contrast enhancement ("lightbulb" sign), areas of calcification, and a dural tail, which is thickening of the dura adjacent to the mass (**Figure 25**).

KEY POINT

- Meningiomas are extraparenchymal tumors that can be identified by characteristic radiographic features such as homogeneous enhancement with contrast ("lightbulb" sign).

Management of Intracranial Tumors

Management of Metastatic Brain Tumors

Patients with multiple brain metastases typically are treated with whole-brain radiation, which is associated with a modest increase in survival and control of local tumor growth and symptoms. Stereotactic radiosurgery (radiation administered to a focal area of brain) also is being used with or without whole-brain radiation to minimize neurotoxicity. Surgical resection has become a major initial management option for patients with a solitary, accessible brain metastasis and controlled extracranial disease. Surgery is the best way to rapidly control mass effect from a tumor and tumor-related edema.

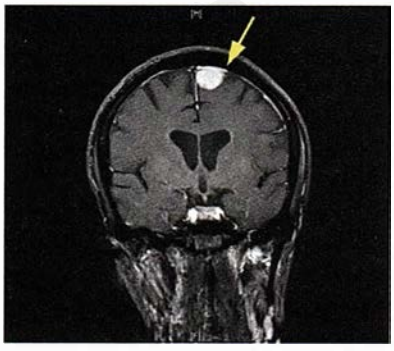

FIGURE 25. Coronal postcontrast T1-weighted MRI showing a left parafalcine meningioma. The tumor enhances homogeneously with contrast, which makes it look like a "lightbulb." Note the "dural tail" (*arrow*).

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CONT. This treatment typically is followed by whole-brain radiation and/or stereotactic radiosurgery.

KEY POINT

- Patients with multiple brain metastases typically are treated with whole-brain radiation, whereas those with a single brain metastasis are usually candidates for surgical resection.

Management of Primary Central Nervous System Gliomas

Whenever possible, the first intervention for primary CNS gliomas is total or near-total resection. The extent of resection is correlated with long-term outcomes. Surgical resection also provides relief of any mass effect and pathologic specimens for diagnosis and prognosis. Patients with glioblastoma multiforme (World Health Organization grade IV astrocytoma) typically receive adjuvant radiation and chemotherapy. Photon radiation is administered to a focal field around the tumor (including a small margin) rather than whole-brain radiation to limit toxicity. Oral temozolomide, an alkylating agent, given in combination with focal radiation has been shown to improve 2- and 5-year survival rates in patients with glioblastoma multiforme compared with radiation alone. Currently, no established standard of care for treatment of grade III gliomas exists. After surgery, chemotherapy and/or radiation often are used and may prolong survival and time to tumor progression. In patients with grade II gliomas, the risks of adjuvant therapies have to be weighed against the potential benefits, particularly in younger patients who typically have longer survivals and greater potential for secondary complications of treatment (such as neurotoxicity or secondary malignancies from radiation or chemotherapy).

Molecular testing of the tumor has had an increasing role in the treatment and prognosis of primary CNS gliomas.

KEY POINT

- Whenever possible, the first intervention for primary central nervous system gliomas is total or near-total resection.

Management of Primary Central Nervous System Lymphoma

The management of primary central nervous system lymphoma (PCNSL) is distinct from the management of CNS gliomas. Resection is not indicated and has been shown to worsen patient outcomes in PCNSL. In patients with PCNSL and HIV infection, the first intervention should be to start antiretroviral therapy; for those who have undergone organ transplantation, immunosuppressive therapy should be stopped, if possible. PCNSL is sensitive to both radiation and chemotherapy. Because PCNSL distribution is universally diffuse throughout the brain, whole-brain (and not focal) radiation is necessary. Most clinicians use systemic methotrexate-based chemotherapy followed by radiation, although in older patients, radiation sometimes is not used because of the risk of neurotoxicity. Although PCNSL is very sensitive to glucocorticoids, these drugs should be avoided early in the disease because they can limit the usefulness of biopsy and subsequent tissue diagnosis.

KEY POINT

- Resection of primary central nervous system lymphoma is not indicated and can worsen patient outcomes.

Management of Meningiomas

Patients with small, asymptomatic meningiomas without evidence of invasion of other intracranial structures and without surrounding edema are usually followed clinically and radiographically, with a first follow-up MRI performed 3 to 6 months after the tumor is identified to ensure that it is not an atypical meningioma exhibiting rapid growth. Patients with large or symptomatic tumors, tumors that invade surrounding parenchyma, or tumors that grow over time may be considered for surgery and/or radiation therapy. If intervention is indicated, surgical resection is usually the first-line therapy, followed by radiation for higher-grade tumors or tumors that could not be resected completely. Rarely, arterial embolization is used to shrink large tumors before resection.

KEY POINT

- Small asymptomatic meningiomas can be followed conservatively with an initial repeat MRI at 3 to 6 months. HVC

Medical Management of Complications of Primary Central Nervous System Tumors

Glucocorticoids often are used to decrease the mass effect associated with edema caused by CNS tumors or by the radiation used to treat them. Drug courses should be kept short to minimize the potentially severe adverse effects of long-term use. All patients taking glucocorticoids should receive calcium and vitamin D supplementation, and bisphosphonates are indicated for those at highest risk of osteoporosis. All patients receiving chronic glucocorticoids or prolonged daily temozolomide should receive prophylaxis for *Pneumocystis jirovecii* pneumonia.

Venous thromboembolism is a common and potentially lethal complication of CNS tumors. Low-molecular-weight heparin is recommended for secondary prevention in patients with these tumors and venous thromboembolism. Inferior vena cava filters should be reserved only for patients with an absolute contraindication to anticoagulation.

Prophylactic use of antiepileptic drugs (AEDs) is not recommended in most patients with brain tumors. AEDs can be used in those with brain tumors and one or more seizures. In these patients, nonenzyme-inducing AEDs, such as lacosamide, lamotrigine, levetiracetam, and valproic acid, are preferred because of their limited interaction with commonly used chemotherapeutic agents.

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KEY POINTS

- For patients with central nervous system tumors who are receiving chronic glucocorticoid or prolonged daily temozolomide therapy, prophylaxis against *Pneumocystis jirovecii* pneumonia is appropriate.

HVC

- Prophylactic use of antiepileptic drugs is not recommended in most patients with brain tumors.

Paraneoplastic Neurologic Syndromes

Paraneoplastic neurologic syndromes (PNSs) are a heterogeneous group of conditions affecting multiple targets in the neuraxis of patients with cancer. Symptomatic progression is typically subacute (over a period of weeks). An immune reaction to the primary tumor is thought to be responsible for the generation of autoantibodies that cross-react with epitopes on specific nervous system structures.

A paraneoplastic antibody syndrome should be suspected in patients with subacute neurologic symptoms that are otherwise unexplained (**Table 40**). Because many of these syndromes are associated with cancers, a first step is to ensure that age-appropriate cancer screening testing is current. Consensus guidelines recommend directing further evaluation on the basis of specific paraneoplastic antibody test results, but this testing may detect only 60% of paraneoplastic antibodies, and it may take several weeks for results to be known. For these reasons, it sometimes may be worthwhile to proceed with whole-body CT and PET scanning or with targeted screening for tumors known to be associated with the patient's constellation of symptoms (such as ovarian ultrasonography or pelvic

TABLE 40. Selected Neuronal Paraneoplastic Antibodies

Paraneoplastic Syndrome	Symptoms	Tumor	Antibody
Cerebellar degeneration	Ataxia, dysarthria, dizziness, vertigo	Breast cancer	ANNA-1 (anti-Hu), ANNA-3, MA, PCA-1 (anti-Yo)
		Hodgkin lymphoma	Tr
		Lung cancer (small-cell)	ANNA-1 (anti-Hu), ANNA-3, CRMP-5, MA, PCA-2, VGCC
		Ovarian cancer	ANNA-1 (anti-Hu), ANNA-3, PCA-1 (anti-Yo)
		Testicular cancer	ANNA-1 (anti-Hu), ANNA-3, CRMP-5, MA
		Thymoma	CRMP-5
Encephalomyelitis	+/– Myelitis (spinal cord syndrome), +/– brainsterm signs (common), +/– limbic encephalitis, +/– neuronopathy, +/– cerebellar degeneration	SCLC	ANNA-1 (anti-Hu)
		Testicular, breast, and lung cancer	Ma2
Lambert-Eaton myasthenic syndrome	Muscle weakness	SCLC	VGCC
Limbic encephalitis	Personality change, psychosis, seizures	SCLC, thymoma	CRMP-5, GABA B receptor
		Tumors of thymus, lung, breast	AMPA receptor
	Personality change, psychosis, seizures, and oral dyskinesias	Ovarian/testicular teratoma	NMDA
	Personality change, psychosis, seizures, and SIADH	Lung cancer, thymoma (although cancer is found in < 20% of patients with limbic encephalitis)	LG1 or CASPR2 (previously known as VGKC)
Opsoclonus-myoclonus	Involuntary eye movements and muscle jerks, ataxia	Breast cancer, lung cancer (small-cell)	ANNA-2 (anti-Ri)
Sensory neuronopathy	Painful sensory neuropathy, sensory ataxia, autonomic dysfunction	Lung cancer (small-cell)	ANNA-1 (anti-Hu)
Stiff-person syndrome	Muscle stiffness and spasms	Breast and lung cancer	Amphiphysin, CRMP-5
		Thymoma	CRMP-5

AMPA = anti-M protein antibody; ANNA = antineuronal nuclear antibody; CASPR2 = contactin-associated protein 2; CRMP-5 = collapsin response mediator protein, GABA B, γ-aminobutyric acid B; MA, mitochondrial antibody, NMDA = *N*-methyl-D-aspartate; PCA = Purkinje cell antibody; SCLC = small cell lung cancer; SIADH = syndrome of inappropriate antidiuretic hormone secretion, VGCC = voltage-gated calcium channel; VGKC = voltage-gated potassium channel.

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CONT.

MRI for suspected anti-*N*-methyl-D-aspartate (NMDA) encephalitis and chest radiography or CT for patients with sensory neuronopathy).

Most commercial laboratories offer antibody testing in panels, so it is vital to include the antibodies corresponding to the patient's clinical syndrome (see Table 40). Generally speaking, serum or CSF samples can be sent for antibody testing because serum provides a similar sensitivity to CSF. Exceptions to this are anti-NMDA and anti-Tr antibodies, for which CSF is more sensitive than serum.

Often, PNS presents well before a cancer is detected, even with the most sensitive evaluations for a systemic malignancy. Notably, some of the syndromes previously thought to be "paraneoplastic" are now understood to be primary autoimmune disorders for which an underlying tumor will never manifest. Clinical guidelines suggest serial cancer screening for up to 5 years after presentation with a classic PNS. In most instances (90%), the tumor manifests within the first year.

Most PNSs respond to treatment of the underlying tumor. Intravenous immune globulin and/or glucocorticoid administration may facilitate recovery from or stabilization of the PNS, particularly if no tumor is identified. In certain syndromes that have a more aggressive course and are principally autoimmune (such as NMDA encephalitis), immunotherapy with rituximab or cyclosporine is often necessary if other therapies do not to control symptoms.

KEY POINT

- A paraneoplastic antibody syndrome should be suspected in patients with subacutely progressive neurologic symptoms that are otherwise unexplained.

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 42-year-old man is evaluated in the emergency department for a 1-week history of bilateral leg weakness and numbness. He has an 8-year history of multiple sclerosis (MS) that is currently well controlled with natalizumab; he has had no MS exacerbations since beginning treatment 2 years ago after unsuccessful trials of interferon beta and glatiramer acetate. The patient also has chronic fatigue and depression. Medications are monthly natalizumab, twice daily amantadine and extended-release bupropion, a daily multivitamin, and a calcium-vitamin D supplement that he rarely takes.

On physical examination, temperature is 36.7 °C (98.1 °F), blood pressure is 124/58 mm Hg, pulse rate is 74/min, and respiration rate is 14/min. Muscle strength is 4/5 in the bilateral hip flexors, knee flexors, and foot dorsiflexors. Decreased pinprick sensation is noted just below the umbilicus.

Laboratory studies performed 3 weeks ago showed no evidence of elevated serum antibody titers against the JC virus. Results of current complete blood count, liver chemistry studies, and a urinalysis show no abnormalities.

An MRI of the brain shows white matter hyperintensities consistent with MS and is unchanged from an MRI obtained 1 year ago.

In addition to a 5-day infusion of intravenous methylprednisolone, which of the following is the most appropriate next step in management?

(A) Discontinuation of natalizumab
(B) Measurement of serum 25-hydroxyvitamin D level
(C) MRI of the lumbar spine
(D) Oral trimethoprim-sulfamethoxazole for 5 days

Item 2

A 67-year-old woman is evaluated for a 1-year history of increasing forgetfulness. She reports greater difficulty keeping track of upcoming appointments, recalling details of recent telephone conversations, and remembering names of new acquaintances. She has completed 16 years of formal education, currently works as a teacher's assistant, and has noticed no change in her ability to perform classroom duties, including carrying out the instructions of the teachers with whom she works. The patient lives alone and is able to care for herself, drive, and manage her finances. She describes her mood as "upbeat," continues to enjoy her life, and has had no other symptoms. She does not take any medication.

On physical examination, vital signs are normal. All other physical examination findings, including those from a neurologic examination, are normal. She scores 24/30 on the Montreal Cognitive Assessment, losing points in the orientation and delayed recall sections.

Which of the following is the most likely diagnosis?

(A) Dementia
(B) Depression
(C) Mild cognitive impairment
(D) Normal aging

Item 3

A 35-year-old man is evaluated in the emergency department for a 7-hour history of midback pain and bilateral leg numbness. He was in a bar fight immediately before symptom onset and sustained forceful kick injuries to the back, head, and limbs; he did not lose consciousness.

On physical examination, temperature is 36.6 °C (97.8 °F), blood pressure is 110/70 mm Hg, pulse rate is 108/min, and respiration rate is 18/min; BMI is 32. The patient is alert without any apparent cognitive deficits. Lacerations on the face, scalp, and extremities are noted, as are hematomas on the midback and chest. No tremors or significant swelling or hematomas on the scalp are detected. Muscle strength is 3/5 in the lower extremities, and muscle tone in the legs is reduced. Muscle tone in the arms is normal, and anal sphincter tone is reduced. Pinprick testing shows a sensory level below T8.

Which of the following is the most appropriate next step in management?

(A) CT of the head
(B) High-dose methylprednisolone
(C) MRI of the thoracic spine
(D) Phenytoin

Item 4

A 55-year-old man is evaluated in the emergency department for a 20-minute episode of left eye visual loss without pain followed by a 5-minute episode of slurred speech. He has no residual symptoms. The patient has hypertension treated with amlodipine. He takes no other medication.

On physical examination, blood pressure is 178/92 mm Hg, pulse rate is 78/min and regular, and respiration rate is 12/min. Carotid upstrokes are normal without bruits. Heart rate is regular, and no murmurs are heard. Other physical examination findings, including those from a neurologic examination, are normal.

Findings on an electrocardiogram and a noncontrast CT scan of the head are normal.

Which of the following is the most appropriate next diagnostic test?

(A) Carotid ultrasonography
(B) CT angiography of the neck
(C) MRI of the brain
(D) Transesophageal echocardiography

Item 5

A 42-year-old man comes to the office to discuss results of imaging studies, which were ordered because of a change in his pattern of chronic migraine. Headache episodes have now improved.

On physical examination, temperature is normal, blood pressure is 110/80 mm Hg, pulse rate is 80/min, and respiration rate is 16/min. All other findings from the general physical and neurologic examinations are normal.

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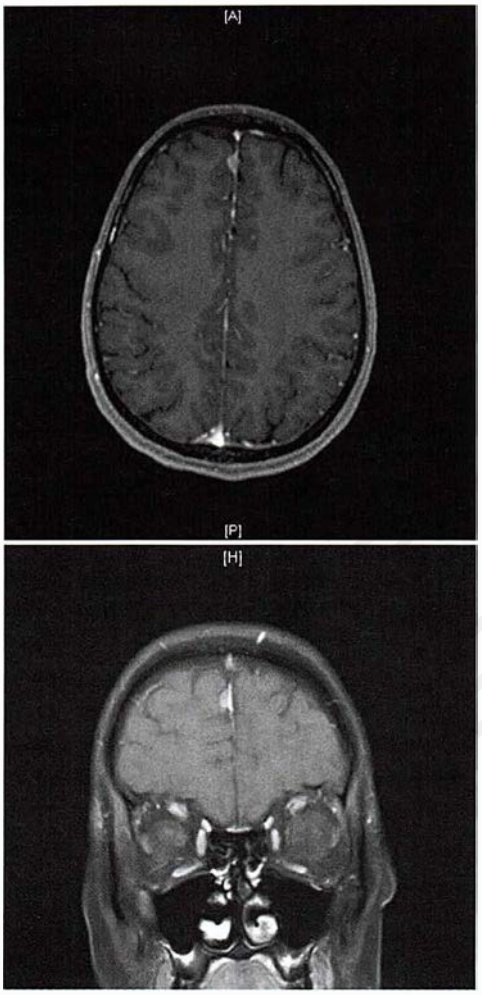
A noncontrast CT scan of the head shows a hyperintense extra-axial lesion located between the frontal lobes (parafalcine), which is confirmed by the axial (*top*) and coronal (*bottom*) MRIs shown.



Which of the following is the most appropriate next step in management?

(A) Lumbar puncture
(B) Radiation therapy
(C) Repeat MRI in 3 to 6 months
(D) Surgical resection

Item 6

A 39-year-old woman is evaluated in the emergency department 45 minutes after having a seizure witnessed by her husband. The seizure, which occurred 10 minutes after she awoke this morning, lasted 90 seconds; she reports now being "back to normal." According to her husband, the seizure was characterized by a loud cry and unilateral stiffening and shaking. She has no memory of the seizure but does recall an intense feeling of déjà vu just before losing consciousness; she reports that she has had a similar sensation lasting 5 to 15 seconds several times over the past few years. She had been at a birthday celebration the night before her seizure, had several alcoholic drinks, and stayed out late, which is unusual for her. She says she fell on ice 1 month ago, striking her head; except for a mild headache that lasted for several days after the fall, she has had no residual symptoms. She has no other significant medical history and takes no medication.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 120/70 mm Hg, pulse rate is 95/min, and respiration rate is 14/min. All other findings from the general physical and neurologic examinations are unremarkable.

Results of laboratory studies are normal, including a blood ethanol level of 0.

Which of the following is the most likely diagnosis?

(A) Alcohol withdrawal seizure
(B) Focal epilepsy
(C) Generalized epilepsy
(D) Posttraumatic seizure

Item 7

A 48-year-old man is evaluated for increasing depression and suicidal ideation. He reports experiencing feelings of hopelessness, lack of initiative, and general disinterest over the past 5 years that recently have worsened and are now accompanied by mood swings, irritability, impatience, verbal abuse, and physical aggression. Thoughts of death and suicide often have been present in the past month. His gait has become slow and shuffling, and his balance is increasingly impaired. His wife says he is more forgetful than ever and unable to perform home repairs that he previously accomplished easily. He has had no hallucinations or delusions. The patient is retired from a 13-year career playing professional football. Other than minor football injuries, he has no significant medical history and has an unremarkable family history, including no neurologic and psychological disorders. The patient takes no medication.

On physical examination, vital signs are normal. Neurologic examination shows slow processing speed, mild dysarthria, slowed rapid alternating movements bilaterally, and a wide-based gait with decreased foot-floor clearance. The patient scores 20/30 on the Montreal Cognitive Assessment, losing points in the visuospatial/executive function, attention, orientation, and delayed recall sections.

Which of the following is the most likely diagnosis?

(A) Chronic traumatic encephalopathy
(B) Dementia with Lewy bodies
(C) Depression-related cognitive impairment
(D) Parkinson disease

Item 8

A 48-year-old woman is evaluated for a 12-month history of increasingly severe headaches. For the past 25 years, she has had monthly migraine without aura. The headaches have occurred one or two times per month, but over the past year, their severity has increased, with NSAIDs now providing only limited, temporary pain relief. Medications are ibuprofen and naproxen as needed (≤5 days/mo).

On physical examination, blood pressure is 116/70 mm Hg and pulse rate is 80/min. Other physical examination findings, including those from a neurologic examination, are normal.

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An MRI of the brain shows several punctate hyperintensities in the bilateral subcortical white matter.

Which of the following is the most appropriate management?

(A) Aspirin
(B) Lumbar puncture
(C) Magnetic resonance angiography
(D) Rizatriptan
(E) Timolol

Item 9

A 26-year-old woman is evaluated for a 10-year history of recurrent episodes of acute-onset feelings of fear and anxiety. These episodes initially occurred approximately four times per year but for the past 3 months have been occurring once or twice per month, especially when she is under stress. She describes the episodes as paroxysmal attacks of fear and anxiety associated with a dry mouth and a consistent "roller coaster" sensation in her stomach that typically last 15 seconds to 1 minute. With more intense attacks, she becomes momentarily confused; her boyfriend says she seems "fidgety" when this occurs. She feels well between episodes. Medical history is otherwise negative, and she takes no medication.

On physical examination, vital signs are normal. All other findings from the general physical and neurologic examinations are unremarkable.

A brain MRI and electroencephalogram are normal.

Which of the following is the most likely diagnosis?

(A) Frontal lobe epilepsy
(B) Juvenile absence epilepsy
(C) Panic disorder
(D) Psychogenic nonepileptic seizures
(E) Temporal lobe epilepsy

Item 10

A 51-year-old woman is evaluated in the emergency department for sudden-onset severe headache and right-sided weakness followed by temporary loss of consciousness that occurred 30 minutes ago. According to her husband, she has hypertension treated with amlodipine and a 20-pack-year smoking history; she stopped smoking 12 years ago.

On physical examination, blood pressure is 158/68 mm Hg, pulse rate is 68/min and regular, and respiration rate is 10/min. Funduscopic examination findings are normal. Nuchal rigidity is noted. On neurologic examination, the patient does not follow commands and has flexor posturing to painful stimuli; pupils are reactive and symmetric in size and shape.

An electrocardiogram shows normal sinus rhythm and no ischemic changes.

Which of the following is the most appropriate next diagnostic test?

(A) Catheter-based cerebral angiography
(B) CT of the head without contrast
(C) Lumbar puncture
(D) MRI of the brain without contrast

Item 11

A 45-year-old man is evaluated for generalized weakness and stiffness. He has had slowly progressive weakness of the lower extremities for the past 5 years. The patient reports that he feels "wobbly" during ambulation, easily becomes fatigued, has bouts of stiffness in the upper and lower extremities, has occasional difficulty holding his hand above his head, and cannot easily stand up from a chair. He has had no diplopia, numbness, or tingling. He says that sometimes it is difficult to release his grip after turning a door knob. Medical history includes cardiomyopathy, first-degree heart block, and cataract surgery 1 year ago. He has a brother with muscle weakness. His only medication is metoprolol.

On physical examination, vital signs are normal. Bilateral ptosis that does not worsen with sustained upward gaze is noted, as is bilateral facial drooping. Speech is dysarthric. Proximal limb muscles are tight, and finger abductors and foot dorsal flexors are weak bilaterally. A delay in releasing his hand grip and slow relaxation of the muscles after percussion are noted. Gait is stiff and unstable.

Which of the following is the most likely diagnosis?

(A) Becker muscular dystrophy
(B) Inclusion body myositis
(C) Lambert-Eaton myasthenic syndrome
(D) Myasthenia gravis
(E) Myotonic dystrophy

Item 12

A 67-year-old man is evaluated in the emergency department for sudden onset of severe headache that has not abated over the past 24 hours.

On physical examination, temperature is 37.4 °C (99.3 °F), blood pressure is 168/78 mm Hg, pulse rate is 68/min and regular, and respiration rate is 12/min. Nuchal rigidity is noted. The left pupil is 5 mm in diameter and unreactive to light, and the right pupil is 3 mm in diameter and reactive to light. A neurologic examination shows normal mental status and motor function.

A CT of the head without contrast is normal.

Which of the following is the most appropriate next diagnostic test?

(A) Lumbar puncture
(B) Magnetic resonance angiography of the brain
(C) Magnetic resonance venography of the brain
(D) MRI of the brain

Item 13

A 69-year-old man is evaluated for a 1-year history of increasing word-finding difficulties. The patient also reports occasional difficulty recalling names of objects and people and has had problems comprehending conversations. His daughter reports sometimes not understanding

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what her father is saying because of his frequent use of filler words, such as "that thing" and "you know"; she says that otherwise his mind seems sharp, his cognition unimpaired, and his memory excellent. He has no other significant medical history, and he takes no medication. His older brother had onset of dementia at age 56 years, and his father developed dementia at age 60 years.

On physical examination, vital signs are normal. General physical examination results are unremarkable, and a neurologic examination yields no focal findings. However, the patient has trouble answering even simple questions about where he lives or what he had for breakfast and is unable to name simple objects.

Results of laboratory studies, including a complete blood count, comprehensive metabolic profile, and thyroid function studies, are normal.

An MRI of the brain is normal.

Which of the following is the most appropriate next step in management?

(A) Determination of apolipoprotein E (*APOE ε4*) status
(B) Observation with reevaluation in 3 to 6 months
(C) Speech and language therapy
(D) Trial of donepezil

Item 14

A 72-year-old woman is evaluated for a 6-month history of gradually worsening, nonsuppressible involuntary movements. The patient first noticed twitching movements of the lower part of the face, with occasional unintended thrusting of the tongue through the lips and biting of the cheeks inside the mouth. She further reports pressure and a pulling sensation at the back of the neck that causes her head to pull backward suddenly and the occasional tendency to drop objects from her hands secondary to uncontrollable jerking movements. The patient has chronic gastroparesis that is treated with metoclopramide and bipolar disorder that is well controlled with lamotrigine and quetiapine. She has no family history of a movement disorder or any neurologic disease.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 145/76 mm Hg, and pulse rate is 80/min. Frequent stereotyped pursing movements of the lips, occasional tongue protrusion and forceful jaw closure, continual slow and nonrhythmic movements of the fingers, and recurrent cervical retrocollis are noted. Occasional rapid jerking movements of the arms and infrequent facial grimacing also are present. Gait is slow and marked by short steps and reduced arm swing.

Which of the following is the most appropriate next step in management?

(A) Change quetiapine to risperidone
(B) Discontinue metoclopramide
(C) Start carbidopa-levodopa
(D) Start tetrabenazine

Item 15

A 40-year-old woman is seen for a follow-up evaluation of multiple sclerosis, which was diagnosed 1 month ago. The patient reports feeling generally well. She has no significant medical history and does not drink or smoke. Her only medication is interferon beta-1a, which she has been taking since diagnosis and tolerates well.

On physical examination, vital signs are normal. Neurologic examination reveals internuclear ophthalmoplegia, right arm weakness, and mild ataxia, which were present at diagnosis and have remained stable. All other physical examination findings are unremarkable.

Which of the following is indicated for periodic monitoring of this patient's disease-modifying therapy?

(A) JC virus antibody measurement
(B) Ophthalmologic evaluation
(C) Serum aminotransferase measurement
(D) Serum amylase and lipase measurement

Item 16

A 68-year-old woman is evaluated 1 month after having an ischemic stroke of the left thalamus. She now has only residual right-sided anesthesia. The patient has hypertension and dyslipidemia, both well controlled by medication, and had been taking a daily aspirin before the stroke. Medications are lisinopril, chlorthalidone, aspirin, and rosuvastatin.

On physical examination, blood pressure is 128/68 mm Hg and pulse rate is 68/min and regular. Findings from the remainder of the general physical examination are normal, including no carotid bruits on cardiac examination. Neurologic examination findings include decreased sensation to light touch and pinprick throughout the right side.

Which of the following is the most appropriate treatment?

(A) Add clopidogrel
(B) Add dipyridamole
(C) Substitute ticlopidine for aspirin
(D) Substitute warfarin for aspirin

Item 17

A 27-year-old woman comes to the office to discuss medications 3 days after experiencing a first seizure. MRI evaluation on the day of the seizure showed left mesial temporal sclerosis, and a subsequent electroencephalogram was significant for temporal sharp waves, findings consistent with temporal lobe epilepsy. She has polycystic ovary syndrome and requires a daily estrogen-progestin combination for symptom management and contraception.

Physical examination findings, including vital signs, are normal.

Which of the following antiepileptic drugs is most appropriate?

(A) Carbamazepine
(B) Lamotrigine
(C) Levetiracetam
(D) Oxcarbazepine
(E) Topiramate

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Item 18

An 83-year-old woman is evaluated in the emergency department for a 36-hour history of left-sided weakness. She has noticed no changes in vision or speech. The patient has hypertension and dyslipidemia. Medications are aspirin, losartan, metoprolol, and atorvastatin.

On physical examination, blood pressure is 168/102 mm Hg, pulse rate is 78/min and regular, and respiration rate is 16/min. Other findings from the general medical examination are normal. Neurologic examination shows grade 4/5 weakness of the left face, arm, and leg; dysarthria; and unsteady gait. Her score on the National Institutes of Health Stroke Scale is 8, indicating a moderate stroke; she coughed after attempting to swallow 30 mL of water.

Results of laboratory studies are normal.

An electrocardiogram is normal. A CT scan of the head without contrast shows an infarct in the right pons.

Which of the following is most likely to reduce the 1-year mortality risk in this patient?

(A) Add clopidogrel
(B) Administer labetalol intravenously
(C) Administer recombinant tissue plasminogen activator (rtPA)
(D) Admit to the stroke unit

Item 19

A 24-year-old man is seen for management of seizures. His first seizure occurred 5 years ago, at which time he had a normal MRI and electroencephalogram. Since that time, he has had two additional seizures, one 2 years ago and the other last week. All seizures have been convulsive and occurred without warning. The patient reports being under stress or sleep deprived around the time of the seizures. He has had no paroxysmal symptoms, including staring spells or morning jerks. He takes no medication.

Physical examination findings, including vital signs, are unremarkable.

Laboratory studies, including a complete blood count, a comprehensive metabolic profile, and measurement of serum thyroid-stimulating hormone level, have normal results.

Which of the following treatments is most appropriate?

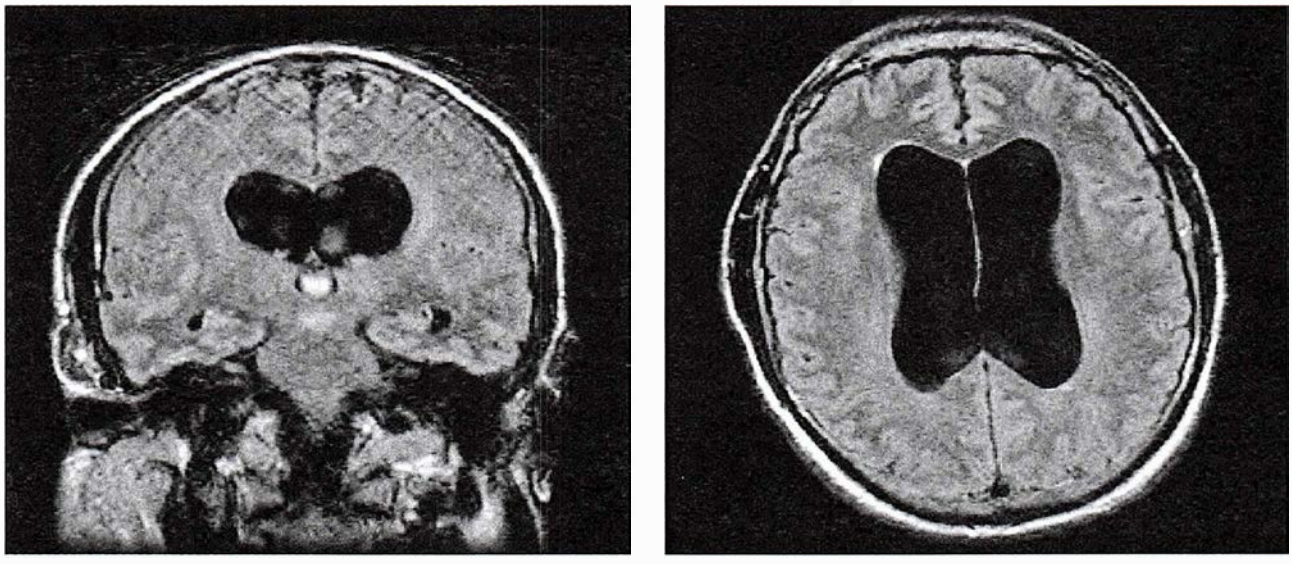
(A) Carbamazepine
(B) Gabapentin
(C) Phenytoin
(D) Topiramate

Item 20

A 72-year-old man is evaluated for a 1-year history of progressively impaired gait and balance. He reports that he walks more slowly and is not as agile as he used to be, attributing a recently increased number of falls to not paying enough attention before tripping. In the past 6 months, he has had occasional problems recalling details of recent conversations and events, completing tasks around the house in a timely manner, and organizing and balancing his checkbook despite having been an accountant before retiring. The patient also reports some urinary urgency and frequency but otherwise feels well. He has hypertension treated with hydrochlorothiazide and no history of traumatic brain injury, meningitis, or intracranial hemorrhage.

On physical examination, vital signs are normal. General medical examination findings are unremarkable. On neurologic examination, gait is slow, with poor foot clearance, shuffling, multistep turns, and intermittent hesitation. Tandem gait is impaired. The remainder of the physical examination is unremarkable. He scores 23/30 on the Mini-Mental State Examination, with points deducted on the delayed recall and serial 7 calculation sections.

An MRI of the brain is shown.



ITEM 20

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CONT.

Which of the following is the most appropriate next step in management?

(A) Brain magnetic resonance angiography
(B) Large-volume lumbar puncture
(C) Trial of donepezil
(D) Trial of levodopa

Item 21

A 40-year-old man is evaluated in the emergency department for a headache that started 1 day ago while he was lifting weights. He first experienced a severe, sharp, right periorbital pain associated with nausea and ipsilateral neck pain. Although the pain has lessened in intensity, it has persisted, and this morning he had an episode of right monocular visual loss resolving spontaneously after several minutes. The patient has a history of monthly migraine without aura that typically lasts 6 hours and is characterized by bilateral frontotemporal throbbing, pain associated with photophobia, and nausea. He says that his current headache pain is "different" from the pain he experiences during migraine episodes and that the neck pain is new. His only medication is naproxen as needed.

On physical examination, blood pressure is 130/86 mm Hg and pulse rate is 72/min. Palpation of the neck elicits pain. Right ptosis and miosis are noted, but all other physical examination findings are unremarkable.

A CT scan of the head shows normal findings.

Which of the following is the most likely diagnosis?

(A) Carotid artery dissection
(B) Cluster headache
(C) Migraine
(D) Vertebral artery dissection

Item 22

A 30-year-old man is evaluated in the hospital for hyponatremia and dizziness. He reports a 3-day history of fatigue, headache, and imbalance. The patient has had difficult-to-manage nonlesional epilepsy since age 9 years and has required multiple drugs to maintain a seizure rate of only two or three per month. He has no other significant medical history. Medications are oxcarbazepine, levetiracetam, topiramate, and clonazepam.

On physical examination, mental status is normal. Temperature is 37.3 °C (99.1 °F), blood pressure is 95/60 mm Hg, pulse rate is 100/min, and respiration rate is 14/min. Examination of the eyes reveals end-gaze nystagmus in both directions of gaze; the optic discs are sharp. Gait is ataxic.

Laboratory studies:

Creatinine	0.7 mg/dL (61.9 µmol/L)
Electrolytes	
Sodium	123 mEq/L (123 mmol/L)
Potassium	3.5 mEq/L (3.5 mmol/L)
Chloride	110 mEq/L (110 mmol/L)
Bicarbonate	23 mEq/L (23 mmol/L)

Which of the following medications is most likely responsible for this patient's findings?

(A) Clonazepam
(B) Levetiracetam
(C) Oxcarbazepine
(D) Topiramate

Item 23

A 68-year-old woman is evaluated for memory deficits. She retired from her position as a high school principal 2 years ago. In the past 6 months, she has had increasing forgetfulness, difficulty organizing her belongings, and problems with concentration and indecisiveness; during this period, she also has noticed fatigue, decreased energy, difficulty falling asleep, diminished interest in reading, and decreased appetite, which has caused her to lose 4.5 kg (10.0 lb). The patient has remained independent in activities of daily living, although she has forgotten to pay several monthly bills. She moved closer to her son last year but now has few opportunities to see her friends, which has resulted in feelings of isolation and sadness. The patient had a depressive episode 28 years ago after her husband's death. She takes no medication.

On physical examination, vital signs and general physical examination findings are normal. Neurologic examination reveals psychomotor slowing without decremental response on repetitive finger tapping. The patient scores 27/30 on the Mini-Mental State Examination, losing three points in the attention and calculation section.

Results of a complete blood count, a comprehensive metabolic profile, thyroid function tests, and urinalysis are normal.

Which of the following is the most appropriate next step in management?

(A) Carbidopa-levodopa
(B) Donepezil
(C) Sertraline
(D) Clinical observation

Item 24

A 27-year-old woman is evaluated for a severe migraine with typical aura and right-sided sensory symptoms that occurred 1 day ago. Migraine was diagnosed at age 13 years, is often preceded by 45 minutes of visual loss (which she describes as "losing half my sight"), is only associated with onset of menses, involves hemicranial throbbing pain associated with nausea and vomiting, and lasts 90 minutes if treated and 24 hours if untreated. Yesterday's migraine was again preceded by the typical visual loss and 40 minutes later by numbness and paresthesia in the right upper extremity, starting in her hand and migrating toward her forearm; these sensations eventually involved her right tongue and throat, lasted an additional 50 minutes, and then resolved completely. The patient has experienced no recurrence of symptoms in the past 24 hours. Medications are rizatriptan and a combined estrogen-progesterone oral contraceptive initiated 3 months ago at a family planning clinic.

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On physical examination, blood pressure is 122/72 mm Hg and pulse rate is 66/min. All other physical examination findings, including those from a neurologic examination, are unremarkable.

Findings on a brain MRI and magnetic resonance angiogram are normal.

Which of the following is the most appropriate next step in management?

(A) Administer daily aspirin
(B) Administer daily topiramate
(C) Discontinue combined oral contraceptive
(D) Discontinue rizatriptan

Item 25

A 54-year-old man is seen for follow-up evaluation of a tremor in his upper extremities that has been present since age 20 years. The tremor was mild for many years and did not interfere with his work but has become more prominent in recent years. He has difficulty writing and using utensils during meals. He has no associated slowness, stiffness, or change in gait. The patient started a trial of propranolol, which provided better control of the tremor, but after a few months, the tremor again worsened. He has subsequently been taking clonazepam without significant relief of symptoms. Alcohol, which the patient uses infrequently, temporarily diminishes the tremor. He also has kidney stones and glaucoma. His father and two sisters have a similar tremor.

On physical examination, vital signs are normal. A persistent large-amplitude tremor of the upper extremities is noted when the patient holds his arms in an outstretched position and during finger-to-nose testing. The tremor is bilateral and absent at rest. Tandem gait cannot be performed, but gait is otherwise normal.

Which of the following is the most appropriate next step in treating this patient's tremor?

(A) Botulinum toxin
(B) Deep brain stimulation
(C) Levodopa
(D) Primidone
(E) Topiramate

Item 26

A 68-year-old man is evaluated in the hospital for midback pain and right leg weakness. A radiograph of the thoracic spine obtained in the emergency department showed a lytic lesion at T7, and an MRI showed extension of an associated mass lesion into the epidural space, which is causing compression of the spinal cord without spinal instability. His only medication is a daily multivitamin.

High-dose glucocorticoids are administered, and results of a stereotactic biopsy of the mass show a plasmacytoma.

On physical examination, temperature is 37.2 °C (99.0 °F). Other vital signs and findings of a general physical examination are normal. Sensory level is to T8.

Which of the following is the most appropriate next step in treatment?

(A) Chemotherapy
(B) Continued high-dose glucocorticoids only
(C) Radiation therapy
(D) Surgery

Item 27

A 34-year-old man is evaluated in the emergency department for worsening headache, nausea, and two episodes of vomiting 2 hours after hitting his head in a fall from the top of a 6-foot ladder.

On physical examination, temperature is normal, blood pressure is 128/84 mm Hg, pulse rate is 86/min, and respiration rate is 14/min. The patient's Glasgow Coma Scale score is 15/15.

Which of the following is the most appropriate immediate step in management?

(A) Head CT with contrast
(B) Head CT without contrast
(C) Hospital observation
(D) MRI of the brain

Item 28

An 82-year-old woman is seen for follow-up evaluation of Alzheimer disease. Since her last visit 12 weeks ago, she has been taking rivastigmine, with a progressively titrated dosage. The patient's only new symptoms are increasing insomnia, loss of appetite, and occasional diarrhea; she has had no feelings of hopelessness, helplessness, sadness, or guilt. Her only other medication is hydrochlorothiazide for hypertension.

On physical examination, vital signs are normal. The patient has lost 6.8 kg (15.0 lb) since her last visit. She scores 20/30 on a Mini-Mental State Examination, losing points in the recall, orientation to time, complex commands, and attention and calculation sections; her score 12 weeks ago was 21/30. All other findings from the general physical and neurologic examinations are normal.

Results of laboratory studies, including a complete blood count, comprehensive metabolic profile, and thyroid function tests, are normal.

Which of the following is the most appropriate next step in management?

(A) Add donepezil
(B) Add memantine
(C) Add mirtazapine at bedtime
(D) Discontinue rivastigmine

Item 29

A 42-year-old woman is evaluated for progressive difficulty with eyelid closure. She initially noticed frequent blinking 3 years ago; within the past year, she also began

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having unintended, prolonged, and forceful closure of both eyes that now prevents her driving. Bright light, prolonged conversation, and psychological stress aggravate her symptoms. The severity of symptoms fluctuates from day to day, but she does not have any symptom-free days. She reports occasional blurry vision but has had no visual field loss or diplopia, has no sensory numbness, and has had no other abnormal movements involving the face, head, limbs, or trunk.

On physical examination, vital signs are normal. Examination of the eyes shows repetitive and bilateral clonic eyelid closures that occasionally involve forceful closure of the eyes that the patient cannot resist or suppress. The intensity of these movements varies during the examination. No facial grimacing, asymmetry, or other abnormal movements are noted. Other findings of the general medical and neurologic examinations are normal.

An MRI of the brain is unremarkable.

Which of the following is the most appropriate treatment?

(A) Botulinum toxin
(B) Clonidine
(C) Deep brain stimulation
(D) Risperidone

Item 30

A 44-year-old man is evaluated for a 6-month history of a persistent burning sensation in the feet. He has had no numbness or weakness. Medical history is significant for hyperlipidemia. His only medication is simvastatin.

On physical examination, blood pressure is 145/85 mm Hg sitting and 130/70 mm Hg standing, pulse rate is 75/min sitting and 65/min standing, and respiration rate is 14/min; BMI is 33. Mild red discoloration and sweating of both palms are noted. Cranial nerve examination findings are normal, motor strength is intact, deep tendon reflexes are normal, and no sensory deficit to light touch, pinprick or vibration is noted. Deep tendon reflexes and gait are normal.

Results of laboratory studies include normal fasting plasma glucose, hemoglobin A_{1c}, vitamin B_{12}, and folate levels.

An electromyogram shows no evidence of neuropathy or myopathy.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Glucose tolerance test
(B) MRI of the lumbosacral spine
(C) Serum vitamin D measurement
(D) Sural nerve biopsy

Item 31

A 40-year-old man is reevaluated for a 1-year history of recurrent tonic-clonic seizures that have not responded to treatment with valproic acid and topiramate. When describing the seizures, his wife says that he usually drops to the ground and begins "shaking all over"; the shaking typically lasts 10 to 15 minutes, with the patient's eyes remaining closed during the event. He subsequently is confused for 30 to 60 minutes. The seizures initially occurred 1 or 2 times per month but recently have been occurring every other day. On several occasions, he has become incontinent. He is a military veteran who sustained a closed head injury in combat 5 years ago and has posttraumatic stress disorder. Medications are twice daily valproic acid and topiramate.

On physical examination, vital signs are normal. General medical examination findings are normal. On neurologic examination, flattening of the nasolabial fold on the right is noted, and right pronator drift is present. Deep tendon reflexes are 3+ in the right upper and lower extremities. A plantar extensor response is noted in the right toe.

Results of laboratory studies are normal, with a serum valproic acid level within the therapeutic range.

An MRI of the brain reveals left frontal lobe encephalomalacia. An electroencephalogram (EEG) shows intermittent left frontal slowing.

Which of the following is the most appropriate management?

(A) Ambulatory EEG monitoring
(B) Carbamazepine
(C) Levetiracetam
(D) Video EEG monitoring

Item 32

A 50-year-old man is evaluated for a 1-year history of increasing urinary frequency and urgency and occasional urge incontinence. He has no symptoms of urinary hesitancy or incomplete emptying. The patient has primary progressive multiple sclerosis. Medications are dalfampridine and vitamin D.

On physical evaluation, temperature is 36.8 °C (98.2 °F), blood pressure is 120/55 mm Hg, and pulse rate is 68/min. Findings of abdominal and digital rectal examinations are normal. Finger-to-nose testing reveals dysmetria bilaterally. Leg tone is increased bilaterally. Muscle strength is 4/5 in both legs. Gait testing reveals spasticity and ataxia.

A urinalysis is negative for infection.

Which of the following is the most appropriate treatment?

(A) Finasteride
(B) Intermittent urinary catheterization
(C) Oxybutynin
(D) Prophylactic antibiotics

Item 33

An 80-year-old man is evaluated for a 5-year history of progressive cognitive decline. According to his daughter, his cognitive difficulties began after a series of "mini-strokes" characterized by the acute onset of slurred speech, difficulty ambulating, and weakness; these symptoms typically improved after onset but never resolved entirely. He recently has had difficulty managing his financial affairs, completing tasks, and understanding abstract concepts; other recent symptoms include a slowed reaction time,

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slowness in speaking and completing tasks, shuffling of gait, urinary incontinence, and sudden involuntary laughing and crying. The patient has hypertension, coronary artery disease, depression, and hyperlipidemia. Medications are lisinopril, aspirin, bupropion, and atorvastatin.

On physical examination, vital signs are normal. Other findings from the general physical examination are unremarkable. Neurologic examination reveals mild right-sided weakness, right-sided hyperreflexia, and difficulty initiating forward movement of the feet ("magnetic gait").

An MRI of the brain shows extensive periventricular white matter lesions and small-vessel disease involving the basal ganglia. The ventricles are normal in size.

Which of the following is the most likely diagnosis?

(A) Alzheimer disease
(B) Normal pressure hydrocephalus
(C) Parkinson disease dementia
(D) Vascular neurocognitive disorder

Item 34

An 80-year-old man is evaluated for a 2-year history of sudden-onset episodes of flashing lights in the right visual field that typically last 10 to 20 seconds. He does not believe that he loses awareness during these events, but his daughter, who accompanied him, reports that he stared and smacked his lips during the two recent episodes she witnessed. Symptoms started 6 months after he had a cryptogenic stroke of the left occipital lobe. The patient also has hypertension. Medications are aspirin, atorvastatin, and lisinopril.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 140/90 mm Hg, and pulse rate is 67/min and irregular. Visual field testing reveals right homonymous hemianopia. All other findings from the general physical and neurologic examinations are within normal limits.

An MRI reveals a chronic infarct in the territory of the left posterior cerebral artery.

Which of the following is the most appropriate treatment?

(A) Carbamazepine
(B) Lamotrigine
(C) Oxcarbazepine
(D) Phenytoin

Item 35

A 57-year-old man is seen for follow-up evaluation after results of a carotid ultrasound obtained to investigate a left neck bruit show a mixed density plaque at the origin of the left internal carotid artery. Stenosis is estimated to be 60% to 80%. He has had no focal neurologic symptoms or visual loss. The patient has coronary artery disease (CAD) with stable angina, hypertension, dyslipidemia, type 2 diabetes mellitus, and mild kidney failure. He has a 30-pack-year smoking history but stopped smoking 7 years ago when CAD was diagnosed. Medications are aspirin, metoprolol, lisinopril, metformin, and nitroglycerin, as needed. He was taking rosuvastatin but discontinued the medication 2 years ago after developing muscle aches.

On physical examination, blood pressure is 132/78 mm Hg, pulse rate is 78/min and regular, and respiration rate is 16/min. The left neck bruit is unchanged. Cardiopulmonary examination has normal results. All other findings from the general medical and neurologic examinations are unremarkable.

Which of the following is the most appropriate next step in management?

(A) Carotid endarterectomy
(B) Magnetic resonance angiography of the neck
(C) Resumption of statin therapy
(D) Substitution of clopidogrel for aspirin

Item 36

H

A 47-year-old woman is evaluated in the emergency department for recurrent attacks of severe holocranial pain that began 2 days ago while she was gardening. She first experienced a rapidly progressive, global, explosive headache that lasted 30 minutes and was associated with photophobia and phonophobia. She had identical symptoms 6 hours ago and additionally had 30 minutes of visual blurring and numbness of the left face and left upper extremity. The patient has attention-deficit disorder for which dextroamphetamine was initiated 2 weeks ago. She has no significant headache history.

On physical examination, blood pressure is 130/90 mm Hg and pulse rate is 86/min. Left homonymous hemianopia is noted.

An MRI of the brain shows bilateral occipital areas of acute infarction.

Cerebrospinal fluid analysis shows 10 erythrocytes, 4 leukocytes, and normal protein and glucose levels.

Four hours after entering the emergency department, the patient has a third abrupt-onset headache with worsening visual blurring. Blood pressure is now 190/115 mm Hg, but physical examination and neuroimaging findings are unchanged.

Which of the following is the most appropriate treatment?

(A) Indomethacin
(B) Normalization of blood pressure
(C) Tissue plasminogen activator
(D) Warfarin

Item 37

H

A 45-year-old man is evaluated in the emergency department for a 3-week history of headache and impaired vision on the right side. He has not previously had frequent headaches, but the current pain has been constant and worsening since onset. The patient thinks that something is wrong with his eyesight because he has been running into or tripping over objects on the right side. He has no significant medical history and takes no medication.

On physical examination, vital signs are normal. No papilledema is noted on funduscopic examination. A slit lamp examination shows no cells in the vitreous humor. Other findings from the general medical examination are

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CONT.

unremarkable. Neurologic examination reveals the presence of right homonymous hemianopia.

An MRI of the brain shows a lesion in the left occipital lobe that is highly suspicious for central nervous system lymphoma.

Results of laboratory studies include a normal leukocyte count and differential and no evidence of HIV antibodies.

Cytologic analysis of cerebrospinal fluid shows no malignant cells.

Which of the following is the most appropriate next step in management?

(A) Bone marrow biopsy
(B) Surgical biopsy of the brain lesion
(C) Surgical resection of the brain lesion
(D) Treatment with dexamethasone
(E) Treatment with photon-beam radiation

Item 38

A 57-year-old woman is evaluated in the emergency department 24 hours after new onset of left hemiparesis and left hemineglect. The patient has hypertension and functional class II New York Heart Association nonischemic heart failure. Medications are enalapril, furosemide, and metoprolol.

On physical examination, temperature is normal, blood pressure is 166/78 mm Hg, pulse rate is 68/min and irregular, and respiration rate is 12/min. A cough is noted. Cardiac examination confirms an irregularly irregular heart rhythm. Neurologic examination shows left visual and tactile extinction, left facial weakness, dysarthria, left arm and leg weakness (muscle strength, 4/5), and normal orientation and language function. She is unable to safely swallow water but can swallow thickened liquids.

Results of laboratory studies are notable for an INR of 1.1 and a serum LDL cholesterol level of 54 mg/dL (1.40 mmol/L).

A CT scan of the head shows an acute infarction in the right parietal and frontal lobes involving half of the hemisphere. An electrocardiogram (ECG) shows atrial fibrillation; an ECG obtained 1 year ago was normal. An echocardiogram shows a left ventricular ejection fraction of 50% without valvular disease or wall motion abnormalities. A chest radiograph and a carotid ultrasound show normal findings.

Which of the following is the most appropriate next step in treatment?

(A) Aspirin
(B) Dabigatran
(C) Intravenous heparin
(D) Warfarin

Item 39

A 65-year-old woman is evaluated in the emergency department for a 2-day history of nausea and vomiting and a 3-week history of increasingly persistent and severe morning headaches. Breast cancer was diagnosed 8 months ago and treated with lumpectomy, radiation therapy, and chemotherapy, which she recently completed. Her most recently measured functional status was good (Karnofsky Performance Score > 70).

On physical examination, temperature is 36.7 °C (98.1 °F), blood pressure is 110/70 mm Hg, pulse rate is 95/min, and respiration rate is 18/min. The patient is awake, appropriately interactive, and fully oriented. Difficulty with tasks requiring attention, such as stating the months of the year backward, is noted. Mild bilateral papilledema is present. Increased tone of the left upper and lower extremities is noted. Deep tendon reflexes are 3+ on the left and 1+ on the right. The left toe exhibits a plantar extensor response.

Results of laboratory studies, including a complete blood count, are normal.

An MRI of the brain shows a 3- × 2- × 2-cm ring-enhancing lesion at the gray-white junction of the right frontal lobe with surrounding edema.

A recent PET scan of the body showed no evidence of metastatic disease.

Which of the following is the most appropriate next step in management?

(A) Brain PET
(B) Lumbar puncture
(C) Surgical resection of the brain lesion
(D) Whole-brain radiation

Item 40

A 62-year-old man is evaluated in the emergency department for a 10-day history of progressively worsening shortness of breath, a 3-month history of difficulty with swallowing at dinnertime that resolves by the morning, and a 5-month history of intermittent blurry vision and fatigue. He had a urinary tract infection 2 weeks ago that was treated with ciprofloxacin, after which the fatigue and other symptoms markedly worsened.

On physical examination, temperature, blood pressure, and pulse rate are normal; respiration rate is 24/min. Other notable findings are bilateral ptosis, diplopia with sustained horizontal gaze, nasal speech, a snarling smile, weakness of cervical flexion, and symmetric weakness of shoulder abduction, arm extension, and hip flexion that becomes more severe with repeated effort. Neurologic examination shows an awake and oriented patient with normal sensation and deep tendon reflexes; no atrophy or fasciculation is noted.

Serum magnesium level is 1.5 mg/dL (0.62 mmol/L). Results of other laboratory studies, including a complete blood count and a comprehensive metabolic profile, are normal.

The patient is admitted to the ICU, where serial respiratory measurements reveal declining vital capacity and negative inspiratory force.

Which of the following is the most appropriate emergent treatment?

(A) High-dose intravenous glucocorticoids
(B) Intravenous magnesium
(C) Intravenous pyridostigmine
(D) Plasmapheresis

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Item 41

A 44-year-old man is evaluated for a 1-week history of severe, recurrent, left periorbital headaches. The patient has experienced a 10- to 12-week period of similar headaches every spring for the past 3 years. Headaches occur once or twice daily, last 2 to 3 hours if untreated, and are accompanied by nausea, photophobia, and ipsilateral tearing but no aura or vomiting. Resting during headache episodes brings no relief; he instead paces the floor. Simple analgesics and prednisone have been ineffective in treating the headache. Although subcutaneous sumatriptan generally relieves symptoms within 5 to 10 minutes, his headache frequency and dosing limitations preclude his using this drug every time he has symptoms. The patient has a 20-pack-year history of smoking. He takes no other medication.

On physical examination, blood pressure is 134/82 mm Hg and pulse rate is 78/min. All other physical examination findings, including those from a neurologic examination, are unremarkable.

Which of the following is the most appropriate next step?

(A) Amitriptyline
(B) Indomethacin
(C) Propranolol
(D) Topiramate
(E) Verapamil

Item 42

A 50-year-old woman is evaluated for a 4-year history of progressively worsening cognitive function. She now has frequent memory deficits and a decreased ability to concentrate and multitask in her work as a lawyer; she has been reprimanded in recent months by her employer for submitting late and disorganized briefs. She has no other symptoms. The patient has a 15-year history of multiple sclerosis and a 5-year history of depression. She reports that her mood is good, and she is not experiencing her typical symptoms of depression, including anhedonia, depressed mood, and sleep disturbance. Medications are dimethyl fumarate, a vitamin D supplement, fluoxetine, and modafinil.

Physical examination reveals a pleasant, interactive woman. Vital signs are normal. Mild gait ataxia is noted. Mental status examination reveals moderate deficiencies in short-term memory, processing speed, and attention.

An MRI of the brain obtained 2 weeks ago showed multiple white matter lesions consistent with multiple sclerosis, with no significant change from an image obtained 1 year ago.

Which of the following is the most appropriate treatment of this patient's cognitive difficulties?

(A) Amantadine
(B) Counseling and cognitive therapy
(C) Donepezil
(D) High-dose intravenous methylprednisolone for 5 days
(E) Increased fluoxetine dosage

Item 43

A 41-year-old man is evaluated for daily headaches. The patient has had migraine with aura since age 15 years and had a mild traumatic brain injury while playing intramural football at age 22 years. Over the past 10 years, migraine frequency has increased from monthly to several days per week. He describes migraine episodes as global, throbbing, and severe in intensity, noting they are often accompanied by nausea, vomiting, and photophobia and sometimes preceded by 30 minutes of visual scintillations. Migraine duration is typically 2 hours with successful treatment. He takes oral sumatriptan as needed for migraine and typically uses his entire monthly allotment; propranolol was added for migraine prophylaxis 2 months ago with no appreciable effect. Ever since lumbar pain with radiculopathy was diagnosed 6 months ago and treated with hydrocodone 3 or 4 days each week, he also has developed a daily, constant, mild bilateral frontotemporal "squeezing" headache associated with maxillary pressure and neck tightness. He occasionally uses the hydrocodone to treat the headaches.

On physical examination, blood pressure is 120/72 mm Hg and pulse rate is 60/min; BMI is 28. Neurologic examination findings are normal, as are other physical examination findings.

A CT scan of the head is normal.

Which of the following is the most likely diagnosis?

(A) Chronic posttraumatic headache
(B) Chronic tension-type headache
(C) Idiopathic intracranial hypertension
(D) Medication overuse headache

Item 44

H

A 35-year-old woman is evaluated in the emergency department for a 3-day history of diplopia, vertigo, and gait imbalance that has prevented her going to work. She reports no additional symptoms. The patient has multiple sclerosis, vitamin D deficiency, and depression. Medications are interferon beta-1a, vitamin D, and extended-release venlafaxine.

On physical examination, temperature is 36.5 °C (97.7 °F), blood pressure is 100/55 mm Hg, pulse rate is 72/min, and respiration rate is 14/min. Incomplete abduction of the right eye is noted when the patient looks to the right. Finger-to-nose testing with the right arm reveals dysmetria. Tandem gait testing results in a near fall.

A T2-weighted MRI of the brain shows multiple new lesions, three of which enhance after administration of intravenous contrast.

Which of the following is the most appropriate next step in treatment?

(A) Glatiramer acetate
(B) Intravenous methylprednisolone, 1 g/d
(C) Oral prednisone, 1 mg/kg
(D) Plasmapheresis

Item 45

H

An 82-year-old man is evaluated in the hospital for right-sided weakness and difficulty speaking. He was found in

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bed by his son, who last saw him well 18 hours ago. The patient does not seek routine medical care. He takes no medication.

On physical examination, blood pressure is 196/88 mm Hg, pulse rate is 84/min and regular, respiration rate is 12/min, and oxygen saturation is 98% on ambient air. Other general physical examination findings, including those from an evaluation of the fundi, are normal. Neurologic examination reveals right-sided facial weakness, severe dysarthria with an inability to swallow, right-sided arm paralysis, 3/5 muscle strength throughout the right leg, and no aphasia.

Results of laboratory studies show normal serum levels of creatinine and troponin T and I.

An electrocardiogram shows normal sinus rhythm with no ischemic changes, and a chest radiograph is normal. A CT scan of the head without contrast shows a left pontine infarct.

Which of the following is the most appropriate acute blood pressure treatment?

(A) Administer oral captopril
(B) Administer oral metoprolol
(C) Administer sublingual nitroglycerin
(D) No pharmacologic treatment is required

Item 46

A 53-year-old man is evaluated for persistent right-sided facial weakness. Three months ago, he first noticed "drooping" of the right side of his lower face, difficulty closing the right eye and wrinkling the forehead, increased sensitivity to loud noises, and occasional slurred speech. Bell palsy was diagnosed, and he began a 10-day course of prednisone. He has noted only limited improvement, with continued facial drooping and mildly dysarthric speech; he now uses an eye patch over his right eye at night. The patient takes no medication.

On physical examination, vital signs are normal. Right-sided facial weakness involving the forehead, orbicularis oculi, and lower facial muscles is noted. Taste recognition is impaired on the anterior right side of the tongue. Facial sensation and the muscles of mastication are intact. The corneal reflex is present bilaterally, and the jaw reflex is normal. Hearing is intact bilaterally, as are extraocular reflexes, motor and sensory function, and deep tendon reflexes.

Which of the following is the most appropriate next step in management?

(A) Acyclovir
(B) Clinical observation
(C) MRI of the brain
(D) Physical therapy

Item 47

A 32-year-old man is evaluated in the emergency department 2 hours after having a witnessed tonic-clonic seizure that lasted 2 minutes. After the seizure, he noted transient weakness of the right arm. The weakness has now resolved, and he feels completely normal. The patient reports that before losing consciousness, he felt a painful numbness in the first and second digits of the right hand, which subsequently assumed a "claw-like" posture. He never has had a similar sensation. He sustained a closed head injury resulting in a brief loss of consciousness 5 years ago in military combat. He takes no medication.

On physical examination, vital signs are normal. The patient's facial features are symmetric. Right pronator drift and difficulty with rapid alternating movements of the right hand are noted. Examination of the right upper extremity shows muscle strength of 4+/5 and 1+ deep tendon reflexes; muscle strength is 5/5 and reflexes are 2+ in all other limbs.

Laboratory studies, including a complete blood count, comprehensive metabolic profile, and urinalysis, have normal results.

An MRI shows encephalomalacia from his previous head trauma in the left parietal lobe and no other acute findings.

Which of the following is the most appropriate next step in management?

(A) Ambulatory electroencephalographic monitoring
(B) Carbamazepine
(C) Clinical observation
(D) Lumbar puncture

Item 48

A 38-year-old man is evaluated for headaches associated with visual changes. He describes intermittent headaches that began 18 years ago, occur three to four times per month, and typically last 12 to 24 hours. The pain is bifrontal, throbbing, occasionally severe, and worsened when he bends forward or ascends stairs. Headaches are accompanied by mild photophobia and phonophobia but no nausea or vomiting. Approximately twice yearly he experiences unilateral visual distortion during a headache attack that he characterizes as "looking through frosted glass"; the visual change typically lasts for only 30 to 40 minutes and then resolves completely. He has taken aspirin, acetaminophen, naproxen, and ibuprofen at various points to relieve his symptoms, but no medication has been effective in relieving either the headaches or visual distortion.

On physical examination, vital signs are normal. All other physical examination findings, including those from a neurologic examination, are unremarkable.

Which of the following is the most appropriate management?

(A) CT of the head
(B) Electroencephalography
(C) Erythrocyte sedimentation rate measurement
(D) MRI of the brain
(E) Sumatriptan administration

Item 49

A 45-year-old man is evaluated for significant fatigue since having a lacunar stroke 6 months ago. He reports not resting well at night and feeling sleepy at work; he does not fall asleep inappropriately during the day. He has been able

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to maintain a daily 20-minute exercise program without difficulty. A recent electrocardiogram and echocardiogram were normal. Since his stroke, the patient has had no depressed mood and has continued to enjoy spending time with family and pursuing his hobbies. He has dyslipidemia, hypertension, and a remote history of depression. Medications are simvastatin, lisinopril, and aspirin.

On physical examination, blood pressure is 146/78 mm Hg, pulse rate is 68/min and regular, and respiration rate is 12/min; BMI is 32. Cardiac examination reveals no carotid bruits or other abnormalities. Neurologic examination shows mild dysarthria and grade 4/5 left-sided weakness throughout.

Which of the following is the most appropriate next step in management?

(A) Cardiovascular stress testing
(B) Citalopram
(C) Dextroamphetamine
(D) Polysomnography

Item 50

A 33-year-old woman is evaluated for a 3-day history of worsening right eye pain and a 1-day history of visual disturbance in the right eye. The pain is aggravated by eye movement. Three years ago, she experienced right arm clumsiness and a mildly unsteady gait but did not seek medical attention; symptoms fully resolved within 1 week. Medical history is otherwise unremarkable, and the patient takes no medication.

On physical examination, temperature is 36.2 °C (97.2 °F), blood pressure is 125/53 mm Hg, pulse rate is 80/min, and respiration rate is 16/min; BMI is 30. Pupillary reactivity is normal when each eye is tested individually; however, when a light is rapidly moved from the left eye to the right, the right pupil dilates by 2 mm. Visual acuity is 20/100 in the right eye and 20/20 in the left. Visual field testing reveals a central scotoma. Slight temporal disc pallor is noted on the right. Other findings from the general medical and neurologic examinations are normal.

Which of the following diagnostic tests is most appropriate to perform next?

(A) Erythrocyte sedimentation rate determination
(B) Lumbar puncture
(C) MRI of the brain
(D) Serum rapid plasma reagin test

Item 51

An 18-year-old man is evaluated for recurrent headaches 1 week after falling on his head during a soccer match at his high school. The patient reports being "dazed" for 15 minutes after the fall but never losing consciousness. Findings from a sideline examination were unremarkable, and the patient was removed from play. Given the temporary alteration in consciousness, a follow-up examination with his internist was recommended. He developed headaches the morning after the injury that for 3 days were severe, global, throbbing, and associated with nausea and dizziness; the nausea and dizziness have gradually resolved, and for the past 2 days, the headache pain has been controlled with acetaminophen. He has had no cognitive symptoms but has not yet resumed school or sports activities.

Results of physical examination, including vital signs and neurologic examination findings, are unremarkable.

Which of the following is the most appropriate management?

(A) Obtain a CT of the head
(B) Obtain an MRI of the brain
(C) Prohibit contact sports
(D) Restrict classroom participation

Item 52

A 29-year-old woman comes to the office to discuss her plans for pregnancy; she hopes to become pregnant before the end of the year. The patient has juvenile myoclonic epilepsy that was diagnosed 13 years ago. She started taking valproic acid at that time to treat the epilepsy and was seizure free until 1 year ago when she decided to stop taking the valproic acid and had a convulsive seizure. After resuming the medication, she has been otherwise asymptomatic except for occasional brief jerks of her hands that occur in the morning when she is sleep deprived but at no other time. Medications are valproic acid and folic acid.

All physical examination findings, including vital signs and results of a neurologic examination, are normal.

In addition to discontinuing valproic acid, which of the following is the most appropriate next step in treatment?

(A) Begin carbamazepine
(B) Begin levetiracetam
(C) Begin topiramate
(D) Withhold AED therapy until after pregnancy

Item 53

A 56-year-old woman is evaluated for a 1-year history of tremor. The tremor is more prominent on the right side. She also reports increasing problems with balance and numerous falls, especially when arising from a chair or turning. The patient does not have any significant cognitive symptoms. She has occasional urinary incontinence, intermittent constipation, and a history of acting out of dreams during sleep.

On physical examination, blood pressure is 115/75 mm Hg sitting and 85/70 mm Hg standing, pulse rate is 65/min sitting and 75/min standing, and respiration rate is 22/min. Bruises over the upper and lower extremities secondary to falls are present. On cranial nerve examination, dysmetric saccades, decreased facial expression, and hypophonic speech are noted. Vertical eye movements are normal. A low-amplitude tremor at rest that is more prominent on the right side is present. Repetitive finger tapping movements are bradykinetic. On finger-to-nose testing, mild dysmetria is present. Gait is ataxic with a wide base and frequent veering to both sides; she is unsteady on turning. Gait speed is normal, but arm swing is decreased. A pull test confirms postural instability. No sensory deficits are noted.

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Which of the following is the most likely diagnosis?

(A) Multiple system atrophy
(B) Parkinson disease
(C) Progressive supranuclear palsy
(D) Vascular parkinsonism

Item 54

A 52-year-old woman is evaluated for a 3-year history of progressively worsening bilateral hand tingling and numbness that are more prominent in the right hand. The numbness involves the thumb and index finger and part of the palm adjacent to the thumb. She says that symptoms are aggravated when she types on a computer keyboard at work, where she is employed as a secretary. She also reports persistent burning and tingling paresthesia over the palmar side of the right thumb and index finger and says she occasionally drops objects with her right hand. The patient has type 2 diabetes mellitus managed by diet and exercise. She takes no medication.

On physical examination, vital signs are normal. Right thumb abductor strength is 4/5; strength in the other muscles of the right hand and right hand grip are normal. Mild atrophy of right thenar eminence in noted. Muscles of the left hand have full strength. Tapping of the right wrist reproduces the symptoms.

Results of nerve conduction studies show ongoing sensorimotor denervation isolated to the right median nerve.

Which of the following is the most appropriate next step in management?

(A) Decompression surgery
(B) Glucocorticoid injection
(C) Nocturnal neutral position wrist splint
(D) Occupational therapy

Item 55

A 58-year-old man is evaluated in the emergency department for a 2-hour history of right-sided weakness. He has hypertension and chronic kidney disease. Medications are amlodipine, lisinopril, and aspirin.

On physical examination, the patient is awake and interactive. Blood pressure is 190/88 mm Hg, pulse rate is 72/min and regular, respiration rate is 16/min, and oxygen saturation is 97% on ambient air. Papilledema is noted. Neurologic examination shows right-sided facial weakness, slurred speech, and absent movement and pinprick sensation in the right arm and leg, but no aphasia.

A CT scan of the head without contrast shows a left thalamic intracerebral hemorrhage.

Results of laboratory studies include a platelet count of 170,000/μL (170×10^9/L), an INR of 0.9, and a serum creatinine level of 1.8 mg/dL (159 μmol/L).

Which of the following is the most appropriate treatment?

(A) Intravenous labetalol
(B) Intravenous nitroprusside
(C) Platelet transfusion
(D) Recombinant factor VIIa

Item 56

A 45-year-old woman is evaluated in the emergency department (ED) 5 minutes after having a witnessed convulsive seizure in the parking lot of the hospital, where she recently started working in the cafeteria. On arrival at the ED, she is obtunded and soon begins to convulse again, exhibiting tonic-clonic movements of both upper extremities. The patient is positioned on her side, and intravenous access is obtained. Medical history cannot be immediately obtained.

On physical examination, temperature is 37.7 °C (99.9 °F), blood pressure is 110/70 mm Hg, pulse rate is 130/min, and oxygen saturation is 93% on ambient air; respiration rate cannot be assessed. This latest seizure has already lasted 6 minutes. Her eyes are open and rolled upward, and the patient is actively convulsing. Initial inspection reveals no evidence of trauma.

Fingerstick blood glucose level is 90 mg/dL (5.0 mmol/L).

Which of the following is the most appropriate intravenous treatment?

(A) Diazepam followed by levetiracetam
(B) Diazepam followed by phenytoin
(C) Lorazepam followed by levetiracetam
(D) Lorazepam followed by phenytoin

Item 57

A 49-year-old man is evaluated for persistent sensorimotor symptoms. Five months ago, he developed tingling and mild bilateral pain in the thighs followed by mild weakness and hand numbness. Over the next 3 months, his lower extremity weakness progressively worsened, and his gait became unstable. He began having difficulty going up stairs and opening jars and had several episodes of presyncopal symptoms on standing; his speech, swallowing, and vision were unaffected. His weakness has plateaued within the past 2 months without any improvement. He continues to have tingling in the lower extremities, but the pain has dissipated. The patient has diabetes mellitus treated with metformin. Family history is noncontributory.

On physical examination, blood pressure is 130/75 mm Hg sitting and 95/60 mm Hg standing; other vital signs are normal. Extraocular movements and muscle tone are normal; no fasciculations are present. Diffuse areflexia is noted, with moderate bilateral symmetric weakness in the distal upper extremities and proximal and distal lower extremities. Decreased sensation to pinprick and vibration is noted in both feet; no evidence of high arches or hammertoes is found.

Results of nerve conduction studies show diffuse and severe slowing of motor nerve conduction velocities and the presence of conduction blocks.

Which of the following is the most likely diagnosis?

(A) Charcot-Marie-Tooth disease type 1
(B) Chronic inflammatory demyelinating polyradiculoneuropathy
(C) Diabetic amyotrophy
(D) Guillain-Barré syndrome

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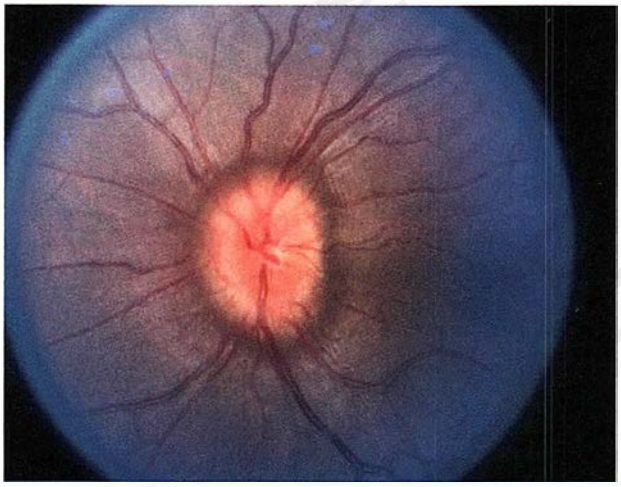
Item 58

A 26-year-old woman is evaluated for progressively worsening headaches that began intermittently 6 months ago and became daily 3 months ago. The patient describes bilateral "vise-like" pain that is steady, moderate in intensity, and unaffected by physical activity. She also has experienced brief, temporal, sharp pains and a few episodes of transient binocular visual dimming. The headaches are accompanied by moderate neck stiffness and mild photophobia but no nausea, phonophobia, or focal neurologic symptoms. She has polycystic ovary syndrome diagnosed 2 years ago and treated with metformin and a combined oral contraceptive but no personal or family history of headache. The patient takes no other medication or supplement.

On physical examination, blood pressure is 124/80 mm Hg and pulse rate is 72/min; BMI is 30. Partial left palsy of the abducens nerve (cranial nerve VI) is noted. A funduscopic photograph is shown.



An MRI is normal. Analysis of cerebrospinal fluid obtained on lumbar puncture shows an opening pressure of 350 mm H_2O.

Which of the following is the most appropriate treatment?

(A) Acetazolamide
(B) Amitriptyline
(C) Epidural blood patch
(D) Optic nerve sheath fenestration
(E) Spironolactone

Item 59

A 71-year-old man is seen for follow-up evaluation 2 weeks after having an ischemic stroke. The patient has hypertension and type 2 diabetes mellitus. Medications are enalapril, chlorthalidone, atorvastatin, metformin, and aspirin.

An MRI of the brain obtained during hospitalization showed a right paramedian frontal lobe acute infarction. A magnetic resonance angiogram of the head and neck showed abrupt termination of the distal right anterior cerebral artery but was otherwise normal. An electrocardiogram was normal, and a transthoracic echocardiogram showed a patent foramen ovale, normal systolic and diastolic function, and no valvular disease. Telemetry findings revealed occasional premature atrial contractions.

On current physical examination, vital signs are normal. On neurologic examination, increased tone in the left leg and weakness below the left knee (muscle strength, 4+/5) are noted; the patient ambulates with a cane.

Which of the following is the most appropriate next step in management?

(A) Addition of clopidogrel
(B) Addition of dabigatran
(C) Cardiac rhythm monitoring
(D) Percutaneous device closure of the patent foramen ovale

Item 60

A 68-year-old man is seen for follow-up evaluation of Parkinson disease, which was diagnosed 10 years ago. Although his symptoms initially were well controlled with medications, he has experienced increasing fluctuations in motor symptoms, specifically tremor at rest and slowness, within the past 3 years. Medications are carbidopa-levodopa, entacapone, and amantadine. He notes marked symptom improvement after taking these medications, but the benefit lasts only for 2 hours. Increased dosing of carbidopa-levodopa causes visual hallucinations.

On physical examination performed 3 hours after the patient took carbidopa-levodopa, blood pressure is 130/65 mm Hg and pulse rate is 85/min. Masked facies, an asymmetric upper extremity tremor at rest, marked bradykinesia, and cogwheel rigidity are noted. Gait is slow, but cognitive assessment findings are normal. Repeat examination performed 1 hour after the patient took carbidopa-levodopa reveals notable improvement in bradykinesia, rigidity, and gait and the emergence of prominent dyskinesia.

Which of the following is the most appropriate treatment of this patient's motor complications?

(A) Deep brain stimulation
(B) Discontinuation of entacapone
(C) Increased amantadine dosage
(D) Ropinirole
(E) Selegiline

Item 61

An 84-year-old woman is evaluated for rapidly increasing confusion and behavioral problems. Alzheimer disease was diagnosed 2 years ago, and she was started on donepezil at that time; symptoms have slowly progressed since diagnosis. Her husband, who is her caregiver, reports that 5 days ago, she began having greater difficulty locating the bathroom in their home, has not recognized members of her immediate family on several occasions, has experienced greater nighttime confusion, has become verbally abusive, and has frequently attempted to leave the house unaccompanied. The patient also has hypertension. Medications are donepezil and enalapril.

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On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 110/70 mm Hg, pulse rate is 84/min and regular, respiration rate is 14/min, and oxygen saturation is 99% on ambient air. Neurologic examination shows a drowsy but easily arousable patient who is oriented to neither time nor place. Her attention is poor, and she has difficulty following even simple commands. Other physical examination findings are unremarkable.

Which of the following is the most appropriate next step in management?

(A) Add quetiapine
(B) Discontinue donepezil
(C) Evaluate for concurrent illness
(D) Order head CT

Item 62

A 49-year-old man has a follow-up evaluation 3 months after an exacerbation of multiple sclerosis (MS) that resulted in bilateral leg weakness. He has had MS for 15 years. The patient reports that for the past 10 weeks, he has had bilateral muscle cramps in the thighs and calves and frequent nighttime episodes of right leg stiffening and spasms that can last from seconds to hours and impair his sleep. He has no other symptoms and no significant family history. Medications are fingolimod and vitamin D supplements.

On physical examination, temperature is 36.4 °C (97.5 °F), blood pressure is 130/50 mm Hg, and pulse rate is 88/min. Increased tone is noted in both legs. Palpation of the leg muscles elicits no pain or fasciculations. Muscle strength is 4/5 in both legs. Patellar and ankle reflexes are 3+. An extensor plantar response is noted on the right. Gait requires the assistance of a cane, and both legs appear stiff when walking.

Results of laboratory studies show a normal serum creatine kinase level.

Which of the following is the most appropriate management?

(A) Electroencephalography
(B) Electromyography
(C) Oral baclofen
(D) Oral pramipexole

Item 63

A 24-year-old woman is seen for a follow-up evaluation of epilepsy first diagnosed 4 years ago. The patient has five or six simple or complex partial seizures annually that have been difficult to control. The epilepsy was first treated with lamotrigine, to which levetiracetam was added 2 years ago. Although both medications decreased the frequency and intensity of the seizures when initiated, the episodes returned to their former state after several months. She cannot drive because the seizures often cause loss of consciousness. She has a history of febrile seizure as an infant. She otherwise has no significant medical history, and her only medications are lamotrigine, levetiracetam, and folic acid.

All physical examination findings are within normal limits.

An MRI shows right mesial temporal sclerosis. Video electroencephalographic monitoring records three complex partial seizures, all originating from the right temporal lobe, and interictal right anterior temporal sharp waves.

Which of the following is the most effective treatment?

(A) Addition of carbamazepine
(B) Ketogenic diet
(C) Right temporal lobectomy
(D) Vagal nerve stimulation

Item 64

H

A 66-year-old man is evaluated in the hospital 3 days after fracturing his hip in a fall. He underwent surgical repair 1 day after admission and had an unremarkable initial postoperative course but now is confused and agitated. Medical history includes anxiety disorder and a 10-year history of Parkinson disease. Medications before hospitalization were levodopa, amantadine, and citalopram. All medications have been withheld since admission.

On physical examination, temperature is 39.5 °C (103.1 °F), blood pressure is 168/80 mm Hg (baseline, 118/70 mm Hg), pulse rate is 90/min, and respiration rate is 28/min. The patient appears rigid, does not follow commands, and is agitated. Deep tendon reflexes are normal, but muscle tone is markedly increased. A resting tremor is present bilaterally but is more pronounced on the right side. No spontaneous or stimulus-induced myoclonus is noted. Dystonic posturing is noted in the right foot.

In addition to continuing supportive care, which of the following is the most appropriate treatment?

(A) Administer baclofen
(B) Administer dantrolene
(C) Restart citalopram
(D) Restart levodopa

Item 65

H

A 23-year-old woman is evaluated in the hospital for a 3-day history of a severe right hemicranial headache that has not responded to medication. She has had recurrent migraine for 17 years that typically involves severe right hemicranial throbbing pain associated with nausea and vomiting. Once or twice annually, the headaches are preceded by visual aura. Since age 13 years, migraine attacks have occurred twice monthly, with menses and ovulation as triggers. Typical duration is 24 hours, although occasionally episodes linger for 4 to 5 days. The patient also has anxiety. Medications are zolmitriptan for acute treatment of headache and alprazolam for anxiety. An infusion of fluids, intravenous prochlorperazine, and ketorolac in the emergency department brought no relief of symptoms.

On physical examination, blood pressure is 108/68 mm Hg and pulse rate is 86/min. All other physical examination findings, including those from a neurologic examination, are normal.

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Which of the following is the most appropriate next step in management?

(A) Brain MRI
(B) Combined oral contraceptives
(C) Dihydroergotamine
(D) Hydromorphone
(E) Sertraline

Item 66

A 29-year-old woman is evaluated during a routine follow-up examination of multiple sclerosis, which was diagnosed 3 years ago. The patient says she wishes to discontinue her oral contraceptive and attempt to become pregnant. She has no other personal or family medical history of note. Medications are fingolimod, vitamin D, and an oral contraceptive.

On physical examination, temperature is 36.9 °C (98.5 °F), blood pressure is 100/50 mm Hg, pulse rate is 66/min, and respiration rate is 14/min; BMI is 27. A right afferent pupillary defect is noted. All other physical examination findings are normal.

Besides discontinuing the oral contraceptive, which of the following is the most appropriate next step in management?

(A) Advise against pregnancy
(B) Discontinue fingolimod
(C) Substitute mitoxantrone for fingolimod
(D) Substitute teriflunomide for fingolimod

Item 67

A 37-year-old woman is admitted to the ICU after a CT scan of the head without contrast obtained in the emergency department showed a thin, diffuse subarachnoid hemorrhage without hydrocephalus or cerebral edema and a subsequent angiogram revealed a 10-mm anterior communicating artery aneurysm. The patient is treated with a coiling procedure without complications.

One day after the procedure, physical examination shows a blood pressure of 134/68 mm Hg, a pulse rate of 96/min, and a respiration rate of 12/min. Nuchal rigidity is noted. The patient has difficulty remaining awake unless spoken to loudly, but no other abnormalities are seen on neurologic examination.

A transcranial ultrasound obtained the same day is normal. Fingerstick blood glucose readings over the next 24 hours range between 120 and 150 mg/dL (6.7-8.3 mmol/L).

Which of the following is the most appropriate next step in treatment?

(A) Intravenous dopamine
(B) Intravenous insulin
(C) Oral nimodipine
(D) Oral simvastatin

Item 68

A 29-year-old woman is seen for a routine follow-up evaluation. Multiple sclerosis (MS) was diagnosed 2 months ago. She has no current symptoms. The patient does not smoke, drinks a glass of wine with dinner three or four times weekly, and exercises at least 3 hours weekly. Her father has hypertension, but she has no other significant family history. Daily medications are glatiramer acetate, a multivitamin, and a calcium-vitamin D supplement.

On physical examination, temperature is 37.3 °C (99.1 °F), blood pressure is 108/48 mm Hg, pulse rate is 62/min, and respiration rate is 12/min; BMI is 20. All other physical examination findings, including those from a neurologic examination, are normal.

Which of the following is the most appropriate preventive or screening strategy for this patient?

(A) Alcohol cessation
(B) Annual influenza vaccination
(C) Urinalysis
(D) Use of an oral contraceptive

Item 69

A 35-year-old man is evaluated for recurrent headaches. For the past 5 years, he has had weekly episodes of headache lasting 6 to 8 hours. The patient describes the pain as a steady pressure affecting the frontal and maxillary regions that is exacerbated by physical activity. When severe, the pain radiates to the temples and occiput. He also experiences nasal congestion and sensitivity to light, noise, and odors with the headaches but has had no gastrointestinal or other neurologic symptoms. Potential headache triggers include drastic weather changes, strong odors, and stress. The patient also has allergic rhinitis. Medications are acetaminophen and fexofenadine, which have been ineffective in relieving the headaches and their associated symptoms.

On physical examination, blood pressure is 114/72 mm Hg and pulse rate is 66/min. Other physical examination findings, including those from a neurologic examination, are normal.

Which of the following is the most appropriate next step in management?

(A) CT of the head
(B) CT of the sinuses
(C) Naproxen
(D) Pseudoephedrine
(E) Sumatriptan

Item 70

A 48-year-old man is evaluated for right upper extremity weakness. For the past 8 months, he has noticed progressive weakness in the right arm that is more prominent in the fingers; proximal strength is preserved. He also has noted frequent, painful muscle cramping in the right arm, lower back, and left lower extremity that recently has been accompanied by muscle twitching. He has had no sensory deficit or significant medical history. The patient takes no medication.

On physical examination, vital signs are normal. The patient's speech is dysarthric. Muscle strength testing

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shows weakness with atrophy in the distal right upper extremity and mild weakness without atrophy in the left lower extremity. Fasciculations are present in the bilateral upper and lower extremities and the paraspinal muscles. Deep tendon reflexes are brisk in all extremities, and the plantar response is extensor. Results of sensory and motor examinations are normal.

Results of laboratory studies—including a complete metabolic profile; serum lead, copper, vitamin B_{12}, and parathyroid hormone levels; and Lyme antibody titers—are unremarkable.

MRIs of the cervical and lumbar spines are normal. Results of needle electrode examination show evidence of lower motoneuron abnormalities in multiple body regions, including the limbs, trunk, and face.

Which of the following is the most appropriate treatment?

(A) Bilevel positive airway pressure
(B) Intravenous immune globulin
(C) Percutaneous endoscopic gastrostomy
(D) Riluzole

Item 71

A 59-year-old woman is evaluated for headaches and occasional double vision. The patient has had episodes of migraine with aura since age 12 years. Aura symptoms include visual blurring and ipsilateral facial numbness lasting approximately 15 minutes. After menopause, migraine attacks became less frequent and intense, declining from 12 to 5 days per month, but over the past 4 months have again become more frequent, increasing to 15 days per month. She describes these recent headaches, which are not associated with her typical aura, as more bilateral and "squeezing" in nature than previous ones and reports intermittent visual blurring and two instances of horizontal diplopia lasting 2 hours. The patient has had no other neurologic symptoms. The recent headaches respond to neither ibuprofen nor to the naratriptan she uses to treat acute migraine episodes. Her only other medication is amitriptyline for migraine prophylaxis.

On physical examination, blood pressure is 128/86 mm Hg and pulse rate is 78/min; BMI is 27. Other results of the general medical and neurologic examinations are normal.

Which of the following is the most appropriate management?

(A) Brain MRI
(B) Discontinuation of ibuprofen
(C) Lumbar puncture
(D) Substitution of sumatriptan for naratriptan
(E) Substitution of topiramate for amitriptyline

Item 72

A 46-year-old woman is evaluated for intermittent left-sided tingling and a subsequent headache. She was seen in an emergency department 3 weeks ago for similar symptoms. At that time, a noncontrast CT scan of the head and an MRI of the brain were normal, but a magnetic resonance angiogram showed a 5-mm left middle cerebral artery aneurysm. Results of cerebrospinal fluid analysis were normal. The patient has hypertension and migraine, but she has no other medical history of note. She has a 15-pack-year smoking history, currently smoking approximately ten cigarettes daily, and does not drink alcoholic beverages. Her only medication is amlodipine.

On physical examination, vital signs are normal. Other results of the general and neurologic examinations are normal.

Which of the following is the most appropriate next step?

(A) Aneurysmal clipping
(B) Endovascular coiling
(C) Smoking cessation counseling
(D) Substitution of nimodipine for amlodipine

Item 73

A 59-year-old man is evaluated for a 10-month history of hand tremor. The tremor is more prominent when he is tired, anxious, or walking. He also reports occasional difficulty with fine-motor movements, a deterioration of his handwriting, and a softening of his voice. His gait is not magnetic, and he has had no problem with balance or falls. The patient does not have urinary incontinence or dementia. His paternal grandfather had essential tremor and his paternal aunt had Parkinson disease.

On physical examination, vital signs are normal. Facial expression is normal, and his voice is low in volume but not tremulous. With the patient at rest, a low-frequency tremor is noted in the right hand and chin. With the arms in an outstretched position, a bilateral tremor emerges after a delay of several seconds that is more prominent on the right side. Finger-to-nose testing reveals a mild bilateral tremor that does not worsen near the target. Rapid alternating movements of the right upper and lower extremities become slower and shorter in amplitude with repetition. Muscle tone is increased bilaterally, with stepwise resistance to passive movements. Gait is normal, but arm swing is decreased and a tremor emerges on the right side during ambulation.

Which of the following is the most appropriate next step in confirming the diagnosis?

(A) Dopamine transporter scan
(B) MRI of the brain
(C) Needle electrode electromyography
(D) No further testing

Item 74

A 52-year-old man is evaluated for worsening leg stiffness and pain. He has secondary progressive multiple sclerosis with associated chronic gait instability, leg weakness, spasticity, and urinary frequency. The patient reports an upper respiratory tract infection over the past week with nasal congestion and rhinorrhea and a mild, nonproductive cough. His leg stiffness and urinary frequency worsened shortly after the onset of respiratory symptoms but

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have persisted despite improvement in his congestion, rhinorrhea, and cough. Medications are interferon beta-1b, a vitamin D supplement, dalfampridine, tizanidine, and oxybutynin.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 139/58 mm Hg, and pulse rate is 98/min. The nasal passages show moderate edema, and postnasal drip is present in the posterior oropharynx. The lungs are clear. Lower extremity spasticity and weakness are noted. All other physical examination findings are unremarkable.

Urinalysis is negative for leukocyte esterase and nitrite.

Bladder ultrasonography shows a postvoid residual urine volume of 180 mL.

Which of the following is the most appropriate treatment?

(A) Amoxicillin-clavulanate
(B) Increased dosage of oxybutynin
(C) Methylprednisolone
(D) Supportive care and clinical observation

Item 75

A 57-year-old man is evaluated in the ICU 7 days after admission for a subarachnoid hemorrhage. An initial noncontrast head CT scan obtained in the emergency department showed a diffuse subarachnoid hemorrhage at the base of the brain that was thickest over the left hemisphere and accompanied by hydrocephalus. An external ventricular drain was placed to treat the hydrocephalus, and he subsequently underwent successful clipping of a 9-mm aneurysm of the left posterior communicating artery. Oral nimodipine was initiated.

On physical examination, temperature is 37.8 °C (100.1 °F), blood pressure is 138/78 mm Hg, pulse rate is 78/min, and respiration rate is 12/min. Neurologic examination shows an extremely somnolent patient who cannot follow commands and is unable to move the right arm and leg; on initial neurologic examination in the emergency department, the patient responded to loud noises, was able to follow simple commands, was oriented to time and place, and exhibited briskly reactive pupils and right arm drift.

Results of standard laboratory studies are normal.

Which of the following is the most appropriate next diagnostic test?

(A) CT angiography of the brain
(B) Electroencephalography
(C) Lumbar puncture
(D) MRI of the brain

Item 76

A 42-year-old man is evaluated for nighttime cramping and crawling sensations in his calves. He experiences these symptoms in the late evening, especially when watching television or getting ready for bed. At times, he feels an urge to stand up and pace around the room, which provides brief relief of symptoms. He has had no pain, weakness, or excessive daytime sleepiness. His mother has similar symptoms. His only medication is loratadine for seasonal allergies.

On physical examination, vital signs are normal. No abnormal movements are noted, and testing of deep tendon reflexes and sensation shows no anomalies.

Results of standard laboratory testing include a normal complete blood count and a serum ferritin level of 120 ng/mL (120 µg/L).

Which of the following is the most appropriate treatment?

(A) Iron supplementation
(B) Pentoxifylline
(C) Ropinirole
(D) Zolpidem

Item 77

A 71-year-old man is evaluated for progressive memory decline. In the past 3 years, he has noticed increasing word-finding difficulties and forgetfulness; he now requires frequent reminders to keep track of appointments. He has remained independent in activities of daily living, except for having to hire an accountant this year to file his taxes. His wife, who accompanied him to the appointment, reports that he is more irritable and impatient than before. The patient describes his mood as upbeat and says he has had no feelings of sadness or hopelessness. He has hyperlipidemia controlled with atorvastatin. His paternal uncle died of Alzheimer disease in his 80s.

On physical examination, vital signs are normal. The patient scores 27/30 on a Mini–Mental State Examination, losing points in the recall section. All other physical examination findings, including those from a neurologic examination, are normal.

Results of laboratory studies, including a complete blood count, a comprehensive metabolic profile, thyroid function tests, and measurement of serum vitamin B_{12} level, are normal.

Which of the following is the most appropriate next step in management?

(A) Amyloid PET imaging
(B) Brain MRI
(C) Carotid Doppler ultrasonography
(D) Determination of apolipoprotein E (*APOE ε4*) status
(E) Fluorodeoxyglucose-PET imaging of the brain

Item 78

A 75-year-old woman is evaluated in the emergency department 90 minutes after onset of right arm weakness and an inability to speak. The patient has atrial fibrillation, hypertension, and dyslipidemia. Medications are warfarin, nifedipine, hydrochlorothiazide, and simvastatin.

On physical examination, blood pressure is 148/78 mm Hg and pulse rate is 86/min and irregular. On neurologic examination, global aphasia, right arm paralysis, antigravity movement in the right leg, left gaze preference, and decreased blink response to threat from the right side are

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noted. Her score on the National Institutes of Health Stroke Scale is high at 22, indicating a severe stroke.

Results of standard laboratory studies include an INR of 1.4 but are otherwise normal.

A noncontrast CT scan of the head shows hyperdensity in the territory of the left middle cerebral artery but is otherwise normal.

After exclusion criteria are ruled out, treatment with intravenous recombinant tissue plasminogen activator (rtPA) is begun 40 minutes after arrival at the emergency department; 60 minutes into the infusion, blood pressure is 168/78 mm Hg, pulse rate is 84/min and irregular, and repeat neurologic examination shows paralysis of the right leg.

Which of the following is the most appropriate next step in management?

(A) Intra-arterial thrombectomy
(B) Intravenous labetalol
(C) Rectal aspirin
(D) Repeat noncontrast CT of the head

Item 79

A 30-year-old woman is evaluated for difficult-to-treat migraine. She has had severe headaches, usually on the first day of menses, since menarche. The pain is hemicranial, pulsatile, and associated with severe nausea and vomiting but no aura. She frequently awakens with the attack already in progress. Ibuprofen was helpful in controlling migraine pain during her teenage years and early 20s but was replaced 5 years ago by oral eletriptan after the pain was no longer controlled; this drug now also is ineffective in relieving symptoms. A trial of oral frovatriptan for menstrual migraine relief also has been unsuccessful. The patient reports receiving intravenous dihydroergotamine and magnesium at an urgent care facility twice in the past 3 months as treatment of refractory headaches.

On physical examination, blood pressure is 98/60 mm Hg and pulse rate is 72/min. All other physical examination findings, including those from a neurologic examination, are normal.

Which of the following is the most appropriate next step in treatment?

(A) Butalbital
(B) Hydrocodone
(C) Naproxen
(D) Orally dissolvable rizatriptan
(E) Subcutaneous sumatriptan

Item 80

A 44-year-old man is evaluated in the emergency department for a severe global headache and blurred vision. Two hours ago, he was struck with a pipe in the right frontotemporal region and anterior neck and knocked to the ground but did not lose consciousness. While describing the assault, the patient becomes stuporous.

On physical examination, blood pressure is 150/100 mm Hg, pulse rate is 50/min, and respiration rate is 10/min. Continued stupor is noted, as are right pupillary dilation, palsy of the oculomotor nerve (cranial nerve III), and an extensor plantar response on the left. The patient withdraws from pain more weakly on the left than the right. No other cranial nerve abnormalities are detected.

Which of the following is the most likely diagnosis?

(A) Epidural hematoma
(B) Left internal carotid artery dissection
(C) Postconcussion syndrome
(D) Posttraumatic seizure

Item 81

A 22-year-old woman is evaluated for a 2-year-history of abnormal involuntary movements. She describes these movements as a quick elevation of the left shoulder followed by a rolling movement of the neck from side to side. The patient is able to suppress the movements completely for brief periods but then feels pressure building at the left shoulder and the urge to release it. She has experienced no other abnormal movements recently but reports uncontrollable blinking 5 years ago and occasional facial grimacing 3 years ago, both of which resolved after 2 years. She also recently has exhibited obsessive-compulsive behavior, such as repeatedly checking that the oven is turned off and all the doors are locked. The patient has anxiety disorder treated with cognitive behavioral therapy. Her father and brother have facial twitching. She takes no medication.

On physical examination, vital signs are normal. The patient is asked to relax and not suppress any movement, after which the left shoulder quickly elevates, followed by the described repeated slower rolling movement of the neck. In the interval between movements, the neck is at midline with no evidence of pulling, tilting, or turning. The movements are more frequent initially but completely disappear during the second half of the visit. She often clears her throat, even during conversation, and frequently blinks. Neurologic examination findings are otherwise unremarkable.

Which of the following is the most likely diagnosis?

(A) Chorea
(B) Dystonia
(C) Myoclonus
(D) Tic disorder

Item 82

A 55-year-old man is evaluated in the hospital for an episode of painful tingling in the right arm followed by clonic jerking of that arm lasting 3 minutes. Medical history is significant for non-small cell lung cancer diagnosed 1 year ago and treated with surgical resection. He was evaluated in the emergency department 1 week ago for a new-onset headache, at which time an isolated brain metastasis in the left parietal area was identified. He subsequently was admitted for planned surgical resection of this lesion, adjuvant local radiation, and systemic chemotherapy.

On physical examination, temperature is 36.6 °C (97.9 °F), blood pressure is 120/92 mm Hg, pulse rate is

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105/min, and respiration rate is 16/min. Right inferior quadrantanopia, right neglect, increased tone in the right arm and leg, and a plantar extensor response in the right toe are noted.

An MRI of the brain shows a stable contrast-enhancing lesion in the left parietal lobe consistent with the patient's known metastasis.

An electroencephalogram shows left hemispheric slowing with no evidence of epileptiform discharges.

Which of the following is the most appropriate management?

(A) Carbamazepine
(B) Phenytoin
(C) Valproic acid
(D) Deferral of antiepileptic drug therapy

H Item 83

A 66-year-old man is evaluated in the emergency department for increasingly difficult-to-manage behaviors. According to his son with whom he lives, he has exhibited intermittent forgetfulness, gotten lost while driving on familiar routes, and had brief but frequent periods of nonsensical speech, excessive daytime sleepiness, and an inability to use familiar objects during the past year. Over the past 3 months, the patient has had increasing visual hallucinations and paranoia accompanied by agitation and restlessness. Medical history is significant for mild depression. His only medication is sertraline. A depression screen is negative for a depressed mood.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 135/70 mm Hg, pulse rate is 80/min, respiration rate is 16/min, and oxygen saturation is 98% on ambient air. General physical examination findings are normal. Neurologic examination shows an agitated man with masked facies, a soft voice, postural instability, and a slow gait. He scores 24/30 on the Mini-Mental State Examination, missing points on orientation to time and place, delayed recall, and figure drawing.

The patient is given haloperidol in the emergency department to treat the agitation, which results in worsening agitation and limb and neck stiffness.

Which of the following is the most likely diagnosis?

(A) Alzheimer disease
(B) Delirium
(C) Dementia with Lewy bodies
(D) Major depression with psychotic features

Item 84

A 36-year-old woman is evaluated for a 1-week history of recurrent episodes of facial pain that are 1 to 3 seconds in duration and occur spontaneously dozens of times throughout the day. The pain is sharp, severe, and located in the right infraorbital area. During this same period, she has developed worsening bilateral lower extremity weakness and urinary incontinence. The patient has an 18-year history of relapsing-remitting multiple sclerosis treated with interferon beta-1a; she also takes baclofen to control spasticity. She has had no nausea, photophobia, phonophobia, nasal congestion, nasal drainage, or ocular/visual changes.

On physical examination, blood pressure is 100/64 mm Hg and pulse rate is 80/min. Moderate bilateral lower extremity weakness and hyperreflexia are noted. Sensory spinal cord level for pain and temperature is T6. Plantar responses are extensor bilaterally. Internuclear ophthalmoplegia is noted, but other findings from an examination of the cranial nerves are unremarkable.

Results of laboratory studies, including a comprehensive metabolic profile, a complete blood count, and urinalysis, are normal.

Which of the following is the most likely cause of the facial pain?

(A) Chronic paroxysmal hemicrania
(B) Herpes zoster
(C) Primary stabbing headache
(D) Trigeminal neuralgia

Item 85

A 64-year-old woman is evaluated for persistent myopathy. Polymyositis was confirmed by muscle biopsy 6 months ago. High-dose prednisone was started, with almost full recovery within 4 months; the glucocorticoid was subsequently tapered to daily low-dose prednisone. For the past month, she has experienced a recurrence of weakness in the deltoid and hip flexor muscle groups. Her only medication is prednisone, 20 mg.

On physical examination, blood pressure is 132/80 mm Hg and pulse rate is 80/min; BMI is 35. Neck extensor, arm abductor, elbow extensor, hip flexor, and knee extensor muscles are moderately weak; distal muscle strength is normal. Muscle tone is flaccid, but sensory examination findings are normal. Deep tendon reflexes are absent at the triceps muscle and patella but normal elsewhere. The plantar response is flexor. Assessment of cranial nerves and mental status shows no abnormalities.

Results of laboratory studies show a serum creatine kinase level of 80 U/L.

Which of the following is the most appropriate management?

(A) Add intravenous immune globulin
(B) Increase prednisone dosage
(C) Taper prednisone dosage
(D) Repeat muscle biopsy

Item 86

H

A 49-year-old woman is evaluated in the emergency department 45 minutes after onset of right-sided weakness and loss of vision. She has dyslipidemia and hypertension. Medications are simvastatin and hydrochlorothiazide.

On physical examination, blood pressure is 160/88 mm Hg, pulse rate is 78/min and irregular, and respiration rate is 12/min. No carotid bruits are heard on cardiac examination. On neurologic examination, speech is fluent with occasional word-finding difficulties. A right inferior visual field deficit, right facial weakness, mild dysarthria, right arm

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CONT. pronator drift, and loss of pinprick sensation on the right arm and face are noted. No right leg weakness is detected. The National Institutes of Health Stroke Scale score is 7 (moderate stroke).

An electrocardiogram shows atrial fibrillation with no ST-segment or T-wave changes. A noncontrast CT scan of the head is normal.

The patient receives intravenous recombinant tissue plasminogen activator 50 minutes after arrival in the emergency department. Three hours after the infusion is completed, her blood pressure is 188/110 mm Hg and pulse rate is 68/min. Other physical examination findings are unchanged.

Which of the following is the most appropriate treatment?

(A) Intravenous nicardipine
(B) Oral aspirin
(C) Subcutaneous heparin
(D) Sublingual nitroglycerin

Item 87

A 39-year-old woman is evaluated for worsening headaches. Headache episodes initially developed while she was in high school but have become increasingly severe and frequent over the past 3 years. She describes these recent headaches as an intense, hemicranial, throbbing pain that occurs two or three times per week and is associated with nausea and photophobia. For the past year, she has experienced additional daily episodes of dull, mild, global head pressure without associated features. The patient also has asthma and mild depression. She stopped taking over-the-counter analgesics 6 months ago when they became ineffective; other medications are albuterol and fluticasone.

On physical examination, blood pressure is 122/78 and pulse rate is 74/min; BMI is 22. Other physical examination findings, including those from a neurologic examination, are unremarkable.

An MRI of the brain is normal.

Which of the following is the most appropriate treatment?

(A) Carbamazepine
(B) Duloxetine
(C) Propranolol
(D) Topiramate
(E) Verapamil

Item 88

A 51-year-old woman is evaluated in the emergency department (ED) for increasingly agitated and paranoid behavior. Over the past 4 weeks, she has exhibited short-term memory loss and has been less organized and more confused, which necessitated her taking a leave from work. Her son also has noticed her occasionally sitting motionless, staring at nothing and smacking her lips. She was brought to the ED after she stopped eating because of a belief that someone was trying to poison her. The patient has no other personal medical history and no family history of dementia or psychiatric disorders. She takes no medication.

On physical examination, temperature is 36.1 °C (97.0 °F), blood pressure is 100/70 mm Hg, pulse rate is 70/min, and respiration rate is 16/min. The patient is agitated, with wandering attention. She does not know the date, often missing it by a decade. She can repeat three of three words but 5 minutes later does not recall any of them. Findings of cranial nerve examination are normal, as are muscle strength, coordination, and reflexes.

Serum sodium level is 128 mEq/L (128 mmol/L). All other results of laboratory studies, including a comprehensive metabolic profile and complete blood count, are normal.

An MRI shows increased flair signal in both mesial temporal regions. Continuous EEG monitoring reveals frequent temporal lobe seizures (8/day) occurring from both the left and right temporal lobes.

Which of the following is the most likely diagnosis?

(A) Alzheimer disease
(B) Human herpesvirus 1 encephalitis
(C) Lewy body dementia
(D) Paraneoplastic limbic encephalitis

Item 89

A 90-year-old man is evaluated in the hospital for disorientation. He was admitted 5 days ago after having a myocardial infarction. Before hospitalization, he was living alone and functioning independently. Since hospitalization, the patient has had periods of daytime sleepiness alternating with periods of agitation. Medications are aspirin, clopidogrel, metoprolol, lisinopril, and atorvastatin.

On physical examination, temperature is normal, blood pressure is 130/82 mm Hg, pulse rate is 70/min, and respiration rate is 16/min. Cardiac examination shows an early systolic murmur and normal heart sounds. Neurologic evaluation shows sudden involuntary jerks of the upper extremities that increase in frequency when the arms are outstretched and wrists are extended. The patient is oriented to self and location but not to date and believes he has been hospitalized for only 1 day. He cannot spell the word "world" backwards, and his responses to questions are at times inappropriate or tangential. He requires frequent redirection during the interview and appears to be distracted by something on the wall. Findings from the rest of the physical examination are otherwise unremarkable.

Laboratory studies:

Complete blood count	Normal
Liver chemistry studies	Normal
Glucose, fasting	Normal
Creatine kinase	Normal
Creatinine	2.9 mg/dL (256 µmol/L) (2.0 mg/dL [177 µmol/L] on admission)

Which of the following is the most likely diagnosis?

(A) Delirium
(B) Dementia
(C) Nonconvulsive status epilepticus
(D) Stroke

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Item 90

A 49-year-old woman is evaluated for a 1-year history of severe fatigue. She often requires a nap in the middle of the day to continue to function and notes that her work productivity is reduced. The patient has multiple sclerosis (MS), which was diagnosed 2 years ago and is well controlled with daily teriflunomide. Other medications are nightly amitriptyline and weekly vitamin D supplementation.

On physical examination, temperature is 36.9 °C (98.4 °F), blood pressure is 105/64 mm Hg, pulse rate is 68/min, and respiration rate is 14/min; BMI is 21. All other physical examination findings are normal, and neurologic examination findings are unchanged from those obtained at her baseline examination.

Results of laboratory studies show a hemoglobin level of 13.1 g/dL (131 g/L), a mean corpuscular volume of 90 fL, and a serum thyroid-stimulating hormone level of 1.4 μU/mL (1.4 mU/L).

An MRI of the brain obtained 1 month ago as part of routine surveillance showed white matter lesions consistent with MS and unchanged from their appearance 1 year ago.

Which of the following is the most appropriate treatment for this patient?

(A) Iron supplementation
(B) Levothyroxine
(C) Modafinil
(D) Nocturnal continuous positive airway pressure
(E) Substitution of dimethyl fumarate for teriflunomide

Item 91

A 74-year-old woman is seen for a follow-up evaluation of generalized muscle pain. She first noticed diffuse myalgia 6 months ago; the pain became more severe over the next 2 months, and she began experiencing mild proximal weakness in both upper and lower extremities. Her serum creatine kinase level at that time was 2200 U/L. She was instructed to discontinue the simvastatin she took for hyperlipidemia, and the muscle pain and weakness resolved. The patient also has coronary artery disease treated with aspirin, metoprolol, and isosorbide dinitrate.

On physical examination, blood pressure is 130/80 mm Hg; other vital signs also are normal. No muscle tenderness is noted. All other findings of the general physical and neurologic examinations are normal.

Laboratory studies show a serum creatine kinase level of 250 U/L.

Which of the following is the most appropriate treatment?

(A) Atorvastatin
(B) Gemfibrozil
(C) Rosuvastatin
(D) Selenium

Item 92

A 56-year-old man is evaluated for a 5-year history of gradually worsening behavioral problems. During this period, the patient has lost four different jobs because of argumentativeness with his bosses and rudeness toward coworkers and customers. According to his wife, he has become increasingly indifferent toward most things, including his family about whom he used to care deeply; has lost all interest in socializing with friends; and has started to drink excessively. He has become preoccupied with counting change and other belongings and has developed compulsive rituals from which he does not diverge. The patient also has begun collecting scrap metals, an activity he greatly enjoys. He says he does not feel down or hopeless and has not had periods of elation, euphoria, or irritability accompanied by an increased energy level. His memory has remained good. During the interview, the patient states that he has not noticed any change in his behavior and contributes little else to the history. His father was institutionalized for an unknown psychiatric illness at age 55 years.

On physical examination, vital signs are normal. The general physical and neurologic examinations are normal. His score on the Mini-Mental State Examination is 29/30, with one point deducted for orientation to date.

Which of the following is the most likely diagnosis?

(A) Alzheimer disease
(B) Dementia with Lewy bodies
(C) Depression
(D) Frontotemporal dementia

Item 93

A 58-year-old woman is evaluated for cognitive impairment. The patient was brought to the office by her daughter because of a progressive inability to care for herself and manage her finances over the past 2 months. She also has become more withdrawn, emotionally blunted, and disinterested in former social activities and hobbies. She previously was successfully employed as a substitute teacher. She has no significant medical history and no family history of a neurologic or psychiatric disorder.

On physical examination, vital signs are normal. Neurologic examination shows generalized slowness, but findings are otherwise normal. She scores 10/30 on the Montreal Cognitive Assessment, losing points in all eight sections.

Results of laboratory studies, including a complete blood count, comprehensive metabolic profile, thyroid function tests, vitamin B_{12} level, erythrocyte sedimentation rate, rapid plasma reagin test, HIV antibody titer, and urinalysis, are normal.

A diffusion-weighted MRI of the brain is shown on page 114.

Which of the following is the most likely diagnosis?

(A) Alzheimer disease
(B) Creutzfeldt-Jakob disease
(C) Herpes simplex virus 1 encephalitis
(D) Vascular neurocognitive disorder

Item 94

A 57-year-old man is evaluated in the emergency department 45 minutes after developing acute-onset left arm

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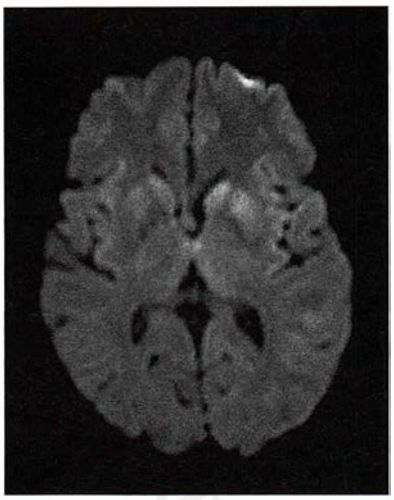

ITEM 93

CONT. weakness. He has type 2 diabetes mellitus and a 50-pack-year smoking history. He has no history of stroke, trauma, bleeding, cardiac disease, or surgery. His only medications are atorvastatin and metformin.

On physical examination, blood pressure is 168/98 mm Hg and pulse rate is 86/min and irregular. Neurologic examination reveals left hemineglect, an inferior left visual field deficit, left facial weakness, mild dysarthria, and left arm and leg drift. He scores 6 on the National Institutes of Health Stroke Scale, indicating a moderate stroke.

Laboratory study findings include a plasma glucose level of 162 mg/dL (9.0 mmol/L); results of a complete blood count, a comprehensive metabolic profile, and coagulation studies are normal.

An electrocardiogram shows atrial fibrillation. A noncontrast CT scan of the head shows no acute infarct or hemorrhage.

Which of the following is the most appropriate next step in treatment?

(A) High-dose aspirin
(B) Insulin
(C) Intravenous heparin
(D) Intravenous recombinant tissue plasminogen activator

Item 95

A 55-year-old man is treated in the emergency department for convulsive status epilepticus. He stops convulsing after receiving intravenous lorazepam and phenytoin but is still confused 30 minutes after treatment. According to his wife who accompanied him, a left temporal cavernous malformation was detected 3 years ago and has been managed conservatively. He has no significant family medical history and takes no chronic medication.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 130/90 mm Hg, pulse rate is 115/min, and respiration rate is 12/min. The patient is generally stuporous but intermittently alert to voice or sternal rub. He occasionally utters nonsensical phrases, mostly consisting of syllables that are not real words, and inconsistently follows some one-step commands. Cranial nerves are intact, and pupils are symmetric and reactive. No weakness is detected in the face or limbs.

A CT of the head shows an acute hemorrhage in the region of the patient's cavernous malformation. The hemorrhage measures 0.5 × 0.5 × 1.0 cm. No significant mass effect or midline shift is noted.

Which of the following is the most appropriate next step in management?

(A) Continuous electroencephalographic monitoring
(B) Intravenous flumazenil
(C) Urgent surgical resection of the vascular malformation
(D) Withholding of further doses of antiepileptic drugs

Item 96

A 65-year-old woman is admitted to the hospital for evaluation of acute kidney injury secondary to dehydration after an episode of severe gastroenteritis. She has type 1 diabetes mellitus, secondary progressive multiple sclerosis, and osteopenia. Medications are irbesartan, insulin glargine, insulin lispro, glatiramer acetate, dalfampridine, baclofen, vitamin D, and calcium.

On physical examination, temperature is normal, blood pressure is 110/60 mm Hg, pulse rate is 108/min, and respiration rate is 14/min. She appears weak and tired. Neck veins are flat. The remainder of the physical examination is normal.

Results of laboratory studies show a serum creatinine level of 3.9 mg/dL (345 µmol/L), which is increased from her baseline level of 1.4 mg/dL (124 µmol/L).

Intravenous fluids are initiated.

In addition to irbesartan, which of the following medications must be discontinued?

(A) Baclofen
(B) Dalfampridine
(C) Glatiramer acetate
(D) Vitamin D

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Answers and Critiques

Item 1 Answer: B

Educational Objective: Diagnose vitamin D deficiency in a patient with multiple sclerosis.

This patient's serum 25-hydroxyvitamin D level should be measured. He most likely has experienced a breakthrough relapse of multiple sclerosis (MS), which should be treated with intravenous methylprednisolone. Given his 2 years without relapses, the MS is relatively well-controlled. However, his care is not fully optimized because he rarely takes the vitamin D supplement. Accumulating evidence suggests that disease activity in MS is highly linked with serum vitamin D levels, with less frequent relapses and fewer new MRI lesions in patients with higher levels. This patient's serum 25-hydroxyvitamin D level should thus be measured to determine if he is vitamin D deficient. Vitamin D supplementation as an adjunctive treatment in MS has been shown to be superior to disease-modifying therapy alone and has become a standard of care for MS patients, especially those who are vitamin D deficient, although the ideal dosing regimen and serum 25-hydroxyvitamin D level are still unknown. Pharmacodynamic studies are under way that may help inform dosing regimens. Vitamin D supplementation also protects against osteoporosis, for which patients with MS are at higher risk.

This patient has no clear indications supporting discontinuation of natalizumab at this time. Natalizumab is the most highly effective drug for MS currently available, which is borne out by his relapse-free status for 2 years and stable brain MRI results. Although this drug is sometimes associated with progressive multifocal leukoencephalopathy (PML), his recent negative result on JC virus antibody testing place him at a very low risk for development of PML, and the spinal cord localization of this current relapse also argues against PML, which does not affect the spinal cord.

The bilateral leg weakness and sensory level around the umbilicus (T10) are consistent with localization to the thoracic spinal cord. Therefore, an MRI of the lumbar spine would not be appropriate.

This patient has no indication for antibiotic therapy, which makes a 5-day course of trimethoprim-sulfamethoxazole inappropriate.

KEY POINT

- Vitamin D supplementation as an adjunctive treatment in multiple sclerosis (MS) has been shown to be superior to disease-modifying therapy alone and has become a standard of care for patients with MS, especially those who are vitamin D deficient.

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Item 2 Answer: C

Educational Objective: Diagnose mild cognitive impairment.

The most likely underlying cause of this patient's symptoms is mild cognitive impairment (MCI). MCI is a cognitive state between normal aging and dementia characterized by a decline in cognitive functioning that is greater than what is expected with normal aging but has not resulted in significant functional disability. For most patients, the onset is insidious, and for some, the course may be progressive; 10% to 15% of patients with MCI transition to dementia per year, compared with 1% to 2% per year of the general population. The Montreal Cognitive Assessment is a screening tool that is more sensitive than the Mini-Mental State Examination in the detection of MCI because it has more cognitively challenging tests of memory/recall and executive function. A score lower than 26/30 generally suggests cognitive impairment, especially in patients with 16 years of formal education. In clinical practice, a careful history and results of a standard mental examination are often sufficient to make a diagnosis of MCI, and extensive cognitive testing is not routinely required. Occasionally, a formal battery of neuropsychological testing beyond the standard mental examination is needed to distinguish particularly mild cases of cognitive impairment from normal aging.

In order to meet criteria for dementia, a patient's cognitive deficits must interfere with daily functioning and result in some loss of independence. A detailed history of the patient's abilities to perform activities of daily living, such as paying bills, managing financial records, assembling tax records, shopping alone, working on hobbies, taking medications, driving, and remembering recent holidays or family events, should be obtained to elicit any change in function. This patient does not meet the criteria for dementia.

The diagnosis of clinical depression is based on patient history and exclusion of alternative diagnoses; no additional tests can confirm the diagnosis. The evaluation must establish whether the patient meets established criteria for major depression, dysthymia, or a different psychiatric condition and also assess for substance abuse. Depressed mood and anhedonia are cardinal symptoms, and the presence of either is highly sensitive but not specific for major depression. Using a two-item questionnaire that assesses for the presence of depressed mood or anhedonia is a quick way to screen for depression. If either depressed mood or anhedonia is present, further inquiry or employing a second tool to diagnose depression should be pursued. This patient, who describes her mood as upbeat and says she enjoys her

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life, has neither depressed mood nor anhedonia. Therefore, depression is unlikely to be the cause of her symptoms.

Patients with memory problems due to normal aging have symptoms, most notably memory loss, that are commonly associated with cognitive impairment, but cognitive testing shows functioning within the normal range. This patient's memory difficulties are greater than what is expected with normal aging, and her score on the Montreal Cognitive Assessment is not in the normal range.

KEY POINT

- A score lower than 26/30 on the Montreal Cognitive Assessment generally suggests cognitive impairment, especially in patients with many years of formal education.

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Item 3 Answer: B

Educational Objective: Treat acute spinal cord injury.

This patient should receive high-dose methylprednisolone as the next step in management. He has an acute spinal cord injury most likely due to traumatic fracture of a thoracic vertebra and subsequent spinal cord compression. The localization of the injury at approximately the T8 level of the spinal cord is clear, given the bilateral leg weakness and reduced tone, reduced anal sphincter tone, and the sensory level on pinprick testing. Large clinical trials have shown improved motor function recovery up to 1 year after administration of an intravenous bolus of methylprednisolone, 30 mg/kg, within the first 8 hours of traumatic spinal cord injury followed by a 5.4-mg/kg infusion over the next 23 hours. A recent trial has shown that extending this infusion for an additional 24 hours further increases recovery. Because of these studies, immediate administration of high-dose methylprednisolone for suspected traumatic spinal cord injury has become standard of care.

Diagnostic studies are not appropriate because of the acuity of the situation. Given that the patient experienced the trauma 7 hours before he was seen in the emergency department, ordering CT or MRI would delay initiation of treatment, which is necessary within the first 8 hours of the traumatic event. Obtaining a confirmatory MRI of the thoracic spine at a later time is appropriate. However, CT of the head is not needed because the injury localizes to the thoracic spine on examination. Although the patient received some trauma to the head, CT is likely unnecessary, given that he had no loss of (or impaired) consciousness, no evidence of significant external head trauma, and no other signs or symptoms of traumatic brain injury.

Phenytoin would not treat this patient's spinal cord injury. Administration of phenytoin after significant head trauma may be indicated to prevent seizures, but this patient does not appear to have significant head trauma, nor is this the most acute issue at this time.

KEY POINT

- High-dose methylprednisolone administered within 8 hours of a traumatic spinal cord injury has been shown to improve motor function recovery.

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Item 4 Answer: A

Educational Objective: Evaluate transient ischemic attack.

The patient should undergo carotid ultrasonography. He most likely has experienced a transient ischemic attack (TIA), which implies the absence of retinal or cerebral infarction. His ABCD^2 score, which is based on a patient's Age, Blood pressure, Clinical presentation, Duration of symptoms, and the presence of Diabetes mellitus, is 2 (one point for elevated blood pressure and one point for the symptom of slurred speech), which indicates a 2-day stroke risk of 1.3%. The antecedent transient monocular blindness in the left eye is concerning for extracranial atherosclerosis of the internal carotid artery. Hospital admission is recommended for all patients with TIAs who have an ABCD^2 score of 3 or greater to expedite diagnostic testing and stroke subtyping; admission is also recommended for patients with a score of 0 to 2 if rapid outpatient evaluation cannot be performed.

Carotid ultrasonography to evaluate for symptomatic extracranial internal carotid artery stenosis is the most appropriate next diagnostic test in this patient with a TIA, given the high risk of early recurrence. Patients with greater than 70% extracranial internal carotid artery atherosclerotic stenosis have the highest risk of stroke in the 2 weeks after a TIA. Carotid Duplex ultrasonography is noninvasive and can effectively rule out significant atherosclerotic disease. If the ultrasound suggests greater than 50% stenosis, hospital admission and a confirmatory test with magnetic resonance or CT angiography is appropriate, with plans for early revascularization. Rapid cardiac testing with transthoracic echocardiography and cardiac rhythm evaluation also is advised within 24 hours for all patients with suspected TIA, as is vascular imaging of the extracranial carotid arteries.

CT angiography of the neck is inappropriate at this point because extracranial internal carotid artery stenosis can be excluded without exposing the patient to a highly invasive procedure with contrast and radiation.

Although an MRI of the brain can distinguish a TIA from an ischemic stroke and reveal infarcts in other arterial territories, it is inappropriate as the next diagnostic test in this patient because results are unlikely to affect immediate management. In addition, MRI may not be readily available and may be contraindicated in some patients.

Transesophageal echocardiography may be indicated to identify embolic sources of a TIA or stroke in patients in whom noninvasive diagnostic testing has been unrevealing. However, the yield of transesophageal echocardiography is

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CONT. low (approximately 1%) in patients who are in sinus rhythm, particularly among those older than age 45 years. Although MRI ultimately may be indicated for this patient, appropriate noninvasive testing should be performed first, including cardiac rhythm evaluation and vascular imaging of the carotid arteries.

KEY POINT

- In a patient with a suspected transient ischemic attack, noninvasive carotid ultrasonography is the most appropriate test to exclude significant atherosclerotic disease.

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Item 5 Answer: C

Educational Objective: Monitor an incidentally discovered meningioma.

Repeat MRI in 3 to 6 months is the most appropriate next step in management. The radiographic features associated with this patient are most consistent with a meningioma, which may be unrelated to his previous headaches, given the tumor's small size and lack of other symptoms. Meningiomas are benign tumors that arise from the meningeal coverings of the brain. They are the most common extra-axial (not in the brain parenchyma) intracranial lesion in adults. Meningiomas are typically slow-growing tumors, and clinical signs tend to be subtle. They also are often discovered incidentally, as in this patient. Meningiomas have characteristic imaging features, including intense homogeneous contrast enhancement ("lightbulb sign"), areas of calcification, and a dural tail, which is thickening of the dura adjacent to the mass. Patients with small, asymptomatic meningiomas without evidence of invasion of other intracranial structures and without surrounding edema are usually followed clinically and radiographically. Meningiomas should be monitored for growth, with a first follow-up scan performed 3 to 6 months after they are identified.

Lumbar puncture is not indicated in this patient whose imaging findings are characteristic of a meningioma. Lumbar puncture may be indicated in patients with suspicious imaging findings (such as partial enhancement or ring enhancement) suggestive of an infectious or inflammatory process. Lumbar puncture is only appropriate in these patients if they also have evidence of increased intracranial pressure, such as papilledema.

Patients with symptomatic tumors, tumors that invade surrounding parenchyma, or tumors that grow over time may be considered for surgery and/or radiation therapy. If intervention is indicated, surgical intervention is usually the first-line therapy, followed by radiation for higher grade tumors or tumors that could not be resected completely. These treatments are not appropriate at this time in this patient who has none of these indications.

KEY POINT

- Meningiomas have characteristic imaging features, including intense homogeneous contrast enhancement ("lightbulb sign") and a dural tail.

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Item 6 Answer: B

Educational Objective: Diagnose focal epilepsy.

This patient most likely has a focal epilepsy syndrome. It is crucial to ask a patient being evaluated for a first seizure about previous more subtle events, such as auras, changes in awareness, and periods of inattention, that may indicate the presence of an as yet unrecognized epilepsy syndrome. The difficult-to-describe sensation of déjà vu that occurred just before this patient's seizure most likely represents an epileptic aura, which is actually a simple partial seizure. The fact that she had the same sensation previously over the past several years suggests that she has had partial seizures before. The features of her current seizure (unilateral shaking and a subjective aura before the onset of convulsion) suggest progression to a secondarily generalized seizure typical of focal epilepsy, although these features are not always present in secondarily generalized seizures.

Alcohol withdrawal is among the many metabolic stressors that can lead to a provoked seizure. Alcohol withdrawal seizures typically occur with other symptoms of withdrawal (behavioral changes and autonomic symptoms) but can sometimes occur in isolation before other withdrawal symptoms. This type of seizure typically does not have the focal features described in this patient, whose previous, recurrent seizures support a diagnosis of epilepsy. In patients with epilepsy, similar triggers, particularly alcohol ingestion and sleep deprivation (as in this patient), can precipitate a seizure or a more serious seizure. However, these seizures are not considered "provoked"; this term is reserved for isolated events in patients without epilepsy.

Distinguishing between focal and generalized epilepsy syndromes may not be possible if a patient has convulsions only. This patient's seizure was preceded by an aura, which is associated with focal epilepsy. The age of onset in this patient (between 30 and 40 years) is also atypical for generalized epilepsy, which usually begins in adolescence or early adulthood.

A posttraumatic seizure can occur within a week of significant head trauma. This patient had head trauma without loss of consciousness 1 month before onset of her first recognized seizure. Her mild head trauma most likely is not

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CONT.

related to her convulsive seizure or the diagnosis of epilepsy, particularly because her auras began before she hit her head.

KEY POINT

- Evaluating a patent with an apparent first seizure should include direct questioning about previous subtle events, such as auras, changes in awareness, and periods of inattention, that may indicate the presence of an as yet unrecognized epilepsy syndrome.

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Item 7 Answer: A

Educational Objective: Diagnose chronic traumatic encephalopathy.

The most likely diagnosis for this patient is chronic traumatic encephalopathy. Chronic traumatic encephalopathy is a progressive neurodegenerative disorder triggered by repetitive mild head injury that has most often been described in military combat veterans and athletes with a history of multiple concussions and subconcussions. This patient's career as a professional football player would have made him particularly susceptible to this type of injury. Clinical symptoms typically manifest years or decades after repeated head trauma and present insidiously. Behavioral symptoms are common and include depression, suicidal ideation, apathy, and irritability. Disinhibition, impulsivity, and aggression can also occur in the later stages. Cognitive symptoms include problems with memory, attention, concentration, and executive function. With disease progression, poor judgment and poor insight become more prominent. Parkinsonism, disturbance of gait, and speech abnormalities often occur later in the disease course.

Although this patient exhibits mild parkinsonism on clinical examination, he lacks other features to support a diagnosis of dementia with Lewy bodies, such as fluctuating cognition, visual hallucinations, rapid eye movement sleep behavior disorder, and autonomic dysfunction. In addition, his age at symptom onset is unusual for dementia with Lewy bodies, which typically presents in the sixth decade of life or later.

Depression-related cognitive impairment refers to the cognitive deficits associated with depression and most often is characterized by frontal-subcortical dysfunction and slowed processing speed. Cognitive symptoms improve with treatment of depression. The patient has depression accompanied by suicidal ideation, but his history and constellation of additional neurologic and behavioral symptoms are more suggestive of chronic traumatic encephalopathy.

Parkinsonism tends to occur in chronic traumatic encephalopathy during the later stages of the disease. Comorbid neurodegenerative disease, such as Alzheimer disease, Lewy body disease, and Parkinson disease, can be seen in a percentage of patients with chronic traumatic encephalopathy at autopsy, and some evidence suggests that repetitive head injury is associated with increased risk of these disorders. This patient has slow and shuffling gait and bradykinesia but lacks the cardinal signs of idiopathic Parkinson disease, including resting tremor or rigidity, a unilateral onset, and asymmetric parkinsonism. The most likely diagnosis for his clinical syndrome of cognitive, behavioral, and motor decline is chronic traumatic encephalopathy.

KEY POINT

- Chronic traumatic encephalopathy is a progressive neurodegenerative disorder triggered by repetitive mild head injury as occurs in military combat veterans and athletes with a history of multiple concussions and subconcussions.

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Item 8 Answer: D

Educational Objective: Treat migraine in a patient with nonspecific MRI abnormalities.

This patient should receive rizatriptan to treat migraine, which is no longer adequately controlled by NSAIDs. Other than increased intensity, the headache pattern has been stable for 25 years. Her history, physical examination findings, and MRI provide no evidence of a secondary headache disorder. The white matter signal abnormalities evident on the MRI are typical of those seen with migraine, specifically in the posterior circulation and particularly in women, as documented in several population-based studies. Data suggest that these lesions are benign and have no correlation with migraine frequency or the appearance of neurologic or cognitive anomalies or deficits. Initiation of a triptan is appropriate in patients with acute migraine who have not responded to treatment with one or more NSAIDs.

Aspirin is unlikely to relieve acute migraine pain that has not responded to two NSAIDs and would be unnecessary for secondary stroke prevention in this patient.

The patient has not reported any clinical events suggestive of stroke or a demyelinating disease, and her normal neurologic examination findings and the absence of any larger or periventricular white matter lesions on MRI would be unusual in multiple sclerosis. Lumbar puncture is thus not warranted in this patient.

Magnetic resonance angiography is also unnecessary. Although migraine is a contributor to stroke risk in women, this patient has no features suggestive of cerebral ischemia and has no aura or other risk factors for cerebrovascular disease.

Timolol is a migraine prophylactic drug that is effective in reducing the frequency of migraine attacks. Pharmacologic prophylaxis of migraine is indicated for headache frequency greater than 2 days per week (or 8 days per month) or use of acute medications, successfully or unsuccessfully, more than 2 days per week. Migraine frequency in this

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patient is too low to warrant introduction of daily migraine preventive medication.

KEY POINT

- White matter signal abnormalities are typically seen on MRIs of patients with migraine, particularly in the posterior circulation and particularly in women; these lesions are benign and unrelated to neurologic examination abnormalities or cognitive anomalies

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Item 9 Answer: E

Educational Objective: Diagnose temporal lobe epilepsy.

This patient most likely has temporal lobe epilepsy. The rising epigastric sensation she describes is the most common epileptic aura that originates in the temporal lobe. Brief episodic anxiety with or without autonomic symptoms, such as dry mouth, also is characteristic of a temporal lobe seizure. These symptoms can occur independently or together (as in this patient) but are typically stereotyped in a given patient. The aura is a simple partial seizure, which can become a complex partial seizure and lead to altered sensorium and automatisms (such as "fidgety" behavior). The absence of focal findings on MRI and electroencephalography (EEG) does not rule-out a diagnosis of epilepsy and is in fact a common finding in temporal lobe epilepsy.

Frontal lobe epilepsy can present with different types of seizures, but a fearful and epigastric aura is not typical. Classically, frontal lobe seizures cause motor manifestations (focal jerking, bicycling movements) that awaken patients from sleep.

Juvenile absence epilepsy is a form of generalized epilepsy beginning at or after puberty that is characterized by absence seizures with or without convulsive seizures. An absence seizure is a brief loss of awareness, typically lasting 3 to 10 seconds. This type of seizure is not preceded by an aura.

Temporal lobe epilepsy is often misdiagnosed as panic disorder, which has some similar features. However, this patient's events are stereotyped and short in duration, characteristics that are more associated with temporal lobe seizures than panic attacks.

Although psychogenic nonepileptic seizures (PNES) can have numerous manifestations and should be part of the differential diagnosis, they are not the most likely cause of this patient's symptoms. PNES are less likely than epileptic seizures to be consistently stereotyped and brief in duration. The fact that episodes can be triggered by stress does not necessarily distinguish between epileptic and nonepileptic seizures. Given the characteristic and consistent features of this patient's events, she should be treated for presumed epilepsy. If the patient does not respond to treatment, inpatient video EEG monitoring should be considered to make a definitive diagnosis.

KEY POINT

- A rising epigastric sensation is the most common epileptic aura that originates in the temporal lobe; electroencephalographic and MRI findings are often normal.

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Item 10 Answer: B

Educational Objective: Obtain CT without contrast in a patient with acute stroke.

CT of the head without contrast is the most appropriate diagnostic test in this patient. She had sudden-onset severe headache followed by impaired consciousness, symptoms that are most concerning for hemorrhagic stroke caused by an aneurysmal subarachnoid hemorrhage or intracerebral hemorrhage. A neurologic examination by itself lacks sufficient predictive value to evaluate the source of impaired consciousness. Rapid imaging is required to initiate rapid treatment. CT of the head is readily available, can be performed quickly, and is the test of choice to rule out intracerebral hemorrhage, subarachnoid bleeding, and hydrocephalus, all of which may necessitate rapid neurosurgical intervention.

Catheter-based angiography is ultimately indicated in most patients with subarachnoid hemorrhage to determine the source of bleeding. However, CT of the head without contrast, which allows for more rapid imaging, should be performed first to evaluate for any condition (such as hydrocephalus from increased intracranial pressure) that can be rapidly reversed with emergency neurosurgical treatment.

Lumbar puncture should not be performed in a patient with stroke symptoms until the presence of a mass lesion has been excluded. If the patient has elevated intracranial pressure from mass effect, particularly in the cerebellum, lumbar puncture may worsen any cerebral herniation.

In the evaluation of a patient with symptoms of a stroke, MRI is time consuming, not readily available, and not cost-effective; this test also leaves the patient in a less monitored setting during the scanning than does CT. In the acute setting, stroke that requires rapid neurosurgical intervention should be diagnosed as quickly as possible.

KEY POINT

- CT of the head without contrast is the most appropriate diagnostic test in a patient with acute stroke.

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Item 11 Answer: E

Educational Objective: Diagnose myotonic dystrophy.

This patient most likely has myotonic dystrophy. Whereas muscle weakness and fatigue are present in a wide range of myopathies, neuromuscular junction disorders, and other conditions, the presence of myotonia—an impairment of muscle relaxation secondary to increased cellular membrane hyperexcitability—narrows the differential diagnosis. Myotonic dystrophy is the most common myotonic disorder, with accompanying symptoms of cataract, cardiomyopathy, cardiac conduction abnormalities, diabetes mellitus, and alopecia. This condition should be considered in all patients with weakness, fatigue, and a myopathic waddling gait who also have muscle stiffness and delayed grip relaxation. The diagnosis should be confirmed by electromyography; confirmatory genetic testing (for myotonic dystrophy type 1) is available commercially. Myotonic dystrophy type 1 is more common and preferentially involves distal limb and facial muscles, whereas the less common type 2 preferentially affects proximal muscles. An increased awareness of comorbidities of myotonic dystrophy and aggressive management of its cardiac complications, which can increase mortality, are recommended.

Becker muscular dystrophy typically starts in childhood, but its progression can be variable. Its pattern of weakness is predominantly proximal, and calf hypertrophy is present; myotonia is not.

Inclusion body myositis is a slowly progressive inflammatory myopathy that predominantly affects distal upper extremity flexors and quadriceps. Asymmetric involvement is common, but myotonia is not a feature.

Although fatigue and weakness can occur in Lambert-Eaton myasthenic syndrome and myasthenia gravis, neither of these conditions is associated with myotonia.

KEY POINT

- Myotonic dystrophy should be considered in all patients with weakness, fatigue, and a myopathic waddling gait who also have muscle stiffness and delayed grip relaxation.

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Item 12 Answer: A

Educational Objective: Diagnose a subarachnoid hemorrhage with lumbar puncture.

This patient should undergo lumbar puncture. He reports sudden onset of a severe headache, most likely a thunderclap headache. Thunderclap headache is defined as a severe headache that reaches maximum intensity within 60 seconds of onset. Although classically associated with subarachnoid hemorrhage (SAH), thunderclap headache also may be caused by other conditions, ranging from benign to life-threatening ones. Because approximately 25% of thunderclap headache presentations result from an SAH, this type of headache should be approached as a neurologic emergency. Although other causes are possible, including dural sinus thrombosis, meningitis, and migraine, the presence of a dilated unreactive pupil suggests external compression of the left oculomotor nerve (cranial nerve III). In the presence of a normal mental status, cerebral herniation and increased intracranial pressure are unlikely, but an aneurysm of the left posterior communicating artery is possible that may not be visible on a noncontrast CT scan of the head. Patients with an aneurysmal SAH may first experience less extensive bleeding that also is not visible on a noncontrast head CT before more significant bleeding occurs. After this initial or "sentinel" bleeding, the patient is at high risk for a clinically significant SAH with associated high morbidity and mortality. Therefore, establishing the diagnosis is a priority.

When the suspicion of an SAH is high and the noncontrast CT scan of the head is normal, a lumbar puncture is required to evaluate the cerebrospinal fluid (CSF) for erythrocytes or xanthochromia. Xanthochromia describes a yellow discoloration of the CSF from breakdown of erythrocytes, which may not develop for at least 6 hours after the initial event.

Magnetic resonance angiography (MRA) is premature before SAH is excluded. Once SAH has been ruled out, MRA may be needed to exclude other arterial causes, such as cervicocephalic arterial dissection. Internal carotid artery dissection can cause pupillary abnormalities, but these are typically from a Horner syndrome, with a smaller pupillary diameter in the affected eye.

Similarly, magnetic resonance venography (MRV) of the brain should not be performed until SAH is excluded. MRV is used to diagnose deep venous thrombosis and cerebral venous sinus thrombosis. Although the latter disorder sometimes presents with thunderclap headache, it is unlikely to cause a dilated unreactive left pupil.

The usefulness of MRI for diagnosing SAH remains under investigation. MRI may ultimately be required if the CSF is normal to rule out other disorders.

KEY POINT

- When the suspicion of a subarachnoid hemorrhage is high and the noncontrast CT scan of the head is normal, a lumbar puncture is required to evaluate the cerebrospinal fluid for erythrocytes or xanthochromia.

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Item 13 Answer: C

Educational Objective: Treat primary progressive aphasia.

This patient should have speech and language therapy. His history is concerning for the initial stages of primary progressive aphasia, which is characterized by the progressive loss of language function with relative sparing of other cognitive domains early in the course of the disease. Primary progressive aphasia is most commonly associated with frontotemporal dementia but also may be a manifestation of Alzheimer disease. Different clinical subtypes of primary progressive aphasia exist that are based on the pattern of language impairment, but each progresses insidiously and eventually results in significant disturbance of communication. The disorder results in significant disability but can be very difficult to diagnose early in its course. Occupational therapy for speech and language can teach the patient and family compensatory strategies to improve communication. This treatment is most beneficial early in the disease when motivation, insight, and learning capabilities are greatest.

Determination of the patient's apolipoprotein E (*APOE ε4*) status could help define his risk for developing Alzheimer disease but would not confirm if he has this disorder. Additionally, the information obtained by assessing his genotype would not be informative if the underlying cause is frontotemporal dementia.

Observation with reevaluation in 3 to 6 months is not the most appropriate next step in management because it would delay intervention that could diminish early symptoms.

Donepezil, a cholinesterase inhibitor, is not FDA approved for the treatment of primary progressive aphasia or frontotemporal dementia. For primary progressive aphasia that is due to underlying Alzheimer disease, standard medications approved by the FDA for Alzheimer disease may be appropriate for symptomatic benefit. However, the first step in management should be occupational therapy for speech and language, especially before a diagnosis of Alzheimer disease is established.

KEY POINT

- In primary progressive aphasia, occupational therapy for speech and language can teach the patient and family compensatory strategies to improve communication.

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Item 14 Answer: B

Educational Objective: Treat drug-induced tardive dyskinesia.

The most appropriate next step is to discontinue the dopamine receptor antagonist metoclopramide. This patient has prominent craniofacial features of chorea and dystonia that are characteristic of tardive dyskinesia. She most likely has medication-related dyskinesia, and discontinuation of the causative dopamine blocker agent is required. Physicians prescribing chronic dopamine blocker antinausea agents should warn their patients about the risk of tardive dyskinesia, a complication that can lead to long-lasting or permanent involuntary movements. Old age and female sex increase the risk of this complication.

Typical and most atypical antipsychotic agents can cause tardive dyskinesia. The main exceptions are quetiapine and clozapine. Because atypical antipsychotic agents also increase the risk of symptoms of tardive dyskinesia becoming permanent, risperidone should be avoided in this patient unless absolutely indicated

Carbidopa-levodopa is appropriate treatment of Parkinson disease, and this patient's slow and narrow-based gait is typical of parkinsonism. However, carbidopa-levodopa can aggravate dyskinetic movements and thus should be avoided in this patient.

Tetrabenazine, a dopamine depleter, has been approved by the FDA for treatment of chorea in Huntington disease. Several studies also have shown its efficacy in reducing tardive dyskinesia, but this remains an off-label use. Because tardive dyskinesia often spontaneously resolves within several months of removal of the causative agent, the immediate use of tetrabenazine in this patient with a mood disorder is unjustified, especially in light of the drug's serious mood-related complications.

KEY POINT

- The most appropriate treatment of medication-related tardive dyskinesia is discontinuation of the causative dopamine blocker agent.

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van Harten PN, Tenback DE. Tardive dyskinesia: clinical presentation and treatment. Int Rev Neurobiol. 2011;98:187-210. [PMID: 21907088]

Item 15 Answer: C

Educational Objective: Monitor patients for adverse effects of multiple sclerosis therapies.

This patient being treated with an interferon beta preparation should have her serum aminotransferase levels measured every 3 to 6 months. Interferon injections are associated with rare autoimmune hepatitis. Therefore, monitoring of liver status by periodic measurement of serum aminotransferase levels is appropriate in patients with multiple sclerosis (MS) who take an interferon beta preparation as a disease-modifying therapy. Although the optimal frequency of monitoring has not been established, most cases of severe hepatotoxicity appear to occur early in therapy. It is also recommended that concurrent use of potentially hepatotoxic agents, such as alcohol, be avoided while taking interferon therapy. Other more common adverse effects include injection site reactions, flu-like symptoms, and depression.

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JC virus antibody screening is currently recommended as a risk mitigation strategy for patients with MS treated with natalizumab because elevated levels of JC virus antibody have been correlated with an increased risk of progressive multifocal leukoencephalopathy (PML) in patients taking this drug. However, no incidences of PML have been reported in patients (such as this one) treated with interferon beta injections. Therefore, monitoring for JC virus antibody is not indicated.

Frequent ophthalmologic examinations are recommended for patients taking fingolimod for MS because of the risk of macular edema. No specific ocular risks are associated with interferon injections.

Teriflunomide has been associated with pancreatitis, and monitoring of the serum amylase and lipase levels is indicated for patients with MS who take this medication. Interferon beta preparations have not been associated with this adverse effect.

KEY POINT

- In patients taking an interferon beta as a disease-modifying therapy for multiple sclerosis, serum aminotransferase levels should be measured every 3 to 6 months to monitor for autoimmune hepatitis.

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Item 16 Answer: B

Educational Objective: Treat with antiplatelet agents for secondary stroke prevention.

Dipyridamole should be added to this patient's medication regimen. She had a small subcortical infarction despite taking daily aspirin before the stroke. The combination of aspirin and dipyridamole has been shown to be superior to aspirin alone in reducing the risk of recurrent stroke.

The combination of aspirin and clopidogrel versus aspirin alone in patients with small subcortical infarcts (lacunes) was associated with increased mortality without the benefit of reducing the risk of recurrent stroke in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial. Similarly, in the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) trial, the combination of dual antiplatelet agents was associated with an increased risk of hemorrhagic complications that offset any potential clinical benefit. The combination of aspirin and clopidogrel thus has limited utility in the secondary prevention of stroke.

Ticlopidine is not first-line treatment for secondary stroke prevention. Although superior to aspirin in preventing a second stroke, ticlopidine is associated with the serious adverse effects of agranulocytosis and thrombotic thrombocytopenic purpura and thus is considered a second-line agent.

Warfarin should not be substituted for aspirin because no evidence of atrial fibrillation or other high-risk cardioembolic sources of stroke was detected in this patient.

KEY POINT

- The combination of aspirin and dipyridamole has been shown to be superior to aspirin alone in reducing the risk of recurrent stroke.

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Furie KL, Kasner SE, Adams RJ, et al; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Car and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011 Jan;42(1):227-76. Epub 2010 Oct 21. [PMID: 20966421]

Item 17 Answer: C

Educational Objective: Treat epilepsy in a woman taking oral contraceptives.

This patient's epilepsy, which is strongly suggested by her MRI and electroencephalographic findings, should be treated with an antiepileptic drug (AED). Of the AEDs listed, levetiracetam is most appropriate for a woman who takes oral contraceptive pills for polycystic ovary syndrome (PCOS) and also relies on them for contraception because it has no significant interactions with synthetic hormones. Most AEDs, particularly older agents, induce hepatic enzymes that alter the metabolism of hormonal contraceptives. This alteration may lead to unpredictable levels of synthetic estrogens and progestin; additionally, when the contraceptives are used to prevent pregnancy, increased failure can occur in women taking AEDs.

Carbamazepine and oxcarbazepine induce cytochrome CYP3A4 and thus affect the metabolism of synthetic estrogens and progestins, which makes many forms of hormonal contraception ineffective. Neither drug is an appropriate treatment for this patient. An intrauterine device (IUD) is the preferred method of contraception for women taking enzyme-inducing AEDs, but an IUD would not address this patient's PCOS symptoms.

Lamotrigine has unique interactions with hormonal contraceptives. Synthetic estrogens induce the clearance of lamotrigine by as much as 50%, which means that higher dosages of lamotrigine have to be administered to patients taking an oral contraceptive and that AED levels will increase during the placebo week of contraceptive therapy. If needed, lamotrigine can be administered with extended-cycle oral contraceptives, but an IUD is the preferred method of contraception for patients taking lamotrigine. Lamotrigine also decreases levels of synthetic progestins by 20%, although the clinical significance of this decrease is unknown.

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Topiramate also increases clearance of synthetic estrogens. Although the clinical significance of this effect with lower doses of topiramate is debated, the World Health Organization advises against combining oral contraceptives with any dose of topiramate and recommends an IUD for contraception in patients taking this drug. Furthermore, topiramate is considered a class D drug for pregnancy because of the increased risk of facial clefting in exposed children, Therefore, it should not be used as a first-line agent in women of childbearing age.

KEY POINT

- Levetiracetam has no major drug-to-drug interactions with hormonal contraceptives and thus is appropriate to use in women with epilepsy who take oral contraceptives.

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Gaffield ME, Culwell KR, Lee CR. The use of hormonal contraception among women taking anticonvulsant therapy. Contraception. 2011 Jan;83(1):16-29. [PMID: 21134499]

Item 18 Answer: D

Educational Objective: Treat stroke with admission to the stroke unit.

This patient has had an acute ischemic stroke and should be admitted to the inpatient stroke unit. Several studies have shown that admission of patients with stroke to an organized inpatient stroke unit compared with a general medical ward is associated with a reduction in mortality at 1 year, with benefits persisting up to several years after stroke. Stroke units are beneficial because of the multidisciplinary nature of care, with an emphasis on specialized nursing, early mobilization, removal of urinary bladder catheters, and adherence to stroke-specific protocols. An important component of the success of stroke units is early referral for rehabilitation services to promote stroke recovery.

Adding clopidogrel to this patient's medication regimen is inappropriate management because the combination of aspirin and clopidogrel has not been shown to be effective and may increase the risk of hemorrhage over the next 3 months. The combination of aspirin and clopidogrel recently was found to reduce the risk of recurrent stroke compared with aspirin alone when administered within 24 hours of transient ischemic attack or minor stroke (National Institutes of Health [NIH] Stroke Scale score less than 5). Because this patient is beyond the 24-hour mark and scored 8 on the NIH Stroke Scale, no evidence supports giving her combination therapy.

This patient's blood pressure is within the acceptable range for someone who has had an acute ischemic stroke. Immediate blood pressure lowering with labetalol or other antihypertensive agents in patients who do not receive intravenous thrombolysis is only recommended if the blood pressure is greater than 220/120 mm Hg or if a high risk or evidence of other end-organ damage exists; neither situation applies.

This patient is well beyond the acceptable timeframe for thrombolysis (3 hours).

KEY POINT

- In patients with newly diagnosed stroke, admission to an organized inpatient stroke unit compared with a general medical ward is associated with a reduction in mortality at 1 year, with benefits persisting up to several years after stroke.

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Item 19 Answer: D

Educational Objective: Treat generalized epilepsy.

This patient should be treated with a broad-spectrum antiepileptic drug (AED), such as topiramate. Given his history of recurrent unprovoked seizures, he clearly has an epilepsy syndrome, but the seizure features and results of ancillary testing do not definitively identify what kind of epilepsy syndrome. When it is unclear if a patient has focal or generalized epilepsy, treatment should be a broad-spectrum AED that can be used to treat both generalized and partial epilepsy syndromes. Topiramate is a broad-spectrum agent appropriate for both focal and generalized epilepsy; other appropriate drugs are lamotrigine, levetiracetam, valproic acid, and zonisamide. Patients starting topiramate should be counseled about the risk of developing kidney stones and the need to stay hydrated. Topiramate may offer additional advantages to patients with comorbid headaches. It also is associated with weight loss and thus may be of added benefit in patients who are overweight. However, the drug may have cognitive adverse effects, such as word-finding difficulty, in some patients. The risk of rash and Stevens-Johnson syndrome should be discussed with all patients starting an AED.

Carbamazepine, gabapentin, and phenytoin are all narrow-spectrum AEDs used to treat partial-onset epilepsies. They have the potential to exacerbate generalized epilepsy and may provoke absence status epilepticus. They should be used when the seizure characteristics or MRI and electroencephalogram clearly support the diagnosis of a partial onset seizure. Typical features suggestive of partial onset include specific auras (déjà vu or a rising epigastric sensation) and unilateral clonic shaking before onset.

KEY POINT

- Topiramate is a broad-spectrum antiepileptic drug that is appropriate for treating both focal and generalized epilepsy, especially when the specific epilepsy syndrome is unknown.

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Item 20 Answer: B

Educational Objective: Diagnose normal pressure hydrocephalus.

Large-volume lumbar puncture is indicated in this patient with likely normal pressure hydrocephalus (NPH). NPH is the most likely diagnosis in the setting of the triad of gait abnormalities, cognitive impairment, and urinary disturbance, especially when neuroimaging studies show enlarged ventricles out of proportion to cortical atrophy. NPH is a potentially reversible cause of cognitive and motor decline. A large-volume lumbar puncture with measurement of intracranial pressure and removal of 30 to 50 mL of cerebrospinal fluid (CSF) should be performed before consideration of placement of a ventriculoperitoneal shunt. Cognitive, balance, and gait examinations before and after the lumbar puncture can be useful to evaluate for potential response to shunting. If a positive response to the initial lumbar puncture is not seen and the clinical suspicion remains high, serial lumbar punctures or continuous lumbar drainage can be considered.

Periventricular white matter changes can be seen on the brain MRI and may have an identical appearance to what is seen in small-vessel vascular disease. However, without additional clinical or neuroradiologic evidence of a previous infarction, extensive evaluation with neurovascular imaging to assess for a cause of these radiologic changes on brain MRI is not warranted. Periventricular hyperintensities are a frequent finding in normal pressure hydrocephalus and are thought to be related to transependymal resorption of CSF.

The cholinesterase inhibitor donepezil is sometimes effective in improving cognitive symptoms and function in patients with Alzheimer disease but has no benefit for the gait and cognitive disturbances typical of normal pressure hydrocephalus.

Although this patient has evidence of lower-body parkinsonism, he lacks other findings that suggest the presence of idiopathic Parkinson disease, such as a resting tremor, asymmetric onset of motor symptoms, and typical nonmotor symptoms. Therefore, levodopa is not likely to result in any symptomatic benefit.

KEY POINT

- Large-volume lumbar puncture should be performed before placement of a ventriculoperitoneal shunt in patients with normal pressure hydrocephalus.

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Williams MA, Relkin NR. Diagnosis and management of idiopathic normal-pressure hydrocephalus. Neurol Clin Pract. 2013 Oct;3(5):375-85. [PMID: 24175154]

Item 21 Answer: A

Educational Objective: Diagnose carotid artery dissection.

The patient most likely has had a carotid artery dissection. Despite his migraine history, the report of a different type of headache should raise suspicion of a secondary headache. Cervicocephalic dissection is an uncommon but important cause of stroke, especially in persons younger than 50 years. The presence of ipsilateral neck pain and ischemic complications, such as transient monocular visual loss and Horner syndrome (miosis, ptosis, and anhidrosis), is characteristic of carotid artery dissection and may not be associated with preceding trauma. The cause of an associated stroke is primarily thrombus formation at the site of dissection with subsequent artery-to-artery embolism. The imaging modality of choice is an MRI of the soft tissues in the neck, which will demonstrate a crescent-shaped hematoma within the internal carotid artery wall on T1-weighted images. Aspirin is considered the treatment of choice to prevent ongoing ischemic complications or stroke.

Cluster headache is a primary headache disorder classified as a trigeminal autonomic cephalalgia. This type of headache presents with unilateral head pain, which is typically periorbital or temporal ("trigeminal") but sometimes may affect the face or neck. Cranial autonomic features, such as ptosis, miosis, tearing, and nasal congestion, are characteristic. Cluster headaches appear in a repetitive fashion, one to eight times daily, and are brief, with durations between 15 minutes and 3 hours. Related trigeminal autonomic cephalgias, such as chronic paroxysmal hemicrania or short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing (SUNCT syndrome), occur with greater frequency and are of shorter duration, lasting minutes and seconds respectively. In this patient, the headache developed abruptly and has lasted an entire day, with no prior pattern indicative of these disorders.

The patient has a history of migraine, but his description of a "different" headache should raise concerns for secondary explanations. The duration of the attack is not outside the acceptable range for migraine (4 to 72 hours), and migraine can present with either unilateral or bilateral discomfort. Visual aura is described by 25% to 35% of those with established migraine, but monocular visual loss is much more uncommon than binocular hemifield impairment. Ptosis and miosis resulting from migraine are quite uncommon. Red flags in this patient's case include the "different" nature of the headache, the new symptoms of neck pain and monocular visual dysfunction, the abrupt onset of pain during physical exertion, and (most importantly) the abnormal physical examination findings. This combination renders migraine unlikely.

Vertebral artery dissection can present with acute head or neck pain associated with physical exertion or trauma but also can occur spontaneously. The most common symptom is headache, but neurologic symptoms or deficits also occur. As many as 25% of ischemic strokes in younger patients result from either carotid or vertebral artery dissection. Because the vertebrobasilar supply of the occipital cortex or cerebellum may be affected, symptoms of loss of vision or balance are common. Although ptosis and miosis may arise from infarction of the lateral medulla (Wallenberg syndrome) in vertebral dissection, they are always accompanied by other findings, such as vertigo, dysarthria, dysphagia, ataxia, and

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CONT.

loss of pain and temperature sensation ipsilaterally in the face and contralaterally in the body.

KEY POINT

- Carotid artery dissection should be suspected in a patient with acute headache and neck pain associated with Horner syndrome.

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Kennedy F, Lanfranconi S, Hicks C, et al; CADISS Investigators. Antiplatelets vs anticoagulation for dissection: CADISS nonrandomized arm and meta-analysis. Neurology. 2012 Aug 14;79(7):686-9. [PMID: 22855862]

Item 22 Answer: C

Educational Objective: Diagnose oxcarbazepine-associated hyponatremia.

Oxcarbazepine is the drug most likely to be responsible for this patient's symptoms and abnormal laboratory findings, and its dosage should be reduced. The drug is associated with hyponatremia in 20% to 30% of the patients taking this medication. In most patients, symptoms associated with hyponatremia are generally mild and not clinically significant. However, severe hyponatremia occurs in 8% to 12% of these patients. Higher doses of oxcarbazepine and polytherapy with other drugs increase the risk of hyponatremia. Although a direct effect on the kidneys has been proposed, the exact mechanism of oxcarbazepine-induced hyponatremia is not well understood. Decreasing the dosage or discontinuing oxcarbazepine, if safe to do so, can help correct hyponatremia. Either of these steps should be taken in conjunction with standard evaluation and management of hyponatremia, including free water restriction. Hyponatremia also can occur with carbamazepine but is much more common and severe with oxcarbazepine use.

This patient's dizziness, end-gaze nystagmus, and ataxia also are likely adverse effects of oxcarbazepine use, although they could be related to the hyponatremia itself. These symptoms and findings can be seen with all antiepileptic drugs (AEDs), particularly in polytherapy, but are most common with AEDs that act on sodium channels, including oxcarbazepine, carbamazepine, lamotrigine, and phenytoin.

Clonazepam, levetiracetam, and topiramate are not associated with hyponatremia. Clonazepam can cause sedation, tolerance, and dependence. The most common adverse effect of levetiracetam is irritability and other adverse effects on mood. Topiramate can cause a mild, usually subclinical acidosis and a low serum bicarbonate level but does not affect the serum sodium level. It is also associated with kidney stones, weight loss, and acute angle-closure glaucoma.

KEY POINT

- Oxcarbazepine is associated with hyponatremia in 20% to 30% of the patients who take it; although symptoms are generally mild and not clinically significant, severe hyponatremia occurs in 8% to 12% of these patients.

Bibliography

Lin CH, Lu CH, Wang FJ, et al. Risk factors of oxcarbazepine-induced hyponatremia in patients with epilepsy. Clin Neuropharmacol. 2010 Nov-Dec;33(6):293-6. [PMID: 20881597]

Item 23 Answer: C

Educational Objective: Treat depression-related cognitive impairment.

The patient's symptoms are consistent with a major depressive episode, which should be treated with sertraline. More than half of patients with late-life major depression exhibit clinically significant cognitive impairment, most frequently affecting processing speed, executive function, and visuospatial ability. Her feelings of isolation and sadness, previous depressive episode, loss of interest in reading, loss of energy, poor concentration, indecisiveness, and significant weight loss are all suggestive of major depression. Depression-related cognitive impairment, historically known as pseudodementia, can be difficult to distinguish from early degenerative diseases. Cognitive testing may show objective impairment of working memory, attention, executive function, and processing speed. Psychomotor slowing, also known as psychomotor retardation, refers to reduced processing speed and motor activity, such as in speech and fine- and gross-motor skills. Psychomotor slowing is a common feature of severe depression. First-line treatment of major depression includes pharmacotherapy, with or without psychotherapy. Each patient should be clinically treated and then monitored for effectiveness of therapy, continued need for pharmacotherapy, and response of cognitive symptoms.

Carbidopa-levodopa is an effective medication for symptomatic treatment of Parkinson disease (PD). This patient exhibits psychomotor slowing but lacks the decremental response (decreased speed and amplitude) on repetitive movements typical of PD and also other defining features of PD. This medication is not effective in treating major depression.

Donepezil is a cholinesterase inhibitor that can be effective in improving cognitive symptoms and function in patients with Alzheimer disease. This patient's history and results of cognitive testing are not consistent with a diagnosis of dementia. Although depression can represent a prodrome to PD, Alzheimer disease, and other neurodegenerative conditions and often accompanies these conditions, cholinesterase inhibitors are not effective in treating major depression.

Depression is often unrecognized and undertreated in the elderly and is not a consequence of normal aging. Late-life depression has been associated with an increased risk of dementia and should be treated aggressively. Therefore, clinical observation is insufficient as management.

KEY POINT

- First-line treatment of major depression in patients with cognitive impairment is pharmacotherapy, with or without psychotherapy.

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Item 24 Answer: C

Educational Objective: Treat migraine with typical aura.

The patient should discontinue taking the combined oral contraceptive. She has a history of migraine with typical aura. Aura is considered typical if it involves any combination of visual, hemisensory, or language dysfunction, with sensory auras most typically affecting the face and upper extremities. Each neurologic feature of a typical aura typically lasts between 5 and 60 minutes before completely resolving and can occur before, during, or independent of a headache. Migraine with typical or other aura is a strong contributor to stroke risk in women. Data suggest that migraine with aura represents the second greatest risk factor for stroke in women (after hypertension), surpassing even diabetes mellitus. Estrogen-containing contraceptives, which further increase stroke risk, should be avoided by women with this diagnosis. Progesterone-only oral contraceptives, injections, implants, and intrauterine devices do not appear to increase the risk of stroke in these patients and are preferred means of contraception in this population.

Findings from physical examination and neuroimaging studies showed no evidence of a stroke in this patient. Therefore, aspirin therapy is unnecessary.

Topiramate is approved for use as migraine prophylaxis. Because this patient typically has a migraine only at onset of menses that is successfully treated with rizatriptan, she has no need for migraine preventive therapies.

Although basilar migraine and hemiplegic migraine are contraindications for triptan therapy, this patient has no symptoms indicating the presence of either subtype. Discontinuation of rizatriptan is thus unnecessary.

KEY POINT

- Because women with migraine with aura have an increased risk of stroke, estrogen-containing oral contraceptives, which further increase stroke risk, should be avoided.

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MacGregor EA. Contraception and headache. Headache. 2013 Feb;53(2):247-76. [PMID: 23432442]

Item 25 Answer: D

Educational Objective: Treat essential tremor.

This patient should begin a trial of primidone for his worsening essential tremor. His long history of a bilateral action tremor, family history of tremor, and ethanol responsiveness are consistent with familial essential tremor. Although the severity of this type of tremor remains stable over a lifetime in most patients, a few experience tremor progression that can become disabling. Primidone and propranolol are FDA-approved first-line treatments of essential tremor. Because propranolol has already been administered without lasting relief, a trial of primidone is warranted.

Botulinum toxin injections can be effective in patients with essential tremor of the voice and head, but its benefit is more limited in the limbs because of the adverse effect of weakness. In this patient, primidone should be initiated first.

In patients with severe medication-refractory essential tremor, deep brain stimulation (DBS) of the thalamus is most likely to maximize tremor control. However, this option should be reserved for those who have not responded to medical therapy or have a marked disabling tremor. In this subset of patients, DBS has the potential to provide significant tremor control beyond that offered by the best medical therapy. DBS is premature for this patient who has not yet had a trial of primidone.

This patient does not have features of Parkinson disease, such as a tremor at rest. Therefore, levodopa therapy is not indicated.

Topiramate is a second-line treatment of essential tremor but is contraindicated in a patient with a history of kidney stones and glaucoma.

KEY POINT

- In patients with essential tremor, propranolol and primidone are FDA approved first-line therapies.

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Item 26 Answer: C

Educational Objective: Treat compressive spinal cord lesions due to plasmacytoma.

This patient should undergo external beam radiation therapy for his epidural plasmacytoma in addition to continued high-dose glucocorticoid treatment. Skeletal lesions that occur as a result of plasmacytoma or myeloma are exquisitely radiosensitive; therefore, radiation therapy is the most appropriate specific and definitive treatment for this tumor type. Patients with compressive myelopathy due to very radiosensitive tumors who have a stable spine and minimal neurologic deficits may respond to this therapy, with recovery or improvement of their neurologic deficits.

Although radiation therapy is the preferred acute treatment for compressive myelopathy in patients with plasmacytomas because of their high level of radiosensitivity and rapid response to treatment, chemotherapy may be a reasonable second-line therapy for selected patients with compressive myelopathy due to myeloma.

High-dose intravenous glucocorticoids administered within the first 8 hours of traumatic spinal cord injury can be useful in the short term to reduce the effect of edema

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within the spinal cord caused by a compressive injury. However, these drugs will not treat the underlying neoplastic disease and thus are inappropriate as monotherapy in this patient.

Immediate surgical decompression is indicated with evidence of spinal instability or with severe neurologic deficits that require removal of the bulk of the tumor to prevent continued injury to the spinal cord. This intervention is usually followed by definitive radiation therapy for treatment of the local tumor.

KEY POINT

- Spinal cord compression by skeletal lesions resulting from plasmacytoma should be treated initially with radiation therapy in patients with no spinal instability and only minor neurologic deficits.

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Item 27 Answer: B

Educational Objective: Evaluate traumatic brain injury with CT of the head.

This patient should have CT of the head without contrast. The American College of Emergency Physicians and the Centers for Disease Control and Prevention have published guidelines for management of mild traumatic brain injury (TBI). Their recommendation is to consider a noncontrast head CT in patients with TBI who have had no loss of consciousness or posttraumatic amnesia but have a focal neurologic deficit, vomiting, severe headache, physical signs of a basilar skull fracture, Glasgow Coma Scale score less than 15, coagulopathy, or a dangerous mechanism of injury, such as ejection from a motor vehicle or a falling from a height of more than 3 feet. This patient sustained a TBI with a dangerous mechanism of injury several hours ago and has developed symptoms (worsening headache and vomiting) mentioned in the guideline. Therefore, noncontrast CT of the head is indicated. A finding of parenchymal, subdural, or epidural hemorrhage requires emergent neurosurgical evaluation and consideration of possible hematoma evacuation.

In the setting of acute head trauma, head CT without contrast is preferable to head CT with contrast and brain MRI because of its lower cost and wider availability. Contrast administration aids in the assessment of certain malignant and vascular lesions of the brain but adds nothing to the evaluation of acute head trauma. Head CT without contrast is also very sensitive for detecting skull fracture or acute hemorrhage, and a CT scan generally requires shorter examination times than a brain MRI requires, both important factors in the evaluation of a patient with acute head injury and symptoms of potential deterioration.

Hospital observation without first ruling out intracranial hemorrhage is inappropriate management of TBI. Untreated intracranial hemorrhage can lead to an accumulation of blood and edema within the skull, which can cause compression or destruction of brain tissue, increased intracranial pressure, and even herniation and death.

KEY POINT

- Head CT without contrast is the appropriate imaging procedure for selected patients with acute traumatic brain injury.

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Item 28 Answer: D

Educational Objective: Recognize adverse effects of cholinesterase inhibitors in a patient with Alzheimer disease.

This patient should stop taking rivastigmine. Given the results of her cognitive testing, she meets criteria for Alzheimer disease of mild severity. She began taking oral rivastigmine, a cholinesterase inhibitor, 12 weeks ago. All of the available cholinesterase inhibitors are approved for mild to moderate Alzheimer disease, except donepezil, which is also approved for the severe stage. Studies of cholinesterase inhibitors and memantine show consistent improvement on measures of cognition and global assessment of dementia, but the effect size is modest and evidence that they improve long-term outcome is lacking. In practice, individual response is variable. There is insufficient evidence to support one cholinesterase inhibitor over another, and choice of treatment in a patient should be based on cost, tolerability, and ease of using the specific formulation. There is also insufficient evidence of the optimal duration of treatment or when therapy should be discontinued. Medication decisions should be made on an individual basis. Cholinesterase inhibitors should be used with caution in patients with cardiac conduction abnormalities, active peptic ulcer disease (because of the risk of bleeding), and seizures. Gastrointestinal adverse effects are common to all cholinesterase inhibitors and include loss of appetite, weight loss, nausea, vomiting, and diarrhea. Insomnia also can occur. This patient has had a significant amount of weight loss, loss of appetite, and insomnia since starting rivastigmine. The most appropriate next step in management would be to discontinue the medication. A trial of a different type of cholinesterase inhibitor could be considered, but only after symptoms subside.

Donepezil, another cholinesterase inhibitor, might be considered as an alternative therapy for this patient. However, no indication supports prescribing multiple cholinesterase inhibitors concomitantly, and rivastigmine should be discontinued as the first step.

Memantine is a noncompetitive *N*-Methyl-D-aspartate receptor antagonist approved by the FDA for the treatment

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of moderate to severe Alzheimer disease. Although this drug could be added in the future, this patient's present symptoms should be addressed first.

Mirtazapine is a nonselective α_2-adrenoceptor antagonist effective in the treatment of depression. Stimulation of appetite, weight gain, and somnolence are frequently associated effects, and thus this medication may be the preferred treatment for depressed patients with Alzheimer disease who have insomnia or loss of appetite. This patient has apathy and loss of interest, which are common symptoms in Alzheimer disease, but lacks additional symptoms to suggest depression.

KEY POINT

- Gastrointestinal adverse effects can occur with cholinesterase inhibitor therapy.

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Item 29 Answer: A

Educational Objective: Treat blepharospasm with botulinum toxin in a patient with focal dystonia.

Botulinum toxin injection is the most effective treatment of focal forms of dystonia, including the blepharospasm experienced by this patient. Blepharospasm is characterized by involuntary and sustained contraction of the orbicularis oculi muscle. Similar to other forms of dystonia, this condition is a result of a dysregulation within a network that involves the basal ganglia, sensorimotor centers, and the cerebellum. Blepharospasm should be distinguished from hemifacial spasm, a form of focal myoclonus resulting from irritation of the facial nerve (cranial nerve VII). Hemifacial spasm is unilateral, involves other facial nerve–innervated muscles, is associated with blinking tics that are suppressible, and usually does not lead to sustained eyelid closure.

Clonidine is appropriate to treat tics but not blepharospasm. Tics are characterized by brief and typically suppressible movements that are distinct from the sustained and forceful contractions seen in dystonia.

Deep brain stimulation for dystonia should be considered only in the treatment of medication-refractory or severe generalized dystonia. Its utility in focal and segmental dystonias is less clear, and treatment with botulinum toxin, with or without other medications, should be attempted first.

Risperidone, an atypical antipsychotic agent, is not effective against dystonic movements and may aggravate them.

KEY POINT

- Botulinum toxin injection is the most effective treatment of focal forms of dystonia, including blepharospasm.

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Tarsy D, Simon DK. Dystonia. New Engl J Med. 2006 Aug 24;355(8):818-29. [PMID: 16928997]

Item 30 Answer: A

Educational Objective: Diagnose small-fiber neuropathy associated with impaired glucose tolerance.

This patient should have a glucose tolerance test. He most likely has small-fiber neuropathy, a condition sometimes associated with impaired glucose tolerance. Although many classic neuropathies associated with diabetes mellitus occur later in the course of the disease, impaired glucose tolerance is being increasingly recognized as an underlying cause of distal peripheral neuropathies, especially those involving the small fibers, which are unmyelinated peripheral nerves that carry sharp pain, temperature, and autonomic nerve fibers. Pure small-fiber neuropathy can present with distal upper and lower extremity pain and paresthesia without sensory or motor deficit. Autonomic deficits also may be present. Clinical examination findings are typically normal, including normal results on sensory, motor, and reflex testing with the possible exception of a mild distal sensory deficit. Results of electromyography (EMG), which assesses the large nerve fibers, can be normal. The presence of glucose intolerance should be confirmed by a glucose tolerance test.

Given the normal results of the clinical examination and EMG, an MRI of the lumbosacral spine to assess for myelopathy and radiculopathy is not warranted.

Although vitamin D deficiency can cause myopathy and central nervous system–related symptoms, it usually does not cause small-fiber neuropathy. Although multiple other conditions may be associated with small-fiber neuropathy, impaired glucose metabolism is one of the most common causes, and evaluating for this possibility should be the initial investigation. Further evaluation of small-fiber neuropathy should consider the possibility of vitamin B_{12} deficiency, HIV infection, amyloidosis, Sjögren syndrome, paraproteinemia, celiac disease, and sarcoidosis.

Sural nerve biopsy has low sensitivity in detecting small-fiber disorders. The diagnosis is instead made on the basis of autonomic testing, including quantitative sudomotor axon reflex testing and skin biopsy, to assess intraepidermal nerve fiber density.

KEY POINT

- Impaired glucose tolerance is an underlying cause of distal peripheral neuropathies, especially those involving the small fibers that carry sharp pain, temperature, and autonomic nerve fibers

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Item 31 Answer: D

Educational Objective: Diagnose nonepileptic seizures.

This patient should have continuous video electroencephalographic (EEG) monitoring for further evaluation of the seizures, which have become increasingly frequent and have not

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responded to two antiepileptic drugs (AEDs). Video EEG monitoring, performed in an epilepsy-monitoring unit, enables correlation of patient behavior with seizure activity on an electroencephalogram. This can lead to better characterization of seizure activity, such as the identification of specific localizing features, and allow assessment of potential non-seizure-related behaviors suggestive of nonepileptic seizures. This patient has several risk factors for psychogenic nonepileptic events. The long duration of the episodes is more typical of nonepileptic than epileptic seizures, as is the fact that his eyes remain closed during the event. The presence of incontinence does not exclude a nonepileptic episode. Although his previous closed head injury puts him at risk for epileptic seizures, it does not exclude the possibility of nonepileptic events. In fact, combat veterans, particularly those with posttraumatic stress disorder (PTSD), are at high risk for nonepileptic seizures. This diagnosis can be overlooked if a history of head trauma is present. Because epileptic and nonepileptic seizures can coexist in the same patient, a thorough description and characterization of the seizures are essential and best achieved by admission to an epilepsy monitoring unit.

Ambulatory EEG monitoring allows more prolonged evaluation of brain activity outside a clinical setting and may be helpful in identifying seizures or interictal epileptiform activity that may not have been seen on a routine interictal EEG study. However, inpatient video EEG monitoring allows analysis of both clinical and EEG characteristics of seizures to assist in diagnosis and management. The latter study is required for a diagnosis of nonepileptic seizures and presurgical evaluations in patients who have not responded to two or more AEDs. The inpatient setting also allows for withdrawal of AEDs in a monitored environment.

A definitive diagnosis is necessary before adding more AEDs, such as carbamazepine or levetiracetam. Furthermore, levetiracetam should be avoided in this patient with PTSD because it can exacerbate anxiety and irritability.

KEY POINT

- Video electroencephalography, performed in an epilepsy-monitoring unit, enables correlation of the patient's behavior with seizure activity on an electroencephalogram, which can lead to better characterization of seizure activity or allow assessment of potential non-seizure-related behaviors suggestive of nonepileptic seizures.

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Salinsky M, Spencer D, Boudreau E, Ferguson F. Psychogenic nonepileptic seizures in US veterans. Neurology. 2011 Sep 6;77(10):945-50.[PMID: 21893668]

Item 32 Answer: C

Educational Objective: Treat urinary dysfunction in multiple sclerosis.

This patient should be treated with an anticholinergic medication, such as oxybutynin, for bladder spasticity due to myelopathy from multiple sclerosis (MS). Several different patterns of bladder dysfunction are associated with MS, with urge incontinence due to uninhibited detrusor function caused by denervation at the level of the spinal cord being the most common. This form of bladder dysfunction responds well to anticholinergic medications, which reduce the intensity and frequency of bladder spasms and reduce urgency, frequency, and incontinence. Other forms of dysfunction include bladder inactivity (leading to overflow incontinence), the loss of the sensation of bladder fullness, and other sensory deficits that also may impair bladder emptying. These conditions are more difficult to treat because anticholinergic agents can impair urinary retention and lead to predisposition to urinary tract infection. Patients with mixed bladder symptoms may require further diagnostic testing to better delineate the cause of incontinence.

Finasteride is a 5α-reductase inhibitor used to treat benign prostatic hyperplasia (BPH) and would have no effect on bladder spasticity. This patient is unlikely to have BPH given the normal findings on digital rectal examination and the absence of urinary hesitancy.

Intermittent urinary catheterization also has no role in isolated bladder spasticity. This patient had no symptoms or signs of urinary retention, which would be relieved by catheterization. It may, however, have a role in selected patients with complex bladder dysfunction due to MS who are not appropriate candidates for or do not respond to medical therapy.

Although patients with bladder dysfunction are at increased risk for urinary tract infection, assessing the type of bladder dysfunction present and providing appropriate treatment are indicated. Prophylactic antibiotics would not be indicated as management of this patient's urinary incontinence in the absence of evidence of infection or recurrent infections due to bladder dysfunction refractory to therapy.

KEY POINT

- In patients with multiple sclerosis, anticholinergic agents reduce the intensity and frequency of bladder spasms and thus may reduce symptoms of urgency, frequency, and incontinence.

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Item 33 Answer: D

Educational Objective: Diagnose cognitive impairment due to cerebrovascular disease.

This patient most likely has cognitive impairment due to cerebrovascular disease, otherwise known as vascular neurocognitive disorder (VND). VND comprises a group of pathophysiologically distinct processes and thus has heterogeneous clinical presentations. Because it encompasses a continuum of cognitive disorders, from mild cognitive

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impairment to dementia, that result from cerebrovascular disease, validated diagnostic criteria do not exist. Widely accepted clinical criteria require evidence of a cognitive disorder plus a previous clinical stroke or neuroimaging evidence that confirms the existence of cerebrovascular disease. A relationship between the cognitive decline and cerebrovascular disease should exist, as it does with this patient. The description of the "ministrokes" experienced by this patient is consistent with a history of previous lacunar strokes. Supportive features include gait disturbance, pseudobulbar affect (a neurologic disorder characterized by involuntary outbursts of laughing and/or crying that are out of proportion to the emotions being experienced), incontinence, depression, and focal neurologic signs. Cognitive impairment generally is characterized by executive dysfunction, slowed mental processing, and impaired attention, as is exhibited by this patient.

Coexisting Alzheimer disease is found at autopsy in a large number of patients with VND. However, the lack of prominent memory impairment, presence of focal neurologic symptoms and signs, and stepwise decline seen in this patient are more consistent with a clinical diagnosis of VND than Alzheimer disease.

Although this patient has some overlapping features typically associated with normal pressure hydrocephalus, such as urinary incontinence, magnetic gait, and cognitive decline, he lacks the neuroimaging findings of enlarged ventricles or hydrocephalus typically seen in this disorder.

This patient has some findings consistent with Parkinson disease, such as shuffling gait and executive dysfunction, but lacks other typical examination findings, such as asymmetric parkinsonism, resting tremor, stooped posture, and decline in fine motor movements. Underlying Parkinson disease is thus unlikely to be the cause of his symptoms.

KEY POINT

- Widely accepted clinical criteria for diagnosing vascular neurocognitive disorder require evidence of a cognitive disorder plus a previous clinical stroke or neuroimaging evidence that confirms the existence of cerebrovascular disease.

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Item 34 Answer: B

Educational Objective: Treat an older patient with seizures.

This patient should be treated with the antiepileptic drug (AED) lamotrigine. He has had several episodes consistent with complex partial seizures and is at high risk for recurrent seizures and associated morbidity, given his history of a previous stroke and age greater than 65 years. Older patients generally have difficulty tolerating the many adverse effects of AEDs. Lamotrigine, levetiracetam, and gabapentin are generally better tolerated in this population and thus are good first-line options. Because these medications have fewer adverse effects, older patients are more likely to continue taking them, which increases the likelihood of seizure freedom.

Carbamazepine, oxcarbazepine, and phenytoin are less well tolerated in older patients and have lower retention and seizure-freedom rates in this population. These drugs are thus inappropriate first-line treatments for this patient. Additionally, these drugs are enzyme-inducers and have drug-drug interactions with many other medications that are taken by older patients.

KEY POINT

- In older patients with seizures who are treated with an antiepileptic drug, lamotrigine, levetiracetam, and gabapentin are generally better tolerated and thus good first-line options.

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Arif H, Buchsbaum R, Pierro J, et al. Comparative effectiveness of 10 antiepileptic drugs in older adults with epilepsy. Arch Neurol. 2010 Apr;67(4):408-15. [PMID: 20385905]

Item 35 Answer: C

Educational Objective: Prophylactically treat asymptomatic extracranial carotid artery stenosis.

This patient should be restarted on statin therapy for primary prevention of stroke and myocardial infarction. The patient has type 2 diabetes mellitus and coronary artery disease, and patients with these disorders benefit from high-intensity statin therapy to reduce the risk of atherosclerotic cardiovascular disease, including myocardial infarction and stroke. High-intensity statins also are recommended for patients with stroke or transient ischemic attack of a presumed atherosclerotic subtype (although this patient is not symptomatic). With improvements in medical therapy, particularly statins, the risk of stroke has been declining in patients with asymptomatic internal carotid artery (ICA) stenosis. In a recent study, the use of a statin in patients with this diagnosis was associated with a stroke risk of less than 2% per year. Although this patient developed apparent statin myopathy from rosuvastatin, switching to another statin less associated with statin myopathy is appropriate.

Although carotid endarterectomy may benefit some patients with greater than 60% asymptomatic ICA stenosis, its effectiveness is highly dependent on the patient's underlying risks and those associated with the procedure itself. The benefit of carotid surgery is modest in patients without symptoms, and this patient's multiple medical comorbidities make him a relatively poor surgical candidate. Some studies have suggested that additional clinical factors increase the risk of stroke further in patients with asymptomatic carotid

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stenosis, including rapidly progressive or greater than 80% stenosis, asymptomatic infarcts on brain imaging, or abnormal results of transcranial Doppler ultrasonography. However, the role that these factors should play in clinical decisions about treatment of asymptomatic carotid stenosis has not been established. Carotid revascularization with either endarterectomy or stenting can be considered in patients at low risk for perioperative cardiovascular morbidity.

Magnetic resonance angiography (MRA) of the neck is inappropriate in this patient because an additional diagnostic test is unlikely to change the medical management of his condition. The accuracy of MRA without contrast is likely similar to that of carotid ultrasonography.

No clear evidence supports the superiority of clopidogrel over aspirin for the primary prevention of stroke in the setting of asymptomatic ICA stenosis.

KEY POINT

- Using a statin to treat patients with asymptomatic internal carotid artery stenosis is associated with a stroke risk of less than 2% per year.

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Item 36 Answer: B

Educational Objective: Treat reversible cerebral vasoconstriction syndrome.

Normalization of blood pressure is recommended for this patient with reversible cerebral vasoconstriction syndrome (RCVS). This condition most commonly presents with thunderclap headaches that recur over several days or weeks. Thunderclap attacks may occur spontaneously or be triggered by bathing, exertion, or Valsalva maneuvers. The headaches may be complicated by focal neurologic deficits with corresponding areas of stroke, parenchymal hemorrhage, or edema visible on neuroimaging studies. The cerebrospinal fluid is typically normal or near normal. Cerebral angiographic studies reveal multifocal areas of vasospasm without evidence of aneurysm. RCVS can occur without an identifiable cause or may be associated with preeclampsia or eclampsia, exposure to certain medications (sympathomimetic agents, ergots, triptans) or blood products (transfused erythrocytes, immune globulin), or catecholamine-secreting tumors. Medications or illicit drugs are associated in up to 40% of affected patients, and women with the syndrome outnumber men at a ratio of 6:1. Migraine may be a predisposing factor. Transient neurologic deficits occur in 30% of patients with RCVS, and 10% may experience persistent deficits from parenchymal damage caused by ischemic or hemorrhagic infarctions.

No clinical trial data are available on which to base therapeutic recommendations. Conservative management, supported by expert consensus, includes headache control with analgesics, careful monitoring of blood pressure to maintain normotensive goals, and serial neurologic examinations.

Primary stabbing headache is a form of benign abrupt-onset headache that may respond to indomethacin. This type of headache typically lasts seconds, not 30 minutes as with this patient. Primary stabbing headache also occurs without visual blurring, focal numbness, or other neurologic symptoms. Although indomethacin is appropriate for treating several additional primary headache syndromes, such as chronic paroxysmal hemicrania, evidence does not support its effectiveness in RCVS.

Because reversible vasoconstriction and not thrombosis is the responsible mechanism for RCVS, tissue plasminogen activator is not indicated in this patient. The use of calcium channel antagonists, such as nimodipine or verapamil, is more appropriate.

No evidence suggests that anticoagulants, such as warfarin, or antiplatelet agents, such as aspirin, affect stroke risk or outcomes in RCVS. The mechanism of cerebral infarction, when present, is likely related to cerebral artery vasospasm and not thrombosis. Given this pathophysiology and the relatively high rate of hemorrhagic infarction in RCVS, antiplatelet or antithrombotic therapy has no role in disease management.

KEY POINT

- Normalization of blood pressure is recommended in patients with reversible cerebral vasoconstriction syndrome, which commonly presents with thunderclap headaches that recur over several days or weeks.

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Item 37 Answer: B

Educational Objective: Diagnose a primary central nervous system lymphoma.

This patient should undergo surgical biopsy of the brain lesion without resection. The MRI is suggestive of primary central nervous system lymphoma (PCNSL), a non-Hodgkin lymphoma that can affect any part of the central nervous system but commonly presents as a focal supratentorial lesion; visual symptoms are common because the tumor often involves the optic radiations. Cerebrospinal fluid (CSF) analysis can be diagnostic in up to 10% of patients, and ocular involvement may be found in 10% to 20%. However, in most patients, including this one with negative results on CSF analysis and slit lamp examination, pathologic analysis of a brain biopsy specimen is required to confirm the diagnosis. Treatment most commonly involves methotrexate-based chemotherapy and possible whole-brain radiation.

Bone marrow biopsy is not indicated in this patient. PCNSL is a whole-organ disease but is not typically systemic.

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CONT.

Therefore, a bone marrow biopsy for diagnostic purposes would have low yield.

Because PCNSL tends to localize to a single organ system and may have multiple associated manifestations, such as diffuse brain and ocular involvement, resection of the presenting lesion is not helpful and can actually worsen patient outcomes.

Dexamethasone and similar glucocorticoids should be avoided if possible before brain biopsy in patients with suspected PCNSL because these agents can significantly decrease the yield of the biopsy. Furthermore, this patient does not have signs or symptoms of increased intracranial pressure that would necessitate urgent glucocorticoids.

Radiation is not indicated for PCNSL until after a tissue diagnosis is made and treatment with methotrexate-based chemotherapy has begun. Additionally, when patients with PCNSL receive radiation, it must be whole-brain radiation, not focal photon-beam radiation, which is more appropriate for gliomas and other primary brain tumors.

KEY POINT

- Pathologic analysis, usually of a brain biopsy specimen, to confirm primary central nervous system lymphoma is required before beginning treatment with methotrexate-based chemotherapy and possible whole-brain radiation.

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Ricard D, Idbaih A, Ducray F, Lahutte M, Hoang-Xuan K, Delattre JY. Primary brain tumours in adults. Lancet. 2012 May 26;379(9830):1984-96. [PMID: 22510398]

Item 38 Answer: A

Educational Objective: Treat ischemic stroke in a patient with atrial fibrillation.

Aspirin should be added to this patient's medication regimen. She has had an acute ischemic stroke and has atrial fibrillation. No other obvious causes of stroke are present, and she is beyond the treatment window for recombinant tissue plasminogen activator therapy. According to two large clinical trials, aspirin administered within 48 hours of ischemic stroke onset modestly reduces the risk of recurrent ischemic stroke within the first 2 weeks without significantly increasing the risk of intracerebral hemorrhage. Administration of aspirin no later than the end of the second day after a stroke is an accepted quality-of-care core metric in primary and comprehensive stroke centers.

Anticoagulation with warfarin or a newer anticoagulant, such as dabigatran, is required to manage this patient's long-term risk of cardioembolic stroke. Some experts will initiate warfarin within 24 hours of stroke onset in medically stable patients with a small infarction, but withholding anticoagulation for 4 days to 2 weeks is typically recommended for patients with moderate to large infarctions. Until that time, patients are managed with aspirin.

In the acute ischemic stroke setting, intravenous heparin was ineffective compared with aspirin in patients with cardioembolic stroke in a randomized clinical trial. Furthermore, this patient's infarct is large enough to be associated with a risk of hemorrhaging into the bed of the infarct within the first 2 weeks of stroke.

KEY POINT

- In patients with acute ischemic stroke who are ineligible for recombinant tissue plasminogen activator therapy, aspirin should be administered within 48 hours of the stroke to reduce the risk of recurrent ischemic stroke.

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Jauch, EC, Saver JL, Adams HP Jr, et al; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Mar;44(3):870-947. [PMID: 23370205]

Item 39 Answer: C

Educational Objective: Treat a solitary metastatic brain tumor.

This patient should undergo surgical resection of the right frontal lesion. Her clinical history and imaging findings are most consistent with a solitary brain metastasis from the breast cancer. Standard-of-care treatment of a solitary brain metastasis in a patient with a good functional status and limited extracranial disease is complete resection of the lesion (when accessible) followed by radiation therapy. This treatment offers better symptom control, longer survival time, and longer periods of independent functional status compared with other therapies, including biopsy followed by radiation.

A PET scan of the brain is unlikely to be of additional diagnostic value in this patient whose MRI clearly reveals the lesion most likely responsible for her symptoms. MRI is more sensitive and specific than other imaging techniques in detecting the presence, location, and number of metastases.

Lumbar puncture is contraindicated in this patient with signs (papilledema) and symptoms (headache, nausea and vomiting) of increased intracranial pressure. Moreover, cerebrospinal fluid analysis is rarely diagnostic of metastatic disease. If an infectious process is also suspected, which often occurs in cancer patients, its presence can be determined by biopsy at the time of surgical resection.

Whole-brain radiation is an appropriate initial therapy for patients with multiple brain metastases but not for this patient whose single metastasis can be resected.

KEY POINT

- Complete resection followed by radiation therapy is standard-of-care treatment of an accessible solitary brain metastasis in patients with good functional status and limited extracranial disease.

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Item 40 Answer: D

Educational Objective: Treat myasthenic crisis.

Treatment with plasmapheresis should be started immediately in this patient with myasthenic crisis. His several-month history of fluctuating proximal weakness with ocular and bulbar involvement is consistent with myasthenia gravis. His rapid decline most likely has been precipitated by recent exposure to ciprofloxacin. Fluoroquinolones can decrease transmission at the neuromuscular junction and exacerbate myasthenia gravis. Although Guillain-Barré syndrome (GBS) also can present with rapidly progressive respiratory failure, the slow clinical course and preserved reflexes in this patient are not consistent with GBS.

Patients with suspected myasthenic crisis (rapid respiratory failure) should be admitted to the ICU and have their respiratory parameters (vital capacity and negative inspiratory force) closely monitored. If myasthenic crisis is confirmed, treatment should be started emergently with either plasmapheresis or intravenous immune globulin (IVIG).

High-dose glucocorticoids can initially aggravate symptoms of myasthenia gravis. These agents can be started after therapy with plasmapheresis or IVIG has been initiated.

Magnesium deficiency usually presents as neuromuscular hyperexcitability, not muscular weakness. Furthermore, because magnesium administration can exacerbate myasthenia gravis by neuromuscular junction blockade, it is inappropriate for this patient. Other medications that need to be used with caution in this setting include fluoroquinolones, aminoglycosides, β-blockers, and calcium channel blockers.

Pyridostigmine can worsen respiratory secretions and should be avoided in the setting of acute respiratory failure with bulbar weakness.

KEY POINT

- Patients in myasthenic crisis should be treated emergently with either plasmapheresis or intravenous immunoglobulin.

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Item 41 Answer: E

Educational Objective: Prevent cluster headache.

The patient should be treated with verapamil for episodic cluster headache. He experiences one or two daily attacks of severe, unilateral, periorbital pain lasting 2 to 3 hours if untreated that is accompanied by at least one ipsilateral cranial autonomic feature, such as ptosis, tearing, or rhinorrhea; he also exhibits motor restlessness during headache episodes. These features meet International Headache Society criteria for cluster headache. Cycles of cluster headache can last weeks to months, with attack frequency varying from 1 event every other day to 8 per day. Cluster headache typically affects young and middle-aged adults. Male sex and tobacco use are risk factors.

Oxygen therapy and subcutaneous sumatriptan are the most effective acute cluster headache treatments. Glucocorticoids can help reduce attack frequency and are effective as a bridge therapy to longer-term prophylactic agents. Verapamil is the drug of choice for cluster headache prevention. Because relatively high doses are sometimes required, regular electrocardiographic assessment for potential prolongation of the P-R interval or heart block is recommended.

Both amitriptyline and propranolol are effective agents for prevention of migraine but not cluster headache. The duration of the headaches described by this patient is too short to meet criteria for migraine.

Indomethacin is an effective treatment for chronic paroxysmal hemicrania (CPH) but not cluster headache. CPH also is characterized by repetitive episodes of unilateral pain with ipsilateral autonomic features but occurs at least 5 times daily with a typical duration between 3 and 20 minutes.

Anticonvulsants, such as topiramate, have limited effectiveness in cluster headache prevention and should be considered only after verapamil therapy proves ineffective or is poorly tolerated.

KEY POINT

- Oxygen therapy and subcutaneous sumatriptan are the most effective acute cluster headache treatments, and verapamil is the drug of choice for cluster headache prevention.

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Item 42 Answer: B

Educational Objective: Treat cognitive dysfunction in multiple sclerosis.

This patient should be referred for counseling and cognitive therapy. Cognitive dysfunction is a common symptom in multiple sclerosis (MS), occurring in at least 50% of affected patients. The most common deficits involve short-term memory, processing speed, and executive function. This cognitive disability can have a significant effect on employment of patients with MS and can reduce their overall quality of life. Unfortunately no trials of pharmacologic therapy to reduce or prevent cognitive dysfunction in MS have as yet been successful. Formal neuropsychological testing, counseling, cognitive therapy, and accommodative strategies (such as creating checklists to overcome memory deficits) sometimes can be of benefit.

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Amantadine is an appropriate treatment of the fatigue associated with MS but has not been shown to improve cognitive function in this disorder.

Donepezil has shown benefit for mild to moderate cognitive dysfunction due to Alzheimer disease. However, a randomized placebo-controlled trial of this medication in patients with MS who also had cognitive dysfunction showed no cognitive benefit.

The use of high-dose intravenous methylprednisolone is indicated only for acute exacerbations of MS, which the patient is not experiencing. The MRI also shows no evidence of breakthrough inflammatory activity.

Increasing the patient's fluoxetine dosage will not affect her cognition. Although depression is a common symptom in MS, and severe depression can be associated with a pseudodementia-like state, the patient did not report any worsening of depression and has a normal affect.

KEY POINT

- Formal neuropsychological testing, counseling, cognitive therapy, and accommodative strategies (such as creating checklists to overcome memory deficits) sometimes can be of benefit in patients with cognitive dysfunction related to multiple sclerosis.

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Item 43 Answer: D

Educational Objective: Diagnose medication overuse headache.

This patient has developed medication overuse headache, which requires the presence of a headache-susceptible patient and excessive exposure to a causative medication. This patient has an underlying history of migraine treated with sumatriptan, and he has been exposed to hydrocodone for back pain. The use of opioid analgesics more than 10 days per month can contribute to the development of medication overuse headache. Daily analgesic exposure is not required. Patients with this condition may develop a worsening of their underlying headache disorder or a new milder, nonspecific headache.

Posttraumatic headaches have been reported to occur in as many as 70% of persons after mild traumatic brain injury (TBI). Posttraumatic headache types are classified similarly to nontraumatic headaches, with migraine and tension-type headaches being the most prevalent. Although this patient has a history of mild TBI, the timing of the TBI and the timing of the headache have no correlation. A true posttraumatic headache must develop within 7 days of the injury.

The headaches described by this patient have phenotypic features of chronic tension-type headache. However, this diagnosis requires the exclusion of secondary headache disorders, such as medication overuse headache, and thus is premature at this time.

Given the absence of papilledema, the diagnosis of idiopathic intracranial hypertension is unlikely.

KEY POINT

- Medication overuse headache requires the presence of a headache-susceptible patient and excessive exposure to a causative medication, such as an opioid analgesic.

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Item 44 Answer: B

Educational Objective: Treat a multiple sclerosis relapse.

This patient should receive intravenous methylprednisolone. Her symptoms are consistent with a new multiple sclerosis (MS) relapse, most likely localizing to a new lesion in the pons and pontocerebellar pathways on the right. The standard of care for MS relapses is a high-dose glucocorticoid, usually intravenous methylprednisolone, 1 g/d for 3 to 5 days. Although this treatment has not been shown to reduce the amount of long-term disability sustained in a relapse, it substantially hastens the rate of recovery. Because of the unclear long-term benefit and the potential for adverse effects, acute high-dose glucocorticoid therapy is usually reserved for attacks resulting in sustained impairment in functional status that interferes substantially with activities of daily living.

In addition to treatment of individual relapses, most patients with relapsing-remitting MS receive chronic maintenance therapy with immunomodulatory or immunosuppressive medications, such as the interferon beta-1a that this patient takes. These disease-modifying therapies have been shown to reduce the relapse rate, slow disability progression, and reduce the accumulation of new demyelinating lesions on MRI. Glatiramer acetate is another disease-modifying drug that has been shown to reduce the relapse rate by approximately one third compared with placebo and appears equivalent to the interferon beta preparations in head-to-head studies. Combining glatiramer acetate with an interferon beta provides no added benefit compared with what either drug achieves alone. Additionally, disease-modifying medications are not effective in hastening recovery in a patient with a functionally significant acute exacerbation of MS.

Although an increasing number of studies suggest the equivalency of oral treatment with prednisone and intravenous treatment with another glucocorticoid for MS, the reported equivalent dose of prednisone is 1250 mg/d, which is a very high dose. In the original Optic Neuritis Treatment Study, which compared treatment of optic neuritis with oral prednisone (1 mg/kg), intravenous methylprednisolone (1 g/d), or placebo, the oral prednisone group had worse outcomes

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after treatment than even the placebo group. Thus, oral prednisone in the range of 1 mg/kg may actually be detrimental in treating acute demyelination.

Relapses that are refractory to glucocorticoid treatment may respond to rescue therapy with plasmapheresis. Since this patient has not received a trial of intravenous methylprednisone, treatment with plasmapheresis is premature.

KEY POINT

- The standard of care for multiple sclerosis relapses is a high-dose glucocorticoid, usually intravenous methylprednisolone.

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Item 45 Answer: D

Educational Objective: Manage hypertension in a patient with acute ischemic stroke.

This patient should receive no pharmacologic treatment. He has an ischemic stroke in the pons, which is commonly caused by hypertensive changes in penetrator vessels originating from the basilar artery. He is not a candidate for intravenous thrombolysis because 18 hours have passed since he was known to be well. He has an elevated blood pressure but no evidence of end-organ damage. Treatment guidelines advise treatment of hypertension in the setting of acute ischemic stroke only if blood pressure is greater than 220/120 mm Hg or evidence of other end-organ damage exists. The rationale for these guidelines is to prevent neurologic worsening from expansion of the cerebral infarct; in recent clinical trials, acute lowering of blood pressure with candesartan within 36 hours of stroke was associated with neurologic worsening. When appropriate, antihypertensive medications are commonly started close to the day of discharge home or to a rehabilitation facility.

Neither oral captopril nor oral metoprolol is appropriate for this patient, who does not require immediate treatment of hypertension. Additionally, he should not be given any oral medication until a dysphagia evaluation documents the ability to swallow.

Sublingual nitroglycerin is also inappropriate because the patient does not require therapy to lower blood pressure at this time.

KEY POINT

- Treatment guidelines advise treatment of hypertension in patients with acute ischemic stroke only if blood pressure is greater than 220/120 mm Hg or evidence of other end-organ damage exists.

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Item 46 Answer: C

Educational Objective: Evaluate facial nerve palsy with incomplete recovery after 3 months.

An MRI of the brain should be obtained in this patient who has limited recovery despite appropriate treatment 3 months after onset of complete facial nerve (cranial nerve VII) palsy to rule out an underlying structural abnormality. He has acute weakness involving both upper and lower facial muscles, which favors a peripheral rather than central weakness. The initial presence of hyperacusis and the impaired taste noted on examination are also consistent with facial nerve involvement. In patients with typical isolated facial nerve paralysis, immediate brain imaging is unnecessary. Most of these patients have idiopathic Bell palsy, and 70% to 90% achieve complete recovery within 3 months. Severe residual weakness occurs in a minority of patients with Bell palsy, but the persistence of significant deficits at 3 months should prompt further investigation, including evaluation for alternative causes of facial nerve paralysis (such as diabetes mellitus, Lyme disease, vasculitis, HIV infection, sarcoidosis, paraproteinemia, and Sjögren syndrome) and an MRI of the brain to rule out structural causes. If results of this evaluation do not reveal a cause of the persistent symptoms, the diagnosis is incomplete recovery after Bell palsy, and clinical monitoring is then recommended.

Acute monotherapy with antiviral medications, such as acyclovir, does not improve prognosis. Early adjunctive use of antiviral therapy in addition to prednisone is favored by some experts, but the evidence supporting this treatment is inconsistent.

Evidence supporting the benefit of physical therapy for rehabilitation after facial nerve palsy is insufficient. In this patient, a structural cause of the deficits should first be excluded.

KEY POINT

- MRI of the brain is an appropriate next step in management for patients with incomplete recovery 3 months after onset of facial nerve palsy despite appropriate initial treatment.

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Item 47 Answer: B

Educational Objective: Evaluate a first seizure in a patient at high risk of recurrent seizure.

This patient should receive an antiepileptic drug (AED), such as carbamazepine. His seizure was unprovoked. The 2-year risk of recurrence after a single unprovoked seizure is approximately 40%. On the basis on this estimate, most experts do not recommend starting an AED for a first seizure unless the patient has risk factors that increase the likelihood for future

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events. This patient, however, has several risk factors for future seizures, including previous head trauma with loss of consciousness, a focal brain lesion on MRI, and postictal Todd paralysis of the right arm (focal weakness after a seizure). His risk of future seizures is high, and he should be treated with an AED. In this patient, the brain injury involving the contralateral parietal lobe is likely the source of the seizure, with the abnormal sensation experienced at seizure onset representing a sensory aura. He most likely had a simple partial seizure starting in the parietal lobe that spread to the motor cortex, which led to the dystonic posture of his hand and subsequent tonic-clonic seizure.

Ambulatory electroencephalography (EEG) is an outpatient test that can be useful to exclude the presence of unrecognized seizures and provide a more sensitive evaluation of interictal discharges than a 30-minute EEG. This test, however, is not performed in the emergency department and does not have to be completed before starting treatment in this patient, who had a witnessed seizure and has a high risk of recurrent seizure.

Clinical observation is appropriate management of a single unprovoked seizure only in patients with no risk factors for future seizures.

A lumbar puncture is indicated in some patients with a first seizure if they have symptoms or signs of infection or have altered mental status. In this patient with a clear reason for a partial seizure, a normal mental status, and no signs of infection, a lumbar puncture is unnecessary.

KEY POINT

- In a patient with a first seizure and risk factors for future seizures, treatment with an antiepileptic drug is appropriate.

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Item 48 Answer: E

Educational Objective: Treat migraine with aura.

The patient has migraine with aura and should be given sumatriptan. The pattern of his headaches has been stable for more than a decade and meets diagnostic criteria for migraine, namely, that migraine attacks should last between 4 and 72 hours if untreated, and the pain must possess two of the following four features: unilateral location, throbbing nature, moderate or severe intensity, and aggravation with physical activity. The quality and duration of the episodic visual distortion are compatible with migraine aura. Aura occurs in 25% to 35% of those with migraine and, most commonly, is visual. By definition, migraine aura should last between 5 and 60 minutes with complete resolution. Symptoms often precede headache but may accompany or even occur separately from the pain of an attack. Episodes of hemisensory symptoms or language disturbance of a similar duration are also described as "typical" aura and warrant no specific restrictions or acute migraine therapy. Because of their lower cost, NSAIDs are considered first-line options in acute migraine management. Because this patient has not responded to NSAIDs, acute treatment with a triptan is now appropriate.

CT of the head and MRI of the brain may be appropriate in the setting of potential secondary headache, but this patient has no "red flags" raising concern for this type of headache and instead exhibits classic signs and symptoms of migraine with aura. The headache pattern is stable, the visual loss is periodic and always reversible over the course of many years, and both headache and visual loss meet diagnostic criteria for migraine with aura. Neuroimaging is inappropriate in the evaluation of uncomplicated headache.

Similarly, electroencephalography has no role in the assessment of headache disorders, according to the American Academy of Neurology's five "Choosing Wisely" initiatives. Compared with standard clinical evaluation, it offers no diagnostic advantage, does not improve outcomes, and adds to medical costs.

Measurement of the erythrocyte sedimentation rate would be reasonable in the setting of suspected temporal arteritis. However, the young age of this patient and stable migraine pattern—episodic headaches with occasional transient visual impairment over 18 years—are incompatible with this diagnosis. Visual loss that occurs with temporal arteritis is typically monocular and more compatible with ischemic events, such as amaurosis fugax. Although the visual loss in typical migraine aura is benign and fully reversible, that noted with temporal arteritis is concerning and may become permanent following retinal artery occlusion.

KEY POINT

- Neuroimaging is inappropriate in the evaluation of uncomplicated headache.

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Item 49 Answer: D

Educational Objective: Diagnose medical complications after stroke.

This patient should be referred for polysomnography. His chief symptom of fatigue is highly prevalent among patients in the poststroke period. Common reversible causes of fatigue after stroke include depression, sleep apnea of the central or obstructive type, and heart failure. This patient has had no recent depression and has normal findings on cardiac examination. He has an elevated BMI and hypertension, both of which are associated with sleep apnea. The diagnosis of sleep apnea is typically confirmed by polysomnography. Appropriate treatment of the sleep apnea can lead to lessening of fatigue symptoms and improved control of hypertension.

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Cardiovascular stress testing is inappropriate in this patient who reports no exercise-induced fatigue and has normal findings on a recent electrocardiogram and echocardiogram. Myocardial ischemia is thus unlikely as an explanation of his symptoms. Patients with ischemic stroke are nonetheless at high risk for myocardial infarction, and a previous ischemic stroke is a coronary risk equivalent for the purposes of cardiovascular disease risk factor management strategies.

Depression is highly prevalent after stroke and is associated with poorer recovery and nonadherence to medical therapy. Use of antidepressant medications or cognitive behavioral psychotherapy (or both) is standard treatment of patients with stroke who experience depression. Although this patient has a remote history of depression, and fatigue can be a symptom of depression, he does not exhibit depressed mood or anhedonia, which are both elements of the two-question depression screening instrument. Treatment with citalopram or another antidepressant medication is therefore not necessary, although he should continue to be screened for this complication on routine visits.

Stimulants, including amphetamines, have shown no clinical benefits in stroke recovery and may exacerbate patients' hypertension. Dextroamphetamine is thus not appropriate in the management of this patient's poststroke fatigue.

KEY POINT

- Common reversible causes of fatigue after stroke include depression, sleep apnea of the central or obstructive type, and heart failure.

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Item 50 Answer: C

Educational Objective: Diagnose multiple sclerosis in a patient with optic neuritis.

This patient should have an MRI of the brain. She has symptoms and signs consistent with optic neuritis, including pain with eye movement, central scotoma, and an afferent pupillary defect. Although idiopathic optic neuritis can occur, the most common cause is multiple sclerosis (MS). An MRI of the brain should be obtained to evaluate for brain lesions consistent with MS. If they are present, a diagnosis of MS is likely on the basis of the official diagnostic criteria. These criteria require clinical and radiologic dissemination of lesions in space and time. In this patient, the occurrence of two disparate clinical events happening at separate times satisfies criteria for dissemination in time, and the presence of an optic nerve (cranial nerve II) lesion (detected on clinical examination) and additional brain lesions (if shown by MRI) would satisfy criteria for dissemination in space.

Determination of the erythrocyte sedimentation rate (ESR) has no role in the evaluation of MS. ESR elevation can occur in giant cell arteritis, a potential cause of visual loss, but this is typically a condition of older patients. In addition, this patient has not had the symptom of a headache.

Although a lumbar puncture is often performed when evaluating a patient for MS, the presence or absence of oligoclonal bands in the cerebrospinal fluid (CSF) is not part of any MS diagnostic criteria. Approximately 10% to 15% of patients with MS do not have these bands in their CSF, and their presence, by itself, is a nonspecific finding. If an MRI confirms the diagnosis of MS, CSF examination is unnecessary.

A rapid plasma reagin test is a screening test for syphilis. The classic pupillary abnormality of neurosyphilis is the Argyll-Robertson pupil, in which pupils are unreactive to light but constrict to accommodation. This patient instead manifested an afferent pupillary defect, which is a sign of reduced optic nerve (cranial nerve II) conductance. Although optic nerve inflammation can be a complication of meningovascular neurosyphilis, this scenario is quite rare, and this patient shows no other concerning signs or symptoms for this condition.

KEY POINT

- In patients with optic neuritis, an MRI of the brain should be obtained to evaluate for brain lesions consistent with multiple sclerosis, which is the most common cause.

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Item 51 Answer: C

Educational Objective: Prevent worsening of traumatic brain injury.

Contact sports should be prohibited for this patient with symptoms after sustaining a mild traumatic brain injury, which occurred when head trauma resulted in a transient alteration of neurologic function. The patient exhibited the typical physical symptoms of this type of injury, including headache, dizziness, and nausea. Although the symptoms have largely resolved, he still requires acetaminophen to control headache pain. Prohibiting contact sports is recommended for a patient who is still symptomatic. This restriction should remain in place even when the patient is in an asymptomatic state after taking medication. Not until the patient is asymptomatic without taking any medication should a return to contact sports be considered.

In the presence of normal findings on physical examination, a head CT scan or MRI of the brain is unlikely to provide any useful information and thus has no role. A noncontrast head CT scan is recommended in the setting of acute head injury when skull fracture or intracranial hemorrhage is suspected. Risk factors for these findings include prolonged loss of consciousness, posttraumatic amnesia, focal neurologic

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deficit(s), vomiting, severe headache, physical evidence of a basilar skull fracture, a Glasgow Coma Scale score less than 15, coagulopathy, or a dangerous mechanism of injury. MRI of the brain may be more sensitive in the detection of small areas of parenchymal damage or hemorrhage in the patient who is seen days or weeks after an injury, but suspicion of such damage would be low in this patient who has shown significant improvement 1 week after the trauma.

Gradual reintroduction of cognitive and normal physical activities is recommended for patients with concussion. Those with significant cognitive symptoms or neuropsychological examination deficits should have restrictions placed on cognitive activity. Immediate resumption of normal levels of cognitive activity (such as full days of classroom work) may delay recovery in some patients. Typically, cognitive rest is recommended for 3 to 7 days, followed by gradual reintroduction of cognitive activity periods. These periods initially should be limited to the threshold of concussion symptom aggravation but, over time, should be lengthened. Given the wide variability of recovery timeframes, management must be individualized. In this patient without any cognitive or significant physical symptoms 1 week after the injury, returning to school is appropriate, and restriction of classroom participation is not required.

KEY POINT

- Contact sports should be prohibited in patients who are symptomatic after sustaining a mild traumatic brain injury.

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Item 52 Answer: B

Educational Objective: Treat generalized epilepsy in a woman of childbearing age.

This patient should begin taking levetiracetam and be weaned off valproic acid. She has juvenile myoclonic epilepsy, which responds particularly well to valproic acid. However, valproic acid should be avoided whenever possible in women of childbearing age because this antiepileptic drug (AED) is associated with a significantly elevated risk (6%-16%) of major congenital malformations, which is much higher than that of other AEDs. In utero exposure to valproic acid also is associated with a 7- to 10-point decrease in intelligence quotient (IQ) on average and an increased risk for autism and autism spectrum disorders in the offspring. Therefore, whenever possible, a trial of another suitable AED should be attempted before pregnancy. This patient should be advised to switch to levetiracetam, which has shown a relatively low risk of birth defects when used in pregnancy. Lamotrigine is another reasonable option, but starting lamotrigine while a patient is still taking valproic acid carries an increased risk of Stevens-Johnson syndrome. If she does not respond to levetiracetam or the drug has adverse effects, lamotrigine, with or without levetiracetam, would be another reasonable choice. If a woman does not respond to treatment with other suitable medications and needs to remain on valproic acid, the dose should be adjusted during pregnancy to the minimum therapeutic dose required. Women should be counseled to use contraception during any period of drug transition from valproic acid because of the drug's significantly increased teratogenic risk.

Carbamazepine is not a good choice for this patient because it is a narrow-spectrum drug used to treat focal epilepsies. Carbamazepine potentially can exacerbate generalized epilepsies, such as juvenile myoclonic epilepsy, and should be avoided in this patient.

Topiramate can be used to treat juvenile myoclonic epilepsy. However, early data suggest that this drug is associated with a moderately increased risk of major congenital abnormalities, particularly cleft lip/cleft palate and small-for-gestational-age infants.

Stopping all AEDs can be considered in some women who have been seizure free for 2 or more years. However, it is rarely an option for patients with juvenile myoclonic epilepsy. These patients typically need life-long AED treatment, and the risk of seizures during pregnancy typically outweighs the potential complications of AED therapy, when selected carefully. The fact that this patient had a seizure after stopping her AED strongly suggests that she should stay on her medication during pregnancy.

KEY POINT

- Valproic acid should not be used by women with epilepsy who are or wish to become pregnant because of its association with a significantly elevated risk of major congenital malformations and other abnormalities in the fetus.

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Item 53 Answer: A

Educational Objective: Diagnose a Parkinson-plus syndrome.

The combination of parkinsonism, cerebellar ataxia, and early postural instability and falls in this patient is most consistent with multiple system atrophy (MSA), a Parkinson-plus syndrome. MSA (Shy-Drager subtype) also can be associated with prominent autonomic deficits, such as orthostatic hypotension and urinary symptoms. Her history of acting out of dreams during sleep (rapid eye movement sleep behavior disorder [RBD]) is another clue suggestive of a synucleinopathy (such as Parkinson disease or MSA). Patients with MSA are at higher risk for falls, dysautonomia, and sleep-related complications, including nocturnal stridor.

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Many of this patient's symptoms also can occur in idiopathic Parkinson disease, but her early prominent imbalance, recurrent falls, and cerebellar features are atypical for this disorder.

Progressive supranuclear palsy is the main differential diagnosis, given the patient's early prominent postural instability. She does not, however, have the characteristic impairment in vertical extraocular movements. Additionally, her cerebellar features, asymmetric tremor, hyposmia, and RBD are more typical of multiple system atrophy than progressive supranuclear palsy.

Patients with vascular parkinsonism have sudden or step-wise onset of symptoms and exhibit disproportionate involvement of the lower extremities. The involvement of the upper body, gradual course, and nonmotor symptoms in this patient make this diagnosis unlikely.

KEY POINT

- The combination of parkinsonism, cerebellar ataxia, and early postural instability and falls is most consistent with a diagnosis of multiple system atrophy.

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Item 54 Answer: A

Educational Objective: Treat carpal tunnel syndrome.

Decompression surgery is the most appropriate treatment for this patient with carpal tunnel syndrome. Patients with this disorder who have active denervation on nerve conduction studies and have muscle weakness and atrophy on clinical examination should undergo decompression surgery to prevent irreversible motor weakness. Uncontrolled pain and sensory symptoms can be another indication for surgery, but in the absence of motor weakness and active denervation, conservative measures to treat pain and control paresthesia should be attempted first.

Symptomatic treatment, such as NSAIDs, gabapentin, and glucocorticoid injections, and conservative treatment, such as nocturnal neutral position wrist splinting and occupational therapy, may be appropriate therapy for patients with mild to moderate carpal tunnel syndrome, but only if they have no evidence of weakness, atrophy, or active motor denervation on nerve conduction studies. Weight reduction also can be helpful in patients with obesity.

Diabetes mellitus can cause (or predispose one to) compressive mononeuropathies, including median neuropathy at the wrist and ulnar neuropathy at the elbow. However, patients with diabetes who experience hand numbness also should be assessed for carpal tunnel syndrome. The criteria for using surgical decompression to treat carpal tunnel syndrome and the expected response to surgery are similar in patients with and without diabetes.

KEY POINT

- Patients with carpal tunnel syndrome who have active denervation on nerve conduction studies and have muscle weakness and atrophy on clinical examination should undergo decompression surgery to prevent irreversible motor weakness.

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Item 55 Answer: A

Educational Objective: Treat hypertension after an intracerebral hemorrhage.

This patient should receive labetalol intravenously. He most likely has an intracerebral hemorrhage induced by hypertension. In patients with this type of hemorrhage and a systolic blood pressure greater than 180 mm Hg, acute blood pressure lowering is indicated. Hematoma expansion is a significant source of morbidity and mortality in intracerebral hemorrhage, particularly with extension into the ventricles, and commonly occurs within the first 3 hours after hemorrhage onset. Uncontrolled hypertension is a strong risk factor for hematoma expansion. In this patient, the blood pressure should be lowered to less than 160/90 mm Hg, according to American Heart Association guidelines. A recent clinical trial even reported that lowering blood pressure to less than 140/80 mm Hg was safe and led to a trend in improvement in neurologic outcomes. Labetalol is a fast-acting agent that can be titrated easily.

Intravenous nitroprusside can increase intracranial pressure and thus should be avoided in this patient with a likely intracerebral hemorrhage. The mechanism of action is thought to be related to an increase in cerebral blood volume from either a direct increase in venous volume or impaired venous drainage.

No evidence supports the use of platelet transfusion to improve outcomes in intracerebral hemorrhage or prevent hematoma expansion in patients taking antiplatelet agents. Associated risks of platelet transfusion include transfusion syndrome and volume overload.

Recombinant factor VIIa is inappropriate treatment for this patient. Studies have not shown a beneficial role of hemostatic agents in intracerebral hemorrhage without coagulopathy. In fact, a phase 3 trial that compared recombinant factor VIIa with placebo showed no improvement in neurologic outcomes but a significant increase in the rate of thrombotic complications.

KEY POINT

- In patients with intracranial hemorrhage and a systolic blood pressure greater than 180 mm Hg, blood pressure should be lowered to less than 160/90 mm Hg.

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Item 56 Answer: D

Educational Objective: Treat convulsive status epilepticus.

This patient should be treated with intravenous (IV) lorazepam followed by IV phenytoin. She is exhibiting convulsive status epilepticus (CSE), which is defined as convulsive seizures lasting longer than 5 minutes without a return to baseline mental status. CSE is a medical emergency requiring immediate treatment. First-line therapy for CSE is IV lorazepam followed by IV phenytoin or fosphenytoin. This combination has been shown to be superior to a benzodiazepine or phenytoin alone for stopping and providing ongoing control of CSE. When available, fosphenytoin, a prodrug of phenytoin, is preferred over phenytoin because it can be administered faster and does not cause the skin necrosis sometimes seen with phenytoin. Valproic acid also can be used after lorazepam to treat CSE, with several studies showing a similar efficacy to phenytoin. In some patients with known generalized epilepsy syndromes, valproic acid may be a better choice because phenytoin has the potential to provoke absence seizures or absence status epilepticus in these patients.

IV diazepam is less effective that IV lorazepam in treating CSE and thus should not be used if IV lorazepam is available. Rectal diazepam can be used if IV access cannot be obtained. Intramuscular midazolam recently also has been shown to be a good alternative to lorazepam for out-of-hospital CSE or patients without IV access. IV access has been established in this patient.

Levetiracetam has not shown efficacy in the treatment of CSE or been approved by the FDA for use in this clinical scenario. No antiepileptic drugs besides fosphenytoin, phenytoin, and valproic acid are recommended as first-line treatment of CSE.

KEY POINT

- First-line therapy for convulsive status epilepticus is intravenous (IV) lorazepam followed by IV phenytoin or fosphenytoin.

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Item 57 Answer: B

Educational Objective: Diagnose chronic inflammatory demyelinating polyradiculoneuropathy.

This patient most likely has chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). His rapidly progressive symmetric distal and proximal weakness that plateaued 3 months after onset is consistent with this diagnosis. The diffuse areflexia and sensory and motor neuropathy noted on physical examination and the demyelinating pattern (conduction blocks and slowing of conduction velocities) detected on nerve conduction studies all support the diagnosis of CIDP. CIDP can be idiopathic or associated with a range of systemic conditions, including diabetes mellitus, paraproteinemia, and HIV infection. Recognition of CIDP is essential because the disorder is responsive to glucocorticoids and other forms of immunomodulatory therapy.

Patients with Charcot-Marie-Tooth disease type 1 also have uniform demyelination on nerve conduction studies. However, the clinical course is much slower than in this patient, and symptoms are more prominent in the distal extremities.

Diabetic amyotrophy, also known as proximal lumbosacral radiculoneuropathy, presents with subacute pain and weakness in the proximal lower extremities. The simultaneous involvement of the upper extremities, diffuse areflexia, and diffuse motor nerve abnormalities on nerve conduction studies in this patient are inconsistent with this diagnosis.

The clinical features of CIDP are very similar to those of Guillain-Barré syndrome, but the latter condition has a faster progression and reaches its nadir within 4 weeks, whereas CIDP progression continues beyond 8 weeks from onset.

KEY POINT

- Progressive weakness, areflexia, and sensorimotor neuropathy with a progression extending beyond 8 weeks since onset of symptoms are characteristic of chronic inflammatory demyelinating polyradiculoneuropathy.

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Item 58 Answer: A

Educational Objective: Treat idiopathic intracranial hypertension.

The patient should be treated with acetazolamide. Although the headache described has many features of a tension-type headache, the findings of papilledema, partial left palsy of the abducens nerve (cranial nerve VI), and a cerebrospinal fluid (CSF) opening pressure of 350 mm H_2O suggests the presence of a secondary headache syndrome. Documentation of an elevated CSF opening pressure without evidence of a space-occupying lesion on neuroimaging confirms the diagnosis of idiopathic intracranial hypertension (IIH). This condition is most frequently seen in young women with an elevated BMI. The use of a combined oral contraceptive is an additional risk factor. Headache is the most common symptom, and papilledema is the most common physical

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examination finding. Carbonic anhydrase inhibitors, such as acetazolamide, are the only reliably effective medications for IIH. These inhibitors have been shown to reduce headache and improve visual impairment in patients with IIH.

Amitriptyline is an effective preventive medication for migraine or tension-type headache but would not address this patient's elevated intracranial pressure and thus is inappropriate.

An epidural blood patch is used in the treatment of intracranial hypotension arising spontaneously or occurring after lumbar puncture. This patient has intracranial hypertension.

Optic nerve sheath fenestration involves an incision in the meninges surrounding the optic nerve (cranial nerve II) to relieve elevated intracranial pressure. Optic nerve sheath fenestration can be used in the treatment of IIH but only after the failure of medical management. If acetazolamide does not relieve this patient's symptoms, then optic nerve fenestration may be appropriate.

Spironolactone is a recognized therapy for polycystic ovary syndrome but has no reported effect on headaches or intracranial pressure.

KEY POINT

- Carbonic anhydrase inhibitors, such as acetazolamide, are the only reliably effective medications for idiopathic intracranial hypertension.

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Item 59 Answer: C

Educational Objective: Monitor for atrial fibrillation in cryptogenic ischemic stroke.

The most appropriate next step is cardiac rhythm monitoring. The patient has an acute infarction in the anterior cerebral artery territory, which is typically the result of artery-to-artery embolic sources or cardiac embolism. This diagnosis is supported by the abrupt termination of the artery seen on magnetic resonance angiography. Until final stroke classification can be confirmed, the patient has a cryptogenic stroke. The patient's vascular imaging did not show extracranial or intracranial internal carotid artery stenosis, which makes cardiac embolism more likely. In several reports, as many as 25% of patients with cryptogenic ischemic stroke have paroxysmal atrial fibrillation on prolonged cardiac monitoring of up to 30 days; patients who have premature atrial contractions and other findings of ectopy on short-term telemetry may be more likely to have this finding. Continued cardiac rhythm monitoring to detect atrial fibrillation is thus advisable in this patient.

Clopidogrel should not be added to this patient's medication regimen because the combination of aspirin and clopidogrel was associated with an increased risk of major hemorrhage without any associated clinical benefit in several clinical trials in the subacute setting.

Dabigatran and other novel anticoagulants have only been approved for stroke prevention in the setting of atrial fibrillation, which has not yet been diagnosed in this patient.

Patent foramen ovale (PFO) closure did not reduce the risk of ischemic stroke more than best medical therapy in patients with cryptogenic stroke in the recently completed CLOSURE I trial. The risk of recurrent stroke in patients with an otherwise isolated PFO, with or without an atrial septal aneurysm, is low in most clinical trials. In older patients, a PFO frequently is an incidental finding and unlikely to be causally related to the infarct.

KEY POINT

- Patients with cryptogenic ischemic stroke require prolonged cardiac monitoring to detect atrial fibrillation, which is found in as many as 25% of these patients.

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Item 60 Answer: A

Educational Objective: Treat advanced Parkinson disease with motor complications.

Deep brain stimulation is the appropriate treatment of this patient with advanced Parkinson disease who continues to benefit from dopaminergic medications but experiences medication-related complications. His initial marked benefit from carbidopa-levodopa wears off before he takes the next dosage. Appropriate initial steps to alleviate this problem included increasing the frequency of carbidopa-levodopa dosing and adding entacapone to prolong the effect of the carbidopa-levodopa after it is taken. However, he developed prominent medication-induced dyskinesia and visual hallucinations, which both limit further medical management. Deep brain stimulation of the subthalamic nucleus is likely to provide more sustained control of his medication-responsive motor deficits and allow a reduction in his medications; this, in turn, should resolve any medication-induced hallucinations or dyskinesia.

Discontinuing entacapone is likely to diminish the patient's dyskinesia but at the same time would remove the beneficial effect of prolonging the action of the carbidopa-levodopa and thus lead to earlier wearing off of its benefit.

Although amantadine can be effective against dyskinesia, increasing the dosage further may worsen the hallucinations.

Adding a dopamine agonist, such as ropinirole, may boost the dopaminergic effect of the carbidopa-levodopa, but this medication also is likely to worsen the patient's hallucinations and dyskinesia and should be avoided.

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Adding a monoamine oxidase B inhibitor, such as selegiline, also is likely to worsen his dyskinesia and thus is inappropriate.

KEY POINT

- Deep brain stimulation is the appropriate treatment of patients with advanced Parkinson disease who continue to benefit from dopaminergic medications but experience medication-related complications.

Bibliography

Okun MS. Deep-brain stimulation for Parkinson's disease. New Engl J Med 2012 Oct 18;367(16):1529-38. [PMID: 23075179]

Item 61 Answer: C

Educational Objective: Identify the cause of delirium in a patient with dementia.

This patient should undergo testing for concurrent illnesses. She has had an acute change in cognitive symptoms accompanied by fluctuating symptoms, inattention, and a depressed level of consciousness. This presentation is consistent with delirium, which should be recognized early and treated by correction of the underlying cause. Underlying cognitive impairment or dementia is a significant risk factor for delirium. The acute change in mental status experienced by this patient is unlikely to be due to worsening dementia, given that the disease course has been slowly progressive to this point. Features of inattention and a depressed level of arousal are not common in Alzheimer disease until late in the disease course. The initial evaluation should focus on ruling out the most common metabolic and infectious causes of delirium in older patients by obtaining a complete blood count, serum electrolyte and plasma glucose levels, liver chemistry and kidney function tests, urinalysis, and a chest radiograph. Additional tests should be tailored to the clinical presentation.

Initiation of quetiapine is premature in this patient. Immediate therapy should focus on identifying and treating the underlying cause of delirium. For agitation, nonpharmacologic interventions should be tried first, such as frequent reorientation, avoiding immobilization and catheterization, restoring normal sleep patterns, and minimizing disruptions in the environment. Only if these steps prove inadequate should treatment with dopamine antagonists be considered.

Although cholinesterase inhibitors, such as donepezil, may be associated with cholinergic adverse effects in some patients, these effects tend to occur shortly after starting the medication or increasing the dose. This patient has tolerated a stable dose of donepezil for at least 1 year, and so it would not be appropriate to attribute her acute delirium to this medication. Evaluation for another cause should be pursued.

Neuroimaging is not indicated in the immediate evaluation of this patient because the findings on neurologic examination were nonfocal. If the initial testing for concurrent illnesses is unrevealing, additional evaluation would include neuroimaging to rule out hemorrhage, territorial infarction, or mass lesion.

KEY POINT

- Underlying cognitive impairment or dementia is a significant risk factor for delirium; identification of any concurrent illness(es) causing the delirium should be the first step in management.

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Item 62 Answer: C

Educational Objective: Treat multiple sclerosis–related spasticity.

This patient should be treated with a skeletal muscle relaxant, such as oral baclofen. He is experiencing muscle spasms and cramps as a long-term consequence of corticospinal tract injury from multiple sclerosis. Damage to upper motoneuron pathways has resulted in reduced inhibition of reflex arcs in the spinal cord, which allows for tonic activation of the lower motoneuron and resultant spasms and cramps. These symptoms can be reduced with the use of skeletal muscle relaxant medications, including baclofen, tizanidine, and cyclobenzaprine. Some patients may require intrathecal baclofen pumps or botulinum toxin injections for refractory symptoms.

Electroencephalography would be an appropriate test if a high suspicion of seizure was present. This patient's history and clinical evaluation do not suggest seizure, and his symptoms are highly consistent with upper motoneuron spasticity.

Because the physical examination findings are clearly consistent with an upper motoneuron injury, electromyography (EMG) (nerve conduction studies and needle electrode examination) is inappropriate. EMG is most appropriate for disorders of the lower motoneuron, neuromuscular junction, or muscle. The lack of fasciculations makes lower motoneuron injury even less likely, and the normal serum creatine kinase level and lack of pain on muscle palpation make an inflammatory myopathy very unlikely.

Pramipexole would be an appropriate treatment for restless legs syndrome (RLS), but this patient is not experiencing RLS symptoms. RLS does not result in upper motoneuron signs on examination or daytime muscle cramps. Also, patients with RLS experience feelings of discomfort in the legs or periodic limb movements while sleeping, not tonic leg spasms and cramps as with this patient.

KEY POINT

- Baclofen is appropriate for treatment of muscle spasms and cramps due to corticospinal tract injury from multiple sclerosis.

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Item 63 Answer: C

Educational Objective: Treat refractory temporal lobe epilepsy.

Right temporal lobectomy is the intervention most likely to make this patient seizure free and thus improve her quality of life. She has refractory epilepsy, defined as the persistence of disabling seizures for longer than 1 year despite treatment with adequate doses of two or more antiepileptic drugs (AEDs). Surgery is the most likely intervention to stop the seizures, and seizure freedom is closely tied to quality of life in a patient with refractory epilepsy. Given her history of febrile seizures in infancy and the presence of mesial temporal sclerosis on the MRI, her chances of seizure freedom 2 years after surgery are at least 70%.

Patients who do not respond to either their first or their second AED (in sequence or conjunction) have a less than 10% chance of experiencing seizure remission with pharmacotherapy. Therefore, adding a third agent, such as carbamazepine, to her medication regimen is unlikely to stop the seizures or improve her quality of life. Although carbamazepine could be offered in an attempt to temporize the situation while she awaits a surgical evaluation, it would not be the most effective management.

The ketogenic diet and vagal nerve stimulation are palliative treatments that can lessen the seizure burden in patients who are not candidates for epilepsy surgery. Both options rarely lead to seizure freedom.

KEY POINT

- In patients with refractory temporal lobe epilepsy, surgery is the most likely intervention to stop seizures and thus improve quality of life.

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Item 64 Answer: D

Educational Objective: Treat parkinsonian-hyperpyrexia syndrome secondary to dopaminergic medication withdrawal.

Levodopa should be restarted in this patient. Sudden withdrawal from dopaminergic medications, as may occur during hospitalization in patients with Parkinson disease, can lead to an acute dopamine agonist withdrawal syndrome, termed parkinsonian-hyperpyrexia syndrome, which resembles neuroleptic malignant syndrome (NMS). Patients who abruptly stop taking dopaminergic medications can develop acute altered mental status, hyperthermia, rhabdomyolysis, and extrapyramidal symptoms, including severe rigidity and dystonia. A high index of suspicion for parkinsonian-hyperpyrexia syndrome is required in these patients because mortality rates of up to 4% have been reported and may be prevented by early recognition and treatment. The differential diagnosis also includes central nervous system infection and status epilepticus. Aggressive supportive care, which may include intensive care and respiratory support, is appropriate. The primary medical therapy is restoration of dopaminergic medication.

Administration of the skeletal muscle relaxant baclofen may be helpful in patients with severe spasticity or progressive encephalomyelitis with rigidity and myoclonus, but not in those with Parkinson disease or disorders due to withdrawal from dopaminergic medications.

Dantrolene is a skeletal muscle relaxant that has proven efficacy in treating malignant hyperthermia and NMS. However, its effectiveness in parkinsonian-hyperpyrexia syndrome has not been established.

The clinical manifestations of serotonin syndrome may overlap with those of parkinsonian-hyperpyrexia syndrome and NMS, although serotonin syndrome is more often associated with hyperreflexia and myoclonus and not extrapyramidal symptoms. It typically occurs in patients taking high doses of serotoninergic agents (such as citalopram) and would not be expected in this patient in whom this medication has been withheld. Restarting the citalopram would not address the underlying disease process in this patient.

KEY POINT

- In hospitalized patients with Parkinson disease, sudden withdrawal of dopaminergic medications can lead to parkinsonian-hyperpyrexia syndrome, an acute syndrome resembling neuroleptic malignant syndrome; restarting the medications is the mainstay of therapy.

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Item 65 Answer: C

Educational Objective: Treat status migrainosus.

The patient has status migrainosus and should receive repetitive intravenous infusions of dihydroergotamine. Status migrainosus is defined as a migraine attack extending beyond 72 hours and is the most common complication of acute migraine. The condition is characterized by persistent severe pain that often is accompanied by protracted nausea with vomiting and profound sensory sensitivities. Hormonal factors are extremely common as inciting events. Life stressors, mood or anxiety disorders, and acute medication overuse may be other contributing factors. Triptans are often unsuccessful in resolving a migraine of this duration, but parenteral hydration and antiemetic medications sometimes provide some relief. Because this patient has not responded to either of

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CONT.

these treatments or to the ketorolac administered in the emergency department, the next step is repetitive administration of intravenous dihydroergotamine. This drug is administered in conjunction with either prochlorperazine or metoclopramide over the course of 1 to 3 days. Outpatient treatment options include a several-day course of oral glucocorticoids.

The patient has normal findings on neurologic examination. An MRI of the brain is unlikely to provide any additional useful information.

Combined oral contraceptives should be avoided in patients with migraine with aura because they further increase stroke risk, which is already elevated in this patient.

Opioids, such as hydromorphone, may provide analgesia but often contribute to worsening migraine frequency or intensity. They should be avoided in patients with acute migraine when other options are available.

Sertraline may help control anxiety but contributes nothing to the acute or preventive treatment of migraine and thus is inappropriate for this patient.

KEY POINT

- Repetitive administration of intravenous dihydroergotamine is the most appropriate in-patient treatment of status migrainosus.

Bibliography

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Item 66 Answer: B

Educational Objective: Modify pharmacologic therapy for multiple sclerosis in the setting of pregnancy.

In addition to discontinuing the oral contraceptive in preparation for attempting conception, fingolimod should be stopped. An oral disease-modifying therapy for multiple sclerosis (MS), fingolimod is a sphingosine-1-phosphate receptor modulator that restricts activated lymphocytes to lymph nodes and may also have direct neuroprotective effects. Fingolimod significantly reduces the relapse rate, risk of disability progression, and accumulation of new lesions on MRI. This drug has been associated with rare but potentially harmful side effects, including increased rates of serious herpesvirus infection, hypertension, bradycardia, lymphopenia, liver function abnormalities, and macular edema. Fingolimod is classified as a pregnancy category C drug, and thus its safety in human pregnancy is not clearly established. Although category C medications are indicated in some patients if the benefits outweigh the risks, the hormonal state of pregnancy itself is protective against MS activity, and thus discontinuing a disease-modifying drug during pregnancy is considered relatively safe.

Advising this patient against pregnancy is clearly inappropriate. The adverse effect of pregnancy on MS progression is a commonly held misconception. In fact, observational studies have found reduced risks for conversion to clinically definite MS from clinically isolated syndromes and reduced risks for conversion from relapsing MS to secondary progressive MS in women with multiple pregnancies.

Mitoxantrone is an anthracenedione chemotherapeutic agent that reduces lymphocyte proliferation and decreases the relapse rate and disability progression in MS. Despite mitoxantrone's efficacy, cardiac toxicity and the risk of secondary leukemia have significantly limited its use. Mitoxantrone is classified as a pregnancy category X drug and is contraindicated during pregnancy.

The MS drug teriflunomide is the active metabolite of leflunomide, which inhibits pyrimidine biosynthesis and interferes with the interaction between T lymphocytes and antigen-presenting cells. Substituting teriflunomide for fingolimod is inappropriate because teriflunomide is classified as pregnancy category X drug and is contraindicated during pregnancy.

KEY POINT

- Fingolimod is classified as a pregnancy category C drug (safety in human pregnancy not clearly established) and thus should not be used by women who are pregnant or planning to become pregnant.

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Item 67 Answer: C

Educational Objective: Prevent neurologic complications with nimodipine after subarachnoid hemorrhage.

This patient should receive oral nimodipine. Nimodipine is an L-type calcium channel blocker that has reduced the incidence of vasospasm in clinical trials involving patients with subarachnoid hemorrhage; morbidity and mortality also were reduced, even among patients who did not have cerebral vasospasm. Nimodipine may improve outcomes by preventing vasospasm and by a neuroprotective mechanism, particularly because calcium influx into neurons is a common pathway of cell injury in ischemia. Administration of oral nimodipine for 21 days after the hemorrhage is indicated in all patients with aneurysmal subarachnoid hemorrhage. This patient had an aneurysmal subarachnoid hemorrhage that was appropriately treated. In the first 48 hours after subarachnoid hemorrhage, rebleeding and hydrocephalus can cause neurologic worsening that is associated with significant morbidity and mortality.

Because the patient has no evidence of cerebral artery vasospasm, such as deterioration in level of consciousness or new focal neurologic deficits, treatment with intravenous dopamine is inappropriate. Vasospasm with subsequent cerebral ischemia is a significant contributor to neurologic worsening and poor long-term outcomes in patients with aneurysmal hemorrhage. Patients with a thick clot in the base of the brain are at higher risk of vasospasm, which can

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H CONT. be detected before symptom onset on a transcranial Doppler ultrasound. This patient, however, has no clinical, objective, or imaging signs of vasospasm that would warrant prophylactic treatment with a vasopressor.

Intravenous insulin should not be given to this patient. Her blood glucose levels are mildly elevated, but acute management of mild hyperglycemia has not shown benefit in patients with all stroke subtypes. Because of the risk of hypoglycemia, the American College of Physicians (ACP) and other organizations recommend not using intensive insulin therapy to normalize blood glucose levels in critically ill patients with or without diabetes mellitus. If insulin therapy is required, the ACP recommends target blood glucose levels of 140 mg/dL to 200 mg/dL (7.8-11.1 mmol/L).

The efficacy of statins for secondary stroke prevention or as a neuroprotective agent in subarachnoid hemorrhage has not been established. Statins are indicated for secondary stroke prevention in patients with ischemic stroke or transient ischemic attack of a presumed atherosclerotic subtype.

KEY POINT

- Oral nimodipine is indicated in all patients with aneurysmal subarachnoid hemorrhage.

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Item 68 Answer: B

Educational Objective: Provide preventive therapy in multiple sclerosis.

This patient should have a yearly influenza vaccination. She takes the disease-modifying drug glatiramer acetate, a pregnancy category B drug, for her multiple sclerosis (MS). The patient already exercises at least 3 hours weekly, takes a daily calcium–vitamin D supplement, and does not smoke, all recommended preventive measures against osteoporosis or conversion to secondary progression in patients with MS. According to a position statement by the American Academy of Neurology, there is no evidence of adverse outcomes of routine vaccinations in patients with MS beyond what is expected in the general population. In fact, these vaccinations are recommended to prevent infections leading to a heightened immune state and potential MS relapse.

Moderate alcohol usage has not been shown to adversely affect MS outcomes and has no effect on the metabolism of glatiramer acetate. Therefore, alcohol cessation is not necessary.

Although urinary tract infections (UTIs) are more common among patients with MS because of neurogenic bladder dysfunction, screening urinalysis is not indicated as a preventive medicine strategy in this patient population, barring UTI symptoms.

Despite the commonly held belief that pregnancy results in adverse events in MS, all evidence points instead toward to the protective effect of the hormonal state of pregnancy. Multiparous women with MS have equivalent, or perhaps better, outcomes than women with MS who have never been pregnant. Initiating an oral contraceptive is indicated only if the patient wishes to avoid pregnancy, but not as a preventive strategy for worsening of MS.

KEY POINT

- Routine vaccinations, such as an annual influenza vaccination, are recommended for patients with multiple sclerosis (MS) to prevent infections leading to a heightened immune state and potential MS relapse.

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Item 69 Answer: C

Educational Objective: Treat migraine without aura with an NSAID.

The patient should receive naproxen to treat his headaches, which meet criteria for migraine without aura. Episodes of migraine without aura typically last between 4 and 72 hours if untreated. Two of four pain features are necessary for the diagnosis to be made: unilateral location, throbbing quality, moderate to severe intensity, and worsening with physical activity. Either nausea or a combination of photophobia and phonophobia also is required. Patients with this diagnosis commonly report sinus pressure or drainage with these episodes, which often leads to the incorrect diagnosis of sinus headache. Common triggers include stress, hormonal or weather changes, alterations in sleep or meal patterns, or strong light, noise, or odor stimuli. Neurologic examination findings are normal. Evidence-based guidelines suggest that NSAIDs (such as naproxen), triptans, and dihydroergotamine are effective therapy for this type of acute migraine but that NSAIDs are preferred as initial treatment because of their greater cost-effectiveness.

In the context of a stable pattern of headaches that meets the criteria for migraine, CT of the head in unnecessary. Similarly, the headache pattern described by this patient—weekly headache episodes lasting 6 to 8 hours—is incompatible with an acute or chronic sinus pathology, which makes CT of the sinuses also unlikely to add any useful information.

Pseudoephedrine is effective in alleviating sinus congestion but has no role in the treatment of migraine. Headache is a relatively late-appearing and minor symptom of acute sinusitis; major symptoms include facial pain, purulent discharge, fever, and hyposmia, none of which this patient reports.

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KEY POINT

- Evidence-based guidelines suggest that NSAIDs, triptans, and dihydroergotamine are effective treatments for acute migraine without aura and that NSAIDs are preferred as initial treatment because of their greater cost-effectiveness.

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Taylor FR, Kaniecki RG. Symptomatic treatment of migraine: when to use NSAIDs, triptans, or opiates. Curr Treat Options Neurol. 2011 Feb;13(1):15-27. [PMID: 21125432]

Item 70 Answer: D

Educational Objective: Treat amyotrophic lateral sclerosis with riluzole.

This patient should receive riluzole. Clinical and electromyographic evidence of simultaneous upper and lower motoneuron signs in multiple body regions is most consistent with a diagnosis of amyotrophic lateral sclerosis (ALS). Onset in a single limb, rapid progression, bulbar involvement, and MRI evidence of a corticospinal tract abnormality further support the diagnosis, which was confirmed by results of the needle electrode examination. The absence of an alternative likely cause of his symptoms, such as Lyme disease, hyperparathyroidism, vitamin B_{12} or copper deficiency, lead intoxication, or combined cervical myelopathy and neuropathy, also suggests the diagnosis.

Riluzole is the only FDA-approved medication for ALS and can increase the survival of affected patients by a modest average of 3 months. It should be offered to all patients with a new diagnosis of ALS who wish to maximize their survival.

Bilevel positive airway pressure and other similarly noninvasive respiratory support methods can increase survival in ALS and should be started in the presence of respiratory symptoms and hypercarbia, which are absent in this patient.

Although intravenous immune globulin (IVIG) can be used in the management of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), this patient's clinical history and findings on needle electrode examination, especially the prominent upper motoneuron signs and absence of sensory deficits, are inconsistent with CIDP. IVIG is not indicated for the management of ALS.

Percutaneous endoscopic gastrostomy should be considered in patients with ALS and dysphagia before they reach the advanced stages of the disease to improve nutrition and increase survival. This intervention would be premature in this patient, however, who has no signs of dysphagia.

KEY POINT

- Riluzole, the only FDA-approved medication for amyotrophic lateral sclerosis, can increase the survival of affected patients by an average of 3 months

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Item 71 Answer: A

Educational Objective: Diagnose a secondary headache.

The patient should undergo brain MRI. Although she has a long-standing history of migraine with aura, the recent escalation in headache frequency and intensity is concerning. The pattern of her headaches has fundamentally changed, and she exhibits several other red flags, such as the development of a new headache condition after age 50 years and neurologic symptoms lasting more than 1 hour, that are compatible with the presence of a secondary headache. Diplopia, when present in migraine aura, should be accompanied by other features seen in migraine with brainstem aura (basilar migraine), such as vertigo, ataxia, dysarthria, diplopia, tinnitus, hyperacusis, or alteration in consciousness; this patient has none of these features. Additionally, the maximum duration of aura in basilar migraine is 60 minutes or less, not the 2 hours she experienced. MRI is the preferred study to confirm the diagnosis of a secondary headache.

Discontinuation of ibuprofen would be helpful in the setting of medication overuse headache. Excessive analgesic intake can result in worsening of the underlying headache or the appearance of a milder, nonspecific headache. However, this medication would not cause new neurologic symptoms, such as diplopia.

In this patient with a probable secondary headache, neuroimaging is necessary before consideration of lumbar puncture to exclude any space-occupying lesion that could affect intracranial pressure.

Switching from naratriptan to sumatriptan may have been a consideration if the diagnosis were only worsening migraine. However, this patient most likely has a secondary headache disorder, so changing triptans in unlikely to be helpful.

Substituting topiramate for amitriptyline may be an appropriate treatment in patients with escalating migraine frequency, but not in those suspected to have a secondary headache disorder.

KEY POINT

- Recent escalation of headache frequency in patients with migraine suggests a secondary headache disorder and should be evaluated with brain MRI.

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Item 72 Answer: C

Educational Objective: Counsel a patient with an unruptured cerebral aneurysm about smoking cessation.

This patient should be counseled about smoking cessation and provided with smoking cessation aids as appropriate, including nicotine replacement or pharmacologic treatment. She has an unruptured intracranial aneurysm of the left

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middle cerebral artery. A subarachnoid hemorrhage (SAH) has been ruled out by neuroimaging and lumbar puncture findings. She has no history of a previous SAH, and the aneurysm measures less than 7 mm, both of which indicate a low risk of rupture. The major risk factors for cerebral aneurysms and their rupture are hypertension and tobacco use. Her hypertension is well controlled by the amlodipine. Smoking cessation is indicated to prevent further aneurysmal expansion and rupture.

Neither aneurysmal clipping nor endovascular coiling is necessary because the aneurysm is less than 12 mm and located in the anterior circulation, which suggests a low risk of rupture (0.05% annually). The surgical morbidity associated with either technique is too great given the low risk of rupture. Repeat neuroimaging on an annual basis can be considered to track any change in the aneurysm's size.

The calcium channel blocker nimodipine has been shown to improve outcomes in SAH and is the standard of care for all patients with aneurysmal SAH. SAH has been ruled out in this patient, whose blood pressure is well controlled by amlodipine. No evidence suggests that switching to nimodipine from amlodipine will prevent aneurysmal expansion or rupture.

KEY POINT

- Patients with unruptured intracranial aneurysms should be counseled to stop smoking because of the increased risk of aneurysmal rupture.

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Item 73 Answer: D

Educational Objective: Diagnose early Parkinson disease.

This patient most likely has early Parkinson disease (PD) on the basis of his clinical examination findings and does not require additional diagnostic testing. This diagnosis requires the presence of bradykinesia (in this patient, the decrements in speed and amplitude of repetitive movements) and at least one other cardinal feature (resting tremor, rigidity, or postural instability, with only postural instability absent in this patient). In addition, the absence of atypical features, such as early dementia, early falls, vertical gaze palsy, or prominent dysautonomia, is consistent with the diagnosis of PD. Reemergence of a resting tremor with posturing and ambulation also is seen in PD. The presence of bilateral kinetic tremor, although more typical of essential tremor, is still consistent with this diagnosis. Further diagnostic testing is not necessary in this patient before a diagnosis can be made.

A dopamine transporter scan can confirm degeneration of nigrostriatal dopaminergic terminals in Parkinson disease and differentiate between Parkinson disease and essential tremor in patients in whom the diagnosis cannot be made on clinical grounds (which is not the case in this patient). The sensitivity of this expensive test, however, is not superior to that of expert clinical assessment.

An MRI of the brain can be used to assess for vascular parkinsonism and hydrocephalus but should not be obtained before a clinical diagnosis is made. This patient does not have symptoms of vascular parkinsonism (predominant lower extremity involvement, gait impairment, and a step-wise course) or normal pressure hydrocephalus (the triad of gait impairment, urinary incontinence, and cognitive impairment), which makes these diagnoses unlikely.

Needle electrode electromyography can be helpful in studies of nerve and muscle disease but has no role in the diagnosis of Parkinson disease.

KEY POINT

- The diagnosis of Parkinson disease can be made on the basis of clinical findings and requires the presence of bradykinesia and at least one of the other cardinal features of resting tremor, rigidity, or postural instability.

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Item 74 Answer: D

Educational Objective: Treat a pseudorelapse of multiple sclerosis, differentiating it from an actual relapse.

This patient should be treated with supportive care and clinical observation. His clinical picture is consistent with a likely viral upper respiratory tract infection, which is causing a pseudorelapse of his multiple sclerosis (MS). MS pseudorelapses involve a worsening of baseline neurologic symptoms (or recurrence of previous symptoms) that occurs in the setting of physiologic stressors. In this patient, the viral syndrome and associated systemic inflammatory response are the underlying cause of the pseudorelapse. Supportive treatment of these symptoms and observation to ensure that the patient returns to baseline status is the most appropriate management to avoid unnecessary treatments or changes in medication. Because actual inflammatory relapses can sometimes be triggered by pseudorelapses (and similar causes), treatment with glucocorticoids can be considered if improvement does not occur within days of resolution of the causative condition.

The patient most likely has a viral upper respiratory tract infection, with no evidence of a urinary tract infection. Without evidence of bacterial infection, antibiotic therapy, such as administration of amoxicillin-clavulanate, is not indicated.

The increased postvoid residual urine volume suggests that this patient has moderate urinary retention. An increase in the oxybutynin dosage would cause relaxation of the

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muscles of the bladder wall and would likely worsen the patient's retention.

Although glucocorticoid therapy might be appropriate therapy for a true MS relapse, treatment with methylprednisolone in this patient with a likely pseudorelapse is inappropriate.

KEY POINT

- A pseudorelapse of multiple sclerosis is a worsening of baseline neurologic symptoms or recurrence of previous symptoms that occurs in the setting of physiologic stressors, such as a superimposed infection.

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Item 75 Answer: A

Educational Objective: Select the appropriate diagnostic test to evaluate for complications after subarachnoid hemorrhage.

This patient should undergo CT angiography of the brain to assess for cerebral vasospasm. He is now at day 7 after a subarachnoid hemorrhage due to a left middle cerebral artery aneurysm. In the first 48 hours after a subarachnoid hemorrhage, rebleeding from an unsecured aneurysm and hydrocephalus are the principal causes of neurologic deterioration. This patient's aneurysm has been successfully clipped, and hydrocephalus is being managed with the use of an external ventricular drain. Potential neurologic complications after the first 48 hours include seizures, hydrocephalus, infection, and symptomatic cerebral vasospasm; the incidence of cerebral vasospasm peaks on days 5 to 10 after a hemorrhage. Cerebral vasospasm can manifest as a decline in neurologic function in patients who are awake enough for a neurologic examination. Although transcranial Doppler ultrasonography may reveal a vasospasm, CT angiography is more sensitive at detecting vasospasm that can be treated with the initiation of vasopressors to augment the blood pressure or with endovascular treatment in more refractory cases. CT angiography has the additional benefit of imaging the brain parenchyma for evidence of cerebral edema or infarction and the ventricles for evidence of hydrocephalus that may be amenable to shunting.

Electroencephalography (EEG) is inappropriate as the next diagnostic step in this patient with an aneurysmal subarachnoid hemorrhage. Convulsive and nonconvulsive status epilepticus is common and underdiagnosed after hemorrhagic stroke and is associated with poor neurologic outcome. If imaging does not identify a clear cause of the patient's decline that can be treated with medical or surgical therapy before irreversible damage occurs, then continuous EEG monitoring may help in diagnosing seizures.

Lumbar puncture may be useful for measuring intracranial pressure in this patient with an external ventricular drain. However, repeat imaging would first be required, independent of the presence of the drain, to rule out mass effect that could precipitate cerebral herniation after a lumbar puncture.

MRI requires too long a time to complete in the setting of a neurologic emergency and may not adequately detect arterial narrowing. Vasospasm is more readily detected with CT angiography.

KEY POINT

- Cerebral vasospasm is a potential complication of subarachnoid hemorrhage that most often occurs 5 to 10 days after the hemorrhage and is best detected by CT angiography of the brain.

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Item 76 Answer: C

Educational Objective: Treat restless legs syndrome.

This patient has restless legs syndrome (RLS) and should be treated with ropinirole. Dopamine agonists, such as ropinirole, pramipexole, or rotigotine, are first-line treatments for RLS. This syndrome is characterized by the clinical features of abnormal sensations in the lower extremities, an urge to move the extremities in response to these sensations (with movement resulting in a transient relief of symptoms), emergence of symptoms at rest, and a circadian pattern (with symptoms more prominent at night). Diagnosis is clinical and based on history. Additional treatment options include gabapentin, gabapentin enacarbil, levodopa, and opioids.

Patients with RLS should be screened for iron deficiency. Iron supplementation can improve or resolve the symptoms of RLS in patients with iron deficiency and those with low-normal (15-45 ng/mL [15-45 µg/L]) serum ferritin levels. This patient's serum ferritin level is well above this range, and no evidence suggests that iron supplementation in this setting is beneficial.

Pentoxifylline is a peripheral vasodilator used in the treatment of peripheral arterial disease. Arterial insufficiency is not associated with RLS, and nothing suggests its presence in this patient. Therefore, this treatment is not indicated.

Zolpidem may help with insomnia but does not treat the underlying problem of RLS.

KEY POINT

- Dopamine agonists, such as ropinirole, pramipexole, or rotigotine, are first-line treatment for restless legs syndrome.

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Item 77 Answer: B

Educational Objective: Evaluate mild cognitive impairment.

This patient should have an MRI of the brain. He most likely has mild cognitive impairment (MCI), as evidenced by cognitive difficulties that are greater than those typical of normal aging but do not impair activities of daily living and have minimal effect on instrumental activities of daily living. MCI is a clinical diagnosis made exclusively on the basis of history and the results of cognitive testing. Although neuroimaging cannot be used to detect whether or not a cognitive disorder is present, structural neuroimaging studies, specifically head CT and brain MRI, can play a key role in the routine diagnostic evaluation of patients with established cognitive impairment to exclude structural lesions of the brain, such as strokes, hematomas, brain tumors, or other mass lesions.

Amyloid PET imaging allows for in vivo detection of amyloid plaques, which are a core pathologic feature of Alzheimer disease. However, positive results are not synonymous with the presence of Alzheimer disease because cognitively normal persons can have abnormal scans. Amyloid PET imaging may provide prognostic information in patients with MCI by identifying those whose cognitive impairment may be related to underlying Alzheimer disease pathology, but much more research is still required before the routine use of this technology in clinical practice.

Screening for carotid stenosis with ultrasonography or any imaging modality has no role in the routine evaluation of cognitive impairment in an asymptomatic patient. An asymptomatic patient in this context is one without previous hemispheric neurologic symptoms—such as transient ischemic attack, stroke, or amaurosis fugax—or the presence of a carotid bruit on examination.

The apolipoprotein E gene (*APOE ε4*) located on chromosome 19 has been identified as a genetic risk factor for late-onset Alzheimer disease. *APOE ε4* genotyping has marginal additive value over clinical diagnoses but is neither necessary nor sufficient to predict who will develop Alzheimer disease and thus is not recommended for broad clinical use.

A fluorodeoxyglucose-PET scan of the brain or any other metabolic scan of the brain cannot determine if a patient's cognitive symptoms indicate cognitive impairment. Abnormal results of fluorodeoxyglucose-PET scanning also occur in persons who are cognitively normal. Although these abnormal results may indicate a future risk of cognitive impairment, this relationship has not been established.

KEY POINT

- Structural neuroimaging studies, specifically head CT and brain MRI, can play a key role in the routine diagnostic evaluation of patients with established cognitive impairment to exclude structural lesions of the brain, such as strokes, hematomas, brain tumors, or other mass lesions.

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Item 78 Answer: D

Educational Objective: Diagnose an acute complication of thrombolytic therapy.

This patient should undergo repeat noncontrast CT of the head. She had an ischemic stroke that was likely due to subtherapeutic anticoagulation. Findings from physical examination, notably an elevated National Institutes of Health Stroke Scale (NIHSS) score, and the initial CT scan of the head suggest a large cerebral infarction in the entire territory of the left middle cerebral artery. She was appropriately given intravenous recombinant tissue plasminogen activator within the recommended treatment window because of the high risk of a poor neurologic outcome. At the time of treatment, she did not meet any exclusion criterion for thrombolysis, such as an elevated blood pressure or an INR greater than 1.7. The patient has several risk factors for intracerebral hemorrhage after thrombolysis, including a high NIHSS score and a cardioembolic cause of the stroke. Any change in the neurologic examination, particularly in patients treated with thrombolysis, should prompt consideration of hemorrhage, which is associated with a high mortality rate. Hemorrhage after thrombolysis can be detected on a noncontrast CT scan of the head.

Intra-arterial thrombectomy is inappropriate in this patient. The new right-leg paralysis noted in the second neurologic examination is most concerning for intracerebral hemorrhage after thrombolysis. However, the benefit of intra-arterial treatment modalities, after or instead of intravenous thrombolysis, has not been established in randomized clinical trials.

This patient also should not be given intravenous labetalol. Administering treatment to lower her blood pressure is inappropriate because her blood pressure is already less than the recommended target of 180/105 mm Hg after thrombolysis.

Aspirin is appropriate stroke therapy in patients not eligible for thrombolysis and can be administered rectally in patients who are unable to swallow. However, in patients who have received thrombolysis, early administration of antiplatelet agents can increase the risk of hemorrhage. In addition, although aspirin is associated with a reduction in recurrent stroke risk when administered within 48 hours of ischemic stroke onset, aspirin has not been shown to prevent or reverse neurologic worsening.

KEY POINT

- Hemorrhage after thrombolysis for ischemic stroke can be detected on a noncontrast CT scan of the head.

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Item 79 Answer: E

Educational Objective: Treat acute refractory migraine.

The patient should be treated with subcutaneous sumatriptan for migraine without aura. She no longer responds to NSAIDs and oral triptans. The headaches are associated with emesis, and she is awakening with attacks. Migraine episodes have been so severe that she has visited an urgent care facility recently for parenteral treatment of refractory migraine. Self-administered injectable migraine medications would be of value for this patient. Although nasal spray options exist for several acute medications, they are less potent than their injectable counterparts. According to guidelines, no first-line agent for acute migraine treatment is available in suppository form.

Neither butalbital compounds nor opioids (such as hydrocodone) are recommended as first-line treatments of recurrent headache disorders. Little evidence of benefit in acute migraine exists for either class of drugs, and both contribute to an increased future risk of transformation into chronic migraine, compared with first-line agents.

Evidence supports the use of naproxen in the management of acute migraine, and the drug is listed by evidence-based guidelines as first-line therapy. In the setting of migraine that occurs upon awakening or with vomiting, however, it is unlikely to be beneficial, especially in a patient who has not responded to another NSAID or oral triptan.

The orally dissolvable versions of rizatriptan and zolmitriptan require gastrointestinal absorption and thus should not be used in the setting of migraine with vomiting.

KEY POINT

- Self-administered subcutaneous sumatriptan is appropriate as therapy for migraine without aura in patients not responding to NSAIDs or oral triptans, especially those with vomiting.

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Item 80 Answer: A

Educational Objective: Diagnose a posttraumatic epidural hematoma.

This patient most likely has an epidural hematoma. Traumatic epidural hematoma classically presents with precipitous neurologic decline after head trauma. Most patients with this diagnosis have a skull fracture with associated rupture of an underlying artery, typically the middle meningeal artery. Blood under arterial pressure accumulates between the inner table of the skull and the dural membranes. The most common symptoms are severe headache and vomiting. Impairment of consciousness may develop immediately or after a lucid interval. Uncal or subfalcine brain herniation can occur and is characterized by ipsilateral occulomotor nerve (cranial nerve III) palsy, contralateral paresis, and stupor or coma. Hypertension with bradycardia (the Cushing response) can be another sign of increased intracranial pressure. A CT scan of the head confirms the diagnosis, and immediate surgical evacuation is required. Mortality rates are commonly reported to be 10% to 20%.

Dissection of the left internal carotid artery typically results in ipsilateral Horner syndrome with ptosis, miosis, and anhidrosis but not oculomotor nerve (cranial nerve III) palsy. Contralateral hemiparesis could result if a secondary stroke were to occur in the left frontal lobe after the dissection, but rapidly declining consciousness would be unexpected.

Postconcussion syndrome is defined by a constellation of neurologic, psychological, and constitutional symptoms without significant abnormalities on physical examination. Minor neurologic findings noted on the examination of a patient with mild traumatic brain injury may include ocular convergence insufficiency or mild ataxia, but typically examination findings are normal. This patient's clinical findings do not fit this pattern.

Seizures occur in approximately 5% of persons hospitalized for acute head trauma. They may be classified as "immediate" if occurring within the first 24 hours, "early" if noted within the first week, or "late" if occurring more than 1 week after the injury. Half of the seizures occurring within the first week will occur in the first 24 hours, and the risk decreases with time. Some correlation between the severity of injury and the risk of posttraumatic seizures exists. This patient shows no signs of involuntary motor activity, so convulsive status epilepticus is not present. Nonconvulsive status epilepticus might manifest as stupor, but the presence of focal cranial nerve and motor deficits in this patient is more indicative of a progressive structural lesion.

KEY POINT

- Traumatic epidural hematoma classically presents with precipitous neurologic decline after head trauma; common symptoms are severe headache and vomiting, with possible impairment of consciousness developing immediately or after a lucid interval.

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Item 81 Answer: D

Educational Objective: Diagnose a tic disorder.

This patient's clinical presentation is most consistent with a tic disorder. Tics are repetitive, stereotyped, suppressible movements typically preceded by an abnormal sensation (premonitory urge). She previously has experienced simple

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motor tics and has a positive family history of facial twitching. The presence of vocal (repetitive throat clearance) and complex motor (shoulder elevation followed by neck rolling) tics, the persistence of symptoms for 1 year, and the comorbid obsessive-compulsive disorder are all consistent with Tourette syndrome. Tics can wax and wane, and old tics can be replaced by new ones over time, but at any given time, a limited number of stereotyped movements are present during clinical examination.

Chorea involves typically random, diffuse, and nonsuppressible involuntary abnormal movements. The focal distribution, suppressibility, and stereotyped character of this patient's movements make chorea unlikely.

Dystonia consists of patterned and directional movements limited to certain parts of the body. However, dystonia is typically sustained and nonsuppressible. The presence of vocal tic, the premonitory urge, and the long history of waxing and waning of various types of movements in this patient also make dystonia unlikely.

Myoclonus consists of a single, rapid, shocklike muscle jerk. Complex stereotyped movements (such as shoulder elevation followed by neck rolling) and suppressibility are inconsistent with myoclonus.

KEY POINT

- Tics are repetitive, stereotyped, suppressible movements typically preceded by an abnormal sensation (premonitory urge).

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Item 82 Answer: C

Educational Objective: Treat seizures in a patient with a brain tumor.

This patient should be treated with valproic acid. In patients with brain tumors and one or more seizures, antiepileptic drug (AED) regimens that do not induce hepatic enzymes and thus have limited interaction with commonly used chemotherapy regimens are favored. Valproic acid is a non–enzyme-inducing AED that is appropriate to treat this patient. Other AEDs that would be reasonable to use include lacosamide, lamotrigine, and levetiracetam.

Carbamazepine and phenytoin are enzyme-inducing AEDs that can diminish the efficacy of the chemotherapy and other drugs this patient may receive. Additionally, because they are metabolized by the same enzyme pathways, chemotherapeutic agents also may alter AED levels unpredictably, which makes them potentially less effective in controlling seizures.

Deferring AED therapy in this patient is not appropriate. He had a clear focal seizure, and the presence of a known brain lesion puts him at risk for subsequent seizures. However, AED treatment is not appropriate as prophylaxis in patients with brain tumors who have not had any clinical seizures.

KEY POINT

- In patients with metastatic brain tumors and one or more seizures, antiepileptic drug regimens that do not induce hepatic enzymes and thus have limited interaction with commonly used chemotherapy regimens are favored.

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Item 83 Answer: C

Educational Objective: Diagnose dementia with Lewy bodies.

This patient most likely has dementia with Lewy bodies, the second most common cause of degenerative dementia. Core features of dementia with Lewy bodies are fluctuating attention and alertness; recurrent, well-formed visual hallucinations; and spontaneous parkinsonism. Sensitivity to neuroleptic medications also is commonly seen. Suggestive features include rapid eye movement sleep behavior disorder and low dopamine transporter uptake in the basal ganglia on single-photon emission CT or PET scans. The patient's features of cognitive fluctuations (episodic disorganized speech and functional disability, daytime sleepiness), parkinsonism, visual hallucinations, and severe sensitivity to haloperidol all support a diagnosis of dementia with Lewy bodies.

Although visual hallucinations and parkinsonism can occur in Alzheimer disease, these features generally present relatively late in the disease course. Severe sensitivity to neuroleptic medications also is less common in Alzheimer disease than dementia with Lewy bodies. Alzheimer disease is predominantly characterized by a decline in memory that can be accompanied by deficits in other cognitive domains. Typical behavioral changes in the earlier stages of Alzheimer disease include irritability, anxiety, and depression.

Delirium is characterized by disturbances of attention, cognition, and perception, with fluctuations in symptoms during the day. These disturbances typically develop over the course of hours to days, rather than over 1 year as occurred in this patient. A careful history obtained from a reliable informant often easily distinguishes delirium from dementia with Lewy bodies.

Major depression with psychotic features is characterized by hallucinations, more often auditory than visual, and delusions that are typically mood congruent, such as guilt, nihilism, or deserved punishment. Although the patient is being treated for depression, no evidence that supports a diagnosis of major depression, such as suicidal ideation, hopelessness, or guilt, has been reported.

KEY POINT

- Core features of dementia with Lewy bodies are fluctuating attention and alertness; recurrent, well-formed visual hallucinations; or spontaneous parkinsonism.

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Item 84 Answer: D

Educational Objective: Diagnose trigeminal neuralgia.

This patient has developed trigeminal neuralgia. Although more common among older patients, trigeminal neuralgia can be seen in young adults, particularly those with multiple sclerosis. Affected patients describe brief episodes of lancinating pain affecting either the second or third distribution of the trigeminal nerve (cranial nerve V_2 or V_3). The pain may occur spontaneously or be triggered by sensory stimulation of the face or mouth. The diagnosis is made clinically. Brain MRI may be indicated in patients with atypical presentations, including those developing symptoms in young adulthood. As many as 15% of patients with trigeminal neuralgia may have a structural explanation for their disease, such as cerebellopontine angle tumors in older patients or demyelinating disease in younger patients. Brain MRI is also indicated in the course of surgical evaluation, if appropriate. Glucocorticoids are typically ineffective. Carbamazepine is the drug of choice for initial management, with a greater than 50% response rate. Oxcarbazepine, a structural derivative of carbamazepine, is also effective and has fewer adverse effects and drug interactions but is a more expensive medication.

Chronic paroxysmal hemicrania is typically expressed along the first branch of the trigeminal nerve (cranial nerve V_1). Pain attacks are brief but generally last a mean of 15 minutes rather than seconds and may recur between 8 to 40 times daily. The diagnosis also requires concomitant ipsilateral autonomic findings, such as tearing, nasal congestion, or rhinorrhea, none of which this patient has.

The eruption of herpes zoster is preceded by a prodrome of constant pain or burning, commonly for up to several days. The patient's intermittent sharp facial pain is most consistent with trigeminal neuralgia.

Primary stabbing headaches are brief paroxysms of pain lasting seconds, without associated autonomic features. The face is typically spared. This patient's pain does not fit this description.

KEY POINT

- Trigeminal neuralgia typically results in brief episodes of lancinating pain affecting either the second or third distribution of the trigeminal nerve (cranial nerve V_2 or V_3); the pain can occur spontaneously or be triggered by sensory stimulation of the face or mouth.

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Item 85 Answer: C

Educational Objective: Adjust medication dosage in glucocorticoid-induced myopathy.

Tapering the prednisone dosage while monitoring the patient's response is the most appropriate method to distinguish between weakness caused by a flare of inflammatory myopathy and glucocorticoid-induced toxic myopathy. The latter diagnosis is more likely in this patient with a normal serum creatine kinase level. In contrast, a flare of inflammatory myopathy, which can present the same way clinically, is associated with a marked increase in the serum creatine kinase level and evidence of irritable myopathy on electromyography (such as abnormal spontaneous necrosis or active muscle membrane damage from inflammation). If weakness improves after prednisone tapering, the patient should be given a glucocorticoid-free holiday or, if needed, switched to another agent. In contrast, if weakness worsens with tapering, an inflammatory flare should be suspected, and increasing the glucocorticoid dosage or adding another immunosuppressive therapy should be considered.

Intravenous immunoglobulin (IVIG) is a second-line therapy for severe inflammatory myopathies that are refractory to treatment with a glucocorticoid and at least one other immunosuppressive agent. Because glucocorticoid-induced myopathy is suspected in this patient, IVIG treatment is not warranted.

Increasing the prednisone dosage without evidence of active inflammation would be inappropriate and could worsen the patient's weakness, which is likely associated with glucocorticoid therapy.

A repeat muscle biopsy might show type 2 muscle fiber atrophy due to glucocorticoid myopathy, but these changes also are seen in disuse atrophy and other conditions and thus are nonspecific. Biopsy is also likely to show inflammatory changes but is unlikely to provide a definitive differentiation between a flare of inflammatory myopathy and glucocorticoid-induced myopathy.

KEY POINT

- Glucocorticoid tapering is the most appropriate method to distinguish between a flare of inflammatory myopathy and glucocorticoid-induced toxic myopathy in a patient with persistent myopathy.

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Item 86 Answer: A

Educational Objective: Treat elevated blood pressure after recombinant tissue plasminogen activator therapy for stroke.

The patient should receive intravenous nicardipine in an attempt to lower her blood pressure to the target range. She

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met no exclusion criteria and was correctly treated with intravenous recombinant tissue plasminogen activator (rtPA) for an acute ischemic stroke within the optimal 3-hour window from onset of symptoms. Her blood pressure before treatment was less than 185/110 mm Hg, as recommended by guidelines. The most serious complication of thrombolysis with intravenous rtPA is intracerebral hemorrhage, which occurs in as many as 6% of patients. The main risk factors for hemorrhage after thrombolysis are a large-volume cerebral infarction, a high National Institutes of Health Stroke Scale score, a cardioembolic origin of the stroke, and protocol violations. The postthrombolysis protocol includes avoiding antiplatelet and anticoagulant agents for 24 hours until a repeat head CT scan shows no hemorrhage, frequent neurologic and vital sign evaluation, and maintenance of the blood pressure at less than 180/105 mm Hg. When the blood pressure exceeds this limit, as in this patient, intravenous labetalol or nicardipine is the best option to reduce the blood pressure and thereby avoid intracerebral hemorrhage.

Oral aspirin and subcutaneous heparin are inappropriate treatments for this patient at this point because antithrombotic medications should not be administered until follow-up CT of the head is obtained 24 hours after rtPA infusion is completed. If the repeat CT scan shows no hemorrhage, and no systemic bleeding complications have occurred, then aspirin should be initiated for secondary stroke prevention and deep venous thrombosis prophylaxis should be started with low-molecular-weight or unfractionated subcutaneous heparin.

Although sublingual nitroglycerin can lower blood pressure, the inability to rapidly titrate the dose to maintain a blood pressure of less than 180/105 mm Hg makes nonintravenous medications a poor choice. Nitrates also have a relative contraindication in the treatment of blood pressure in acute stroke, particularly hemorrhagic stroke, because of the possibility of raising intracranial pressure.

KEY POINT

- After patients with acute ischemic stroke are treated with intravenous recombinant tissue plasminogen activator, their blood pressure should be maintained at less than 180/105 mm Hg to avoid intracerebral hemorrhage.

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Item 87 Answer: D

Educational Objective: Treat chronic migraine.

The patient should be treated with topiramate for chronic migraine, which is headache occurring on 15 or more days per month for more than 3 months. Chronic migraine is characterized by increasingly frequent attacks of migraine that are eventually accompanied by an interval milder headache. By definition, on at least 8 days of the month, the headache of chronic migraine must be severe, possess migraine features, or respond to migraine-specific therapy. The interval headache may have no migraine features and appear to be a tension-type or sinus headache. A medication overuse element is often present and may interfere with the efficacy of preventive and acute migraine treatments. Headache frequency and acute medication use of greater than 10 days per month are significant risk factors for transformation to chronic migraine. Because the development of secondary brain pathology also occasionally may contribute to the transformation to chronic migraine, MRI of the brain is indicated.

Topiramate has level A evidence of effectiveness in treating episodic migraine. Topiramate and onabotulinumtoxinA are the only agents that have shown efficacy in studies of chronic migraine. Topiramate is less expensive than onabotulinumtoxinA.

Carbamazepine is the drug of choice for treating trigeminal neuralgia but has shown no effect on migraine prevention.

Although the serotonin-norepinephrine reuptake inhibitor venlafaxine has demonstrated benefit in migraine prevention studies, no such data are available for duloxetine, which is in the same drug class and is used to treat major depressive disorder and generalized anxiety disorder.

Propranolol has level A evidence of effectiveness in the prevention of episodic migraine but has the potential to worsen both depression and asthma. No evidence supports it use for chronic migraine.

Verapamil is the treatment of choice in cluster headache prevention. The drug, however, has neither level A (effective) nor level B (probably effective) evidence supporting its use in migraine prevention.

KEY POINT

- Topiramate and onabotulinumtoxinA are the only agents that have shown efficacy in studies of chronic migraine.

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Item 88 Answer: D

Educational Objective: Diagnose paraneoplastic limbic encephalitis.

This patient has limbic encephalitis, or inflammation of the emotional and memory structures of the brain. The subacute progression of this patient's symptoms of personality change,

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psychosis, and seizures is most consistent with a paraneoplastic antibody syndrome, which is usually mediated by autoantibodies. Paraneoplastic limbic encephalitis is most commonly associated with lung tumors (usually small cell lung cancer), breast cancer, thymoma, germ cell tumors, and Hodgkin lymphoma. Patients frequently have the neurologic symptoms before discovery of the causative tumor. In this patient, the possible presence of the concomitant syndrome of inappropriate antidiuretic hormone secretion (SIADH), as suggested by the low serum sodium level, makes the particular diagnosis of anti-LG1 (formerly anti–voltage-gated potassium channel) antibody syndrome most likely because it is associated with both limbic encephalitis and SIADH. A definitive diagnosis is usually made after laboratory testing of serum and/or cerebrospinal fluid (CSF) for paraneoplastic antibodies in the appropriate clinical context. Treatment involves immunotherapy and treatment of the underlying tumor, if available. Although these syndromes traditionally have been characterized as "paraneoplastic" because they often are associated with an underlying cancer, many, including most anti-LG1 syndromes, are primarily autoimmune.

Although paranoia and seizures can be seen in Alzheimer disease, they typically occur late in the disease course. Alzheimer disease also is not generally associated with mesial temporal MRI changes.

Reactivation of human herpesvirus 1 also can cause an encephalitis with cognitive problems, psychiatric disturbance, and bitemporal seizures. However, the progression of this type of encephalitis is acute, occurring over days, not weeks. If not treated emergently, herpes encephalitis is lethal. Patients suspected of having human herpesvirus 6 encephalitis will need a lumbar puncture to rule out other viral causes of limbic encephalitis, such as human herpesvirus 3 (varicella-zoster virus), human herpesvirus 8, and cytomegalovirus.

The course of Lewy body dementia is typically longer than that described in this patient. Also, the seizures and imaging findings would be atypical.

KEY POINT

- The subacute progression of the symptoms of personality change, psychosis, and seizures is most consistent with an antibody-mediated cause, such as a paraneoplastic antibody syndrome.

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Tüzün E, Dalmau J. Limbic encephalitis and variants: classification, diagnosis and treatment. Neurologist. 2007 Sep;13(5):261-71. [PMID: 17848866]

Item 89 Answer: A

Educational Objective: Diagnose delirium.

This patient most likely has delirium. Tests such as spelling a word backwards or reciting the days of the week in reverse are rapid ways to measure attention at the bedside. Frequent redirection during the course of an interview is another indicator of inattention. A tangential thought process is often misinterpreted as part of normal aging, but it actually is an indicator of disorganized thinking. Acute onset of cognitive dysfunction over hours to days, impairment of attention, disorganized thinking, and fluctuating mental status are core features of delirium. Increased or decreased psychomotor activity, disorientation, and perceptual disturbances are other supportive features. The use of a screening instrument (such as the Confusion Assessment Method) allows for improved recognition and diagnosis of delirium.

Delirium is an underrecognized disorder in older patients who are hospitalized and may result from various causes, including organ failure (such as the worsening kidney function in this patient), metabolic disturbances, medications, or infection. A key to the likely cause of delirium in this patient is myoclonus seen on physical examination. Myoclonus is a sudden involuntary muscle contraction (positive myoclonus) or sudden brief loss of muscle activity (negative myoclonus, or asterixis); this patient's examination shows asterixis, a common finding in metabolic disturbances (uremia, liver failure, or hypoglycemia) and toxic encephalopathy (due to antibiotics, pain medications, and immunosuppressants).

Although the presence of delirium significantly increases the risk of developing dementia and, conversely, dementia is a significant risk factor for developing delirium, this patient was previously functioning independently. The onset of dementia is typically insidious. The diagnosis of dementia requires 6 months of progressive cognitive decline.

Nonconvulsive status epilepticus (NCSE), or alteration in mental status without overt convulsive activity as a result of continuous or near continuous epileptiform discharges, is often unrecognized in older patients with mental status changes and should be considered as part of the differential diagnosis of acute confusional state if the cause remains unknown. However, the cause of delirium is often identifiable by a careful history, physical examination, and review of medical conditions or interventions that may be contributing to a change in mental status. Additionally, the negative myoclonus seen in this patient would be unlikely in a patient with NCSE without a history of preexisting epilepsy.

Although stroke presents with an abrupt onset, and this patient is at higher risk for stroke because of his recent myocardial infarction, this patient does not have any focal neurologic signs, such as dysarthria, facial droop, hemiparesis, or dysmetria, to suggest that a stroke has occurred.

KEY POINT

- Acute onset of cognitive dysfunction over hours to days, impairment of attention, disorganized thinking, and fluctuating mental status are core features of delirium, an underrecognized disorder in older patients who are hospitalized.

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Young J, Murthy L, Westby M, Akunne A, O'Mahony R; Guideline Development Group. Diagnosis, prevention, and management of delirium: summary of NICE guidance. BMJ. 2010 Jul 28;341:c3704. [PMID: 20667955]

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Item 90 Answer: C

Educational Objective: Treat fatigue in multiple sclerosis.

This patient should be treated with modafinil. She is experiencing fatigue related to her multiple sclerosis (MS). Fatigue is a very common symptom of MS but is often underevaluated and undertreated. Given this patient's decreased work performance and need for daytime sleep, pharmacologic treatment is indicated. The stimulant medications modafinil and armodafinil are frequently used in patients with MS. Amantadine also is an effective therapy for fatigue. For fatigue refractory to these medications, methylphenidate or other amphetamines may be considered.

Iron supplementation is an appropriate treatment for iron deficiency anemia, which can sometimes result in fatigue and always should be excluded as a cause in patients with MS. However, this patient's normal hemoglobin level and normal mean corpuscular volume argue against her being iron deficient.

Although hypothyroidism also can result in fatigue, this patient is clinically euthyroid, and her thyroid-stimulating hormone level is normal. Thyroid hormone supplementation in the absence of hypothyroidism is not appropriate treatment for the fatigue associated with MS.

Nocturnal continuous positive airway pressure (CPAP) can be an appropriate treatment of obstructive sleep apnea (OSA) and other causes of daytime sleepiness, such as primary sleep disorder. OSA should be considered in patients with MS and severe fatigue. However, this patient has no clinical history consistent with OSA, and thus prescribing CPAP without diagnostic polysomnography would not be appropriate.

This patient's history, physical examination, and imaging findings give no indication that her disease-modifying drug is resulting in treatment failure. Therefore, the teriflunomide does not have to be replaced with dimethyl fumarate or any other drug. In addition, fatigue is not a known adverse effect of teriflunomide, and this patient's fatigue is not a sign of medication intolerance.

KEY POINT

- Modafinil is often a successful treatment of fatigue in multiple sclerosis.

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Amato MP, Portaccio E. Management options in multiple sclerosis-associated fatigue. Expert Opin Pharmacother. 2012 Feb;13(2):207-16. [PMID: 22220738]

Item 91 Answer: C

Educational Objective: Treat statin-related toxic myopathy with a hydrophilic statin.

Rosuvastatin is the most appropriate treatment for this patient with hyperlipidemia. Hydrophilic statins, especially rosuvastatin but also pravastatin and fluvastatin, are less likely than lipophilic statins (such as atorvastatin, simvastatin, and lovastatin) to cause statin-induced myopathy and can be used at low doses in patients with previous statin-related myalgia, myopathy, or mild rhabdomyolysis. Hydrophilic statins also are much less likely than lipophilic statins to cause muscle weakness and elevated serum creatine kinase levels. Lipophilic statins should be avoided in patients with previous statin-related myopathy or rhabdomyolysis. Recently, an immune-mediated necrotizing form of statin myopathy that is associated with anti-HMGCR autoantibodies has been identified in some statin-exposed patients; this form continues to progress even after removal of the statin and may require immunosuppression as treatment. This patient, whose symptoms have resolved after discontinuation of the simvastatin, has no evidence of this type of statin myopathy.

Gemfibrozil is a fibric acid derivative that is typically used for the treatment of hypertriglyceridemia. If added to statin therapy, gemfibrozil raises the serum concentration of statins by twofold, which increases the risk of rhabdomyolysis. Cytochrome P3A4 inhibitors, such as antifungal agents, macrolides, immunophilin ligands, and tricyclic antidepressants, also can increase risk of statin-induced myopathy.

Although selenium supplementation does not treat hyperlipidemia, it has been suggested as a potential method of preventing statin-induced myopathy. Available evidence, however, does not allow a definitive conclusion to be drawn.

KEY POINT

- Hydrophilic statins, such as rosuvastatin, are less likely than lipophilic statins to cause statin-induced myopathy.

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Mohassel P, Mammen AL. Statin-associated autoimmune myopathy and anti-HMGCR autoantibodies. Muscle Nerve. 2013 Oct;48(4): 477-83. [PMID: 23519993]

Item 92 Answer: D

Educational Objective: Diagnose behavioral variant frontotemporal dementia.

This patient likely has the behavioral variant type of frontotemporal dementia (FTD). This form of FTD is a clinical syndrome characterized by the insidious onset of changes in behavior, personality, and executive function. This patient demonstrates the typical features of hyperorality (as evidenced by excessive alcohol intake), loss of insight, loss of empathy, compulsive behaviors, and impaired social conduct. An early age of onset is typical for the disease. Behavioral variant FTD is the second most common cause of early-onset dementia, second only to Alzheimer disease. A family history of a related neuropsychiatric disorder is evident in approximately 40% of patients with FTD; this patient's family history of a father being institutionalized in his 50s is thus concerning. Patients with behavioral variant FTD typically do well on the Mini-Mental State Examination because executive function is not well assessed by this

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screening test, and this cognitive domain is most likely to be impaired in patients with FTD.

Although Alzheimer disease is the most common cause of early-onset dementia, the disease presentation in this patient is not typical for this diagnosis. On cognitive testing, patients with Alzheimer disease typically exhibit impairment on tests of learning, memory, and visuospatial function. This patient showed none of these impairments.

This patient's decline in functioning can be attributed to behavioral dysfunction rather than cognitive impairment, which is the cause of impaired functioning in patients with dementia with Lewy bodies. In addition, he lacks other supportive features of dementia with Lewy bodies, such as parkinsonism, formed visual hallucinations, fluctuating cognition, rapid eye movement sleep behavior disorder, or autonomic dysfunction.

Patients with behavioral variant FTD are frequently misdiagnosed with a psychiatric illness, such as depression, bipolar disorder, or another mood or personality disturbance, especially early in the disease course. Although this patient has a few symptoms of depression, such as apathy and loss of interest, the prominent changes in behavior and lack of additional depressive symptoms make behavioral variant FTD the more likely diagnosis.

KEY POINT

- Behavioral variant frontotemporal dementia is characterized by the typical features of hyperorality, loss of insight, loss of empathy, compulsive behaviors, impaired social conduct, and an early age of onset.

Bibliography

Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011 Sep;134(Pt 9):2456-77. [PMID: 21810890]

Item 93 Answer: B

Educational Objective: Diagnose Creutzfeldt-Jakob disease.

This patient most likely has Creutzfeldt-Jakob disease (CJD), a dementing illness that occurs subacutely over weeks to months and is classified as a rapidly progressive dementia. This patient has the hallmark neuroradiologic finding of sporadic CJD, namely, hyperintensities on diffusion-weighted imaging (DWI), in this instance involving the basal ganglia and insular and left parietal cortices. DWI hyperintensities also can occur in the cerebral cortex (as cortical ribboning) and thalamus in CJD. DWI is highly sensitive and specific for the diagnosis of sporadic CJD.

Alzheimer disease can present as a rapidly progressive dementia, but not commonly. The MRI findings seen in this patient are not consistent with Alzheimer disease, in which the MRI is typically normal or shows focal atrophy involving the temporal and/or parietal lobes.

Rapidly progressive dementias are relatively uncommon and are more likely to be due to treatable, reversible causes than are the more typical dementing conditions that develop over years. Herpes simplex virus 1 (HSV-1) encephalitis typically results in an acute neurologic decline occurring over days to 1 week rather than months as with this patient. Fever, focal neurologic findings, and focal seizures are common. T2 hyperintensities (and occasionally DWI hyperintensities), with a predilection for the temporal lobes, are strongly suggestive of HSV-1 encephalitis, rather than the DWI abnormalities seen in this patient.

Vascular neurocognitive disorder is characterized by cognitive impairment occurring after a clinical stroke or in the presence of neuroimaging findings of cerebrovascular disease. The prevalence of poststroke dementia is approximately 30%. This patient has neither the history nor focal neurologic signs (such as hemiparesis, facial droop, or dysarthria) to suggest that a clinical stroke has occurred. Although DWI is very sensitive in the detection of early ischemic infarction, the DWI abnormalities seen in this patient do not follow vascular territories and are instead classic for sporadic CJD.

KEY POINT

- Creutzfeldt-Jakob disease can be diagnosed by the presence of hyperintensities in the cerebral cortex (cortical ribboning), basal ganglia, or thalamus on diffusion-weighted imaging, which is highly sensitive and specific for the diagnosis.

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Paterson RW, Takada LT, Geschwind MD. Diagnosis and treatment of rapidly progressive dementias. Neurol Clin Pract. 2012 Sep;2(3):187-200. [PMID: 23634367]

Item 94 Answer: D

Educational Objective: Treat acute ischemic stroke with thrombolysis.

This patient should receive intravenous recombinant tissue plasminogen activator (rtPA). He is within the 3-hour window for treatment of patients who do not meet any of the exclusion criteria for thrombolysis. In the National Institute of Neurological Diseases and Stroke (NINDS) rtPA trial, patients who received intravenous rtPA within 3 hours of stroke onset had a greater likelihood of clinical improvement at 3 months compared with those who received placebo. The trial included patients with atrial fibrillation and all ischemic stroke subtypes and showed no significant safety difference between stroke subtypes. Because he has no contraindications to thrombolysis, it is the treatment of choice in this patient.

High-dose (325-mg) aspirin would be an appropriate initial treatment if the patient met any of the exclusion criteria for thrombolysis, which he does not. As long as a follow-up CT scan of the head shows no hemorrhage, aspirin should be initiated 24 hours after administration of rtPA.

Hyperglycemia is common in patients with acute ischemic stroke and, if persistent in the first 24 hours

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after stroke onset, is associated with poor functional outcomes. To date, no definitive clinical trials have outlined the best approach to treatment or the most appropriate targets. Acute ischemic stroke guidelines are thus in keeping with general recommendations for all critically ill hospitalized patients who have mild hypertension, with or without diabetes mellitus, which are not to use intensive insulin therapy to normalize plasma glucose levels. If insulin therapy is required, the American College of Physicians recommends target plasma glucose levels of 140 mg/dL to 200 mg/dL (7.8-11.1 mmol/L) while monitoring carefully for hypoglycemia. Insulin therapy is thus not indicated in this patient whose plasma glucose level falls in the target range.

Intravenous heparin does not reduce the 14-day risk of recurrent stroke or mortality in patients with atrial fibrillation who have a new stroke and is therefore not indicated.

KEY POINT

- In patients with focal neurologic symptoms suggestive of an acute ischemic stroke, recombinant tissue plasminogen activator should be administered within 3 hours of symptom onset to patients who do not meet any of the exclusion criteria.

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Item 95 Answer: A

Educational Objective: Diagnose nonconvulsive status epilepticus with continuous electroencephalographic monitoring.

This patient should have continuous monitoring with electroencephalography (EEG) because his presentation is concerning for nonconvulsive status epilepticus (NCSE). Approximately 48% of patients treated for convulsive status epilepticus (CSE) will continue to have subtle or subclinical seizures on EEG. Persistently altered mental status, particularly with waxing and waning features and focal neurologic deficits (such as aphasia), is a characteristic feature of NCSE. Patients with intracranial structural abnormalities who are comatose also are at high risk for this disorder. Intracerebral hemorrhage is an additional risk factor for nonconvulsive seizures and status epilepticus.

Continuous EEG monitoring is twice as sensitive as a routine 30-minute EEG for detecting seizures, especially the intermittent seizures that are common in patients already treated for CSE. All patients with altered mental status after CSE should have continuous EEG monitoring for at least 24 hours to detect nonconvulsive seizures or a changed status. Comatose patients should be evaluated for 24 to 48 hours. Continuous EEG monitoring is indicated in patients with acute structural intracranial lesions and altered mental status, even if clinically evident seizures have not occurred.

Flumazenil should not be administered to any patient with seizures or at risk for seizures because the drug can precipitate status epilepticus. Because the patient is not showing any signs of respiratory depression or other adverse effects of medication, there is no urgent need to reverse the benzodiazepine he received as part of appropriate CSE treatment.

Cavernous malformations usually have self-limited bleeding, and this patient does not have any mass effect or other urgent need for surgery. Although he ultimately may be a surgical candidate, given that refractory seizures are associated with cavernous malformations, surgical resection is not the most appropriate next step. He first should be evaluated and treated for NCSE.

Maintenance antiepileptic drugs (AEDs) should not be withheld in a patient with CSE at presentation unless the drugs are clearly causing severe adverse effects. In this patient, NCSE is a more likely explanation of the patient's mental state than is an adverse effect of the AED.

KEY POINT

- All patients with altered mental status after convulsive status epilepticus should have continuous electroencephalographic monitoring for at least 24 hours to detect nonconvulsive seizures.

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Kennedy JD, Gerard EE. Continuous EEG monitoring in the intensive care unit. Curr Neurol Neurosci Rep. 2012 Aug;12(4):419-28. [PMID: 22653639]

Item 96 Answer: B

Educational Objective: Anticipate the potential adverse effects of medications used for symptomatic treatment of patients with multiple sclerosis.

This patient's dalfampridine (4-aminopyridine) should be discontinued. Dalfampridine is a voltage-gated potassium channel antagonist that can potentiate action potentials along demyelinated axons and is used in patients with multiple sclerosis (MS) for potassium channel blockade. This medication can improve lower extremity function and walking speed and endurance. Because of its mechanism of action, seizures have been reported as a rare, dose-dependent adverse effect of this medication. Dalfampridine is excreted through the kidneys and thus is contraindicated in patients with kidney disease because its resultant decreased clearance would significantly increase the seizure risk. For this reason, this medication should be discontinued in this patient.

Baclofen can alleviate the spasticity often associated with MS. There is no reason to discontinue the drug in this patient with acute kidney injury because no specific adverse effects of this drug due to kidney toxicity or related to kidney

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clearance have been reported. Dosing may have to be modified in patients with severe kidney failure, however.

Glatiramer acetate is a disease-modifying medication used in the treatment of MS to impede disease activity and prevent relapses. This drug has no known adverse effects on the kidneys due to poor clearance or direct toxicity.

Vitamin D supplementation is now suggested for all patients with MS to reduce the accumulation of new lesions on MRI. No adverse effects on kidney function or kidney clearance have been reported.

KEY POINT

- Dalfampridine is renally excreted and thus is contraindicated in patients with kidney disease.

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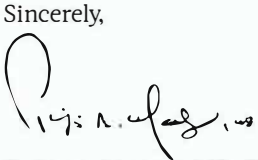

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Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon (**HVC**).

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Errata for MKSAP 17 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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Pulmonary and Critical Care Medicine High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 17 in several important ways. MKSAP 17 now includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Pulmonary and Critical Care Medicine section of MKSAP 17.

- Low-dose chest CT utilizes a lower total radiation dose than standard chest CT and remains as effective for lung cancer screening and for imaging lung nodules and lung parenchyma.
- Vocal cord dysfunction, characterized by (1) mid-chest tightness with exposure to triggers, (2) difficulty breathing in, and (3) partial response to asthma medications, is often misdiagnosed as severe asthma resulting in unnecessary intubations and high health care utilization.
- Although expensive, omalizumab has been shown to reduce emergency department visits and is cost effective in moderate to severe persistent asthma with: (1) symptoms inadequately controlled with inhaled glucocorticoids, (2) allergies to perennial aeroallergens, and (3) serum IgE levels between 30 and 700 U/mL (30-700 kU/L).
- Smoking cessation is the single most clinically efficacious and cost-effective way to prevent COPD, to slow progression of established disease, and to improve survival.
- Screening for COPD with spirometry should not be performed in asymptomatic patients.
- Because inhaled medications are a mainstay of COPD management, good inhaler technique should be ensured (particularly in patients with suboptimal symptom control) before making changes to the drug regimen.
- Long-acting bronchodilators in COPD improve FEV_1, improve health status, and significantly reduce the frequency of exacerbations, but have not been shown to affect mortality.
- The use of inhaled glucocorticoids is not effective as primary therapy or monotherapy in COPD and should only be used in combination with other proven therapies.
- Roflumilast is an oral selective phosphodiestarase-4 (PDE-4) inhibitor and its use should be limited to add-on therapy in severe COPD associated with chronic bronchitis and a history of recurrent exacerbations; it is not a bronchodilator, is expensive, and has not been shown to be effective in other groups of patients with COPD.
- Home treatment of a COPD exacerbation is reasonable in patients with less severe lung disease who do not have significant accompanying illnesses and who are experiencing mild to moderate exacerbations.
- Glucocorticoids for acute exacerbations of COPD have been shown to reduce recovery time, improve lung function and arterial hypoxemia, decrease risk of early relapse, decrease treatment failure, and decrease length of hospital stay; a frequently used regimen is oral prednisone 40 mg/d for 5 days and intravenous glucocorticoids should be reserved for patients unable to tolerate oral therapy.
- Antibiotic use in acute exacerbations of COPD should be limited to patients with increased dyspnea and purulent sputum or those who require mechanical ventilation (invasive or noninvasive).
- Patients with COPD should receive inactivated influenza vaccination annually, and the 23-valent polysaccharide pneumococcal vaccine (PPSV23) should be given to all patients aged 19 to 64 years with COPD, with revaccination at age 65 years or older if 5 years have elapsed since the previous pneumococcal immunization; the 13-valent pneumococcal conjugate vaccine should also be administered at age 65 years or older if 1 year has elapsed since the last PPSV23 immunization (see Item 98).
- There are no data to support the routine use of short- or long-acting bronchodilators or the long term use of systemic glucocorticoids in patients with bronchiectasis.

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- Pulmonary rehabilitation programs are effective in patients with bronchiectasis and are associated with significant improvements in exercise capacity and fewer outpatient and emergency department visits.
- High-resolution CT is the diagnostic tool of choice for evaluation of diffuse parenchymal lung disease; there is little role for plain chest radiography or conventional CT imaging (5-mm slice thickness) given the limits of their resolution (see Item 11).
- Cessation of smoking is the primary management for smoking-related diffuse parenchymal lung disease.
- The most recent evidence-based consensus statement recommends against mechanical ventilation for individuals with acute respiratory failure due to either progression or an acute exacerbation of idiopathic pulmonary fibrosis.
- The American Thoracic Society recommends palliation of symptoms rather than intubation and mechanical ventilation for patients with respiratory failure due to progressive idiopathic pulmonary fibrosis (see Item 44).
- In patients with COPD, parameters that portend a poor prognosis and trigger more extensive discussions regarding end-of-life care include an FEV_1 of less than 30% of predicted, oxygen dependence, multiple hospital admissions for COPD exacerbations, significant comorbidities, weight loss and cachexia, decreased functional status, and increasing dependence on others (see Item 69).
- The first step in management of shift work sleep disorder is to address sleep-related behaviors and the sleep environment, referred to as sleep hygiene (see Item 90).
- The overriding principle in management of occupational lung disease is prevention, consisting of interventions in the workplace to avoid exposures as well as early identification of coworkers who may also be at risk.
- Spirometry before and after rechallenge with workplace exposures is a cost-effective way to confirm the diagnosis of occupational asthma (see Item 29).
- Chest radiograph and thoracic ultrasound are important tests in the evaluation of pleural effusion; ultrasound has a higher sensitivity for pleural fluid and no associated radiation exposure.
- Bedside ultrasound is recommended for thoracentesis as it enhances procedural accuracy and safety.
- Observation alone has been shown to be safe for small pneumothoraces in patients with minimal symptoms.
- Advanced therapy for pulmonary hypertension with vasodilators should be reserved for patients with pulmonary arterial hypertension (group 1) as they have not been shown to be efficacious and may be harmful in this group.
- Ventilation-perfusion scanning is a sensitive indicator of chronic thromboembolic pulmonary hypertension and is generally the preferred first imaging modality.
- If prior imaging of the chest is available, it should be reviewed as a low-risk and inexpensive way to assess the stability or growth of the solitary pulmonary nodule.
- In patients with a subcentimeter pulmonary nodule, any previous imaging of the chest should be obtained to establish whether the nodule has remained stable or has grown over time (see Item 3).
- If imaging demonstrates stability of a solitary pulmonary nodule (and no other new findings) for 24 months, no further imaging is required (see Item 65).
- Smoking prevention and cessation are the most important steps in preventing lung cancer.
- The United States Preventive Services Task Force recommends low-dose CT screening for lung cancer in patients between the ages of 55 and 79 years who have a 30-pack-year or more history of smoking and who are currently smoking or quit within the last 15 years.
- Overnight pulse oximetry alone has a high rate of false-positive and false-negative results and has not been validated as a screening tool for obstructive sleep apnea; its use should be limited to patients with low pretest probability, few symptoms, or in patients who prefer to avoid treatment.
- A cost-effective approach to a patient with an inadequate response to obstructive sleep apnea treatment with continuous positive airway pressure (CPAP) therapy is to first check the level of adherence to therapy by downloading and reviewing data from the CPAP device (see Item 49).
- Noninvasive ventilation is associated with decreased ICU mortality, intubation rate, and ICU length of stay in immunocompromised patients and should be considered as an alternative to endotracheal intubation in patients who are appropriate candidates.
- In patients with hypoxemic respiratory failure due to heart failure, noninvasive positive pressure ventilation decreases the need for mechanical ventilation, improves respiratory parameters, and may decrease mortality (see Item 15).
- Bedside ultrasound to assess vena caval dimensions induced by positive-pressure ventilation appears to be highly predictive of volume responsiveness and is a noninvasive alternative to a pulmonary artery catheter.
- Ultrasound-guided central line insertion is associated with a reduction in failure of catheter placement and vessel injury, as well as prevention of pneumothorax.
- When compared with deep sedation, light sedation (a drowsy and cooperative patient) reduces ICU-related posttraumatic stress disorder, time on the ventilator, and mortality.
- Do not routinely transfuse erythrocytes in nonbleeding, hemodynamically stable patients in the ICU with a hemoglobin concentration greater than 7 g/dL (70 g/L) (see Item 93).
- Large-caliber peripheral intravenous access is the preferred route of infusion when large volumes of crystalloid fluid and blood are needed quickly (see Item 8).
- The association between opioid analgesics and central sleep apnea (CSA) is increasingly recognized; reduction or withdrawal of opioids improves CSA (see Item 41).

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Pulmonary and Critical Care Medicine

Pulmonary Diagnostic Tests

Pulmonary Function Testing

Pulmonary function testing is essential to the diagnosis and management of respiratory symptoms and pulmonary diseases. Pulmonary function tests are also used in the evaluation and screening of patients who are at risk for lung disease, such as those with occupational exposures or drug toxicity.

Spirometry

Spirometry, the measurement of pulmonary airflow, is a readily available and essential initial test. Spirometry may be performed in the office setting or more formally in a pulmonary function testing laboratory. The results of spirometry are highly dependent on technique and patient effort; therefore, patients should be carefully instructed in the proper technique prior to testing. Proper technique consists of the patient sitting upright with the head erect and the mouthpiece held tightly between the lips. Measurements should be repeated to ensure reproducibility; the two largest values within 150 mL of each other should be used. Normal reference values for spirometry are dependent on age, gender, height, and race.

Measures of interest are the forced expiratory volume exhaled in 1 second (FEV_1) and forced expiratory volume until full exhalation, or forced vital capacity (FVC). The FEV_1/FVC ratio is used to assess for airway obstruction; a value less than 70% (the lower limit of normal) is consistent with airflow obstruction. With evidence of obstruction, the degree of reduction in FEV_1 is used to characterize the degree of obstruction. An FEV_1 of 50% to 80% of predicted is classified as moderately reduced, 34% to 49% of predicted is severely reduced, and less than 34% of predicted is very severely reduced. In patients with evidence of obstruction, a bronchodilator challenge (2 to 4 puffs of a short-acting β_2-agonist) is often given to determine the reversibility of obstruction (which may be helpful in differentiating between asthma and COPD); an increase in FEV_1 of 12% or 200 mL is considered a positive bronchodilator response.

A normal FEV_1/FVC ratio may reflect normal lung function or may indicate a restrictive lung defect. However, if the FEV_1 and the FVC are reduced proportionately with each other and are below the predicted normal values, the spirometry results are consistent with a restrictive defect, which may be confirmed by further testing demonstrating low lung volumes (see Lung Volumes).

Flow-volume loops graphically plot pulmonary airflow during exhalation and inspiration, with characteristic patterns associated with specific clinical conditions (**Figure 1**).

KEY POINT

- An FEV_1/FVC ratio of less than 70% on spirometry is consistent with airflow obstruction.

Bronchial Challenge Testing

In patients with clinical symptoms suggestive of bronchospastic disease (such as cough or unexplained dyspnea) but with normal spirometry, bronchial challenge testing may be diagnostically helpful. Bronchial challenge testing uses a controlled inhaled stimulus to induce bronchospasm in association with spirometry; a positive test is indicated by a drop in the measured FEV_1. Because bronchial challenge testing may induce severe bronchospasm, it should only be performed in a controlled environment such as a pulmonary function testing laboratory.

Methacholine is a commonly used agent that induces cholinergic bronchospasm at low concentrations in patients with asthma. The provocative dose 20% (PD20) is the dose of methacholine that causes a significant drop in the FEV_1 of 20% or greater. The ability to achieve a PD20 at low concentrations of methacholine indicates more easily induced obstruction and is sensitive for detecting asthma.

Similar principles apply to other forms of bronchial challenge testing, such as after exposure to cold air or exercise, in which case a 10% drop in FEV_1 from baseline in the context of a supporting clinical picture is diagnostic.

KEY POINT

- Bronchial challenge testing with a controlled stimulus is helpful in patients with dyspnea or cough of uncertain cause when spirometry results are normal.

Lung Volumes

Lung volume testing directly and indirectly measures the static amount of air in the lungs and can be helpful in the diagnostic evaluation of dyspnea and abnormal spirometry results. Key measures include the total lung capacity (TLC), or the amount of air in the lungs after maximal inhalation, and residual volume (RV), the volume of air remaining in the lungs after a maximal exhalation. Lung volume tests are performed most commonly using body plethysmography. The components that are directly measurable by plethysmography are the functional residual capacity (air in the lungs after a

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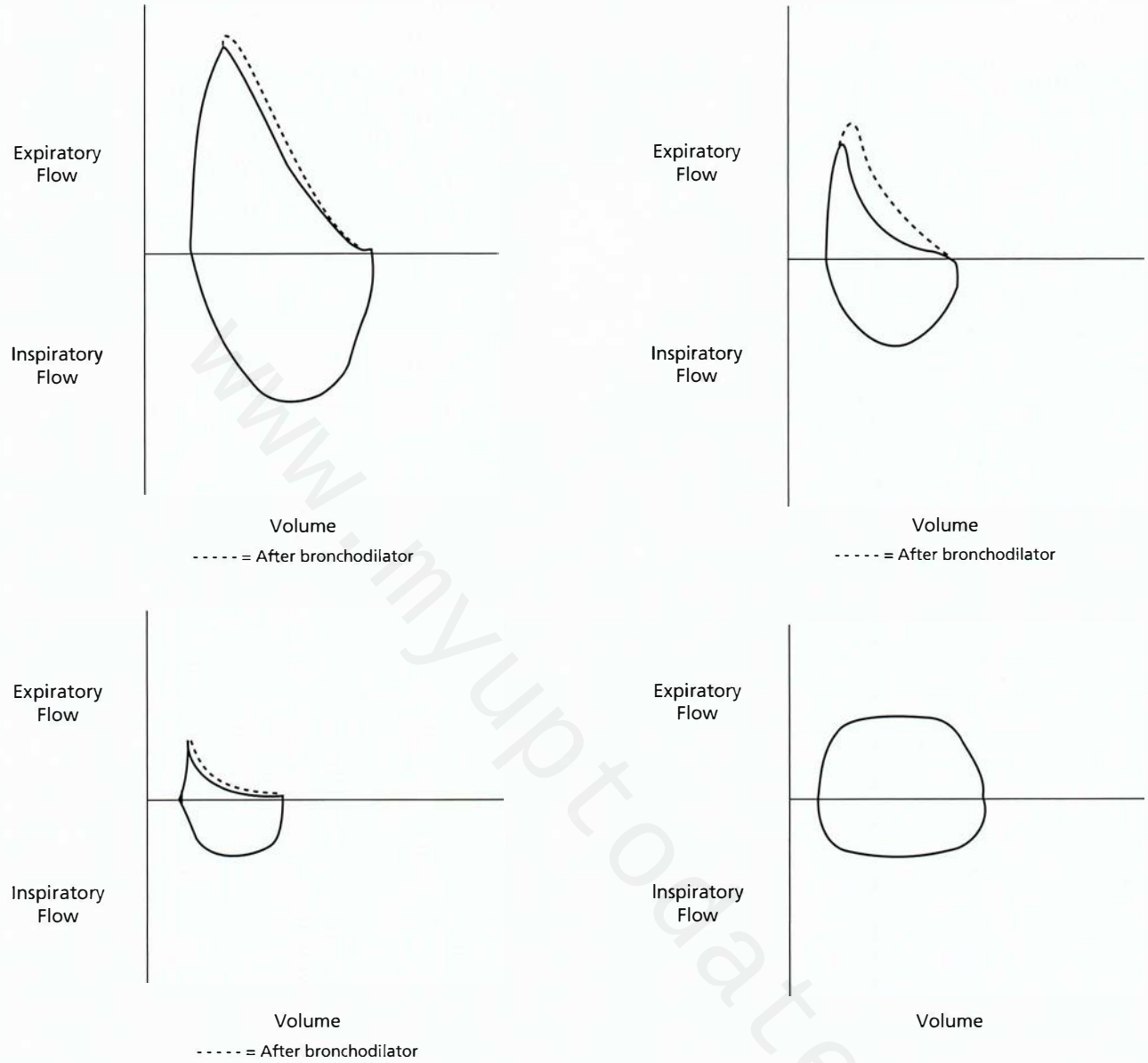

FIGURE 1. *Top left panel*: Flow-volume loop demonstrating normal spirometry, with similar maximum inspiratory and expiratory flows; no significant change is seen after bronchodilator administration. *Top right panel*: Flow-volume loop demonstrating asthma, with a reduction in peak expiratory flow and concave curvature for the expiratory limb while the inspiratory limb remains normal; improvement is seen in expiratory flows (particularly the increase in peak flow) after bronchodilator administration. *Bottom left panel*: Flow-volume loop demonstrating COPD, with a significant reduction in peak expiratory flow and concave appearance of the expiratory limb; no significant change is seen after bronchodilator administration. *Bottom right panel*: Flow-volume loop demonstrating fixed obstruction/tracheal stenosis, with flattening of the peak inspiratory and expiratory flows.

normal expiration), expiratory reserve volume (air in the lungs that is still able to be exhaled after normal expiration), and slow vital capacity (the volume of air maximally exhaled during expiration with a slow exhalation). These measures are then used to calculate the RV and TLC. In the setting of restrictive lung patterns on spirometry, TLC measurement can determine whether restriction is due to a primary parenchymal process or chest cage restriction from factors such as obesity, muscle weakness, or scoliosis. In obstructive lung diseases, an increased TLC is suggestive of hyperinflation and high compliance, and an increased RV is suggestive of air trapping.

Diffusing Capacity for Carbon Monoxide

The diffusing capacity for carbon monoxide (DLCO) is performed by having the patient take a single, deep breath containing a very low percentage of carbon monoxide and measuring the amount of subsequently exhaled carbon monoxide following a short period of breath holding. Carbon monoxide is rapidly and efficiently taken

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up by hemoglobin, and the amount absorbed is determined by the amount of blood recruited to the pulmonary alveolar capillary bed and the surface area available for diffusion. DLCO is therefore useful as a measure of the capacity for gas transfer through the alveolar-capillary membrane. Clinical disorders that recruit blood to the alveoli (cardiac shunt, asthma, erythrocytosis, alveolar hemorrhage) can elevate DLCO levels. In contrast, conditions that decrease the surface area available for diffusion, decrease permeability across the alveolar-capillary membrane, or otherwise interfere with gas transfer can reduce DLCO. For example, a reduced DLCO in a patient with a low TLC or restriction on spirometry is suggestive of a parenchymal or interstitial process. The DLCO may also be diminished in COPD (from parenchymal destruction) or in conditions that affect the pulmonary vasculature such as pulmonary hypertension or chronic pulmonary thromboembolic disease.

6-Minute Walk Test

Lung function during exertion using the 6-minute walk test (6MWT) is helpful to assess disability and prognosis in chronic lung conditions. Simple pulse oximetry and oxygen desaturation studies performed at rest and with exertion assess the need for oxygen supplementation. During a 6MWT, oxygen saturation, heart rate, dyspnea and fatigue level, and distance walked at a normal pace in 6 minutes are recorded. This relatively simple maneuver quantifies exercise tolerance, determines effective interventions, and helps predict morbidity and mortality. The 6MWT is routinely used before, during, and after pulmonary rehabilitation programs.

Pulse Oximetry

Pulse oximetry is a noninvasive measurement of arterial hemoglobin saturation. Pulse oximeters have two light-emitting diodes and a photodetector that measures the pulsatile fraction of hemoglobin and algorithmically estimates the arterial hemoglobin saturation. In general, resting oxygen saturation less than or equal to 95% or a desaturation with exercise greater than or equal to 5% is considered abnormal.

Pulse oximetry cannot distinguish between oxygen saturation of hemoglobin and similar abnormal hemoglobins such as carboxyhemoglobin. In patients with high levels of carboxyhemoglobin, as seen in carbon monoxide poisoning, pulse oximetry will provide false-negative results. If the presence of carboxyhemoglobin is suspected, co-oximetry is the preferred test to measure oxyhemoglobin.

Imaging and Bronchoscopy

Imaging

Chest Radiography

A plain chest radiograph allows visualization of the bony structures and contents of the thoracic cavity, including the airways, lungs, heart, pleura, and great vessels (**Figure 2**). It is therefore often the first diagnostic test performed when evaluating any symptoms potentially explained by pathology to any of these structures. The cost and risks to the patient, such as subsequent consequences of radiation exposure (**Table 1**), are lower compared with other chest imaging studies. However, because of the low sensitivity of plain chest radiography in diagnosing

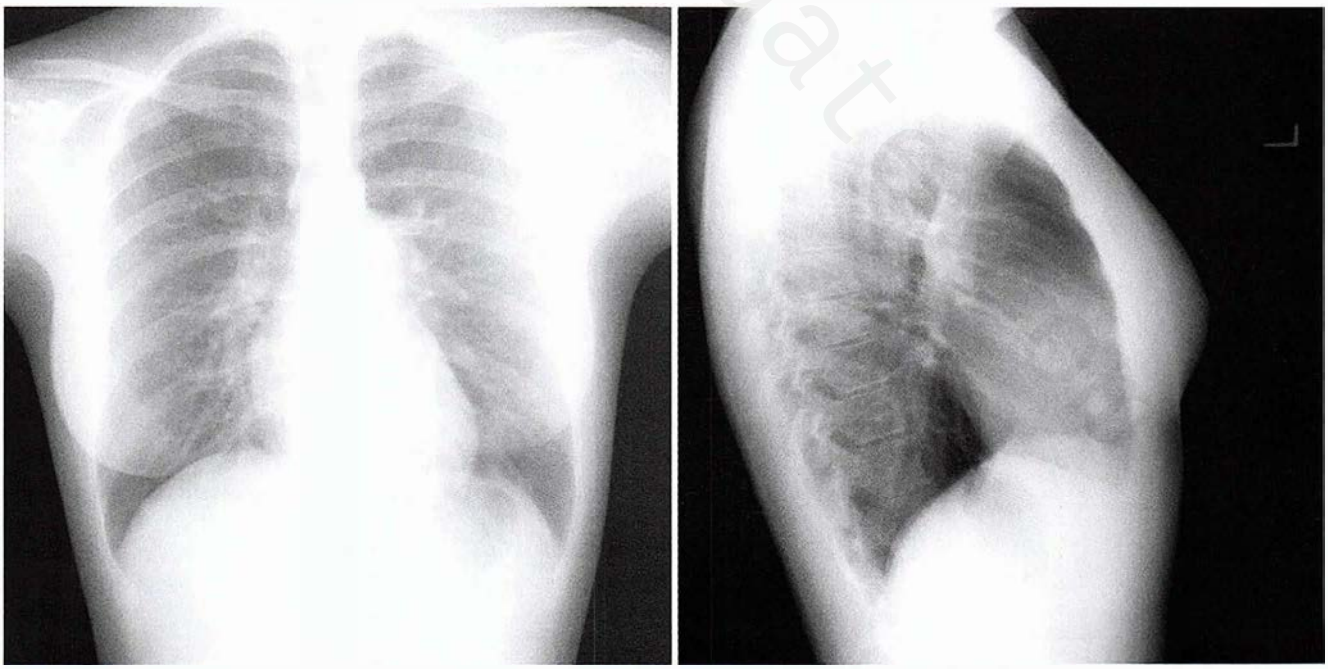

FIGURE 2. Posteroanterior and lateral chest radiographs showing normal cardiopulmonary and skeletal structures.

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TABLE 1. Comparison of Radiation Exposure of Chest Imaging Techniques

Imaging Modality	Equivalent Daytime Radiation	Equivalent Number of Chest Radiographs
PA/lateral radiograph	10 days	N/A
Routine CT	3 years	400
HRCT	89 days	43
CTPA	4.3 years	750
Low-dose CT	68 days	33
FDG-PET/CT	5.4 years	809

CTPA = CT pulmonary angiogram; FDG = fluorodeoxyglucose; HRCT = high-resolution CT; N/A = not applicable; PA = posteroanterior.

several cardiopulmonary conditions, CT of the chest is often obtained if the chest radiograph is normal or if clarification of an abnormal chest radiograph finding is needed.

Computed Tomography

The choice of unenhanced CT, contrast-enhanced CT, high-resolution CT (HRCT), or CT pulmonary angiography is dependent on the information being sought based on the differential diagnosis. Contrast may be added to the study to better evaluate the mediastinal structures (for example, to assess for lymphadenopathy) whereas HRCT is indicated if diffuse parenchymal lung disease is suspected. HRCT can help narrow the differential diagnosis based on the distribution of the lung parenchymal abnormalities and the presence or absence of associated findings. Because the HRCT protocol employs thin sections obtained at wide intervals (typically 1 cm between imaged cross sections), this type of CT should not be performed to evaluate suspected lung disease with a focal abnormality or to evaluate pulmonary nodules. CT pulmonary angiography uses a timed bolus of intravenous contrast to opacify the pulmonary arteries and is mainly used in the diagnosis of pulmonary embolism or aortic dissection. Patients who meet criteria for lung cancer screening should undergo imaging with low-dose chest CT to minimize radiation exposure (see Table 1). Low-dose chest CT images utilize a lower total radiation dose than standard CT chest protocols. The lower dose of radiation decreases the radiation to patients and is as effective in imaging lung nodules and lung parenchyma owing to the high inherent contrast between lung tissue and air.

KEY POINT

- Low-dose chest CT utilizes a lower total radiation dose than standard chest CT and remains as effective for lung cancer screening and for imaging lung nodules and lung parenchyma. HVC

Positron Emission Tomography

Patients with a pulmonary nodule or other findings suggestive of malignancy may require PET/CT. This test most commonly uses fluorodeoxyglucose (FDG) as a metabolic marker to identify rapidly dividing cells such as tumor cells and, to a lesser degree, any inflammatory lesion (**Figure 3**). For example, if a pulmonary nodule is identified but no previous imaging is available, PET/CT can help determine the activity of the nodule, as long as the nodule is approximately 1 cm or larger. At smaller sizes, PET/CT imaging may be falsely negative. A nodule that demonstrates no FDG uptake is unlikely to be malignant. Any disease with metabolic activity, including infection, inflammation, and malignancy, can cause an FDG-avid nodule. PET/CT imaging can also be used in the management of known cancer. It can be used for staging the cancer (by determining the presence or absence of metastatic disease), monitoring response to treatments (not only by assessing for a decrease in size but also for a decrease in metabolic activity), and surveillance for recurrence.

Bronchoscopy

Fiberoptic bronchoscopy is an endoscopic technique that allows for the visualization of the tracheobronchial lumen and sampling of suspected areas of disease, including the

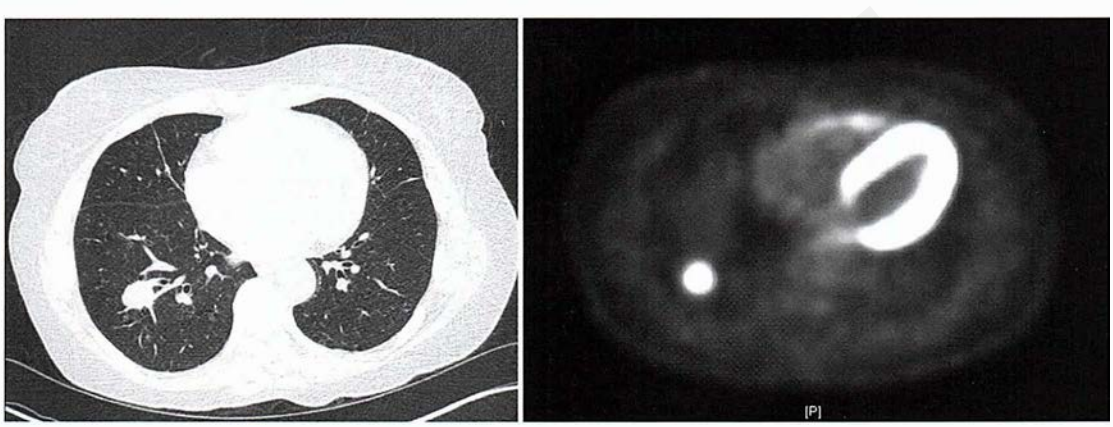

FIGURE 3. A right lower lobe lobulated nodule was identified on an unenhanced chest CT (*left panel*). A high metabolic rate was confirmed on PET/CT (*right panel*) and the patient was subsequently diagnosed with adenocarcinoma of the lung.

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CONT.

endobronchial mucosa, lung parenchyma, and accessible lymph nodes. For diagnostic purposes, a flexible bronchoscope is used more commonly than a rigid bronchoscope. A rigid bronchoscope requires general anesthesia, but its larger lumen may be necessary for some therapeutic bronchoscopies such as attempted retrieval of a foreign body. Flexible bronchoscopy can be performed under light to moderate sedation, and, although the flexible bronchoscope's lumen is smaller than that of a rigid bronchoscope, it does allow instruments to be used to help increase its diagnostic yield. Bronchoscopic diagnostic procedures are described in **Table 2**.

The most common indications for a bronchoscopy are (1) evaluation of new respiratory symptoms associated with airway pathology (for example, hemoptysis, stridor); (2) pulmonary infections, especially if they are progressive despite appropriate empiric therapy or occur in immunocompromised patients; (3) diagnosis or staging of primary or metastatic cancer of the lung; (4) diagnosis of an abnormal imaging finding such as a pulmonary nodule, persistent infiltrate, or atelectasis; and (5) diffuse parenchymal lung disease of unknown cause (**Table 3**). A flexible or rigid bronchoscope may also be used therapeutically, such as in instances of airway stenosis (placement of stents or dilation), foreign-body aspiration, or mucus plugging, or to treat a lesion locally with electrocoagulation, laser therapy, or cryotherapy.

Major complications of bronchoscopy are rare and depend on the intervention undertaken; complications include pneumothorax (1%–4%) and significant bleeding (1%) with the use of transbronchial lung biopsy. Patients may also have adverse effects from topical anesthetics and systemic sedatives. Bronchoscopy should be avoided in patients who cannot tolerate possible adverse events, which include hypotension, tachycardia, severe hypoxemia, and bronchospasm. For example, bronchoscopy should be postponed in a patient with a recent myocardial infarction or who requires high amounts of supplemental oxygen. Although hypoxemia, even when severe, is not an absolute contraindication, patients who require high concentrations of supplemental oxygen may require mechanical ventilation to safely perform the bronchoscopy; patients should be informed about this concern in advance of the procedure.

TABLE 2. Bronchoscopic Diagnostic Procedures

Technique	Description	Examples of Indications
Airway inspection	Visualization of the tracheobronchial tree to the level of segmental airways	Hemoptysis Localized wheeze Persistent atelectasis Diagnosis of tracheobronchomalacia
Bronchial washings	Samples from large airways	Diagnosis of infections Cell counts in diagnosis of parenchymal lung disease
Bronchoalveolar lavage	Samples from small bronchi and alveoli	Diagnosis of infections Cell counts in diagnosis of parenchymal lung disease
Bronchial brushings	Brushings of the endobronchial mucosa for cells	Endobronchial lesions
Endobronchial biopsy	Biopsy of the lumen of the airway	Endobronchial mass or nodules
Transbronchial lung biopsy	Biopsy of the parenchyma	Diffuse lung disease Persistent infiltrates Posttransplant rejection
Transbronchial needle aspiration	Aspiration of a lymph node or mass adjacent to the airway	Lymphadenopathy Pulmonary mass Mediastinal mass
Endobronchial ultrasound	Use of an ultrasound probe at the distal end of the bronchoscope	Lymphadenopathy Pulmonary mass
Electromagnetic navigation	Images from a recent CT are used to create a 3D model of the patient's airways. During the bronchoscopy, the patient's airways are "linked" with the 3D model whenever the bronchoscope reaches a locatable anatomic landmark. An electromagnetic guidance system at the bronchoscope is then used to create a map of the airways and guide the physician to the area of interest.	Pulmonary mass or nodule

3D = three-dimensional.

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TABLE 3. Common Indications for Diagnostic Bronchoscopy

Indication	Comments
Hemoptysis	Patients with active hemoptysis without an obvious explanation warrant an airway inspection via bronchoscopy and chest imaging. Bronchoscopy may be useful in localizing an active bleeding source as well as for treatment of endobronchial abnormalities causing bleeding. However, bronchoscopy is not indicated for all patients presenting with hemoptysis from known causes, including respiratory infection or heart failure exacerbation.
Stridor or localized wheeze	Bronchoscopy can identify the location of airway obstruction and may also treat the underlying cause (for example, removal of a foreign body or balloon dilation of a stricture).
Pulmonary infections	Bronchoscopy can provide microbiologic data in patients who have respiratory infections of diverse causes. Most pulmonary infections do not require bronchoscopy for diagnosis, especially if the patient is otherwise healthy and is improving with therapy. However, bronchoscopy should be considered for all patients with a pulmonary infection who are immunocompromised and do not respond to empiric treatment. These patients commonly have opportunistic infections including *Pneumocystis jivorecii* pneumonia and fungal infections.
Diagnosis and/or staging of bronchogenic carcinoma	Bronchoscopic biopsy of lung nodules and masses coupled with lymph node aspiration can help diagnose and stage lung cancers.
Diagnosis of pulmonary metastases	Diagnosis of metastatic disease may be made by bronchoscopy and biopsy in patients presenting with new pulmonary nodules in the setting of a known primary cancer.
Evaluation of a pulmonary nodule	Diagnostic specimens can be obtained via bronchoscopic biopsy for tissue diagnosis.
Persistent pulmonary infiltrate	Patients with a persistent pulmonary infiltrate may benefit from bronchoscopy to diagnose or exclude noninfectious causes of pulmonary infiltrates, such as eosinophilic lung disease, cryptogenic organizing pneumonia, and cancer.
Mucus plugging	When mucus plugging is severe enough to cause atelectasis and interfere with oxygenation or ventilation, bronchoscopy may evacuate the mucus plug.
Foreign-body aspiration	Bronchoscopy is the intervention of choice to extract foreign bodies wedged in airways.
Diffuse parenchymal lung disease	Surgical lung biopsy is the diagnostic method of choice for most patients with diffuse parenchymal/interstitial lung diseases. However, selected diseases, including sarcoidosis, are diagnosed with a high degree of accuracy via bronchoscopic techniques, which may obviate the need for a more invasive surgical biopsy.

KEY POINT

- Fiberoptic bronchoscopy is an endoscopic technique that allows for the visualization of the tracheobronchial lumen and sampling of suspected areas of disease, including the endobronchial mucosa, lung parenchyma, and accessible lymph nodes.

Endobronchial Ultrasound

Endobronchial ultrasound is a bronchoscopic technique that involves the use of an ultrasound probe at the distal end of the bronchoscope. The ultrasound-tipped bronchoscope can identify mediastinal lymph nodes and increase the yield of a transbronchial needle aspiration by allowing direct visualization of the needle entering the lymph node. This can be used to visualize and biopsy structures adjacent to an airway. For example, endobronchial ultrasound has been particularly useful in the staging of lung cancer, given its high specificity and sensitivity in identifying and staging lymph node involvement of the mediastinum and hila. Peripheral bronchoscopic ultrasound techniques can also aid in the successful biopsy of any lesion adjacent to an airway, including pulmonary nodules.

Airways Disease

Asthma

Asthma is a common chronic respiratory condition characterized by reversible airway obstruction that is caused by airway inflammation and bronchial hyperresponsiveness.

The current view of asthma is that it is a heterogeneous disorder with various phenotypes rather than one condition. Differentiation of asthma subtypes may allow therapeutic approaches to be tailored for the individual patient, resulting in maximal treatment efficacy with minimal adverse effects. Commonly observed clinical syndromes of asthma as well as confounding factors that worsen underlying asthma will be discussed in this chapter.

Epidemiology and Natural History

Asthma affects approximately 8% of the population in the United States. Allergic asthma is strongly associated with a personal or family history of allergies or atopy (maternal asthma in particular), maternal smoking while pregnant, and exposure to environmental tobacco smoke in childhood. Children with allergic asthma are commonly diagnosed

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during preschool years, and many have mild symptoms that resolve. However, some individuals with childhood allergic asthma progress to chronic airflow obstruction with increasingly severe symptoms that persist into adulthood. Although the cause is unclear, this worsening of asthma into adulthood is likely related to environmental stimuli such as viral infections, workplace exposures, or exposure to tobacco smoke (first-hand or second-hand) as well as individual predisposition (for example, family history, antioxidant activity in the lung). Importantly, adult-onset asthma can occur with or without a history of childhood asthma and may be underrecognized in older adults. Therefore, an initial clinical suspicion should be followed by diagnostic testing, particularly in those without a previous history of asthma. Asthma can present in a variety of ways, from early-onset childhood asthma with allergies, to very late-onset adult nonallergic asthma associated with obesity or chronic sinus infections.

There is a higher prevalence and severity of asthma in people with lower income, children, and black populations. This difference is likely related to multiple factors, including limited access to primary and specialty care, delayed disease recognition and suboptimal management, expectations about disease control, unhealthy dietary patterns, and ongoing exposure to triggers and environmental elements.

KEY POINT

- Asthma affects approximately 8% of the population in the United States.

Pathogenesis

The underlying pathophysiology in asthma is airway inflammation. Chronic airway inflammation results in the production and release of multiple mediators that may result in epithelial damage, smooth muscle hypertrophy, airway fibrosis, and remodeling in some patients (**Figure 4**).

Airway inflammation is usually triggered at the epithelial level. In allergic asthma, exposure of the airway to allergens following sensitization causes mast cell degranulation and initiation of an inflammatory cascade. In nonallergic asthma, epithelial stimulation and initiation of inflammation can occur with viral or bacterial infections or exposure to noxious chemicals.

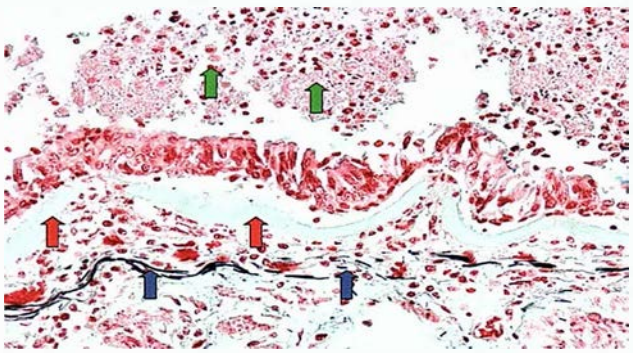

FIGURE 4. Airway tissue in a patient with severe asthma demonstrating subbasement membrane thickening (*red arrows*), disruption of elastic fibers (*blue arrows*), and infiltration with inflammatory cells and filling of the airway lumen with mucus and inflammatory cells (*green arrows*).

In allergic asthma, allergen exposure triggers mast cell activation and a robust response from the T-helper 2 (Th2) subset of lymphocytes. Immediate release of histamine and interleukins recruits other cell types, and the activation of Th2 lymphocytes further potentiates airway inflammation. The Th2 response appears to be modulated by Treg cells, a newly discovered, seemingly protective lymphocyte subset. Some patients also experience a late-phase asthmatic response, which manifests as a secondary decrease in FEV_1 4 to 8 hours after immediate exposure.

Bronchial biopsies in patients with allergic and even nonallergic asthma demonstrate accumulation of eosinophils, mast cells, and CD4+ T lymphocytes. When chronic, this results in airway remodeling with structural changes such as mucus cell hyperplasia, subepithelial thickening of basement membrane, smooth muscle hypertrophy, connective tissue deposition, and airway fibrosis.

Risk Factors

The degree to which individual predisposition and environmental factors play a role in asthma is unclear. Genetic susceptibility may be modulated through DNA methylation, which can be altered by environmental factors such as diet and in utero exposures. Genetic studies have identified gene clusters, some of which have been associated with childhood but not adult asthma. However, no single gene or gene cluster accounts for all types of asthma.

Exposures to indoor environmental allergens, environmental tobacco smoke, and viruses can predispose individuals to asthma. Common allergens are indoor mold, house dust, domestic animals, and cockroaches. Maternal smoking during pregnancy and after delivery increases immune responsiveness and the risk for asthma in the infant. Rhinovirus infections in early childhood may also play a role in increasing airway inflammation.

The hygiene hypothesis suggests that exposure to microbial diversity appears to protect against asthma by shifting Th cells to a Th1 instead of a predominantly Th2 phenotype. Breast feeding, exposure to microbial diversity, and avoidance of environmental tobacco smoke have been associated with reduced incidences of asthma; however, a definitive strategy to prevent the development of asthma has not been established.

KEY POINT

- Exposures to indoor environmental allergens, environmental tobacco smoke, and viruses can predispose individuals to asthma.

Symptoms and Clinical Evaluation

Patients with asthma classically present with a history of episodes of coughing, chest tightness, shortness of breath, and wheezing. The cough may be spastic and dry or may be

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productive of mucus. Some patients have only cough or shortness of breath, as asthma presents differently in different patients. For example, some patients may have an unremitting cough after exposure to cold air or after respiratory tract infections, and other patients with asthma may have significant breathlessness even without cough that is worse with any activity. Patients may identify the onset of symptoms with specific triggers, such as known allergen exposure, inhaled irritants, respiratory tract infections, and exercise. Other conditions that mimic asthma should be considered (**Table 4**).

In patients with suspected asthma, the first step in evaluation is usually spirometry to assess for the presence and severity of airway obstruction (as indicated by a reduced FEV_1/FVC ratio) and its reversibility (with a 12% or greater improvement in FEV_1 after administration of a bronchodilator).

TABLE 4. Differential Diagnosis of Asthma

Condition	Characteristics
COPD	Airway obstruction is less reversible; typically seen in older patients with smoking history
Vocal cord dysfunction	Abrupt onset and end of symptoms; monophonic wheeze; more common in younger patients; confirm with laryngoscopy or flow-volume loop
Heart failure	Dyspnea and often wheezing; crackles on auscultation; limited response to asthma therapy; cardiomegaly; edema; elevated BNP; other features of heart failure
Bronchiectasis	Cough productive of large amount of purulent sputum; rhonchi and crackles are common; may have wheezing and clubbing; confirmed by CT imaging
Allergic bronchopulmonary aspergillosis	Recurrent infiltrates on chest radiograph; eosinophilia; positive skin testing to *Aspergillus* antigens, high IgE levels, positive to *Aspergillus*; frequent need for glucocorticoid treatment
Cystic fibrosis	Cough productive of large amount of purulent sputum; rhonchi and crackles are common; prominent clubbing; may have wheezing. GI symptoms due to pancreatic insufficiency with possible sinus diseases are common, but recurrent respiratory tract infections may be present without GI or other systemic involvement.
Mechanical obstruction	More localized wheezing; if central in location, flow-volume loop may provide a clue
Eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome)	Autoimmune small-vessel vasculitis presents with peripheral eosinophilia, lung symptoms similar to asthma; skin changes such as purpura and sensory or motor neuropathy are other systemic symptoms; + ANCA in 40%-60% patients, mostly p-ANCA

ANCA = antineutrophil cytoplasmic antibodies; BNP = B-type natriuretic peptide; GI = gastrointestinal; p-ANCA = perinuclear antineutrophil cytoplasmic antibodies.

Although not routinely tested, some patients with asthma may have lung volumes evaluated for dyspnea or cough; patients with air trapping associated with asthma-related airway obstruction may demonstrate an increase in residual volume. Between attacks and exacerbations, spirometry can be normal in patients with suspected asthma. Therefore, a bronchial challenge test may be helpful for diagnosis if positive or make the diagnosis less likely if negative (see Pulmonary Diagnostic Tests).

Chest radiographs are often normal or may demonstrate widened rib spaces and a flattened diaphragm, resulting from air trapping due to chronic airflow obstruction. Eosinophils can be found in sputum, and allergy evaluation with skin testing or blood testing for specific IgE antibodies may aid in the assessment of risk and management of asthma. For individuals in whom allergies may be a trigger or contributing factor, referral to an allergist for allergen skin testing or blood tests for common inhaled allergens may enable patients to avoid exposures. Exhaled nitric oxide testing is a newer noninvasive breath test. Nitric oxide is normally present in airways but is increased in certain types of airway inflammation (asthma, eosinophilic airway inflammation). When elevated, it supports the diagnosis of asthma in the appropriate clinical context.

KEY POINTS

- Patients with asthma classically present with episodic symptoms of cough, chest tightness, shortness of breath, and wheezing.
- In patients with suspected asthma, the first step in evaluation is usually spirometry to assess for the presence and severity of airway obstruction (as indicated by a reduced FEV_1/FVC ratio) and its reversibility (with a 12% or greater improvement in FEV_1 after administration of a bronchodilator).

Asthma Syndromes

Allergic Asthma

Allergic asthma is the most common form of asthma in adults. Patients with atopy may present with allergic asthma early in life, experience a period of stability, and then may have recurrence later. However, allergic asthma can also manifest initially during adulthood. Family history is often positive for allergies and asthma. Symptoms may be seasonal, requiring trigger avoidance and stepping up of asthma therapy during times of known exacerbations. Individuals with perennial allergies may need more sustained controller therapy, with modification (stepping up or stepping down) of treatment based upon sequential monitoring and assessment. Additionally, superimposed viral infections or other nonallergic triggers (such as sinus diseases) may exacerbate underlying allergic asthma.

Cough-Variant Asthma

Asthma can present with a persistent or episodic cough in the absence of other common symptoms usually associated with asthma. Extrinsic triggers such as cold air or irritants can

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stimulate or make the cough worse. Spirometry and bronchial challenge testing can be helpful to establish the diagnosis and distinguish asthma from other causes of cough, such as upper airway cough syndrome (rhinosinusitis, postnasal drip) and gastroesophageal reflux. Treatment of cough-variant asthma is similar to usual guideline-based therapy for asthma.

See MKSAP 17 General Internal Medicine for a discussion of chronic cough.

Exercise-Induced Bronchospasm

In exercise-induced bronchospasm (EIB), symptoms occur in patients with asthma with exercise that requires increased respiratory ventilation. Increased ventilation, particularly of cool, dry air, causes drying of airway surfaces, which triggers bronchoconstriction via several mechanisms. When the airway-drying phenomenon is reversed, a rebound effect (with recruitment and infiltration of inflammatory cells) causes asthma symptoms. In patients with dyspnea with exercise but normal spirometry, methacholine challenge testing can be useful to assess the degree to which symptoms are related to hyperreactivity of the lungs.

If symptoms occur only a few times per week, EIB can be managed with inhaled short-acting β_2-agonists (such as albuterol) given 5 to 20 minutes prior to exercise; this therapy can be protective for 2 to 4 hours. Inhaled glucocorticoids are useful in minimizing the number and severity of exercise-induced asthma episodes. Antileukotriene therapy is also effective for the chronic management of patients with EIB.

Nonpharmacologic management includes warming and humidifying inhaled air with nasal breathing, as well as covering the nose and mouth during exercise in colder environments. A 10-minute pre-exercise warmup (to achieve a 60% to 80% of maximum heart rate) may decrease the occurrence of exercise-related bronchospasm for up to 4 hours.

KEY POINT

- If symptoms occur only a few times per week, exercise-induced bronchospasm can be managed with inhaled short-acting β_2-agonists (such as albuterol) given 5 to 20 minutes prior to exercise; this therapy can be protective for 2 to 4 hours.

Occupational Asthma

Occupational asthma, related to workplace exposures to agents associated with airway hyperreactivity, should be suspected in all adults with asthma because it may be preventable in most cases. Approximately 10% of workers exposed to known sensitizing agents develop asthma; farmers, factory workers, and hairdressers, among others, are at risk. Exposure to animal allergens, plants, grains, wood dust, and chemicals (diisocyanates from spray paint, persulfates), even at low levels, can act as sensitizers through responses similar to other forms of asthma (T lymphocytes, eosinophils, interleukins, mast cells, histamine). Early recognition of an association of asthma symptoms with potential workplace exposure, and testing if indicated, is important for diagnosis and to guide therapy. Serial monitoring of peak flows throughout the workday, with comparison to a baseline time period away from exposures, can be helpful to support the diagnosis. Similarly, spirometry before and after rechallenge with workplace exposures is helpful to confirm the diagnosis. Treatment of occupational asthma should follow guidelines for typical asthma, and allergen exposure should be controlled or eliminated if possible.

KEY POINT

- Approximately 10% of workers exposed to known sensitizing agents have asthma; farmers, factory workers, and hairdressers, among others, are at risk.

Aspirin-Sensitive Asthma

Also known as aspirin-exacerbated respiratory disease or Samter triad, aspirin-sensitive asthma includes severe persistent asthma, aspirin sensitivity, and hyperplastic eosinophilic sinusitis with nasal polyposis. Asthma is worsened by exposure to aspirin or other NSAIDs, likely because of the inhibition of cyclooxygenase and the resulting increase in leukotriene synthesis. Treatment consists of avoidance of aspirin or NSAIDs along with typical asthma management. For patients who require aspirin use (such as those with coronary artery disease), an aspirin desensitization procedure can be performed. Successful desensitization down-regulates leukotriene receptors and modifies interleukin sensitivity, which may improve asthma symptoms in some patients.

Reactive Airways Dysfunction Syndrome

Reactive airways dysfunction syndrome (RADS) is the development of respiratory symptoms in the minutes or hours after a single inhalation of a high concentration of irritant; airway hyperresponsiveness then persists for an extended period of time. RADS is not a form of typical asthma; it may be a temporary phenomenon that occurs after a short-lived and/or high-dose exposure to an irritant in a patient without asthma. Examples of exposures include inhalation of strong fumes, particulate matter (such as wood smoke), or chemical irritants (such as cleaning supplies). Spirometry may reveal evidence of bronchoconstriction that is reversible. Initial treatment is similar to that of asthma. The clinical course and recovery may allow reduction of medications relatively quickly; however, initial symptoms may also be early manifestations of new-onset asthma that will require chronic management.

Virus-Induced Bronchospasm

A viral respiratory infection can lead to airway hyperresponsiveness and obstruction through nonallergic mechanisms in patients without a history of asthma, and the associated bronchospasm may be limited only to the duration of the infection. Virus-induced bronchospasm in patients without asthma typically resolves 6 to 8 weeks after a respiratory infection. Viral respiratory infections may also exacerbate disease in patients with allergic asthma, with up to half of asthma

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exacerbations being related to human rhinovirus infection. Patients with asthma often exhibit more severe symptoms from influenza infections (especially the recent H1N1 strain), possibly owing to differential responses of airway epithelial cells in nonasthmatic versus asthmatic airways. Because of this, annual influenza vaccinations are a key part of the management of patients with asthma.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a chronic hypersensitivity reaction that occurs in response to colonization of the lower airways with *Aspergillus* species. The resulting inflammation causes impaired mucociliary clearance with expectoration of mucus plugs, destruction of pulmonary parenchyma with bronchiectasis, difficult-to-control asthma, and weight loss. Diagnosis is determined by clinical history, testing (positive skin testing to *Aspergillus* antigens, high IgE titers to *Aspergillus*, peripheral eosinophilia), and radiographic findings (proximal bronchiectasis, pleural thickening, transient infiltrates, or atelectasis). Treatment includes systemic glucocorticoids; inhaled glucocorticoids may reduce the need for higher doses of systemic glucocorticoids. Antifungal therapy (such as fluconazole) may be helpful in conjunction with glucocorticoid therapy, and anti-IgE therapy (such as omalizumab) may be used as adjunctive treatment in selected patients.

Common Contributing Factors

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) can make underlying asthma worse through direct reflux of acidic gastric contents into the respiratory system, resulting in upper airway inflammation or direct airway injury. The reflux of gastric contents into the lower part of the esophagus can also cause a reflex bronchoconstriction. There is evidence that treating GERD in patients with asthma improves asthma control. In most patients with asthma and suboptimal control of symptoms, a history consistent with GERD is adequate to justify a trial of empiric antacid therapy without further testing for evidence of reflux. Management of GERD in patients with asthma is an important component of therapy; see MKSAP 17 Gastroenterology and Hepatology for a discussion of the diagnosis and management of GERD.

Sinus Disease

Because disorders affecting the upper respiratory tract may affect the lower tract (unified airway concept), sinus disorders may be associated with worsening control of asthma. Patients with frequent asthma exacerbations should be evaluated for occult sinus disease, as untreated upper airway inflammation may contribute to poor asthma control. Treatment of bacterial sinusitis or allergic sinusitis with nasal glucocorticoids can reduce bronchial hyperresponsiveness, shortness of breath, and wheezing.

Obstructive Sleep Apnea

Asthma has been associated with obstructive sleep apnea (OSA), and the relationship appears to be bidirectional. OSA appears to affect asthma control, and continuous positive airway pressure treatment for comorbid OSA improves asthma symptoms, frequency of rescue inhaler use, and quality-of-life scores. In difficult-to-control asthma, OSA is a significant risk factor for frequent exacerbations. Treatment of OSA affects both daytime and nighttime asthma symptoms, suggesting that local and systemic inflammatory pathways are implicated in the association. See Sleep Medicine for a discussion of the diagnosis and management of OSA.

Vocal Cord Dysfunction

The clinical suspicion of paradoxical vocal fold motion (PVFM) disorder, also known as vocal cord dysfunction, should be high when patients describe (1) mid-chest tightness with exposure to particular triggers such as strong irritants or emotions, (2) difficulty breathing in, and (3) symptoms that only partially respond to asthma medications. Symptoms include mid-chest tightness, dyspnea, and lack of symptom relief with asthma treatment. Patients may also note cough and dysphonia, and stridor may be present that may be detected on examination as inspiratory monophonic wheezing. PVFM disorder can occur suddenly; although it can be present with asthma, it is often misdiagnosed as asthma, resulting in high health care utilization and multiple intubations. Adduction of vocal cords during inspiration as seen on laryngoscopy is the gold standard for diagnosis (**Figure 5**); however, the diagnosis is often made clinically based on history. It may also be diagnosed if spirometry happens to capture a flat inspiratory limb on the flow-volume loop. Speech therapy training exercises (to control the laryngeal area and maintain airflow) and treatment of GERD can result in dramatic improvement in PVFM disorder symptoms.

KEY POINT

- Vocal cord dysfunction, characterized by (1) mid-chest tightness with exposure to triggers, (2) difficulty breathing in, and (3) partial response to asthma medications, is often misdiagnosed as severe asthma resulting in unnecessary intubations and high health care utilization. **HVC**

Obesity

Obesity is one of the strongest risk factors for developing asthma, may have a causal role, and affects prognosis and outcomes in asthma. Obese patients with asthma experience more severe asthma with increased symptoms, worse quality of life, and increased health care utilization. Obesity can worsen childhood-onset allergic asthma. Mechanical strain (breathing against the pressure of added chest or abdominal girth) and obesity-related cytokines, called adipokines, can also affect late-onset nonallergic asthma. Dramatic weight loss

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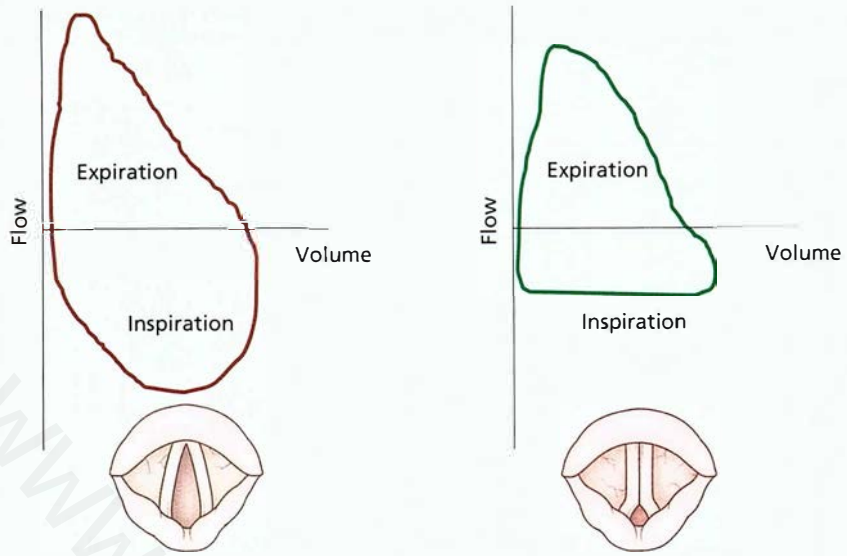

FIGURE 5. Flow-volume loops showing maximum inspiratory and expiratory flow-volume relationships in a patient with vocal cord dysfunction during asymptomatic (*left*) and symptomatic (*right*) periods. Note also the marked adduction of the vocal cords with severe reduction of the glottic aperture during a symptomatic period of airway obstruction (*right*).

has proved to be successful in controlling the disease, particularly in a subgroup of middle-aged obese women with nonallergic asthma.

Chronic Management

Goals for the management of asthma outlined by the National Heart, Lung, and Blood Institute include assessment and monitoring, control of factors contributing to symptom exacerbation, pharmacotherapy, and education for partnership in care.

On initial diagnosis of asthma, severity of disease should be determined based on the level of impairment and risk of future exacerbations using the frequency of symptoms, need for quick-relief medications, and degree of obstruction on spirometry (**Table 5**). Appropriate treatment should be initiated based on this assessment (**Figure 6**). Symptoms should be monitored after treatment is initiated; therapy may need to be adjusted as symptom patterns may change over time. If changes in symptoms occur, it is reasonable to reevaluate lung function with spirometry. During times of symptom stability, spirometry should be performed yearly.

Depression is significantly associated with asthma and is present more commonly in patients with asthma than in those with other chronic diseases. A high index of suspicion for and treatment of depression can reduce impairment from asthma. Depression in patients with asthma is underrecognized and has been associated with increased emergency department visits and hospitalizations, decreased lung function, higher medication nonadherence, and increased asthma-related deaths.

Medications

Inhaled glucocorticoids are the mainstay of therapy because of the inflammatory mechanisms underlying asthma. β_2-Agonists are used for symptom relief, and additional medications such as systemic glucocorticoids and anticholinergic agents may be useful in managing asthma in specific situations. Owing to the dynamic nature of asthma, pharmacologic management may require stepwise modification based on periodic assessment of asthma severity.

Quick-Relief Medications

β_2-Agonists are sympathomimetic agents that act on airway β receptors that activate adenylate cyclase, increasing cyclic adenosine monophosphate levels. These activate protein kinase A, which phosphorylates regulatory proteins that mediate bronchodilation. Short-acting β_2-agonists (for example, albuterol, salbutamol) help relieve the acute symptoms of chest tightness, wheeze, shortness of breath, and cough but do not treat or improve the underlying problem of airway inflammation. Long-acting β_2-agonists (LABAs) (for example, salmeterol) are available and should be used in conjunction with inhaled glucocorticoids to avoid potential tolerance to bronchodilators.

Anticholinergic agents dilate bronchial smooth muscle by decreasing the constrictive cholinergic tone in the airways. Although it is less effective than β_2-agonists, the short-acting agent ipratropium can be used as adjunctive quick-relief therapy during asthma exacerbations.

KEY POINT

- In patients with asthma, short-acting β_2-agonists (albuterol, salbutamol) help relieve the acute symptoms of chest tightness, wheeze, shortness of breath, and cough but do not treat or improve the underlying problem of airway inflammation.

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TABLE 5. Classification of Asthma Severity

Components of Severity	Intermittent	Persistent		
		Mild	Moderate	Severe
Impairment[a]				
Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
Nighttime awakenings	≤2 ×/month	3-4 ×/month	>1 ×/week but not nightly	Often 7 ×/week
SABA use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not more than 1 ×/d	Daily	Several times a day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function	Normal FEV_1 between exacerbations FEV_1 ≥80% of predicted FEV_1/FVC normal	FEV_1 ≥80% of predicted FEV_1/FVC normal	FEV_1 ≥60% but <80% of predicted FEV_1/FVC reduced ≤5%	FEV_1 <60% of predicted FEV_1/FVC reduced >5%
Risk				
Exacerbations (consider frequency and severity)[b,c]	0-1/year	>2/year	>2/year	>2/year
Recommended step for initiating treatment (see Figure 6 for treatment steps)[d]	Step 1	Step 2	Step 3; consider short courses of systemic glucocorticoids	Step 4 or 5; consider short courses of systemic glucocorticoids

EIB = exercise-induced bronchospasm; SABA = short-acting β_2-agonist.

[a]Normal FEV_1/FVC ratio: 8-19 years old, 85%; 20-39 years old, 80%; 40-59 years old, 75%; 60-80 years old, 70%.

[b]Frequency and severity may fluctuate over time for patients in any severity category.

[c]Relative annual risk for exacerbations may be related to FEV_1.

[d]In 2 to 6 weeks, evaluate the level of asthma control that is achieved and adjust therapy accordingly.

Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma. http://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf. Published 2007. Accessed June 15, 2015.

Controller Medications

When symptoms related to asthma occur more than twice per week or one night per week, asthma is considered persistent. At this stage, it is appropriate to start controller therapy to reduce airway inflammation from asthma. Inhaled glucocorticoids are the mainstay of controller asthma treatment. They have been shown to improve and control symptoms, reduce exacerbations, and improve lung function. These agents treat the underlying inflammatory disease process, and the inhaled formulation allows drug delivery with minimal systemic absorption and limited side effects. Newer formulations require twice-daily dosing, and varying potency allows careful titration of treatment to minimize potential side effects. Differences in delivery devices (traditional inhaler versus dry powder inhalation formulations) can accommodate patient preferences and capabilities. Traditional inhalers use a pump, and aerosolized medication is delivered. With inhalers, proper (slow and steady) inhalation technique, inhalation chambers (known as spacers), and a breath hold can improve drug delivery and avoid side effects such as thrush. Dry powder inhalers deliver a fine powder to the lungs; they require less coordination but require more forceful inhalation than with a traditional inhaler.

When inhaled glucocorticoids alone do not achieve asthma control, the addition of a LABA has proved to be effective as step-up therapy. Combination preparations that contain an inhaled glucocorticoid and a LABA are available. In addition to bronchodilation, LABAs appear to potentiate anti-inflammatory effects of inhaled glucocorticoids when taken together. However, the LABA portion of the combination preparation can cause side effects (for example, anxiety, tremor, and headache); therefore, stepping down LABA therapy should be considered after a period of sustained asthma control.

In conjunction with inhaled glucocorticoids, long-acting anticholinergic agents (such as tiotropium) may have an anti-inflammatory effect, which has been shown to increase time to severe exacerbation and result in modest

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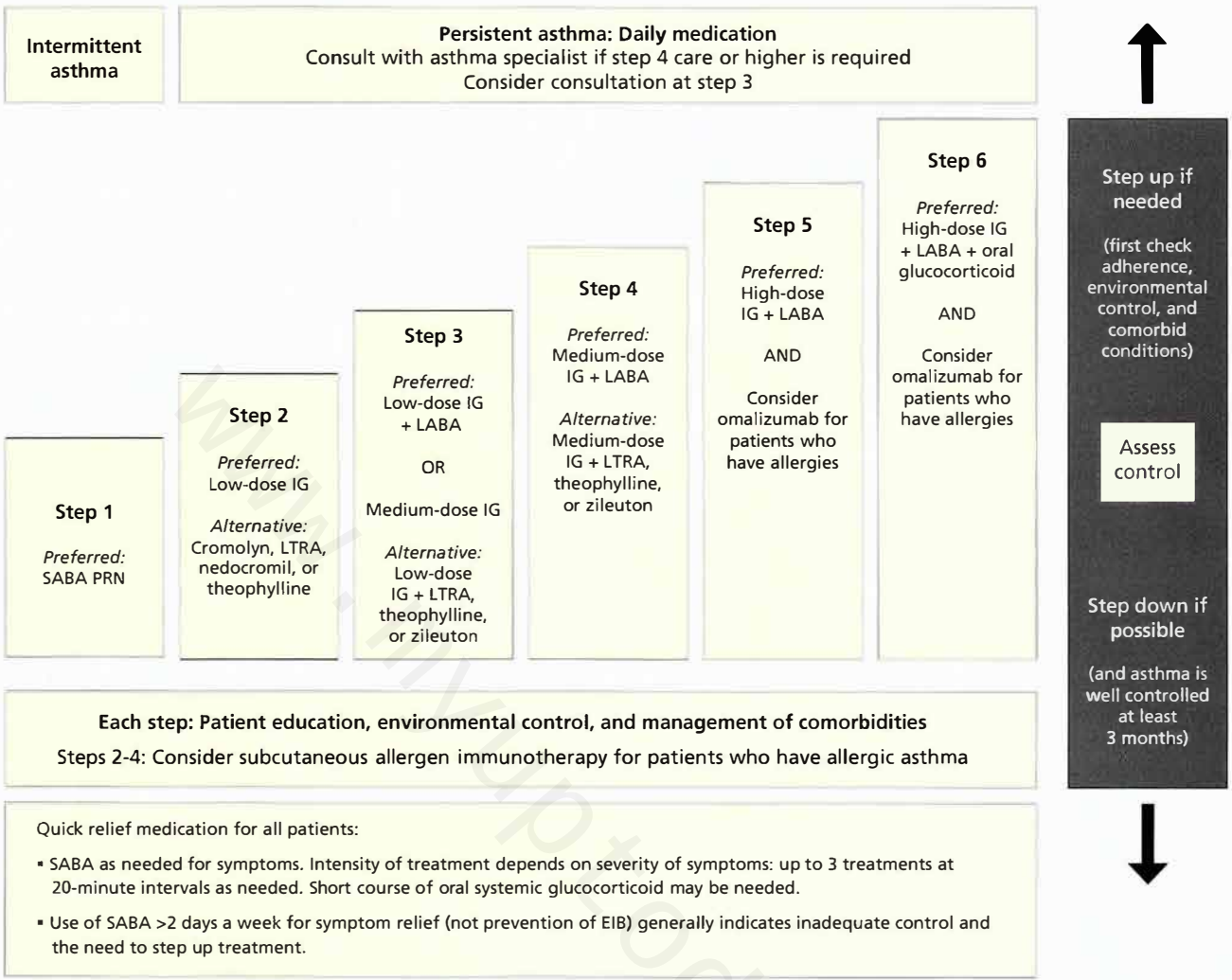

FIGURE 6. Stepwise approach to asthma therapy. EIB = exercise-induced bronchospasm; IG = inhaled glucocorticoids; LABA = long-acting β_2-agonist; LTRA = leukotriene receptor antagonist; PRN = as needed; SABA = short-acting β_2-agonist.

Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma. www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf. Published 2007. Accessed June 15, 2015.

sustained bronchodilation. These agents should be considered when inhaled glucocorticoids, LABAs, and leukotriene receptor antagonists (LTRAs) do not provide sufficient control.

LTRAs are not considered first-line controller therapy in any asthma population but can be used as an add-on to inhaled glucocorticoid therapy. LTRAs have a particular role in EIB and aspirin-sensitive asthma, and they can be helpful in sinus disease because they target a different area of the inflammatory cascade.

Theophylline is an older drug from the methylxanthine drug class. Methylxanthines inhibit phosphodiesterase, which is normally responsible for degradation of cyclic adenosine monophosphate, and therefore may have effects on bronchodilation, with potential for some anti-inflammatory capability. Owing to drug toxicity and side effects and improved availability of inhaled glucocorticoids, methylxanthines (such as theophylline) are not commonly used.

Some patients experience severe asthma such that even the optimal inhaled glucocorticoid therapies may not provide sufficient control, and in those situations chronic oral glucocorticoids may be necessary.

Omalizumab, a humanized monoclonal antibody directed at IgE, is the first biologic agent approved by the FDA for use in asthma. Administered subcutaneously every 2 to 4 weeks, omalizumab is indicated in patients with moderate to severe persistent asthma with the following characteristics: (1) symptoms inadequately controlled with inhaled glucocorticoids, (2) evidence of allergies to perennial aeroallergens, and (3) serum IgE levels between 30 and 700 U/mL (30-700 kU/L) (normal range, 0-90 U/mL [0-90 kU/L]). Although it is expensive, omalizumab has been shown to reduce emergency department visits and appears to be cost effective in appropriately selected patients; it is not indicated for use in patients other than those meeting these treatment parameters. This

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agent can also be useful in the treatment of ABPA. Other biologic agents that target various cytokines such as interleukin-5 and interleukin-13 are being explored, and emerging characterization of biomarkers in individual patients may help guide appropriate use of these specific agents.

KEY POINTS

- Inhaled glucocorticoids are the mainstay of asthma treatment; they have been shown to improve and control symptoms, reduce exacerbations, and improve lung function.
- When inhaled glucocorticoids alone do not achieve asthma control, the addition of a long-acting β_2-agonist has proved to be effective as step-up therapy.
- HVC Although expensive, omalizumab has been shown to reduce emergency department visits and is cost effective in moderate to severe persistent asthma with: (1) symptoms inadequately controlled with inhaled glucocorticoids, (2) allergies to perennial aeroallergens, and (3) serum IgE levels between 30 and 700 U/mL (30-700 kU/L).

Nonpharmacologic Therapy

Comprehensive asthma care strategies include avoidance of triggers with allergen management (mold abatement, pest control, air filters), reduced exposure to environmental tobacco smoke, and a healthy diet and exercise program. Stress management and counseling may be helpful adjuncts to disease management. Vitamin D insufficiency is associated with a lower level of asthma control, and supplementation has been associated with greater response to inhaled glucocorticoid therapy. Yearly influenza vaccination reduces the risk of asthma exacerbations from influenza.

It is important to address potential barriers to optimal asthma management. For example, prescription of complex treatment regimens may impair adherence, and financial issues associated with acquiring medications may pose a challenge in some patients.

Bronchial thermoplasty (BT) was recently approved by the FDA as an adjunctive therapy for patients with asthma who remain symptomatic despite optimization of medications. A bronchoscopically-introduced catheter is used to apply thermal energy to conducting airways 3 mm or greater in diameter with the goal of reducing smooth muscle thickening in the airway walls. Three bronchoscopic sessions, spaced at least 3 weeks apart, are performed to treat different sections of the lung. After treatment, measures of lung function remain unchanged, but notable outcomes from BT include improved asthma-related symptoms, reduced emergency department visits, and improvement in severity of exacerbations. Adverse effects include a temporary worsening of asthma after the procedure is performed. As experience increases, it is likely that careful patient selection will play an important role in BT outcomes.

KEY POINTS

- Comprehensive asthma care strategies include avoidance of triggers with allergen management (mold abatement, pest control, air filters), reduced exposure to environmental tobacco smoke, and a healthy diet and exercise program.
- Bronchial thermoplasty was recently approved by the FDA as an adjunctive therapy for patients with asthma who remain symptomatic despite optimization of medications.

Management of Asthma Exacerbations

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With appropriate education and development of a patient-implemented asthma action plan, many patients can manage early signs of an exacerbation at home. Measurement of airflow with serial peak flow measurements may be particularly helpful in patients who are appropriate candidates for home management by providing a more objective assessment of disease status than the subjective perception of symptoms. At early signs of asthma instability (increased shortness of breath, cough, wheezing, chest tightness, or reduced peak flows to less than 50% of baseline), starting a course of systemic glucocorticoids may improve asthma control. In most cases, antibiotic agents are not necessary unless bronchitis, pneumonia, or sinusitis is suspected. Patients attempting self-management should be given individualized, clear parameters regarding when to seek emergency treatment when treating asthma exacerbations at home (for example, lack of resolution despite three nebulized albuterol treatments, failure to improve with systemic glucocorticoids, early self-referral for patients with a history of respiratory failure or need for intubation).

When evaluating patients with an acute exacerbation, it is important to consider factors that increase the risk of poorer outcomes, which include a history of frequent emergency department visits for asthma, the need for endotracheal intubation and mechanical ventilation to treat previous exacerbations, and poor perception of the presence of reduced lung function. Patients who are not responding to initial treatment and have persistently high work of breathing, particularly high-risk patients (those with lack of improvement with outpatient management, poor access to care, or a history of intubation or near-fatal asthma), should be admitted to the hospital and considered for intensive care management (see Critical Care Medicine). Management should include close monitoring of dyspnea, work of breathing, and vital signs; frequent bronchodilator treatment; and systemic glucocorticoids. Pulse oximetry may be falsely reassuring because patients maintain normal oxygen levels despite high work of breathing, and hypoxia is a late sign of pending respiratory failure. In patients who are at high risk or have lack of symptom resolution with initial therapies, arterial blood gas assessment is vital and may initially reveal hyperventilation with a low arterial P_{CO_2}. Normalization of the P_{CO_2} could be an early indicator of airway muscle fatigue and impending respiratory arrest.

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Severe Refractory Asthma

CONT.

Although most patients with asthma achieve symptom control, approximately 10% of patients have severe refractory asthma. Patients are considered to have severe refractory asthma if they have multiple exacerbations per year, a need for high-dose inhaled or oral glucocorticoids, an inability to step down therapy without compromising asthma control, or a history of multiple hospitalizations or intubations. The cause of severe asthma is heterogeneous, and appropriate therapy should be tailored to the specific characteristics of a patient's asthma syndrome. These patients usually require multidisciplinary and specialist care to manage their disease; this may consist of a team of social workers, pulmonary rehabilitation specialists/respiratory therapists, allergists, otolaryngologists, gastroenterologists, and pulmonary specialists.

KEY POINT

- Patients are considered to have severe refractory asthma if they have multiple exacerbations per year, a need for high-dose inhaled or oral glucocorticoids, an inability to step down therapy without compromising asthma control, or a history of multiple hospitalizations or intubations.

Asthma in Pregnancy

Approximately one third of pregnant women with asthma experience worsening asthma symptoms, one third have no change in symptoms, and another third have improvement in symptoms. Lack of asthma control increases the risk for preeclampsia and preterm labor for mothers and low birth weight, small gestational size, and preterm delivery for the infant. Asthma management during pregnancy should consist of optimization of anti-inflammatory therapy, management of gastroesophageal reflux, and smoking cessation. Inhaled glucocorticoids are considered safe in pregnancy, and abundant long-term safety evidence exists for budesonide. Most LTRAs are also considered safe in pregnancy.

KEY POINT

- Inhaled glucocorticoids are considered safe for asthma therapy during pregnancy, and abundant long-term safety evidence exists for budesonide.

Chronic Obstructive Pulmonary Disease

Definition

COPD is characterized by persistent, progressive airflow limitation, which arises from structural lung changes due to chronic inflammation as a result of inhaling noxious particles or gases. Chronic inflammation causes narrowing of the small airways and decreased elastic recoil of the lung, which diminishes the capacity of the airways to remain open during expiration. The resulting increase in air trapping and hyperinflation contributes to progressive airflow limitation. The characteristic symptoms of COPD are chronic dyspnea, cough, and sputum production.

Epidemiology

COPD is the third most common cause of death worldwide and a major cause of chronic morbidity, resulting in an increasingly substantial economic and social burden.

Evidence suggests that up to 50% of the total population with COPD remain undiagnosed. In populations with diagnosed COPD, studies indicate that patients frequently are undertreated, with an estimated 30% to 70% receiving no therapy or suboptimal treatment.

Pathophysiology

The underlying pathophysiology in COPD is chronic inflammation triggered and maintained by inhalation of toxic particles and gases, most commonly from tobacco smoke. Inflammation disrupts normal repair mechanisms and results in thickening and narrowing of the small airways (obstructive bronchiolitis). The inflammatory response also causes release of proteases that dissolve a portion of the adjacent lung tissue, including elastin, the major component of the connective tissue in the lung parenchyma that tethers the small airways open. The loss of elastin causes a decrease in the elastic recoil of the lungs that normally keeps airways open during exhalation. Proteases also damage the airspaces distal to the terminal bronchioles, resulting in permanent enlargement of airspaces with loss of diffusing surface (emphysema). Multiple factors influence the severity of the inflammatory process, including genetics, the level of oxidative stress, and a reduced presence of endogenous antioxidants. However, the degree of inflammation intensifies as disease progresses and the risk of exacerbations increases.

The decreased elasticity of the lung parenchyma causes both static and dynamic hyperinflation. Static hyperinflation occurs because of the loss of the recoil properties of the lung resulting in the inability to fully exhale, leading to permanent increases in end-expiratory lung volumes. In contrast, dynamic hyperinflation occurs when patients begin to inhale before full exhalation of the previous breath has been completed, such that inspiratory air volume exceeds expiratory volume, trapping air within the lungs with each successive breath. The ability to fully exhale is dependent on the degree of airflow obstruction (associated with the degree of structural changes, inflammation, increases in cholinergic tone, and mucus plugging) and rate of breathing. Both can vary and cause greater hyperinflation during periods of exertion and exacerbation. When the demand for greater minute ventilation occurs, increases in tidal volume and respiration rate ensue, and the available time for exhalation can become insufficient, creating a cycle of air trapping and progressive dynamic hyperinflation. Progressive hyperinflation expands the lungs, flattening and reducing the mechanical effectiveness of the diaphragm, making use of accessory muscles of breathing more crucial, and

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markedly increasing the work of breathing as chest wall compliance decreases. Because of these changes, the ability to increase minute ventilation is severely compromised in patients with COPD. As disease progresses, dynamic hyperinflation occurs even during quiet breathing, causing worsening dyspnea and significant impairment of exercise and activity intolerance.

Gas diffusion by the lung is also impaired in COPD. The ability to exchange CO_2 and oxygen correlates with the degree of functional impairment of gas exchange and reduction of the available capillary bed for gas diffusion owing to a loss of lung parenchyma.

Risk Factors

Essentially all risk for development and progression of COPD results from an interaction between patient and environmental factors.

It is estimated that up to 20% or more of COPD occurs in non- and never-smokers. However, smoking cessation is the single most clinically efficacious and cost-effective way to prevent COPD. Discontinuation of smoking in patients with established COPD slows disease progression and improves survival. The age at which patients start to smoke, total pack-years smoked, and current smoking status are cumulative predictors of COPD morbidity and mortality.

Relatives of patients with COPD have a higher prevalence of the disease, which cannot be attributed to personal or environmental risk factors. Additionally, there is a higher prevalence of reduced lung function among the children of patients with COPD than in their spouses; this is not well understood but is thought to be related to genetic predisposition. COPD is affected by multiple genes and genetic predisposition, but nongenetic factors (for example, childhood viral respiratory infections, childhood asthma, environmental and occupational pollution, and worldwide use of biomass fuels) likely contribute to increased susceptibility in this subset of patients.

KEY POINT

- Smoking cessation is the single most clinically efficacious and cost-effective way to prevent COPD, to slow progression of established disease, and to improve survival.

Heterogeneity of COPD

Patients with COPD have traditionally been categorized by the predominant manifestation of their disease; this is typically the degree of irreversible airway obstruction present (emphysema) or the presence of significant inflammation (chronic bronchitis), with or without a component of reversible airways disease (asthma). However, the clinical manifestations of COPD vary significantly between patients, suggesting that COPD is a conglomerate of several different disease processes.

Patients with COPD also typically demonstrate different clinical patterns, or phenotypes, of disease, with variations in severity of symptoms, response to treatment, and outcomes that may occur independent of genetic background. For example, some patients experience more rapid disease progression and more frequent exacerbations despite similar history, monitoring, and treatment. In addition to the "exacerbator" phenotype, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015 guidelines has added a phenotype called asthma COPD overlap syndrome (ACOS), as these patients have features of both asthma and COPD.

Role of Comorbid Conditions

Patients with COPD have a high frequency of comorbid conditions that adversely affect prognosis and significantly contribute to morbidity and mortality. It has been shown that the lung disease is frequently not appropriately treated in patients with COPD and significant comorbid conditions.

Cardiovascular disease is one of the most common comorbid conditions of COPD, and it is the leading cause of mortality in patients with mild to moderate COPD. The risk of cardiovascular injury is also significantly increased in patients with COPD who experience frequent exacerbations. During and immediately following an acute exacerbation of COPD, patients are particularly vulnerable to ischemic heart disease and acute myocardial infarction. Weight loss, muscle wasting, muscle weakness, and osteopenia are also common in patients with severe COPD. The rates of early hospital readmission for COPD exacerbation increase as the number of comorbidities increases.

KEY POINT

- Patients with COPD have a high frequency of comorbid conditions (such as cardiovascular disease, weight loss, muscle wasting, weakness, and osteopenia) that adversely affect prognosis and significantly contribute to morbidity and mortality.

Diagnosis

Spirometric evaluation is required for the clinical diagnosis of COPD. Spirometry is warranted in any patient presenting with dyspnea, chronic cough, or sputum production. Screening for COPD with spirometry should not be performed in asymptomatic patients.

For diagnosis of COPD, spirometry should be performed both before and after administration of an inhaled bronchodilator. A postbronchodilator fixed FEV_1/FVC ratio less than 70% is diagnostic for COPD in a consistent clinical context and differentiates COPD from asthma, which shows reversible airflow obstruction.

Patients with an FEV_1 of less than 35% of predicted should be assessed for adequacy of oxygenation with either arterial blood gas studies or measurement of oxyhemoglobin saturation with pulse oximetry.

Patients who develop symptoms of COPD and have a reduced FEV_1/FVC ratio at a young age (≤40 years of age) should be considered for α_1-antitrypsin deficiency testing. Patients with this disorder are often misdiagnosed with asthma for many years. They may have a modest smoking

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history and basilar emphysema (although they may present with any pattern of emphysema), and they may have concurrent liver disease. Patients with α_1-antitrypsin deficiency who never smoke may develop symptoms later in life. The pattern of basilar emphysema, liver disease, and family history of emphysema in patients with COPD should prompt consideration of α_1-antitrypsin deficiency in middle age and older patients.

KEY POINTS

HVC
- Screening for COPD with spirometry should not be performed in asymptomatic patients.
- A postbronchodilator fixed FEV_1/FVC ratio less than 70% is diagnostic for COPD in the correct clinical context and differentiates COPD from asthma, which shows reversible airflow obstruction.

Assessment and Monitoring

Initial assessment of patients with COPD includes a comprehensive medical history and physical examination to characterize the degree of impairment of lung function and identify potential comorbidities.

Patient symptoms and their impact on function may be more objectively assessed with either the Modified Medical Research Council (mMRC) Questionnaire or the COPD Assessment Test (CAT). The mMRC (**Table 6**) grades the degree of breathlessness using a 0 to 4 scale, with higher values indicating decreasing exercise tolerance. The CAT provides a numeric scale relating to eight functional parameters (for example, cough, sputum, walking, sleeping, energy level); lower scores indicate fewer symptoms and higher scores indicate more symptoms. The 2015 GOLD classification uses spirometric measures to provide a more objective classification of COPD severity (**Table 7**); a higher GOLD category indicates increased risk.

TABLE 6. Modified Medical Research Council (mMRC) Questionnaire for Assessing Severity of Breathlessness

Score	Description of Dyspnea	Severity
0	I get breathless only with strenuous exercise	None
1	I get short of breath when hurrying on level ground or walking up a slight hill	Mild
2	On level ground, I walk slower than other people my age because of breathlessness, or I have to stop for breath when walking at my own pace	Moderate
3	I stop for breath after walking approximately 100 yards or after a few minutes on level ground	Severe
4	I am too breathless to leave the house, or breathless when dressing	Very severe

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TABLE 7. Classification of COPD Severity by Spirometry (In Patients with FEV_1/FVC <70%)

Category	Severity	Spirometry
GOLD 1	Mild	FEV_1 ≥80% of predicted
GOLD 2	Moderate	50% ≤ FEV_1 < 80% of predicted
GOLD 3	Severe	30% ≤ FEV_1 < 50% of predicted
GOLD 4	Very severe	FEV_1 <30% of predicted

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The updated GOLD guidelines introduced a new model for classifying the severity of disease using more objective measures. The new classification scheme combines four parameters to categorize the level of risk in an individual patient (**Table 8**):

- Degree of patient symptoms as rated on a numeric scale (the CAT or mMRC questionnaire)
- GOLD classification of airflow obstruction
- Exacerbation risk based on the frequency and severity of previous episodes
- Presence of individual patient comorbidities

Exacerbation risk is determined by assessing exacerbations occurring in the past year; patients are considered high risk if they had any exacerbation leading to hospitalization, or two or more COPD exacerbations that did not require hospitalization.

Although comorbidities are not numerically incorporated into the new model, their presence is important for understanding the effect of COPD in specific patients; this information may be useful in assigning overall risk and in making patient-specific treatment decisions.

These parameters are used to assign a patient to a specific risk group, as outlined in Table 8.

Monitoring of patients with COPD includes ongoing review of symptoms, evaluation for complications of COPD, and assessment of frequency and severity of exacerbations, if present. Patients should be asked about changes in sputum volume, the occurrence of worsening dyspnea, and their psychological wellbeing. In patients on pharmacologic therapy, medication dosage(s) should be confirmed, and therapeutic adherence, side effects of treatment, and level of symptom control should be assessed. Because inhaled medications are a mainstay of COPD management, good inhaler technique should be ensured (particularly in patients with suboptimal symptom control) before making changes to the drug regimen. Follow-up visits should also include periodic reevaluation with spirometry, which is usually performed at least annually in stable patients to document changes in lung function and disease progression. Based on these elements, the efficacy of the therapeutic regimen should be reassessed and adjusted if needed.

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TABLE 8. GOLD Model for Classifying Severity of Disease in COPD

Patient Category	Characteristics	Spirometric Classification[a]	Exacerbations Per Year	CAT Score	mMRC Score
A	Low risk, fewer symptoms	GOLD 1-2	≤1	<10	0-1
B	Low risk, more symptoms	GOLD 1-2	≤1	≥10	≥2
C	High risk, fewer symptoms	GOLD 3-4	≥2	<10	0-1
D	High risk, more symptoms	GOLD 3-4	≥2/≥1 with hospital admission	≥10	≥2

CAT = COPD Assessment Test; mMRC = Modified Medical Research Council.

[a]See Table 7 for definitions of spirometric classifications.

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Some patients may experience worsening symptoms and significant declines in lung function over time. **Table 9** provides criteria that can be useful for determining whether and when to refer to a pulmonary specialist.

KEY POINTS

- Monitoring of patients with COPD includes ongoing review of symptoms, evaluation for complications of COPD, and assessment of frequency and severity of exacerbations, if present.
- HVC Because inhaled medications are a mainstay of COPD management, good inhaler technique should be ensured (particularly in patients with suboptimal symptom control) before making changes to the drug regimen.

TABLE 9. Criteria for Potential Referral of Patients with COPD to a Pulmonary Specialist

Diagnosis of COPD at ≤40 years of age
Frequent exacerbations (≥2/year) despite adequate treatment
Rapid disease course (decline in FEV_1, progressive dyspnea, decreased exercise tolerance, unintentional weight loss)
Severe COPD (FEV_1 <50% of predicted) despite optimal treatment
Need for oxygen therapy
Onset of a comorbid condition (especially cardiovascular disease or event)
Diagnostic uncertainty (for example, coexisting COPD and asthma)
Symptoms disproportionate to severity of airflow obstruction
Confirmed or suspected α_1-antitrypsin deficiency
Patient request for a second opinion
Patient is a potential candidate for lung transplant or lung-volume reduction surgery
Patient has very severe disease and requires elective surgery that may impair respiratory function

Source: Littner MR. In the clinic. Chronic obstructive pulmonary disease. Ann Intern Med. 2011 Apr 5;154(7):ITC4-1-ITC4-15. [PMID: 21464346]

Chronic Management

Therapeutic interventions in COPD have traditionally been guided by the degree of airflow obstruction as determined by spirometry, the subjective assessment of the severity of disease, and consideration of individual patient factors that might affect treatment. However, the new GOLD classification model (see Table 8) allows for risk- and symptom-based, individualized therapy for COPD. This classification scheme is helpful in selecting the level of therapeutic intervention appropriate for the patient's risk and symptom level. Management recommendations for the different categories are outlined in **Table 10**.

The American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society offer a simple, evidence-based classification and treatment scheme for stable COPD (**Table 11**, on page 20).

Pharmacologic Treatment

No pharmacologic agent is able to reduce the progressive decline in lung function seen in patients with COPD. However, a variety of medical treatments may reduce symptoms, diminish the frequency and severity of exacerbations, reduce the frequency of hospitalization, and improve exercise tolerance and health status. Medications used to treat COPD are summarized in **Table 12** on page 21.

Bronchodilators

Bronchodilators are the mainstay of therapy in COPD; they relax airway smooth muscle, increase airway diameter, and decrease breathlessness, hyperinflation, and air trapping. Bronchodilators may also improve exercise tolerance, quality of sleep, and quality of life.

β_2-Agonists or anticholinergic agents are generally preferred over methylxanthines, which have a more extensive side-effect profile. Additionally, inhaled agents are recommended over oral agents based on efficacy and decreased side effects. However, the predominance of data does not support the superiority of any one inhaled bronchodilator over another. Inhaled bronchodilators are available in both short- and long-acting forms.

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TABLE 10. Initial Pharmacologic Management of COPD[a]

Patient Category[b]	Recommended First Choice	Alternative Choice	Other Possible Treatments[c]
A	Short-acting anticholinergic PRN ***or*** Short-acting β_2-agonist PRN	Long-acting anticholinergic ***or*** Long-acting β_2-agonist ***or*** Short-acting β_2-agonist ***and*** Short-acting anticholinergic	Theophylline
B	Long-acting anticholinergic ***or*** Long-acting β_2-agonist	Long-acting anticholinergic ***and*** Long-acting β_2-agonist	Short-acting β_2-agonist ***and/or*** Short-acting anticholinergic ***or*** Theophylline
C	Inhaled glucocorticoid + Long-acting β_2-agonist ***or*** Long-acting anticholinergic	Long-acting anticholinergic ***and*** Long-acting β_2-agonist ***or*** Long-acting anticholinergic ***and*** Phosphodiesterase-4 inhibitor ***or*** Long-acting β_2-agonist ***and*** Phosphodiesterase-4 inhibitor	Short-acting β_2-agonist ***and/or*** Short-acting anticholinergic ***or*** Theophylline
D	***Inhaled*** glucocorticoid + Long-acting β_2-agonist ***and/or*** Long-acting anticholinergic	Inhaled glucocorticoid + Long-acting β_2-agonist ***and*** Long-acting anticholinergic ***or*** Inhaled glucocorticoid + Long-acting β_2-agonist ***and*** Phosphodiesterase-4 inhibitor ***or*** Long-acting anticholinergic ***and*** Long-acting β_2-agonist ***or*** Long-acting anticholinergic ***and*** Phosphodiesterase-4 inhibitor	*N*-acetylcysteine ***or*** Short-acting β_2-agonist ***and/or*** Short-acting anticholinergic ***or*** Theophylline

PRN = as needed.

[a]Medications in each box are listed in alphabetical order, not necessarily in order of preference.

[b]See Table 8 for definitions of patient categories.

[c]Medications in this column can be used alone or in combination with other options in the Recommended First Choice and Alternative Choice columns.

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Short-acting bronchodilators (short-acting β_2-agonists [SABAs]) and short-acting anticholinergics [also known as short-acting muscarinic agents [SAMAs]) provide rapid onset of action (within minutes of administration) and have a duration of action of 3 to 6 hours. They are recommended as initial monotherapy, administered on an as-needed basis, in patients with mild COPD and intermittent and/or exertional symptoms of disease (category A) (see Table 10). Short-acting bronchodilators also have an important role as add-on therapy, either alone or in combination, with other recommended therapies in higher-risk (categories B, C, and D) disease.

Long-acting bronchodilators consist of long-acting β_2-agonists (LABAs) and long-acting anticholinergics (also known as long-acting muscarinic agents [LAMAs]). These agents have demonstrated efficacy in improving FEV_1,

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TABLE 11. ACP, ACCP, ATS, and ERS Treatment Recommendations for Patients with Symptomatic, Stable COPD

Degree of Airflow Obstruction	Recommendation	Strength of Recommendation/ Quality of Evidence
FEV_1 60%-80% of predicted	Inhaled bronchodilators	Weak/Low
FEV_1 <60% of predicted	Monotherapy with either a long-acting inhaled anticholinergic or a long-acting β_2-agonist[a]	Strong/Moderate
	Combination therapy (long-acting inhaled anticholinergics, long-acting β_2-agonists, or inhaled glucocorticoids)	Weak/Moderate
FEV_1 <50%[b] of predicted	Pulmonary rehabilitation[c]	Strong/Moderate

ACP = American College of Physicians; ACCP = American College of Chest Physicians; ATS = American Thoracic Society; ERS = European Respiratory Society.

[a]Choice of specific monotherapy should be based on patient preference, cost, and adverse effect profile.

[b]Clinicians should consider pulmonary rehabilitation for symptomatic or exercise-limited patients with an FEV_1 ≥50% of predicted (weak recommendation/moderate evidence).

[c]In addition to pharmacologic therapy.

Source: Qaseem A, Wilt TJ, Weinberger SE, et al; American College of Physicians; American College of Chest Physicians; American Thoracic Society; European Respiratory Society. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. 2011 Aug 2;155(3):179-91. [PMID: 21810710]

improving health status, and significantly reducing the frequency of exacerbations; however, long-acting bronchodilators have not been shown to affect mortality. Some LABAs have a slower onset of action than SABAs, but the duration of action is greater. Salmeterol and formoterol have a 12-hour duration of action, whereas indacaterol and olodaterol have a 24-hour duration of action and provide significantly greater bronchodilating effects than salmeterol or formoterol. Agents with a duration of action of at least 24 hours are sometimes referred to as ultra-LABAs. LAMAs also have a slower onset of action compared with SAMAs, but they provide a 12- to 24-hour duration of action (aclidinium and glycopyrronium are 12 hours; umeclidinium and tiotropium are 24 hours). Newer 24-hour agents are sometimes referred to as ultra-LAMAs. Long-acting bronchodilators are used in the treatment of COPD when patients remain symptomatic on SABAs or require frequent SABA use to control symptoms, as outlined in Table 10. All patients using long-acting bronchodilators should also have a short-acting bronchodilator (SABA or SAMA) available for rescue use.

KEY POINTS

- Bronchodilators are the mainstay of therapy in COPD; all patients with COPD using long-acting bronchodilators should also have a short-acting bronchodilator available for rescue use.
- Long-acting bronchodilators in COPD improve FEV_1, improve health status, and significantly reduce the frequency of exacerbations, but have not been shown to affect mortality. HVC

Inhaled Glucocorticoids

The use of inhaled glucocorticoids is not considered appropriate as primary therapy or monotherapy in COPD, which differentiates COPD treatment from asthma treatment. However, combination treatment with an inhaled glucocorticoid and LABA or LAMA is recommended for highly symptomatic patients with frequent exacerbations (category C and D disease) (see Table 10).

In older patients with advanced COPD, inhaled glucocorticoids appear to be associated with an increased incidence of pneumonia, but this association has been difficult to confirm in this high-respiratory-risk population and has not been associated with increased mortality. Routine treatment with inhaled glucocorticoids does not improve decline of lung function, and the safety data with long-term use are not definitive. Patients taking inhaled glucocorticoids should be monitored for adverse drug effects, such as osteopenia, hyperglycemia, and cataracts. The potential for harm in treating patients with advanced COPD with inhaled glucocorticoids needs to be balanced against the potential benefit of reducing exacerbations and improving respiratory symptoms and quality of life.

A short-term trial of oral glucocorticoids is not recommended as a means of identifying patients who may respond to inhaled glucocorticoids.

KEY POINT

- The use of inhaled glucocorticoids is not considered appropriate as primary therapy or monotherapy in COPD. HVC

Systemic Glucocorticoids

Oral glucocorticoids are reserved for limited periodic use in treating exacerbations of COPD and may provide some benefit in decreasing hospital readmission rates after exacerbation. Long-term oral glucocorticoid therapy has limited, if any, benefit in COPD and carries a high risk for other significant side effects (such as muscle weakness and decreased functional status) in addition to those associated with inhaled glucocorticoids. Long-term oral glucocorticoids should not be used to treat COPD. However, select patients with ACOS may benefit from oral glucocorticoids, provided they have a reversible asthma component that predominates their symptomatic disease.

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TABLE 12. Drug Treatment for COPD

Agent	Side Effects	Notes
Bronchodilators		
Inhaled short-acting β_2-agonists (albuterol, fenoterol, levalbuterol, metaproterenol, pirbuterol, terbutaline)	Tachycardia and hypokalemia (usually dose dependent), but generally well tolerated by most patients	Generally used as needed for mild disease with few symptoms
Inhaled short-acting anticholinergic agents (ipratropium)	Dry mouth, mydriasis on contact with eye, tachycardia, tremors, rarely acute narrow angle glaucoma; this drug class has been shown to be safe in a wide range of doses and clinical settings	Not to be used with tiotropium; generally used as needed for mild disease with few symptoms; avoid using both short- and long-acting anticholinergics
Inhaled long-acting anticholinergic agents (tiotropium, aclidinium, umeclidinium, glycopyrronium)	Dry mouth, mydriasis on contact with eye, tachycardia, tremors, rarely acute narrow angle glaucoma	Not to be used with ipratropium; use when short-acting bronchodilators provide insufficient control of symptoms for patients with an FEV_1 <60% of predicted
Inhaled long-acting β_2-agonists (salmeterol, formoterol, arformoterol, indacaterol, olodaterol)	Sympathomimetic symptoms such as tremor and tachycardia; overdose can be fatal	Use as maintenance therapy when short-acting bronchodilators provide insufficient control of symptoms for patients with an FEV_1 <60% of predicted; not intended to be used for treatment of exacerbations of COPD or acute bronchospasm
Methylxanthines (theophylline, aminophylline; sustained and short-acting)	Tachycardia, nausea, vomiting, disturbed pulmonary function, and disturbed sleep; narrow therapeutic index; overdose can be fatal with seizures and arrhythmias	Used as maintenance therapy; generally use only after long-acting bronchodilator treatment to provide additional symptomatic relief of exacerbations; may also improve respiratory muscle function
Oral β_2-agonists (albuterol, metaproterenol, terbutaline)	Sympathomimetic symptoms such as tremor and tachycardia	Used as maintenance therapy; rarely used because of side effects but may be beneficial for patients who cannot use inhalers
Oral Phosophodiesterase-4 Inhibitor		
Roflumilast	Diarrhea, nausea, backache, decreased appetite, dizziness	Used to reduce risk for exacerbations in patients with severe COPD (blood levels not required) with chronic bronchitis and history of exacerbations; roflumilast should not be used with methylxanthines owing to potential toxicity; very expensive and should be used only in select patients
Anti-Inflammatory Agents		
Inhaled glucocorticoids (fluticasone, budesonide, mometasone, ciclesonide, beclomethasone)	Dysphonia, skin bruising, oral candidiasis, rarely side effects of oral glucocorticoids (see below)	Most effective in patients with a history of frequent exacerbations and when used in conjunction with long-acting bronchodilators; not approved by the FDA for treatment for COPD
Oral glucocorticoids (prednisone, prednisolone)	Skin bruising, adrenal suppression, glaucoma, osteoporosis, diabetes mellitus, systemic hypertension, pneumonia, cataracts, opportunistic infection, insomnia, mood disturbance	Use for significant exacerbations of COPD with taper; avoid, if possible, in stable COPD to limit glucocorticoid toxicity; consider inhaled glucocorticoids to facilitate weaning of systemic glucocorticoids
Combination Agents		
Combined inhaled long-acting β_2-agonist and inhaled glucocorticoid in a single inhaler (fluticasone/salmeterol, budesonide/formoterol)	Same/combined effects of both drug classes	Fluticasone/salmeterol is approved by the FDA as maintenance therapy and for prevention of exacerbations; budesonide/formoterol metered-dose inhaler is approved by the FDA as maintenance therapy; combinations are not to be used for treatment of acute bronchospasm
Combined short-acting β_2-agonist plus anticholinergic in a single inhaler (fenoterol/ipratropium, salbutamol/ipratropium)	Same/combined effects of both drug classes	Not to be used with tiotropium; generally used as needed for mild disease with few symptoms; avoid using both short- and long-acting anticholinergics; this combination therapy may be used for maintenance therapy only if patients have well-controlled disease on this combination treatment and do not require rescue therapy if/when expense is a determining factor

(Continued on the next page)

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TABLE 12. Drug Treatment for COPD *(Continued)*

Agent	Side Effects	Notes
Combined inhaled glucocorticoid and ultra-long-acting β_2-agonist in a single inhaler (fluticasone/vilanterol)	Same/combined effects of both drug classes	Not to be used for treatment of acute bronchospasm
Combined anticholinergic plus ultra-long-acting β_2-agonist in a single inhaler (umeclidinium/vilanterol)	Same/combined effects of both drug classes	Not to be used for treatment of acute bronchospasm

CONT.

Oral or intravenous glucocorticoids may be used in the management of acute exacerbations of COPD that require hospital admission. Although oral therapy has been shown to be noninferior to intravenous therapy, critically ill patients and those with nausea are candidates for intravenous therapy. Patients responding to intravenous glucocorticoids should be switched to oral glucocorticoids, and the dose of oral glucocorticoid should be tapered after discharge. The optimal dose and duration of glucocorticoid therapy in management of an acute exacerbation remains uncertain. Recent clinical trials continue to demonstrate a pattern that supports noninferiority of shortened duration of therapy and low-dose regimens. A recent systematic review found no significant differences in clinical outcomes between short-duration (<7 days) and longer-duration (>7 days) glucocorticoid treatment. Additionally, a recent randomized clinical trial showed that prednisone, 40 mg orally daily for 5 days, was not inferior to prednisone, 40 mg orally daily for 14 days, with regard to re-exacerbation within 6 months. Although the optimal dose and duration is not known, these data demonstrate shortened duration and reduced daily dosing of glucocorticoid therapy can decrease the total glucocorticoid exposure without worsening outcomes. H

Methylxanthines

Methylxanthines have shown modest treatment benefit in COPD, likely due to a bronchodilating effect mediated by nonselective inhibition of phosphodiesterase. However, the potential toxicity of this class of drugs coupled with their reduced efficacy has led to increasingly limited use. Although they may be helpful in any classification of COPD, they tend to be used in selected patients with late-stage disease or for patients in whom other preferred therapies have proved ineffective for symptomatic relief; they may also be used when other medications are not available or affordable. Methylxanthines are available in oral and intravenous formulations. However, they have a narrow therapeutic window, are poorly tolerated in older patients, and have multiple drug interactions.

Phosphodiesterase-4 Inhibitors

Inhibition of phosphodiestarase-4 (PDE-4) decreases inflammation, which may be helpful in a limited number of patients with COPD in whom inflammation is a significant factor. Roflumilast is an oral selective PDE-4 inhibitor and is currently the only available drug in this class. It is used primarily as add-on therapy in severe COPD (categories C and D) associated with chronic bronchitis and a history of recurrent exacerbations despite other therapies; it has been shown to improve symptoms and reduce risk and frequency of exacerbations in these individuals. However, it is not a bronchodilator, is expensive, and has not been shown to be effective in other groups of patients with COPD; therefore, it is not indicated for acute bronchospasm, rescue, or treatment of primary emphysema. Common side effects include diarrhea, nausea, weight loss, headache, and some psychiatric adverse events (anxiety, depression, insomnia). Roflumilast is contraindicated in patients with liver impairment and has significant drug interactions.

α_1-Antitrypsin Augmentation Therapy

α_1-Antitrypsin replacement therapy has been shown to slow the progression of COPD in select young patients with severe hereditary α_1-antitrypsin deficiency and established emphysema. However, this therapy is not recommended for patients with COPD that is unrelated to this deficiency.

Antibiotics

Use of antibiotics, other than for the treatment of infectious exacerbations, is currently not indicated.

There has been increasing interest in the chronic use of macrolide antibiotics to prevent COPD exacerbations based on their dual antimicrobial and anti-inflammatory effects. Several clinical trials to assess prophylactic use and benefit have demonstrated a reduction in the rate of exacerbation in patients with moderate to severe COPD with one or more exacerbations in the previous year despite optimal maintenance inhaler therapy; further evaluation is needed before routine use can be recommended in this patient population. Benefit and use of prophylactic macrolide therapy for patients with stable COPD has not been demonstrated and is presently not recommended. Macrolide antibiotics have the potential to precipitate growth of macrolide-resistant bacterial organisms and/or development of macrolide-resistant strains of nontuberculous mycobacteria and should be used with caution. In addition, potentially fatal arrhythmias have occurred in association with azithromycin.

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Other Agents

Routine use of antitussive agents is not recommended because there is no evidence of their efficacy.

Mucolytic drugs reduce sputum viscosity and are often prescribed in patients with COPD. *N*-acetylcysteine is an oral mucolytic drug that has been shown to improve mucociliary clearance and modulate the inflammatory response. It has antioxidant properties and may be helpful in preventing exacerbations in patients with moderate to severe COPD. However, further evaluation is needed before routine use of *N*-acetylcysteine can be recommended for treatment of patients with stable COPD. In other patients, the overall benefit of mucolytic therapy appears to be minimal, and routine use of mucolytics is not recommended.

The use of statins is not recommended in patients with moderate to severe COPD who are at risk for COPD exacerbations; however, some patients with COPD may meet accepted criteria for initiation of statins owing to the presence of cardiovascular risk factors.

Use of oral and parenteral opioids is very effective to treat dyspnea in severe COPD; however, data on nebulized delivery are insufficient. Use of opioids is common in patients in hospice care. Patients with refractory or disabling dyspnea who are not enrolled in hospice also benefit from symptom relief provided by opioids, which are likely underutilized in this population.

Use of pulmonary vasodilators (phosphodiesterase-5 inhibitors, calcium channel blockers, nitric oxide) is not recommended until further safety and efficacy data are available. There is no evidence supporting the use of leukotriene-modifying agents in COPD treatment.

Vaccination

Influenza vaccination has been shown to reduce serious illness (such as lower respiratory tract infections that require hospitalization) and death in patients with COPD. These vaccines should be administered annually in all patients with COPD.

Pneumococcal vaccination with the 23-valent polysaccharide vaccine should be given to all patients aged 19 to 64 years with COPD, with revaccination at age 65 years if 5 years have elapsed since the previous pneumococcal immunization. All patients (with or without COPD) should also receive the 13-valent pneumococcal conjugate vaccine at age 65 years, although the polysaccharide and conjugate vaccines should be given sequentially rather than together for optimal effect (see MKSAP 17 General Internal Medicine).

Nonpharmacologic Therapy

Smoking Cessation

Smoking cessation has been demonstrated to reduce the rate of decline in FEV_1 and risk of exacerbations in COPD. Smoking cessation is the most important goal in the management of COPD in patients who smoke, regardless of the level of disease severity. Counseling and pharmacotherapy can be effective to increase cessation success (see MKSAP 17 General Internal Medicine).

KEY POINTS

- Smoking cessation is the most important goal in the management of COPD in patients who smoke, regardless of the level of disease severity. HVC
- The use of antibiotics in COPD should be limited to infectious exacerbations. HVC
- Roflumilast is an oral selective phosphodiestarase-4 (PDE-4) inhibitor and its use should be limited to add-on therapy in severe COPD associated with chronic bronchitis and a history of recurrent exacerbations; it is not a bronchodilator, is expensive, and has not been shown to be effective in other groups of patients with COPD. HVC

Pulmonary Rehabilitation

All patients with COPD can benefit from exercise maintenance. Pulmonary rehabilitation is recommended for all symptomatic patients with an FEV_1 less than 50% of predicted and specifically for those hospitalized with an acute exacerbation of COPD. Pulmonary rehabilitation may also be considered in symptomatic or exercise-limited patients with an FEV_1 greater than or equal to 50% of predicted. These programs include education, functional assessment, nutrition counseling, and follow-up to reinforce behavioral techniques for change. They also include an exercise training component (≥30 minutes three times weekly for 6 to 8 weeks) that has been shown to improve endurance, flexibility, and upper and lower body strength. Exercise training can provide sustained benefit for post-exacerbation symptoms such as breathlessness following the completion of even a single rehabilitation program. This benefit does not wane after a rehabilitation program ends; however, sustaining benefit requires continuation of routine exercise. When combined with other forms of therapy (medical therapy, smoking cessation, nutrition counseling, and education), pulmonary rehabilitation has been shown to decrease patients' perceived intensity of breathlessness, reduce dyspnea and fatigue, facilitate increased participation in daily activities, and enhance health-related quality of life, including improvements in anxiety and depression.

KEY POINT

- All patients with COPD can benefit from pulmonary rehabilitation and exercise maintenance; pulmonary rehabilitation is recommended for all symptomatic patients with an FEV_1 less than 50% of predicted and specifically for those hospitalized with an acute exacerbation of COPD.

Oxygen Therapy

Long-term oxygen therapy in specific patients with COPD improves survival and has beneficial effects on hemodynamics,

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hematologic characteristics, exercise capacity, general alertness, mental status, hand grip, and motor speed. When provided during exercise, oxygen therapy can increase duration of endurance and reduce breathlessness at the end of exercise.

The need for oxygen therapy should be evaluated in all stable patients with an FEV_1 less than 35% of predicted or in patients with clinical symptoms or signs suggestive of respiratory failure or right-sided heart failure. A determination of the need for long-term oxygen therapy is initially based on resting arterial Po_2 or oxygen saturation values, which should be repeated and confirmed twice over a 3-week period. If resting oxygen saturation is less than 88%, arterial blood gas studies should be performed and long-term oxygen therapy should be initiated. When starting long-term oxygen therapy, a 6-minute walk test should be performed to assess and titrate oxygen levels with activity. The use of ambulatory oxygen is not supported for patients who do not meet the selection criteria.

Use of long-term oxygen therapy (>15 hours per day) has been shown to prolong life in patients meeting the following criteria: (1) chronic respiratory failure and/or severe resting hypoxemia, defined as an arterial Po_2 less than or equal to 55 mm Hg (7.3 kPa) or oxygen saturation less than or equal to 88% breathing ambient air, with or without hypercapnia; and/or (2) if there is evidence of pulmonary hypertension, peripheral edema suggesting right-sided heart failure, or polycythemia, in combination with an arterial Po_2 less than 60 mm Hg (8.0 kPa) or oxygen saturation less than 88% breathing ambient air.

Noninvasive Mechanical Ventilation

In select patients with COPD, noninvasive positive pressure ventilation may improve breathing pattern, diminish dyspnea, and increase oxygenation, resulting in improved sleep continuity, symptoms of daytime somnolence, exertional dyspnea, and awake arterial Po_2 levels. Candidates for this therapy are patients with stable severe and very severe COPD. The combination of noninvasive ventilation with long-term oxygen therapy is used in a select subset of patients with pronounced daytime hypercapnia. In patients with both COPD and obstructive sleep apnea, continuous positive airway pressure improves both survival and risk of hospital admissions. In addition to performing arterial blood gas studies to assess changes in Pco_2, dyspnea and exercise capacity should also be evaluated.

Noninvasive ventilation also has a significant role in management for patients with very severe COPD during an acute exacerbation and/or acute respiratory infection (for example, chronic bronchitis, pneumonia) and may be helpful to avoid intubation (see Critical Care Medicine).

Lung Volume Reduction Surgery

Lung volume reduction surgery is a palliative procedure that carries a high risk of perioperative mortality, and it is indicated only in a very clearly defined group of patients (**Table 13**). This surgery improves the mechanical efficiency of respiratory muscles and increases the elastic recoil of the lungs to improve expiratory flow and reduce exacerbations. Although lung volume reduction surgery may improve exercise capacity, lung function, dyspnea, and health-related quality of life in some patients, it has not been shown to increase survival when compared with pharmacologic therapy alone.

TABLE 13. Eligibility Criteria for Lung Volume Reduction Surgery in Patients with COPD

Severe COPD
Remain symptomatic despite maximal pharmacologic therapy
Completed pulmonary rehabilitation
Evidence of bilateral predominant upper-lobe emphysema on CT scan
Postbronchodilator total lung capacity of >100% ***and*** residual lung volume >150% of predicted
Maximum FEV_1 >20% and ≤45% of predicted and DLCO ≥20% of predicted
Ambient air arterial Pco_2 ≤60 mm Hg (8.0 kPa) ***and*** arterial Po_2 ≥45 mm Hg (6.0 kPa)

Information from Global Initiative for Chronic Obstructive Lung Disease (GOLD), Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html. Updated 2015. Accessed July 1, 2015.

Lung Transplantation

Lung transplantation improves quality of life and functional capacity in select patients with very severe COPD. Patients who may be considered appropriate candidates for lung transplantation should meet the criteria described in **Table 14**.

Common complications of lung transplantation include acute rejection, opportunistic infections (such as cytomegalovirus), fungal infections (such as *Candida, Aspergillus, Cryptococcus, Pneumocystis*), bacterial infections (such as *Pseudomonas, Staphylococcus* species), bronchiolitis obliterans, lymphoproliferative disease, and overall increased postoperative mortality. Double lung transplantation has similar or slightly higher survival rates compared with single lung transplantation.

TABLE 14. Recommended Criteria for Lung Transplantation in Patients with COPD

History of exacerbation associated with acute hypercapnia (arterial Pco_2 >50 mm Hg [6.7 kPa])
Pulmonary hypertension
Cor pulmonale
Pulmonary hypertension and cor pulmonale
FEV_1 <20% of predicted with DLCO <20% of predicted ***or*** homogeneous distribution of emphysema

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Acute Exacerbations

Definition

An exacerbation of COPD is defined as a sustained worsening of the patient's COPD. Exacerbations are marked by increased breathlessness and are usually accompanied by increased cough and sputum production. The degree of exacerbation is considered mild when a change in the clinical condition is noted but no change in medication is necessary. An exacerbation is considered moderate when medication changes are made. A severe exacerbation results in hospitalization.

KEY POINT

- An exacerbation of COPD is defined as a sustained worsening of the patient's COPD; exacerbations are marked by increased breathlessness and are usually accompanied by increased cough and sputum production.

Prevention

The strongest predictors of exacerbation are: (1) a history of previous exacerbation and (2) the baseline severity of airflow limitation. However, exacerbations of COPD can be prevented by optimizing treatment with appropriate interventions based on risk classification and overall disease management; this includes immunizations and lifestyle changes such as maintaining physical activity and addressing anxiety and depression. Interruption of maintenance therapy for COPD is associated with an increased risk of exacerbation. Smoking cessation has the greatest capacity to influence the natural history of COPD and reduce future exacerbations; therefore, all measures (including counseling and pharmacologic support) should be given to assist patients in stopping smoking. Exacerbations may also commonly be precipitated by respiratory infections (either bacterial or viral), and efforts should be made to minimize exposure to possible sources of infection. Additionally, environmental exposures, such as to pollutants, may trigger exacerbations and should be avoided.

In patients who experience an exacerbation, early outpatient pulmonary rehabilitation is safe and produces clinically significant improvements in health status at 3 months, possibly decreasing the risk of future exacerbations.

KEY POINT

- The strongest predictors of exacerbation of COPD are (1) a history of previous exacerbation and (2) the baseline severity of airflow limitation.

Initial Assessment and Setting of Care

Initial assessment of the severity of an exacerbation is based on the patient's medical history and clinical signs of severity (**Table 15**). Studies helpful in the evaluation may include pulse oximetry to assess oxygenation or guide oxygen therapy; a chest radiograph to rule out an alternative diagnosis; a complete blood count to identify the presence of polycythemia, anemia, or leukocytosis; arterial blood gas studies; a biochemical panel to assess for electrolyte and glycemic abnormalities; and an electrocardiogram to evaluate for a possible cardiac comorbidity.

TABLE 15. Criteria for Assessment of COPD Exacerbations

Medical History
Severity of COPD based on degree of airflow limitation
Duration of worsening or new symptoms
Number of previous episodes (exacerbations/hospitalizations)
Comorbidities
Current treatment regimen
Previous requirement for mechanical ventilation
Signs/Degree of Severity
Use of accessory respiratory muscles
Paradoxical chest wall movements
Worsening or new onset of central cyanosis
Development of peripheral edema
Hemodynamic instability
Deteriorated mental status

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The decision regarding the appropriate setting of treatment is usually based on the severity of the underlying lung disease, the severity of the exacerbation, and the presence of comorbidities.

Up to 80% of COPD exacerbations may appropriately be treated at home. The risk of dying from an exacerbation is closely related to the development of acidotic respiratory failure and possible need for ventilatory support in addition to the presence of significant comorbid conditions; therefore, treatment at home is reasonable in patients with less severe lung disease who do not have significant accompanying illnesses and who are experiencing mild to moderate exacerbations. Patients with more severe disease (symptom/risk evaluation categories C or D) without evidence of impending respiratory failure may also be candidates for home therapy, particularly if professionally administered home care services are available. However, the exact criteria for this approach (versus hospitalization) are not well defined and vary by health care setting, requiring individualization of setting of care decisions for these patients.

The criteria for hospital admission are described in **Table 16**. If an exacerbation is life-threatening, the patient should be immediately admitted to the ICU (see Critical Care Medicine). Criteria for ICU admission are discussed in **Table 17**.

KEY POINTS

- Home treatment of a COPD exacerbation is reasonable in patients with less severe lung disease who do not have significant accompanying illnesses and who are experiencing mild to moderate exacerbations. HVC

(Continued)

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TABLE 16. Criteria for Hospital Assessment of an Acute Exacerbation of COPD

Marked increase in intensity of symptoms (such as sudden onset of resting dyspnea)
Severe underlying COPD
Onset of new physical signs (such as cyanosis, peripheral edema)
An exacerbation that fails to respond to initial medical management
Presence of high-risk comorbid conditions (such as heart failure or newly occurring arrhythmias)
Frequent exacerbations
Advanced age
Patient inability to care for him- or herself
Inadequate home care available

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TABLE 17. Criteria for ICU Admission for an Acute Exacerbation of COPD

Despite adequate, appropriate treatment (oxygen, noninvasive ventilation), the patient experiences:
Persistent/worsening hypoxemia (arterial Po_2 <40 mm Hg [5.3 kPa]), ***and/or***
Severe/worsening respiratory acidosis (pH <7.25) and requires endotracheal intubation with mechanical ventilation
Severe dyspnea that responds inadequately to initial emergency therapy
Changes in mental status (such as confusion, lethargy, coma)
Hemodynamic instability with need for vasopressors

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KEY POINTS *(continued)*

- The criteria for hospital admission in patients with a COPD exacerbation include a marked increase in the severity of symptoms, the presence of severe underlying COPD, failure to respond to initial medical treatment or a change in medications, advanced age, and/or lack of sufficient in-home care.

Goals and Therapeutic Management

A primary goal of treatment is to minimize the overall impact of an exacerbation, and a secondary goal is to prevent future episodes. When an exacerbation occurs, components of treatment include both respiratory support and pharmacologic treatments.

Supplemental oxygen therapy should be provided to maintain an arterial Po_2 greater than 60 mm Hg (8.0 kPa) or an oxygen saturation of 88% to 92%. In patients with severe underlying lung disease who are at risk for acidotic respiratory failure, arterial blood gases should be checked 30 to 60 minutes after initiating oxygen therapy to assess for carbon dioxide retention and development of acidosis. Patients with severe underlying lung disease or severe exacerbations should be monitored closely for evidence of respiratory decompensation and the need for ventilatory support.

In patients with impending respiratory failure, noninvasive mechanical ventilation may be helpful in avoiding intubation. However, endotracheal intubation and mechanical ventilation are indicated in patients experiencing life-threatening hypoxemia, progressive hypercapnia, and/or severely altered mental status in whom a decision has been made to pursue invasive therapy (see Critical Care Medicine).

Short-acting bronchodilator therapy is a mainstay of therapy for treating COPD exacerbation, and a SABA or SAMA should be administered either alone or as combination therapy. The role of long-acting bronchodilators for treating COPD exacerbations has not been defined.

Glucocorticoids for acute exacerbations of COPD have been shown to reduce recovery time, improve lung function and arterial hypoxemia, decrease risk of early relapse, decrease treatment failure, and decrease length of hospital stay. Guidelines recommend oral glucocorticoids, although intravenous glucocorticoids are frequently administered in hospitalized patients. The optimal dose and duration of glucocorticoid therapy for COPD exacerbation has not been established, but a frequently used regimen is prednisone, 40 mg/d for 5 days. Tapering during the post-discharge period is reasonable.

Although the role of antibiotics in treating COPD exacerbations is not well defined, they appear to be most effective in patients with (1) increased dyspnea, sputum volume, and sputum purulence; (2) two of the preceding symptoms if one of the two symptoms is increased purulence; or (3) a requirement for mechanical ventilation (invasive or noninvasive). Empiric antibiotic therapy should be chosen on the basis of local bacterial resistance patterns. Commonly used regimens include an advanced macrolide, a cephalosporin, or doxycycline. If symptoms do not respond to initial antibiotic therapy, sputum cultures should be obtained, particularly to assess if *Pseudomonas aeruginosa* is present. The length of antibiotic treatment is usually 5 to 10 days.

Palliative Care and Hospice

Progressive respiratory failure, comorbid cardiovascular disease, malignancies, and the presence of other disease continue to be the primary cause of death in patients with COPD hospitalized for an exacerbation. Therefore, palliative and hospice care are important components of care for patients with advanced and complicated COPD.

Palliative care should be made available to all patients with advanced COPD early in their clinical course. Hospice services are focused on patients with very advanced COPD and a limited life expectancy; these services may be provided in either inpatient or home settings.

In patients with COPD, parameters that portend a poor prognosis and should trigger more extensive discussions regarding end-of-life care include an FEV_1 of less than 30% of predicted, oxygen dependence, multiple hospital admissions

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H CONT. for COPD exacerbations, significant comorbidities, weight loss and cachexia, decreased functional status, and increasing dependence on care takers. H

KEY POINTS

HVC • Glucocorticoids for acute exacerbations of COPD have been shown to reduce recovery time, improve lung function and arterial hypoxemia, decrease risk of early relapse, decrease treatment failure, and decrease length of hospital stay; a frequently used regimen is oral prednisone 40 mg/d for 5 days.

HVC • Antibiotic use in acute exacerbations of COPD should be limited to patients with increased dyspnea and purulent sputum or those who require mechanical ventilation (invasive or noninvasive).

Bronchiectasis

Definition

Bronchiectasis is irreversible pathologic dilation of the bronchi or bronchioles resulting from an infectious process occurring in the context of airway obstruction, impaired drainage, or abnormality in antimicrobial defenses. The pattern of lung involvement varies greatly with the underlying cause and may be focal or diffuse. Focal bronchiectasis may occur owing to either extrinsic changes (airway tumor, aspirated foreign body, scarred or stenotic airway) or intrinsic changes (bronchial atresia) to the airway. Diffuse bronchiectasis is more commonly associated with underlying systemic or infectious disease (bacterial infection, nontuberculous mycobacterial [NTM] infection, reactivated tuberculosis, cystic fibrosis [CF]).

Causes

The causes of bronchiectasis are listed in **Table 18**. The affected area of the lung may be helpful in defining the associated underlying disease. For example, CF-related bronchiectasis has more pronounced involvement of the upper lung fields. Upper lobe predominance is also suggestive of allergic bronchopulmonary aspergillosis, congenital causes, and causes associated with autoimmune or connective tissue diseases/syndromes. The mid-lung fields may be preferentially affected with NTM or *Mycobacterium avium* complex (MAC) infection (see MKSAP 17 Infectious Disease). Chronic recurrent aspiration, end-stage fibrotic disease, or recurrent infections associated with immunodeficiency more commonly affect the lower lung fields. Primary ciliary dyskinesia can be either central or diffuse. Bronchiectasis is associated with postradiation fibrosis, which corresponds with the lung tissue included in the radiation port.

TABLE 18. Causes of Bronchiectasis

Categories	Causes
Congenital	Cystic fibrosis
	Primary ciliary dyskinesia
Infections	Typical and atypical mycobacterial infection
	Recurrent infection, postinfectious (viral, bacterial, fungal)
Inhalation	Recurrent aspiration
	Chronic hypersensitivity pneumonitis
	Smoke inhalation
Traction (scarring)	Usual and nonspecific interstitial pneumonias
	Asbestosis
	Radiation therapy
Systemic inflammatory disorders	Collagen vascular disease (rheumatoid arthritis, scleroderma, systemic lupus erythematosus)
	Sarcoidosis
Local immunologic reactions	Allergic bronchopulmonary aspergillosis
	Asthma
	Lung transplant rejection
Autoimmune disease	Rheumatoid arthritis
	Sjögren syndrome
Connective tissue disease	Tracheobronchomegaly (Mounier-Kuhn syndrome)
	Cartilage deficiency (Williams-Campbell syndrome)
	Marfan syndrome
Immune deficiency	Immunoglobulin deficiency
	HIV infection
	Job syndrome (elevated IgE, eczema, and recurrent respiratory infection)
	Agammaglobulinemia
	Common variable immune deficiency
	Secondary immunodeficiency (chronic lymphocytic leukemia, HIV)
Inflammatory bowel disease	Ulcerative colitis
	Crohn disease
Obstruction	Tumor
	Foreign body
	Lymphadenopathy
Other	α_1-Antitrypsin deficiency
	Yellow nail syndrome (nail dystrophy, lymphedema, and pleural effusions)
	Young syndrome (azoospermia and recurrent sino-pulmonary infections due to ciliary dysfunction)

Presentation

Symptoms of bronchiectasis include chronic cough with purulent sputum and recurrent pneumonia (in both smokers and nonsmokers). Pulmonary function tests commonly detect mild to moderate airflow obstruction, which may overlap with other disease findings (COPD). Physical findings may include crackles and/or wheezing on lung auscultation. Some patients present with digital clubbing.

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Diagnosis

High-resolution CT (HRCT) is diagnostically definitive for bronchiectasis. For every diagnosed patient, it should be determined whether there is an underlying cause that can be treated. This may involve testing for chronic bacterial or mycobacterial infections, assessing for the presence of connective tissue disease, and evaluating immune function. In selected patients, testing for CF or α_1-antitrypsin deficiency may be appropriate if suspected. However, even with rigorous evaluation, more than half of all cases are still considered idiopathic.

KEY POINTS

- Symptoms of bronchiectasis include chronic cough with purulent sputum and recurrent pneumonia (in both smokers and nonsmokers).
- High-resolution CT is diagnostically definitive for bronchiectasis.

Treatment

Overall goals of therapy for bronchiectasis are to reduce symptoms, improve quality of life, and prevent acute exacerbations. If a modifiable cause for bronchiectasis is identified, treating the cause is the primary priority.

Inhaled hypertonic saline in conjunction with chest physiotherapy is often used for airway clearance. Mucolytic agents such as acetylcysteine may be used to reduce viscosity and liquefy sputum secretions but are not routinely recommended owing to lack of definitive benefit. Dornase alfa (an enzyme that selectively cleaves DNA in sputum from degenerating neutrophils and reduces sputum viscosity) is beneficial in patients with CF-related bronchiectasis but not in patients with bronchiectasis due to other causes.

Pulmonary rehabilitation programs are effective in patients with bronchiectasis; they are associated with significant improvements in exercise capacity and fewer outpatient and emergency department visits.

Although some patients with bronchiectasis show significant improvement in FEV_1 following administration of a bronchodilator, there are no data to support the routine use of short- or long-acting bronchodilators in bronchiectasis.

Anti-inflammatory therapy with inhaled glucocorticoids may be used in the treatment of bronchiectasis. In patients with non-CF bronchiectasis who also have COPD, inhaled glucocorticoids combined with SABA/LABA have a role for those patients who have two or more exacerbations annually. There is no evidence to support inhaled glucocorticoids alone in treating bronchiectasis. Short-duration systemic glucocorticoids have been used for exacerbations of bronchiectasis. However, because of side effects, long-term systemic glucocorticoids should not be used.

The macrolide antibiotic azithromycin has demonstrated clinical benefit in treatment of bronchiectasis; however, because of the potential to foster significant increases in antibiotic-resistant organisms, chronic NTM infection should be ruled out before initiating chronic macrolide therapy in bronchiectasis.

Oral, inhaled, and/or intravenous antibiotics are increasingly used in the management of bronchiectasis owing to a better understanding of the role of mucus stasis in bacterial colonization of the lung. In patients with bronchiectasis who experience recurrent exacerbations (≥3 episodes per year), use of oral or inhaled antibiotics to suppress microbial load and reduce future exacerbations is best supported in patients with CF rather than non-CF bronchiectasis. If *Pseudomonas aeruginosa* and/or methicillin-resistant *Staphylococcus aureus* is detected, consensus-based guidelines suggest treatment to attempt eradication.

KEY POINTS

- If a modifiable cause for bronchiectasis has been identified, treating the cause is the primary priority.
- There are no data to support the routine use of short- or long-acting bronchodilators or the long term use of systemic glucocorticoids in patients with bronchiectasis. HVC
- Pulmonary rehabilitation programs are effective in patients with bronchiectasis and are associated with significant improvements in exercise capacity and fewer outpatient and emergency department visits. HVC

Treatment of Exacerbations

Exacerbations of bronchiectasis may be difficult to differentiate from baseline symptoms. However, changes in sputum volume, viscosity, or purulence; increased cough; wheezing; shortness of breath; hemoptysis; and/or declines in lung function are considered evidence of exacerbation.

Therapy for an exacerbation is ideally guided by routine sputum and acid-fast bacilli culture results to identify a possible predominant organism for treatment. Empiric therapy should be based on previous respiratory cultures until current culture data are available, as resistant organisms commonly colonize bronchiectatic airways. Once culture and sensitivity data are available, antimicrobial therapy should be tailored to treat known pathogens. Although there is no clear evidence for determining the appropriate length of the therapeutic course, 2 weeks is commonly suggested.

Cystic Fibrosis in Adults

CF results from mutations in the CF transmembrane conductance regulator (*CFTR*) gene. It causes epithelial mucus dehydration and viscous secretions, which then cause occlusion of respiratory airways and contribute to the persistent airway infections and progressive tissue destruction that characterizes CF. However, CF is a multisystem disease that may also involve obstruction of the pancreatic ducts, biliary tree, and vas deferens.

CF is an autosomal recessive disorder that occurs with a frequency of 1 in 2000 to 3000 live births. Approximately 1000 new cases of CF are diagnosed annually, and approximately

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70,000 people are affected worldwide. Approximately 7% of patients with CF remain undiagnosed until adulthood (≥18 years of age).

Because of late diagnosis and treatment advances, CF is no longer considered a pediatric disease. By 2012, adults made up nearly 50% of the population with CF, and it is expected that adult patients with CF will very soon outnumber pediatric patients. The mean predicted survival age has increased over the last decade by almost 10 years, to 41.1 years of age as of 2012.

Diagnosis

Diagnosis of CF in adults may be obscured by an atypical and/or delayed presentation. However, the presence of certain conditions in an adult should increase suspicion for CF (**Table 19**).

Diagnosis is based on a combination of CF-compatible clinical findings in conjunction with either biochemical (sweat testing, nasal potential difference) or genetic (*CFTR* mutations) techniques. Use of the sweat test has been the mainstay of laboratory confirmation, although infection with *Burkholderia cepacia* is pathognomonic for CF. Once a CF diagnosis is confirmed, all patients should undergo *CFTR* mutational analysis to determine if *CFTR* modulator therapy may be an option.

Associated comorbidities in adults with CF include diabetes mellitus (present in up to 30% of patients), infertility due to azoospermia (present in 95% of men) and multifactorial causes in women, osteoporosis (present in 23% of patients), and liver disease. Liver disease occurs in 10% of patients with CF. The most common abnormality is fatty infiltration and intrahepatic cholestasis, with up to 5% to 15% of patients developing multilobular cirrhosis and portal hypertension.

Treatment

The pillars of CF management are airway clearance, antibiotic therapy, nutritional support, and psychosocial support. The primary objectives of CF treatment are maintaining lung health and controlling/minimizing the impact of CF-affected organ disease.

The vast majority (95%) of patients with CF die from complications of lung infection. The cardinal feature of CF lung disease is pulmonary exacerbation, which serves as a significant predictor of lung function decline, decreased quality of life, and increased morbidity. The Cystic Fibrosis Foundation (CFF) practice guidelines recommend use of chronic medications to improve lung function and reduce exacerbations. These medications include mucolytics, hydrating agents, inhaled antibiotics, oral macrolide antibiotics, and *CFTR* potentiators. Despite monitoring and management, patients may still experience exacerbations. Treatment for end-stage lung disease is with transplantation.

The goals of antibiotic treatment of CF bacterial infection(s) are to reduce bacterial burden, attempt/achieve early bacterial eradication, and/or prevent bacterial colonization of the lung (such as with *P. aeruginosa*). The CFF practice guidelines recommend that antibiotic treatment be provided for a minimum of 10 days, but a 14- to 21-day course is often necessary. Therapy may be extended even longer in patients with severe disease.

Similarly, additional recommendations are provided by the CFF for managing other CF-affected organ disease (pancreatic insufficiency; need for transplantation; sinus, liver, and bone disease; reproductive issues); these can be found on the CFF website (www.cff.org).

TABLE 19. Conditions Suggesting the Possible Diagnosis of Cystic Fibrosis in Adults

Recurrent pancreatitis
Male infertility
Chronic sinusitis
Severe nasal polyposis
Nontuberculous mycobacterial infection
Allergic bronchopulmonary aspergillosis
Bronchiectasis
Positive sputum culture for *Burkholderia cepacia*

KEY POINTS

- The diagnosis of cystic fibrosis is based on a combination of compatible clinical findings in conjunction with either biochemical (sweat testing, nasal potential difference) or genetic (*CFTR* mutations) techniques.
- The pillars of cystic fibrosis management are airway clearance, antibiotic therapy, nutritional support, and psychosocial support.

Diffuse Parenchymal Lung Disease

Overview

Interstitial lung diseases were initially named because of abnormalities identified in the pulmonary interstitium on histopathology. However, these disorders also typically involve the distal lung parenchyma, smaller airways, vasculature, and pleura. As a result, diffuse parenchymal lung disease (DPLD) is a more accurate and inclusive term for describing these diseases than is interstitial lung disease. DPLD represents a heterogeneous group of disorders that are classified based on similar clinical, radiographic, physiologic, and pathologic criteria. The term DPLD excludes pulmonary hypertension and COPD. In general, DPLDs are not infectious in origin, they most commonly present with dyspnea and cough, and imaging abnormalities are most often diffuse rather than focal.

Classification and Epidemiology

In comparison with the prevalence of either COPD or cardiogenic causes of shortness of breath, the DPLDs are extremely

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rare. Accurate estimates of the prevalence of DPLD remain elusive. Current estimates place the prevalence of DPLD at approximately 70 per 100,000 persons. Although this is the most widely accepted prevalence, it likely underestimates the true prevalence of the disorder. Approximately 30% to 40% of cases are idiopathic.

There are hundreds of DPLDs, which often leads to confusion on how best to diagnose them. The most useful classification system defines those with a known cause or association versus those that are idiopathic (**Table 20**). Pulmonary pathology specimens are the gold standard for diagnosis of DPLD of both unknown and known causes; however, for the idiopathic

TABLE 20. Classification and Distinguishing Features of Select Forms of Diffuse Parenchymal Lung Disease

Known Causes	
Drug induced	Examples: amiodarone, methotrexate, nitrofurantoin, chemotherapeutic agents (see www.pneumotox.com for a complete listing)
Smoking related	"Smokers" respiratory bronchiolitis characterized by gradual onset of persistent cough and dyspnea. Radiograph shows ground-glass opacities and thickened interstitium. Smoking cessation improves prognosis.
	Desquamative interstitial pneumonitis and pulmonary Langerhans cell histiocytosis are other histopathologic patterns associated with smoking and DPLD.
Radiation	May occur 6 weeks to months following radiation therapy
Chronic aspiration	Aspiration is often subclinical and may exacerbate other forms of DPLD
Pneumoconioses	Asbestosis, silicosis, berylliosis
Connective tissue diseases	
Rheumatoid arthritis	May affect the pleura (pleuritis and pleural effusion), parenchyma, airways (bronchitis, bronchiectasis), and vasculature. The parenchymal disease can range from nodules to organizing pneumonia to usual interstitial pneumonitis.
Systemic sclerosis	Nonspecific interstitial pneumonia pathology is most common; may be exacerbated by aspiration due to esophageal involvement; antibody to Scl-70 or pulmonary hypertension portends a poor prognosis. Monitoring of diffusing capacity for early involvement is warranted.
Polymyositis/ dermatomyositis	Many different types of histology; poor prognosis.
Other connective tissue diseases	Varying degrees of lung involvement and pathology can be seen in other forms of connective tissue disease.
Hypersensitivity pneumonitis	Immune reaction to an inhaled low-molecular-weight antigen; may be acute, subacute, or chronic. Noncaseating granulomas are seen.
Unknown Causes	
Idiopathic interstitial pneumonias	
Idiopathic pulmonary fibrosis	Chronic, insidious onset of cough and dyspnea, usually in a patient aged >50 y. Usual interstitial pneumonia pathology (honeycombing, bibasilar infiltrates with fibrosis). Diagnosis of exclusion.
Acute interstitial pneumonia	Dense bilateral acute lung injury similar to acute respiratory distress syndrome; 50% mortality rate.
Cryptogenic organizing pneumonia	May be preceded by flu-like illness. Radiograph shows focal areas of consolidation that may migrate from one location to another.
Sarcoidosis	Variable clinical presentation, ranging from asymptomatic to multiorgan involvement. Stage 1: hilar lymphadenopathy. Stage 2: hilar lymphadenopathy plus interstitial lung disease. Stage 3: interstitial lung disease. Stage 4: fibrosis. Noncaseating granulomas are hallmarks.
Rare DPLD with Well-Defined Features	
Lymphangioleiomyomatosis	Affects women in their 30s and 40s. Associated with spontaneous pneumothorax and chylous effusions. Chest CT shows cystic disease.
Chronic eosinophilic pneumonia	Chest radiograph shows "radiographic negative" heart failure, with peripheral alveolar infiltrates predominating. Other findings may include peripheral blood eosinophilia and eosinophilia on bronchoalveolar lavage.
Pulmonary alveolar proteinosis	Median age of 39 years, and males predominate among smokers but not in nonsmokers. Diagnosed via bronchoalveolar lavage, which shows abundant protein in the airspaces. Chest CT shows "crazy paving" pattern.

DPLD = diffuse parenchymal lung disease.

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forms of disease, histopathologic patterns correlate with disease prognosis as well as response to anti-inflammatory treatment (such as glucocorticoids).

Diagnostic Approach and Evaluation

Patients with DPLD most often present with nonspecific symptoms of dyspnea and cough. A careful history with attention to time course is useful in raising the suspicion for DPLD and narrowing the differential diagnosis. For symptoms of shorter duration, lasting days to weeks rather than over months, infection and heart failure remain the most likely cause. If these causes are excluded or empiric treatment in this population is unsuccessful, the acute- or subacute-onset DPLDs should be considered.

Causes of DPLD can be classified into several broad categories, which include connective tissue diseases, occupational or other exposures, drug-induced lung injuries, idiopathic disorders, and primary disorders (**Figure 7**). For each of these categories, the differential diagnoses overlap with the idiopathic interstitial pneumonias. Therefore, in patients with suspected DPLD, a careful history that includes the time course of symptoms, smoking and exposure history, rheumatologic review of systems, family history of autoimmune and lung disease, and past medication use helps assess potential risk and focus the differential diagnosis.

Plain chest radiography findings may be highly variable in patients with DPLD. Chest films may show increased interstitial reticular or nodular infiltrates in different patterns of distribution, but they may be normal in up to 20% of patients. Therefore, if clinical suspicion for DPLD exists, the evaluation should not stop if the chest radiograph is normal.

Characteristics on high-resolution CT (HRCT) of the chest have pulmonary pathology correlates that can help narrow the differential diagnosis. HRCT provides detailed resolution of the pulmonary parenchymal architecture. Advances in HRCT imaging techniques along with improved understanding of the correlation between HRCT findings and surgical biopsy histopathology findings have made HRCT the diagnostic tool of choice for evaluation of DPLD. There is little role for the use of conventional CT imaging (5-mm slice thickness) for this population given the limits of its resolution. HRCT, clinical presentation (including time course of symptoms), physical findings, and, when necessary, lung biopsy and histopathology allow clinicians to reach selected diagnoses from hundreds of DPLDs.

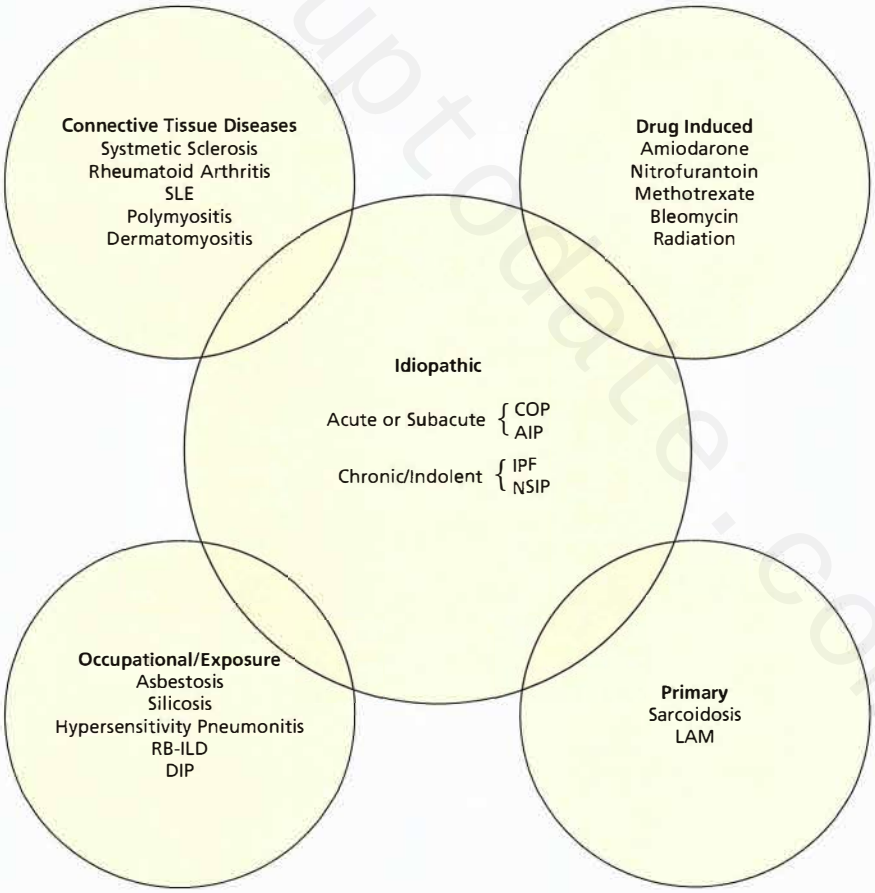

FIGURE 7. Broad categories of diffuse parenchymal lung disease. AIP = acute interstitial pneumonia; COP = cryptogenic organizing pneumonia; DIP = desquamative interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; LAM = lymphangioleiomyomatosis; NSIP = nonspecific interstitial pneumonia; RB-ILD = respiratory bronchiolitis-associated interstitial lung disease; SLE = systemic lupus erythematosus.

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For patients with more chronic symptoms, pulmonary function testing is helpful diagnostically to exclude obstructive lung disease as a primary cause of a patient's dyspnea symptoms. When restrictive or combined obstructive/restrictive diseases are identified and the presentation is more insidious (>6 months), DPLD should be considered.

Once there is clinical suspicion of DPLD, pulmonary consultation is appropriate.

KEY POINTS

- Causes of diffuse parenchymal lung disease can be classified into several broad categories, which include connective tissue diseases, occupational or other exposures, drug-induced lung injuries, idiopathic disorders, and primary disorders.
- The diagnosis of diffuse parenchymal lung disease should be considered in patients with insidious onset dyspnea and cough (>6 months) once infection, heart failure, and COPD are ruled out; consistent pulmonary function testing has a restrictive or combined obstructive/restrictive pattern.
- HVC High-resolution CT is the diagnostic tool of choice for evaluation of diffuse parenchymal lung disease; there is little role for plain chest radiography or conventional CT imaging (5-mm slice thickness) given the limits of their resolution.

High-Resolution CT Scanning

Patterns and Distribution

Disease patterns on HRCT generally correlate with pathologic findings on open lung biopsy. Specific terminology is used to describe findings noted on HRCT (**Table 21**). This terminology, in conjunction with the distribution of disease, allows the thoracic radiologist to describe patterns of disease associated with specific pathology (**Table 22**). Coexisting patterns of disease are common and can make definitive characterization from the CT scan imaging alone difficult. The combination of history, physical examination, serologic evaluation, and HRCT can obviate the need for diagnostic lung biopsy in 60% or more of patients. For those without a clear diagnosis following this evaluation, surgical lung biopsy may be considered.

Associated Findings

Outside of the lung parenchyma, additional findings may be present in the mediastinum, pleura, and soft tissues that assist in making a diagnosis. For example, mediastinal and hilar lymphadenopathy is a common finding in sarcoidosis, whereas significantly enlarged lymph nodes are a rare finding in patients with idiopathic pulmonary fibrosis (IPF). Similarly, pleural effusions are rare in IPF but can be seen in connective tissue disease–associated DPLD such as systemic lupus erythematosus. Pleural plaques can help identify a history of asbestos

TABLE 21. Thoracic Radiology Terminology for Parenchymal Findings in DPLD

Pattern	Characteristics	Pathophysiology
Septal	Peripheral: short lines that extend to the pleura	Disease affecting any component of the septum (connective tissue containing lymphatics and pulmonary venules)
	Central: polygonal arcades that outline the secondary pulmonary lobule	
Reticular	On radiograph: interlacing lines that suggest a net	HRCT further defines the abnormality, whether septal lines or walls of a cyst
Nodular	Spherical lesions (<1 cm) with widespread distribution	Centrilobular: artery and small airway pathology
	Locations: centrilobular, lymphatic (septal), or random	Septal (see above)
Reticulonodular	On radiograph: intersection of innumerable lines producing the effect of micronodules	As above
	HRCT: Discerns the location of nodules as either septal or centrilobular	
Ground glass	Hazy increased opacity with preservation of bronchial and vascular markings	Partial filling of airspaces; interstitial thickening from fluid, cells, and/or fibrosis; partial collapse of alveoli; increased capillary blood volume or a combination of these
Consolidation	Denser opacity that obscures vascular markings, unlike ground-glass opacity	Exudate or other product that replaces alveolar air
	Air bronchograms may be present	
Honeycomb change	Closely approximated ring shadows that resemble a honeycomb; typically subpleural with well-defined walls	Destroyed and fibrotic lung containing cystic airspaces
Mosaic attenuation	Patchy regions of differing attenuation	On expiratory images, decreased areas of attenuation represent bronchial or bronchiolar obstruction

DPLD = diffuse parenchymal lung disease; HRCT = high-resolution CT.

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TABLE 22. Patterns of Disease Associated with Diagnosis of DPLD

Lung Disease	Imaging	Comments
Acute interstitial pneumonia	Diffuse ground-glass with consolidation	Indistinguishable from ARDS with a risk factor
Organizing pneumonia	Patchy ground glass, consolidation, peripheral and basal predominance	Connective tissue diseases, infections, vasculitis, lymphoma, adenocarcinoma
Idiopathic pulmonary fibrosis/usual interstitial pneumonia	Basal- and peripheral-predominant septal line thickening with traction bronchiectasis and honeycomb changes	This is the usual interstitial pneumonia pattern and can be seen in connective tissue disease, asbestosis, and chronic hypersensitivity pneumonitis; idiopathic pulmonary fibrosis is a diagnosis of exclusion
Nonspecific interstitial pneumonia	Ground glass, basal predominance	Idiopathic and common finding in connective tissue disease
Respiratory bronchiolitis	Centrilobular nodules and ground-glass opacity in an upper-lung predominant distribution	May be an asymptomatic finding in an active smoker
Desquamative interstitial pneumonia	Basal- and peripheral-predominant ground-glass opacity with occasional cysts	—
Hypersensitivity pneumonitis	Acute: centrilobular micronodules that are upper- and mid-lung predominant Chronic: mid- and upper-lung predominant septal lung thickening with traction bronchiectasis; usual interstitial pneumonia pattern may be seen	Acute: associated with flulike illness Chronic: often cannot identify a causative antigen
Sarcoidosis	Upper-lobe predominant fibrosis; mediastinal and hilar lymphadenopathy; cystic changes including development of aspergilloma; airways-centered changes	Findings for sarcoidosis are often not specific; DPLD with diffuse mediastinal and hilar lymphadenopathy greater than 2 cm in size should raise suspicion

ARDS = acute respiratory distress syndrome; DPLD = diffuse parenchymal lung disease.

exposure and possible asbestosis. Bone abnormalities are notable in individuals with ankylosing spondylitis.

Surgical Lung Biopsy

Video assisted thoracoscopic lung biopsy is an option for patients who have disparate findings on history, physical examination, imaging, and laboratory studies. Although generally well tolerated, there are reports of individuals whose disease has worsened after the procedure. Therefore, risk stratification and assessment of potential benefit are necessary when deciding whether to pursue biopsy.

Diffuse Parenchymal Lung Diseases with a Known Cause

Smoking-Related Diffuse Parenchymal Lung Disease

Tobacco smoke is associated with the development of multiple DPLDs, including IPF. There are also several disorders that generally only develop in individuals who have an active smoking history.

Respiratory bronchiolitis–associated interstitial lung disease is used to describe disease in active smokers who have imaging findings of centrilobular micronodules with a pathologic finding of respiratory bronchiolitis on biopsy. Desquamative interstitial pneumonia is due to extensive, diffuse macrophage filling of alveolar spaces with predominant cough and dyspnea symptoms and bilateral ground-glass opacities on chest imaging. Pulmonary Langerhans cell histiocytosis is characterized by thin-walled cysts with accompanying nodules and is often associated with pulmonary hypertension. All of these diseases are subacute and present in active smokers. Pulmonary function tests usually reveal an obstructive pattern with a severely decreased DLCO in individuals with more severe disease. For those with milder disease, pulmonary function tests can be normal, restrictive, or obstructive. Cessation of smoking is the primary management. Although glucocorticoids are used in individuals with more severe disease, the benefit of their use is uncertain.

KEY POINTS

- Tobacco smoke is associated with the development of multiple diffuse parenchymal lung diseases, including idiopathic pulmonary fibrosis.
- Cessation of smoking is the primary management for smoking-related diffuse parenchymal lung disease. HVC

Connective Tissue Diseases

The prevalence of pulmonary manifestations in individuals with known connective tissue diseases is extremely high.

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Patients with DPLD associated with connective tissue disease typically present with dyspnea.

DPLD is most often identified after an established diagnosis of connective tissue disease, although occasionally DPLD will be the first manifestation of connective tissue disease. As a result, all patients with suspected DPLD should be screened with a careful rheumatologic review of systems and physical examination to assess for the possibility of connective tissue disease. It is important to identify an underlying autoimmune disorder because of its effect on prognosis, drug therapy recommendations, and management of comorbidities that may adversely affect pulmonary outcomes.

For example, progressive pulmonary disease is now the primary cause of mortality in systemic sclerosis. Cyclophosphamide may have some short-term benefit in treating the lung disease, and managing the gastroesophageal dysmotility associated with systemic sclerosis may help avoid aspiration and further lung injury.

Another connective tissue disease commonly associated with DPLD is rheumatoid arthritis. DPLD associated with rheumatoid arthritis is more common in males than females and, as with other autoimmune diseases, may present prior to manifestations of arthritis. Parenchymal lung disease may include pleural disease, rheumatoid nodules, bronchitis, bronchiectasis, organizing pneumonia, and bronchiolitis, as well as a pattern of usual interstitial pneumonia (UIP). Similar to individuals with IPF, a UIP pattern on CT imaging indicates a poor prognosis. Currently, these manifestations of rheumatoid arthritis are often treated with glucocorticoids and disease-modifying agents; however, there are little data to suggest clear efficacy for this strategy.

KEY POINTS

- The prevalence of pulmonary manifestations in individuals with known connective tissue diseases is extremely high, and these patients typically present with dyspnea.
- All patients with diffuse parenchymal lung disease should be clinically assessed for an underlying autoimmune disorder because of its effect on prognosis, drug therapy recommendations, and management of comorbidities.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is the result of an immunologic response to repetitive inhalation of antigens. The most common sources of antigens are thermophilic actinomyces, fungi, and bird droppings. Antigens, however, are not limited to these origins and can include bacterial, protozoal, animal, or insect proteins, and even small molecular chemical compounds.

The acute form of HP presents within 48 hours of a high-level exposure and will often be associated with fevers, flulike symptoms, cough, and shortness of breath. Radiographic imaging can demonstrate bilateral hazy opacities, while HRCT imaging of the chest shows findings of ground-glass opacities and centrilobular micronodules that are upper- and mid-lung predominant (**Figure 8**). Symptoms typically wane within 24 to 48 hours after removal from the exposure. Recurrence of symptoms with exposure to the respiratory antigen is the hallmark of this disorder, and careful attention to the history will help identify the cause.

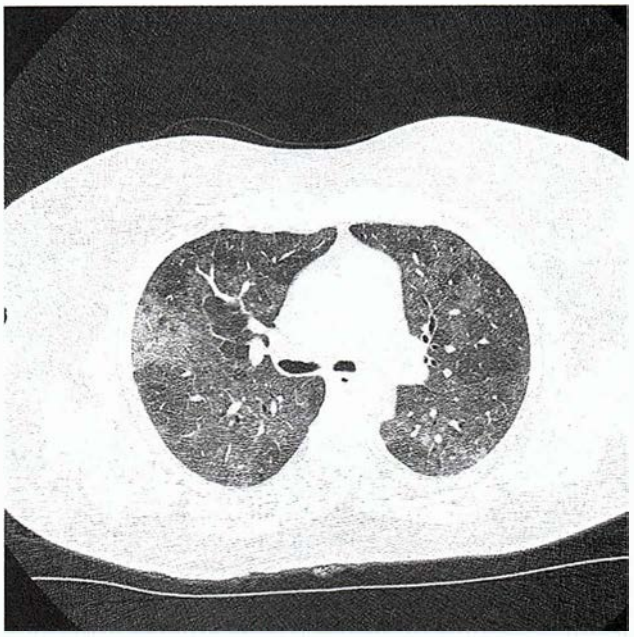

FIGURE 8. Chest CT demonstrating hypersensitivity pneumonitis with patchy, bilateral ground-glass opacities and centrilobular micronodules in this mid-lung section.

Subacute and chronic forms of the disease also occur and are believed to be associated with more chronic low-level exposures to inhaled antigen. Bird fancier's disease is the classic example of this disorder, in which individuals are chronically exposed to an antigen from a domestic bird within the home. Patients will ultimately present with cough, dyspnea, malaise, and weight loss. HRCT findings include centrilobular micronodules in upper- and mid-lung distribution as well as evidence of septal line thickening and fibrosis.

The primary treatment is to remove the offending antigen. For this reason, it is extremely important to obtain a careful history to identify potential exposures. Glucocorticoids are used for patients with more severe symptoms and for those with evidence of fibrosis.

KEY POINTS

- The most common sources of antigens causing hypersensitivity pneumonitis are thermophilic actinomyces, fungi, and bird droppings; symptoms wane 24 to 48 hours after removal from exposure and recur with re-exposure to respiratory antigens.
- Radiographic imaging in hypersensitivity pneumonitis may demonstrate bilateral hazy opacities, while high-resolution CT imaging of the chest shows findings of ground-glass opacities and centrilobar micronodules that are upper- and mid-lung predominant.

(Continued)

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KEY POINTS *(continued)*

- The primary treatment for hypersensitivity pneumonitis is to remove the offending antigen; glucocorticoids are used for patients with more severe symptoms and for those with evidence of fibrosis.

Drug-Induced Parenchymal Lung Disease

In patients who present with diffuse abnormalities on chest imaging, drug-induced parenchymal lung disease should be considered and investigated. Hundreds of drugs have been described in association with drug-induced lung disease. A few classic drug-induced lung syndromes are described in **Table 23**. Symptoms can develop acutely after drug initiation, but some medications have more subacute symptoms. Therefore, a careful medication history should be taken and should include medications that may have been discontinued after chronic treatment. The primary management of these disorders is removal of the offending agent.

Radiation-Induced Parenchymal Lung Disease

Symptoms of acute radiation pneumonitis typically occur 6 to 12 weeks after exposure. Patients present with cough, dyspnea, and occasionally fever and malaise. Differentiating these symptoms from infection and drug-induced pneumonitis is difficult given the common use of chemotherapy in combination with radiation. HRCT shows hazy ground-glass opacities.

TABLE 23. Select Drug-Induced Parenchymal Lung Diseases

Drug	Clinical Points	Radiographic Findings and Treatment
Amiodarone	More common in: Older patients Increased dosage and higher cumulative dose First year of therapy (but can occur late)	Multiple radiographic presentations possible including ground-glass opacities, subpleural nodules, and reticular abnormalities Very long half-life prevents clearance from the pulmonary parenchyma: Rare improvement with discontinuation of the drug alone High risk of recurrence with tapering of glucocorticoids
Methotrexate	Occurs in less than 5% of patients treated Unpredictable time to presentation No clear correlation between dose and disease severity	Diffuse reticular and ground-glass attenuation Patients generally do well after stopping medication Glucocorticoids are often given and duration is based on response
Nitrofurantoin	Acute (more common): Fevers, chills, cough, shortness of breath, chest pain; rash can occur in 10%-20% of patients Peripheral eosinophils common Chronic: Distinct from the acute form Onset months to years after prolonged exposure	Acute: Faint bilateral lower lobe septal lines; moderate pleural effusions may be present. Treatment: Often will resolve with discontinuation but will recur with repeat exposure. Chronic: Reticular opacities with subpleural lines and thickened peri-bronchovascular areas. Treatment: Possible benefit of glucocorticoids from anecdotal reports.
Busulfan	Occurs in less than 8% of patients treated Used solely as a conditioning regimen for HSCT today; often combined with other agents associated with pulmonary toxicity Injury typically occurs 30 days to 1 year after exposure	Multiple patterns including: ground glass opacities, reticulation, bibasilar septal lines, asymmetric peripheral and peribronchial consolidation, centrilobar nodules, and dependent consolidation Optimal treatment unknown and is often supportive Glucocorticoids may be used for more progressive disease
Bleomycin	Risk significantly increases with cumulative dose Increased age, renal insufficiency, concomitant chemotherapy and/or radiation also increases risk of toxicity Typically subacute presentation 1 to 6 months after exposure; may resemble hypersensitivity pneumonitis but with more rapid onset and progressive course	Imaging patterns suggest the multiple possible pathologic findings seen: Consolidation with ground glass (diffuse alveolar damage) Septal line thickening, traction bronchiectasis, and honey comb change (end-stage fibrosis) Patchy ground glass with subpleural consolidation or peribronchial consolidation (organizing pneumonia) Diffuse ground glass with centrilobar micronodules (hypersensitivity pneumonitis) Glucocorticoids are used for more severe disease and disease may recur with tapering of steroids

HSCT = hematopoietic stem cell transplantation.

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CONT.

The factor that is most pathognomonic of radiation pneumonitis is the imaging finding of a nonanatomic straight line demarcating involved versus uninvolved lung parenchyma. Although abnormalities most often occur within the radiation field, it is possible for changes to occur outside of the field as well. Typically, acute changes will resolve within 6 months, but some patients may be left with a well-demarcated area of fibrosis, volume loss, and bronchiectasis.

Treatment of radiation pneumonitis is determined by the severity of symptoms. For patients with evidence of organizing pneumonia, there is likely a benefit to the use of glucocorticoids. Glucocorticoid therapy use is based on animal data suggesting a beneficial effect by suppressing the inflammatory response from acute radiation. For those with milder disease, the inflammation may resolve, obviating the need for glucocorticoids.

KEY POINTS

- In patients who present with diffuse abnormalities on chest imaging, drug-induced lung disease should be considered and investigated.
- Radiation pneumonitis presents with cough, dyspnea, and hazy ground-glass opacities (pathognomonic finding is a nonanatomic straight line between involved and uninvolved lung) on high-resolution CT 6 to 12 weeks after radiation exposure.

Diffuse Parenchymal Lung Diseases with an Unknown Cause

Idiopathic Pulmonary Fibrosis

IPF is the most common idiopathic interstitial pneumonia. It occurs predominantly in older individuals; the diagnosis of IPF is rare in those younger than 60 years of age. Gradual onset of dyspnea and cough over months to years is typical. Physical examination reveals dry inspiratory crackles at the bases. Nearly 50% of patients will have clubbing. More severe disease is associated with secondary pulmonary hypertension and evidence of right-sided heart failure on examination. Initial evaluation findings are often similar to more common conditions such as heart failure (due to crackles on lung examination) or COPD (a smoking history is common). Pulmonary function testing will most often show a restrictive abnormality with a reduced diffusing capacity; however, an isolated reduction in diffusing capacity and normal pulmonary function can also be seen (see Pulmonary Diagnostic Tests). All other identifiable causes of fibrotic lung disease must be excluded before the diagnosis can be made. When select HRCT features are present that establish a definite pattern of UIP (see Table 22) in the appropriate clinical setting, the diagnosis of IPF is established.

Prognosis remains poor, and individuals diagnosed with IPF have an estimated average survival of 3 to 5 years. There is, however, variability in the disease course. Some individuals will have slowly progressive declines in their forced vital capacity, while others can have a rapid decline leading to death. Still others will demonstrate stepwise declines in their pulmonary function tests with acute declines followed by subsequent stabilization.

An acute decline may manifest as an acute exacerbation of IPF. This is a well-defined clinical syndrome that develops in a small portion of patients with IPF. The clinical course of an acute exacerbation is acute to subacute onset (typically <30 days) of worsening dyspnea, and the medical evaluation does not reveal another cause for dyspnea such as infection, heart failure, or pulmonary embolism. HRCT shows new-onset diffuse ground-glass opacities. Patients may develop frank respiratory failure due to an exacerbation or stabilize at a new, worsened baseline.

The most common cause of death in IPF is respiratory failure. For individuals who develop severe respiratory distress for which there is no underlying reversible cause, supportive mechanical ventilation is of little long-term benefit. Therefore, the most recent evidence-based consensus statement recommends against mechanical ventilation for individuals with acute respiratory failure due to either progression or an acute exacerbation of IPF. In these circumstances, the focus should be on palliation of the patient's underlying dyspnea.

Treatment of IPF is primarily supportive, with optimization of fitness and oxygenation, as well as treatment of associated conditions. Recent clinical trials have led to a clearer understanding of the pharmacologic approach to patients with carefully diagnosed IPF. Therapies used in the past focused on anti-inflammatory therapy (for example, prednisone), with or without immune modulators (such as azathioprine). These therapies should be avoided because they were associated with increased mortality when compared with placebo in patients with mild to moderate respiratory impairment due to IPF. Antioxidant therapy with *N*-acetylcysteine was not found to be beneficial in decreasing the progression of IPF or reducing the frequency of exacerbations of IPF.

The most current models of disease focus on the interplay among alveolar epithelial cells, the extracellular matrix, and myofibroblasts that lead to fibrosis. Knowledge of these pathways has led to the development of two newly approved FDA therapies for the treatment of IPF: nintedanib and pirfenidone. Nintedanib is a tyrosine kinase inhibitor known to block pathways that lead to activation of the fibroblast. Similarly, pirfenidone is a novel therapeutic agent that regulates transforming growth factor β (TGF-β) and tumor necrosis factor α (TNF-α) activity through an unknown mechanism. Although these therapies are an important step forward in the management of IPF, they are not curative.

Lung transplantation remains the only therapy that clearly prolongs life in a select subset of patients with IPF. Early referral to a lung transplant center for suitable individuals interested in transplantation remains an appropriate early intervention for individuals with IPF.

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KEY POINTS

- Treatment of idiopathic pulmonary fibrosis is supportive, with optimization of fitness and oxygenation, as well as treatment of associated conditions; lung transplantation may be appropriate in a select subset of patients.

HVC

- The most recent evidence-based consensus statement recommends against mechanical ventilation for individuals with acute respiratory failure due to either progression or an acute exacerbation of idiopathic pulmonary fibrosis.

Nonspecific Interstitial Pneumonia

Similar to IPF, NSIP is a disease that predominantly affects the lower lobes of the lung. Unlike IPF, NSIP tends to affect a younger patient population and is strongly associated with connective tissue disease. The largest group of patients with NSIP is those with systemic sclerosis; however, many autoimmune disorders have been associated with NSIP, including rheumatoid arthritis, systemic lupus erythematosus, polymyositis/dermatomyositis, and undifferentiated connective tissue disease. Some patients may initially present with only pulmonary manifestations of their underlying autoimmune disorder. For these individuals, the initial diagnosis may be idiopathic NSIP. This cohort of patients should receive continued surveillance for development of connective tissue disease. A careful review of systems is a key component of patient follow-up; new-onset symptoms should prompt further diagnostic assessments. A definitive diagnosis may help to better define the prognosis. The basis for immunosuppressive/immune-modulatory medications in patients with NSIP stems from the treatment response observed in the Scleroderma Lung Study, which was specific for patients with scleroderma and the inflammatory form of NSIP. The generalizability of these data in patients with NSIP due to other causes is less understood. In general, the prognosis for patients with an underlying autoimmune disorder is better than those with IPF; however, more severely affected pulmonary function and more extensive disease on CT imaging portend a worse prognosis.

KEY POINT

- Nonspecific interstitial pneumonia predominantly affects the lower lobes of the lung, tends to affect a younger patient population, and is strongly associated with connective tissue disease (most often systemic sclerosis).

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Cryptogenic Organizing Pneumonia

Organizing pneumonia is a patchy process that involves proliferation of granulation tissue within alveolar ducts, alveolar spaces, and surrounding areas of chronic inflammation. There are many known causes of this pattern, including acute infections and autoimmune disorders like rheumatoid arthritis. The term cryptogenic organizing pneumonia (COP) is reserved for individuals who have this pattern but do not have a clear associated cause.

Patients with COP will typically present with symptoms over 6 to 8 weeks that mimic community acquired pneumonia. The vast majority of individuals will present with symptoms of less than 3 months' duration. Patients typically present with bilateral diffuse alveolar opacities on chest radiograph with normal lung volumes (**Figure 9**). Patients may also present with multiple large nodules or masses that are predominantly peripheral. Although these findings are suggestive of an organizing pneumonia pattern, they are not specific to this disease. Typically, an initial empiric treatment for infection is given but fails; subsequently, noninfectious causes are then considered. Because the imaging findings are not specific, a bronchoscopic or surgical lung biopsy may be necessary to establish the diagnosis.

The prognosis for COP is typically favorable with a good response to glucocorticoids. Similar to idiopathic NSIP, individuals with COP should undergo examination and careful review of systems to ensure that there is not an underlying connective tissue disease. Also similar to idiopathic NSIP, individuals may develop manifestations of an underlying autoimmune disease subsequent to their initial pulmonary presentation.

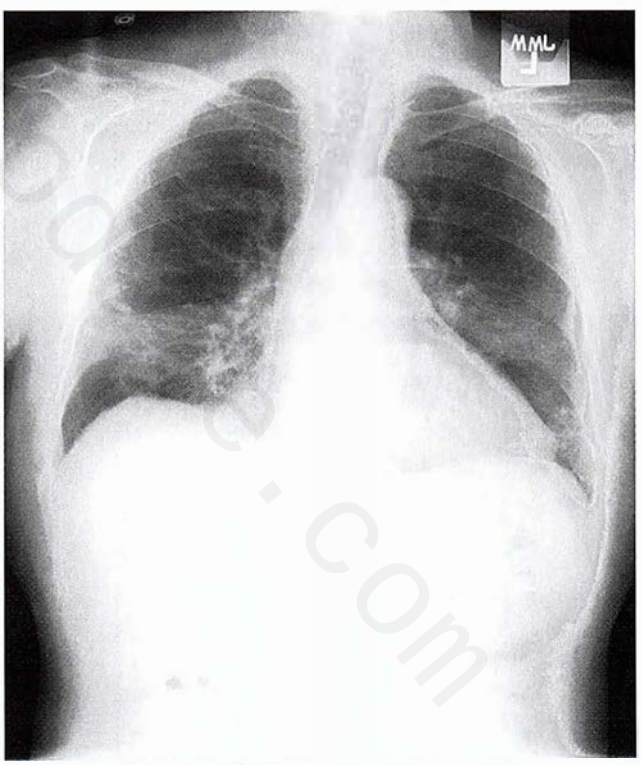

FIGURE 9. Chest radiograph showing cryptogenic organizing pneumonia with multiple patchy bilateral alveolar opacities that are nonspecific and may be difficult to distinguish from more typical infectious pneumonia. Infiltrates may be migratory with resolution of established opacities as new areas appear on serial imaging. Imaging may also be nonspecific, showing interstitial infiltrates and alveolar opacification or showing one or more rounded nodules that may be interpreted as malignancy.

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CONT.

In COP, recurrence with tapering of the glucocorticoid dosage is common; however, these recurrences most often respond to readministration and tapering of glucocorticoids. For those with multiple recurrences, careful re-examination for an underlying cause (such as an autoimmune disorder or ongoing exposure) is necessary. This group of patients may require long-term immunosuppressive therapy.

KEY POINT

- The prognosis for cryptogenic organizing pneumonia is typically favorable with a good response to glucocorticoids.

Acute Interstitial Pneumonia

Acute interstitial pneumonia develops rapidly over days to weeks and results in progressive hypoxemic respiratory failure. Radiographic examination reveals bilateral alveolar opacities consistent with pulmonary edema; these findings cannot be reliably discerned from acute respiratory distress syndrome. Similarly, open lung biopsy specimens demonstrate diffuse alveolar damage. Unlike acute respiratory distress syndrome, there are no clearly associated risk factors for respiratory failure. Therefore, the history should be carefully reviewed to ensure that there is nothing to suggest aspiration, sepsis, pneumonia, or inhalational injury that might be amenable to treatment. Consensus recommendations advocate treatment with glucocorticoids. Although little evidence-based data exist, anecdotal reports suggest an improved outcome with this therapy. In addition to glucocorticoids, supportive care (with low tidal volume ventilation and careful attention to avoid complications of critical illness) remains the mainstay of therapy. Mortality rates remain extremely high (approximately 50%). Individuals who recover from the initial illness may relapse or develop chronic lung disease.

KEY POINT

- Acute interstitial pneumonia develops rapidly over days to weeks and results in progressive hypoxemic respiratory failure; treatment consists of glucocorticoids and supportive care, but mortality is still high at 50%.

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unclear cause with a predilection for the lung; pulmonary involvement occurs in more than 90% of patients.

Many patients with pulmonary sarcoidosis are asymptomatic, and lung involvement is frequently discovered incidentally on chest imaging (**Figure 10**). Pulmonary sarcoidosis is classified based on the radiographic pattern (**Table 24**), and spontaneous regression of disease is common. For example, greater than 90% of those with stage I findings have radiographic resolution of their findings within 2 years, whereas 20% of those with stage II or III had spontaneous improvement in their imaging findings over this same time interval.

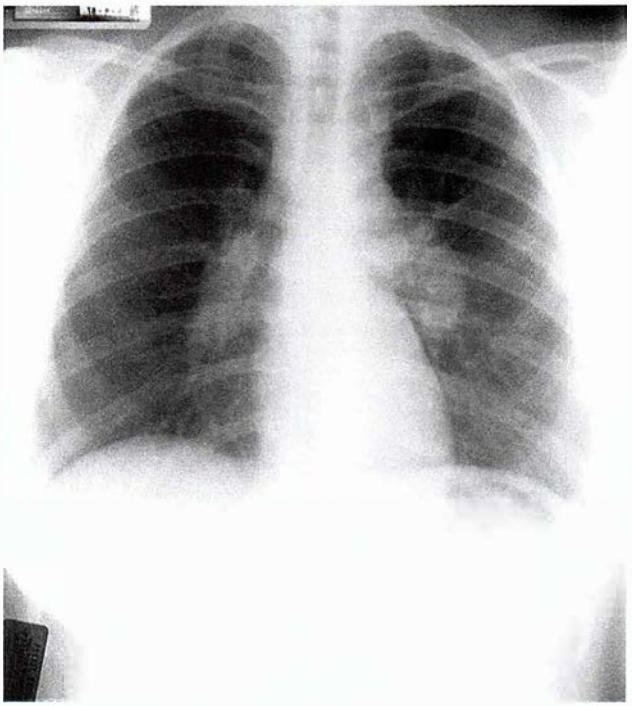

FIGURE 10. Chest radiograph showing stage I pulmonary sarcoidosis with hilar lymphadenopathy and normal lung parenchyma.

TABLE 24. Plain Radiographic Staging of Pulmonary Sarcoidosis

Stage	Radiographic Pattern	Clinical Course and Comments
0	Normal	—
I	Hilar lymphadenopathy with normal lung parenchyma	>90% will have spontaneous resolution without treatment
II	Hilar lymphadenopathy with abnormal lung parenchyma	Approximately 20% rate of spontaneous improvement without treatment
III	No lymphadenopathy with abnormal lung parenchyma	Approximately 20% rate of spontaneous improvement without treatment
IV	Parenchymal changes with fibrosis and architectural distortion	—

Pulmonary function tests will often be abnormal with obstructive, restrictive, or combined physiology on testing. Because sarcoidosis is a diagnosis of exclusion, a careful assessment is warranted in all patients to clarify the diagnosis. Although tissue biopsy (most often via bronchoscopy with transbronchial and lymph node biopsy) is usually required to diagnose sarcoidosis and exclude significant alternative diagnoses, there are several specific clinical situations in which biopsy is not considered necessary (**Table 25**).

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TABLE 25. Clinical Presentations of Sarcoidosis that Do Not Warrant a Biopsy

Syndrome/Sign	Comments
Asymptomatic bilateral hilar lymphadenopathy	No evidence of fevers, malaise, or night sweats to suggest a malignancy
Löfgren syndrome	Bilateral hilar lymphadenopathy, migratory polyarthralgia, erythema nodosum, and fevers
Heerfordt syndrome	Anterior uveitis, parotiditis, fevers (uveoparotid fever), and facial nerve palsy

CONT.

Glucocorticoids are the mainstay of therapy. Treatment is usually limited to those with evidence of clinical symptoms from organ dysfunction. Because there is a high rate of spontaneous remission and stability, most treatment protocols favor a period of observation without therapy. The decision to initiate glucocorticoid therapy for sarcoidosis should be based on symptoms or physiologic impairment that is attributable to sarcoid disease. There is a paucity of randomized controlled trials to provide guidance regarding whether glucocorticoid therapy will provide definitive benefit. Retrospective data suggest that treatment with glucocorticoids may have short-term symptomatic benefit but does not clearly affect long-term disease outcomes. If glucocorticoids are used for treatment of sarcoidosis, studies suggest that low-dose or alternate-day treatment strategies are as efficacious as higher-dose strategies and appear to have fewer side effects. Studies also show that once glucocorticoid therapy has begun, many patients will remain on this therapy for prolonged periods. Tapering regimens are often prolonged and should be based on clear, attributable symptoms or physiologic metrics in conjunction with careful and frequent follow-up.

Pulmonary hypertension may develop in some individuals with sarcoidosis owing to multiple physiologic reasons, including DPLD, pulmonary vascular disease, pulmonary artery compression from significant lymphadenopathy, left ventricular dysfunction, and pulmonary venous occlusion. For individuals who develop pulmonary hypertension without evidence of left ventricular dysfunction, mortality is significantly higher, with a median survival of approximately 3 years. For this group of patients, as well as individuals with significant limitations due to pulmonary disease, lung transplantation is a viable therapeutic option.

For a discussion of the musculoskeletal manifestations of sarcoidosis, see MKSAP 17 Rheumatology.

KEY POINTS

- Pulmonary involvement occurs in more than 90% of patients with sarcoidosis, but is often asymptomatic.
- Glucocorticoids are the mainstay of therapy for symptomatic pulmonary sarcoidosis.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis is a rare disorder that occurs sporadically in women or in association with tuberous sclerosis. It manifests as a diffuse cystic lung disease due to infiltration of smooth muscle cells into the pulmonary parenchyma. Genetic mutations within the cells lead to activation of the mammalian target of rapamycin (mTOR) pathway. Diagnosis is based on imaging studies with diffuse thin-walled cysts (**Figure 11**) as well as spontaneous pneumothorax, angiomyolipomas, and elevated vascular endothelial growth factor-D (VEGF-D). Hormonal therapy, which was used in the past, is not effective in altering the disease course. Immunosuppression with sirolimus has demonstrated promise in limiting progression of pulmonary disease in patients with lymphangioleiomyomatosis.

Occupational Lung Disease

When to Suspect an Occupational Lung Disease

Occupational lung diseases affect all aspects of the respiratory tract, from the upper airways to the lower airways and interstitium. Clinical manifestations may include rhinitis, asthma, COPD, constrictive bronchiolitis, and restrictive diseases. Symptom onset following exposure can be acute (reactive airways disease/small airways dysfunction as occurs in acute chlorine gas exposure) as well as prolonged or subacute with a significant latent period (as with asbestosis). Because the clinical presentation of occupational lung disease is highly variable and dependent on the particular exposure, a high index of suspicion is necessary to identify this disorder.

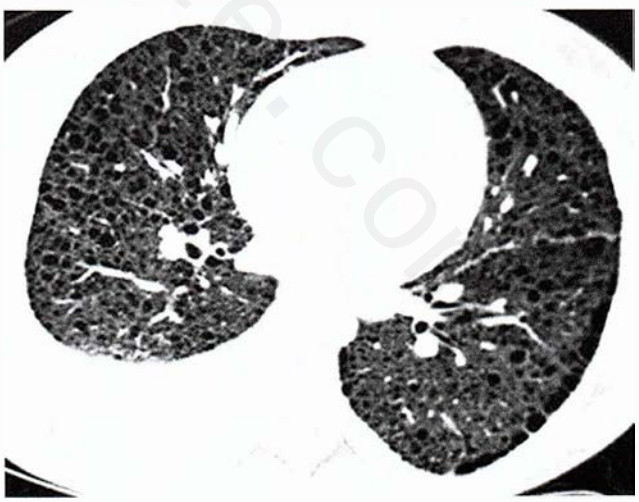

FIGURE 11. CT image of a patient with lymphangioleiomyomatosis showing diffuse thin-walled cysts and a right chylothorax.

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Key Elements of the Exposure History

Factors that should raise the index of suspicion for an occupational-associated lung disease are shown in **Table 26**. Careful attention to historical details and a comprehensive occupational history are often crucial to identification of these disorders. In addition to identification of specific exposures, the duration and concentrations of exposures should be elicited. Owing to the variable time of onset of symptoms, the history should include exposures that date back many years. Furthermore, the interviewer should inquire about any potential additional exposures outside the work environment that may affect respiratory health (**Table 27**).

For individuals who work with potentially harmful substances, the U.S. Occupational Safety and Health Administration (OSHA) requires that employers maintain Material Safety Data Sheets (MSDS). These documents outline chemical properties of substances and the known potential health risks. OSHA requires that employers provide the MSDS upon request. These documents may be helpful in determining the risk of lung disease associated with a particular exposure.

When concern for an occupational disease persists but the history is unrevealing, referral to an occupational/environmental lung disease specialist is appropriate.

KEY POINT

- Careful attention to historical details and a comprehensive occupational history are often crucial to identification of occupational lung disease; in addition to identification of specific exposures, the duration and concentrations of exposures should be elicited.

Management

The overriding principle in management of occupational lung disease is prevention. This includes interventions in the workplace to avoid exposures as well as early identification of coworkers who may also be at risk. For those who are affected, removal of the offending agent is essential. Symptomatic management often includes pharmacologic interventions.

Workers' compensation issues may require an assessment of the extent to which symptoms and physiologic impairment are directly attributable to a work exposure. These assessments are challenging, and referral to a specialist may be most appropriate.

KEY POINT

- The overriding principle in management of occupational lung disease is prevention, consisting of interventions in the workplace to avoid exposures as well as early identification of coworkers who may also be at risk. HVC

TABLE 26. Conditions that Should Increase Clinical Suspicion of Occupational Lung Disease

The patient raises a concern about possible exposures at work
There is a temporal relationship to clinical symptoms and work:
Symptoms worsen during or after work
Symptoms abate or improve with time off or away from the workplace
Coworkers are affected with similar symptoms
There are known respiratory hazards at work (these can be identified by Material Safety Data Sheets [MSDS] from the workplace)
Failure to respond to initial therapy or symptoms that are further exacerbated upon returning to work
Onset of a respiratory disorder without typical risk factors
Clustering of disease in one geographic area

TABLE 27. Elements of a Thorough Patient History for Suspected Occupational Lung Disease

Understand the Occupation
What tasks do you perform at your current job?
How long have you been working at your current job?
What other jobs have you had in the past and for how long?
Understand the Type and Extent of Exposure
Are you exposed to vapors, gases, dust, or fumes in your work?
Do you know the amount and type of chemicals used?
Do you have Material Safety Data Sheets (MSDS) from your workplace?
Is your work environment well ventilated?
Does your employer require you to wear protective equipment? Do you wear it for the full duration of your exposure?
Is there visible dust in the air or on surrounding equipment?
Understand the Temporal Relationship of Symptoms to the Work Environment
Were there any changes to your work process prior to the onset of symptoms?
Do symptoms improve when you are away from the work environment? With vacation?
Understand Other Relevant Exposures
What are your hobbies?
Do you have pets in the home?
What is your travel history?

Surveillance

When primary prevention fails or when a new potential threat is identified, surveillance programs including health screening and serial pulmonary function testing are appropriate. A recent example is the assessment of returning war veterans from Afghanistan and Iraq. Sentinel cases of constrictive

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bronchiolitis have identified multiple potential exposures (open fire pits, diesel exhaust, particulate matter from sand storms, and exposure to rocket fuel) that may result in lung disease. Because of this, a thorough assessment of war veterans for possible evidence of lung disease is recommended and should include symptom review and serial pulmonary function tests for those who are symptomatic. Identification of patients with mild or early disease allows for earlier intervention and counseling.

Asbestos-Related Lung Disease

Asbestos is a silicate mineral fiber previously used as an insulating material that is a major cause of lung disease. Although asbestos use in the United States has been virtually eliminated since its peak in the 1980s, asbestos-related diseases will persist well into this century owing to the long latency period between exposure and disease development (15-35 years). Although developed nations have nearly eliminated its use, asbestos inhalation remains at roughly 2 million metric tons per year worldwide. The result is that asbestos-related diseases will continue to be a major public health concern in the developing world for many years. Currently, approximately 107,000 people die each year owing to asbestos-related mesothelioma, lung cancer, and interstitial lung disease (asbestosis).

Risk Factors

The extent of asbestos exposure correlates with risk for disease, with the most common occupational exposures occurring in the construction, automotive servicing, and shipbuilding industries. Asbestos-related diseases are also commonly found in mining workers and in areas where manufacturing of asbestos has led to contamination of the environment. In this instance, individuals will not have an occupational exposure history.

KEY POINT

- Asbestos exposures are most commonly associated with the construction, automotive servicing, shipbuilding, and mining industries.

Pathophysiology

Asbestos fibers are inhaled and are deposited at the level of airway bifurcations and the alveolus. The lung may clear fibers (typically shorter fibers), whereas others are transported to the interstitium or via the lymphatics to the pleura. Parietal plaques are the most common finding, and the mechanism by which fibers transmigrate and develop plaques remains unclear. Diffuse parenchymal lung disease due to asbestos (asbestosis) is secondary to the extent of the fiber burden. The initial process begins with an alveolitis. If the fiber burden is low, this can resolve spontaneously. With a higher burden, proinflammatory and cytotoxic agents are released by macrophages with resultant recruitment of fibroblasts. If the process is sustained, collagen deposition leads to irreversible chronic fibrosis.

Asbestos-Related Pleural Diseases

Asbestos is associated with multiple forms of pleural disease. Pleural plaques are the most common form of disease and are characterized by smooth, white, raised, irregular lesions affecting predominantly the parietal and, very rarely, the visceral pleura (**Figure 12**). Pleural plaques are asymptomatic in the absence of parenchymal disease and are typically incidentally identified on routine chest radiograph.

Pleural fibrosis is a visceroparietal pleural reaction that may be either localized or diffuse. When the process is diffuse, it can lead to symptomatic restrictive disease. Treatment options for this are limited, and there is little benefit to surgical removal of the pleural layer (decortication) in this cohort. Pleural fibrosis may also lead to the development of rounded atelectasis (**Figure 13**). This is a process in which the lung becomes atelectatic in the region of the pleural fibrosis. The area forms a mass-like lesion that includes bronchi and vessels. These are often asymptomatic but may lead to respiratory impairment if they become large enough. Although these lesions may be concerning for a possible malignancy, they are often distinguished radiographically by a thoracic radiologist as benign.

Benign asbestos pleural effusion may occur either early or late after asbestos exposure. It may be asymptomatic or associated with chest pain. The pleural fluid analysis will be exudative and is often hemorrhagic. Further, eosinophils are present in nearly one third of patients. Benign asbestos pleural effusion is diagnosed only after exclusion of infection, pulmonary

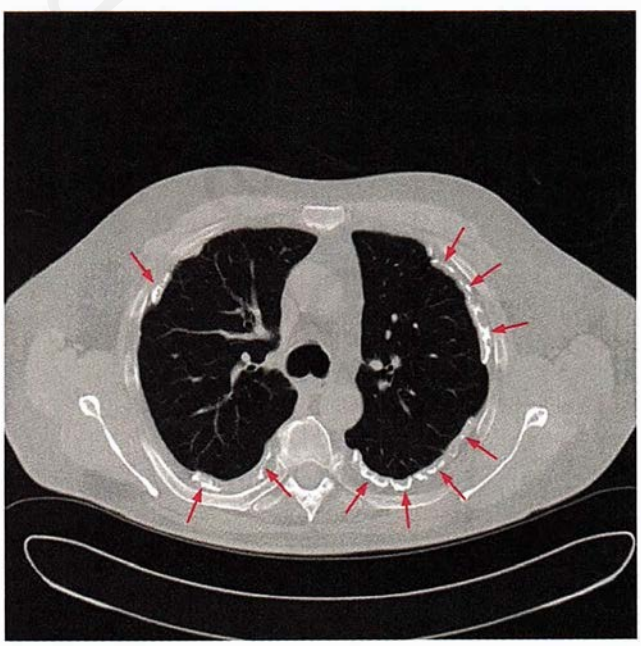

FIGURE 12. Chest CT showing extensive calcified pleural plaques (*arrows*) associated with asbestos exposure.

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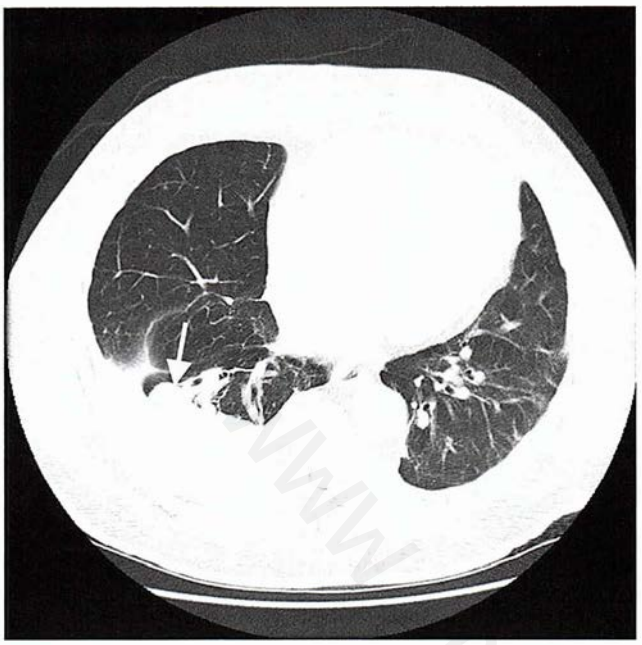

FIGURE 13. Chest CT showing rounded atelectasis (*arrow*) with its typical findings of a round area of lung parenchyma associated with a pleural abnormality and a comet tail that extends into the lung parenchyma.

embolism, and malignancy. Exclusion of mesothelioma is difficult owing to the low sensitivity of cytology and the presence of "reactive" mesothelial cells. Clinicians should have a low threshold to refer for consideration of pleuroscopy for these patients. An experienced thoracic surgeon or interventional pulmonologist can often discern mesothelioma on direct inspection. See Lung Tumors for a discussion of mesothelioma.

Asbestos exposure significantly increases the risk of lung cancer. In a recent report, 19% of patients with extensive asbestos exposure died secondary to lung cancer. For those that were nonsmokers, the risk of lung cancer mortality was 3.6-fold higher than controls. For those with a combined history of smoking and asbestos exposure, the risk of lung cancer mortality was 14.4 times higher than controls. For patients with a history of asbestosis, however, the additional risk of smoking was supra-additive (36.8 times higher than controls). The risk of developing cancer was mitigated by discontinuing smoking at any point. This new information further encourages smoking cessation and highlights the potential importance of lung cancer screening in those with the combined risk factors of smoking and asbestosis.

KEY POINTS

- Asbestos exposure is associated with multiple forms of pleural disease, including pleural plaques, pleural fibrosis, benign asbestos pleural effusion, and mesothelioma.
- Asbestos exposure significantly increases the risk of lung cancer and lung cancer mortality, particularly when combined with smoking.

Silicosis

Silicosis is a spectrum of fibrotic lung diseases related to the inhalation of silica dust. The most common form of silica is quartz, and any occupation that disturbs the earth's crust involves potential risk. Workers in industries that process silica-containing rock or sand are also at risk. Simple silicosis is marked by profusion of small rounded nodules that are upper-lobe predominant. The disease course may be accelerated (3-10 years after exposure) or latent (>10 years after exposure). The lesions may become confluent and lead to progressive massive fibrosis. Although individuals with simple silicosis may be asymptomatic, those with progressive massive fibrosis develop symptomatic shortness of breath.

The incidence of tuberculosis is increased in those with silicosis, and symptoms should prompt an evaluation for possible infection. In addition, altered cellular immunity may account for the increased prevalence of connective tissue disease in those with silicosis. Mine workers are often exposed to multiple dusts and radon, and they have high rates of tobacco use; however, the development of silicosis is also an independent risk factor for the development of lung cancer.

Once fibrotic disease develops, there are no clear therapeutic interventions to alter the disease course. Individuals with continued exposure to silica dust should change to a silica-free environment. Because airways disease and cancer are also associated with silica exposure, smoking cessation is always an appropriate recommendation. Symptomatic treatment includes inhaled bronchodilators, antibiotics for infections, and supplemental oxygen for hypoxemia. For individuals with progressive disease, consideration of lung transplantation referral is appropriate.

KEY POINT

- The incidence of tuberculosis is increased in patients with silicosis, and symptoms should prompt an evaluation for possible infection.

Pleural Disease

There are two main types of abnormalities that affect the pleura: increased fluid (pleural effusion) and air (pneumothorax) in the pleural space.

Pleural Effusion

Pleural effusion is the most common disorder affecting the pleura, with approximately 1.5 million pleural effusions diagnosed each year. These occur as a result of increased fluid formation and/or decreased fluid resorption in the pleural space. There are over 50 known causes and the pathophysiology varies depending on the cause. The vast majority of pleural effusions in the United States are the result of heart failure, pneumonia, or malignancy. A systematic approach to diagnosis is necessary based on the clinical presentation of the patient.

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KEY POINT

- The vast majority of pleural effusions in the United States are the result of heart failure, pneumonia, or malignancy.

Evaluation

History and Physical Examination

The history and physical examination guide the initial evaluation of pleural effusion. Signs and symptoms vary depending on the cause but commonly include dyspnea, cough, and pleuritic chest pain. Additional features such as fever, orthopnea, or concurrent arthralgia may provide clues to the underlying cause and can help narrow the differential diagnosis. History of travel, prior and current occupation, medication use, prior surgery (such as coronary artery bypass surgery), malignancy, place of residency, and prior asbestos exposure should also be elicited.

Clinical examination hallmarks include diminished breath sounds, dullness to percussion, and decreased tactile fremitus over the area of the pleural effusion; these findings generally occur only in effusions larger than 300 mL. Other clues on examination include distended neck veins, peripheral edema, right ventricular heave or deep venous thrombosis, stigmata of end-stage liver disease, joint deformities, or synovitis. Each of these findings may help narrow the differential diagnosis and guide additional testing.

Diagnostic Imaging

A chest radiograph is usually the first imaging study obtained when evaluating a pleural effusion. Posteroanterior radiographs will generally show evidence of pleural effusion when there is approximately 200 mL of pleural fluid present, and lateral films will be abnormal when approximately 50 mL of pleural fluid is present.

Thoracic ultrasound also has an increasingly important role in the evaluation of pleural effusion because of its higher sensitivity in the detection of pleural fluid than the clinical examination or chest radiography. Characteristics that can also be seen on ultrasound can help define whether the effusion is simple or complex. A simple effusion can be identified as fluid in the pleural space with homogeneous echotexture as seen in most transudative effusions, whereas a complex effusion is echogenic, frequently with septations (loculations) within the fluid, and is always an exudate. Bedside ultrasound is recommended when performing thoracentesis, as it enhances procedural accuracy and safety.

KEY POINTS

HVC
- Chest radiograph and thoracic ultrasound are important tests in the evaluation of pleural effusion; ultrasound has a higher sensitivity for pleural fluid and no associated radiation exposure.

HVC
- Bedside ultrasound is recommended for thoracentesis as it enhances procedural accuracy and safety.

Indications for Thoracentesis

A thoracentesis is indicated for any new unexplained pleural effusion. Observation and initiation of therapy without diagnostic thoracentesis are reasonable in the setting of known heart failure or small parapneumonic effusions, or following coronary artery bypass surgery. However, any atypical features (such as fever, pleurisy) or failure to respond to therapy in these patients should prompt consideration of a diagnostic thoracentesis.

Pleural Fluid Analysis

The gross appearance of pleural fluid should be noted while performing a thoracentesis, as it may reveal the diagnosis. Fluid can appear serous, serosanguineous (blood stained), hemorrhagic, or purulent. Bloody fluid is often seen in malignancy, pulmonary embolism with lung infarction, trauma, benign asbestos effusion, or post–cardiac injury syndrome. Purulent fluid can be seen in empyema and lipid effusions. In addition, a putrid odor can point to an anaerobic infection and the smell of ammonia to an urinothorax.

The characterization of pleural fluid as a transudate or exudate helps narrow the differential diagnosis and direct subsequent investigations. The most common criteria used to make this differentiation are the Light criteria (**Table 28**). Initial testing should include measurement of the pleural fluid total protein and lactate dehydrogenase with concurrent measurement of serum total protein and lactate dehydrogenase to allow assessment of the Light criteria.

Other initial pleural fluid studies include the cell count with differential, pH, and glucose levels. If infection is suspected, Gram stain and microbiologic culture should be performed, and cytology is appropriate in patients with possible malignancy. Additional tests performed in selected patients include amylase, cholesterol, triglycerides, acid-fast bacilli, and *Mycobacterium tuberculosis* culture.

Transudates are usually the result of an imbalance between hydrostatic and oncotic pressures, whereas exudates result primarily from inflammation or impaired lymphatic drainage (such as infections, inflammation, or malignancy) (**Table 29**). Light criteria can occasionally misclassify transudative effusions as exudates in the setting of ongoing diuresis. In this case it is reasonable to determine the serum albumin to pleural fluid albumin gradient. If it is greater than 1.2 g/dL (12 g/L), the underlying process is likely transudative.

TABLE 28. Light Criteria

An effusion is considered an exudate if any of the following are met:
Pleural fluid total protein/serum total protein >0.5
Pleural fluid LDH/serum LDH >0.6
Pleural fluid LDH >2/3 the upper limit of normal for serum LDH

LDH = lactate dehydrogenase.

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TABLE 29. Common Causes of Transudates and Exudates

Transudates	Exudates
Heart failure	Parapneumonic effusions
Hepatic hydrothorax	Malignancy
Nephrotic syndrome	Pulmonary embolism
Hypoalbuminemia	Tuberculosis
Unexpandable (trapped) lung	Autoimmune diseases (RA, SLE)
Urinothorax	Benign asbestos effusion
Atelectasis	Post-coronary artery bypass
Peritoneal dialysis	Pancreatitis
	Post-myocardial infarction
	Yellow nail syndrome (lymphatic disorders)
	Drugs

RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

KEY POINT

- The characterization of pleural fluid as a transudate or exudate helps narrow the differential diagnosis and direct subsequent investigations.

Cell Counts and Differential

Pleural fluid cell counts with differential are helpful in narrowing the diagnosis but are not disease specific (**Table 30**).

Blood Chemistry Studies

Glucose concentration in pleural fluid is equivalent to that of the blood in the absence of pleural pathology. Therefore, a low pleural fluid glucose concentration can be very helpful in the analysis of pleural fluid. A low pleural fluid glucose level results from either increased utilization within the pleural space (bacteria, malignant cells) or decreased transport into the pleural space (rheumatoid pleurisy), and a concentration less than 60 mg/dL (3.3 mmol/L) narrows the differential diagnosis significantly (**Table 31**).

Pleural fluid acidosis (pH <7.30) is seen in complicated parapneumonic effusions, malignancy, tuberculous pleuritis, rheumatoid and lupus pleuritis, and esophageal rupture. By itself it does not distinguish between these entities, but it implies high metabolic activity in the pleural space. In malignancy, a low pH correlates with a poor prognosis and predicts pleurodesis failure. In suspected pleural infection, a pH less than 7.20 should be treated with pleural drainage. Collection and processing of samples for pH must be done carefully. Exposure of the fluid to air in the syringe can increase the pleural fluid pH, and very small amounts of lidocaine can lower pH significantly. It is recommended that pleural fluid pH be tested on a blood gas analyzer within 1 hour of collection.

Pleural fluid amylase is elevated if the pleural fluid to serum amylase ratio is greater than 1.0 and suggests pancreatic disease, esophageal rupture, and malignant effusions. It should not be routinely measured but can be useful when an esophageal or pancreatic cause for the effusion is suspected.

A pleural fluid triglyceride level greater than 110 mg/dL (1.24 mmol/L) is characteristic of a chylothorax, and a level less

TABLE 30. Clinical Significance of Cell Counts in Pleural Fluid

Cell Type	Cell Count	Clinical Significance
Erythrocytes	5000-10,000/μL ($5\text{-}10 \times 10^9$/L)	Bloody appearance, hemothorax if pleural fluid hematocrit >50% peripheral hematocrit; most commonly associated with cancer, pulmonary infarction, asbestos-related effusions, or trauma
Nucleated cells	>50,000/μL (50×10^9/L)	Complicated parapneumonic effusions and empyema
	>10,000/μL (10×10^9/L)	Bacterial pneumonia, acute pancreatitis, and lupus pleuritis
	<5000/μL (5×10^9/L)	Chronic exudates (TB pleurisy and malignancy)
Lymphocytes	>80%	Suggests TB, lymphoma, chronic rheumatoid pleurisy, sarcoidosis, and late post-CABG effusions. Pleural biopsy is indicated if no diagnosis.
Eosinophils	>10%	Suggests air or blood in the pleural space but is nonspecific. Can be seen in parapneumonic effusions, drug-induced pleurisy, eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome), benign asbestos effusions, malignancy (lymphoma), pulmonary infarction, fungal disease (coccidioidomycosis, cryptococcosis, histoplasmosis), and parasitic disease

CABG = coronary artery bypass graft; TB = tuberculosis.

TABLE 31. Pleural Effusions with Glucose Level Less than 60 mg/dL (3.3 mmol/L)

Rheumatoid pleurisy
Complicated parapneumonic effusion or empyema
Malignant effusion
Tuberculous pleurisy
Lupus pleuritis
Esophageal rupture

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than 50 mg/dL (0.56 mmol/L) reasonably excludes the diagnosis. An intermediate level (between 50–110 mg/dL [0.56–1.24 mmol/L]) should be investigated with a lipoprotein analysis looking for chylomicrons. It is also not a routine pleural fluid study but is appropriate in patients with suspected chylothorax.

Tests for Tuberculous Effusions

Tuberculous pleuritis continues to be a common problem worldwide and should be considered as part of the differential diagnosis in patients with undiagnosed lymphocyte predominant exudative effusions. Smear and culture of pleural fluid for acid-fast bacilli are very specific but have a low sensitivity (5% and 20%, respectively). Adenosine deaminase is an enzyme present in lymphocytes that is elevated in most tuberculous pleural effusions (sensitivity 95%). In countries with a low incidence of tuberculosis, testing for adenosine deaminase can be useful as a test to rule out tuberculosis. Pleural biopsy is the most likely test to yield a positive mycobacterial culture (>70%).

Tests for Pleural Malignancy

Cytology should be performed on any effusion in which malignancy is suspected. When the suspicion for malignancy is high, it is appropriate to repeat cytology if the first specimen is negative. The overall mean sensitivity is approximately 60%, and the yield from sending more than two samples is very low. One study demonstrated an additional yield of 27% on the second sample and only 5% on the third. The diagnostic rate is higher for adenocarcinoma than mesothelioma and lymphoma. If lymphoma is suspected, flow cytometry should be performed to further characterize the cells present.

Thoracoscopy is the next step in the evaluation of an exudative pleural effusion that is indeterminate and malignancy is suspected. Medical thoracoscopy allows for the direct visualization of the pleural surface and allows for biopsy of pleural sites likely to have a high diagnostic yield. It therefore has a diagnostic sensitivity for malignant disease of greater than 90%. Blind closed pleural biopsy is less sensitive than cytology and should not be performed.

Management

Parapneumonic Effusions and Empyema

Pleural space infections are increasing worldwide and are associated with 20% mortality rates; the reason for this increase in adults is not known. Parapneumonic effusions are exudative pleural effusions that occur adjacent to a bacterial pneumonia and result from migration of excess interstitial lung fluid across the visceral pleura; although inflammatory cells are present, parapneumonic infections are sterile. Typically these are small and uncomplicated and resolve with resolution of the pneumonia. If bacteria from the pneumonia invade the pleural space, a complicated parapneumonic effusion or empyema will result. A complicated parapneumonic effusion involves persistent invasion of bacteria resulting in an increase in inflammatory cells and decreased pH and glucose levels. However, because bacteria may be cleared rapidly from the pleural space, cultures are usually sterile. Empyema represents clear infection of the pleural space with the presence of pus. Pleural effusions greater than 10 mm in depth on chest radiograph and associated with a pneumonic illness should be sampled. In general, these require thoracostomy tube drainage when the pH is less than 7.2 or the pleural fluid glucose level is less than 60 mg/dL (3.3 mmol/L) (**Table 32**).

A wide range of organisms may cause pleural space infection; the most typical are *Streptococcus pneumoniae*, *Streptococcus milleri*, *Staphylococcus aureus*, and Enterobacteriaceae. Anaerobes have also been cultured in 36% to 72% of empyemas. Consequently, empiric antimicrobial coverage for suspected pleural infection should include anaerobic coverage. The use of intrapleural fibrinolytics has been studied in complicated parapneumonic effusions and has shown limited utility. When combined with a mucolytic agent (deoxyribonuclease), it resulted in a greater decrease in the size of the effusion and lower rate of surgical referral. The size of the drainage tube remains controversial, but several studies have demonstrated equal efficacy

TABLE 32. Parapneumonic Effusions

Type	Pleural Characteristics	Pleural Fluid Chemistry	Management
Uncomplicated	Small (<10 mm on lateral decubitus radiographic view), free flowing	pH: unknown Glucose: unknown	Antibiotics and serial follow-up to ensure resolution; if no resolution or ongoing sepsis, consider thoracentesis
	Small to moderate effusion (>10 mm to <1/2 hemithorax), free flowing	pH >7.2 Glucose >60 mg/dL (3.3 mmol/L)	Antibiotics, thoracentesis, and serial follow-up to ensure resolution; if no resolution or ongoing sepsis, consider repeat thoracentesis and need for drainage
Complicated	Loculated or thickened pleura	pH <7.2 ***or*** glucose <60 mg/dL (3.3 mmol/L)	Antibiotics, thoracostomy tube drainage, serial follow-up; if no resolution, consult thoracic surgeon for possible thorascopic debridement
Empyema	Bacterial organisms seen on Gram stain or aspiration of pus on thoracentesis	pH <7.0	Antibiotics, thoracostomy tube drainage, early consultation with a thoracic surgeon for possible thorascopic debridement

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and improved patient comfort with the use of smaller, 10 to 14 Fr (3.3 to 4.7 mm) thoracostomy tubes. Effusions refractory to antibiotics and drainage alone require surgical debridement.

KEY POINTS

- Parapneumonic pleural effusion requires thoracostomy tube drainage when the pH is less than 7.2 or the pleural fluid glucose level is less than 60 mg/dL (3.3 mmol/L).
- Anaerobes are cultured in 36% to 72% of empyemas, and empiric antibiotic therapy should include anaerobic coverage.

Malignant Pleural Effusion

The goal of management in malignant pleural effusions is palliation of symptoms. The choice of therapy should be dependent on prognosis, rate of reaccumulation, and the severity of the patient's symptoms. Repeat therapeutic thoracentesis is appropriate for patients with poor prognosis (<3 months) and slow reaccumulation of fluid. In patients with more rapid recurrence of fluid, more definitive measures are warranted. Indwelling pleural catheters with intermittent drainage (managed as an outpatient) is commonly the procedure of choice for management of malignant pleural effusions. Indwelling pleural catheters have been demonstrated to provide significant symptom relief, and 50% to 70% of patients achieve spontaneous obliteration of the pleural space (pleurodesis) after 2 to 6 weeks. Chemical pleurodesis with talc is also very effective, with a success rate of 60% to 90% depending on the degree of lung reexpansion. Pleurectomy and pleuroperitoneal shunt are other management options but are rarely performed.

Pneumothorax

Pneumothorax (air in the pleural space) can occur spontaneously, as a result of trauma, or iatrogenically. Spontaneous pneumothorax is further characterized as a primary spontaneous pneumothorax (PSP) in a person without underlying lung disease or a secondary spontaneous pneumothorax (SSP) in a person with underlying lung disease. Risk factors for PSP are smoking, tall stature, family history, Marfan syndrome, and thoracic endometriosis. SSP is most commonly associated with COPD and presents with increased symptoms and breathlessness due to decreased respiratory reserve.

Physical examination usually reveals reduced lung expansion, hyperresonance to percussion, and diminished breath sounds on the side of the pneumothorax. Tension pneumothorax should be suspected in patients presenting with significant cardiorespiratory distress.

Pneumothorax is diagnosed by detection of a visceral pleural line on a standard chest radiograph (**Figure 14**). The size of the pneumothorax is determined by measuring the distance between the lung margin and the inner chest wall at the level of the hilum. A distance of greater than 2 cm is considered a large pneumothorax.

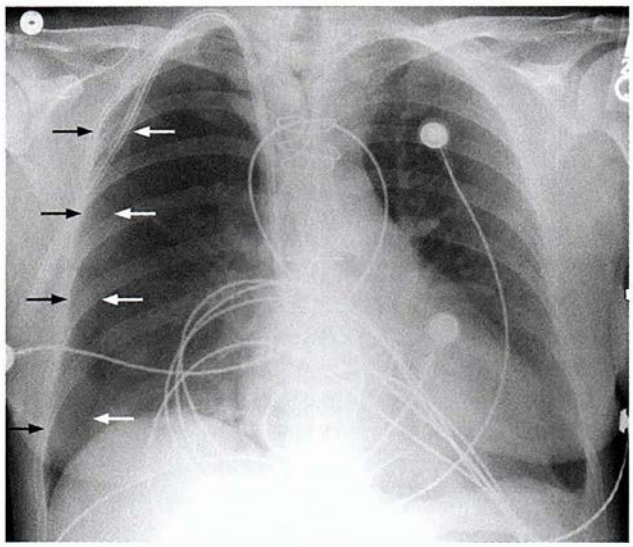

FIGURE 14. This chest radiograph demonstrates a right pneumothorax following the placement of a central venous catheter. The chest wall and parietal pleura are indicated by the black arrows, and the visceral pleura and lung border are indicated by the white arrows. The air in the pleural space is darker than the adjacent lung and also lacks normal lung markings.

Management of a pneumothorax depends on the degree of clinical compromise, size, and whether the pneumothorax is primary or secondary. Breathlessness indicates the need for active intervention as well as supportive treatment (high-flow supplemental oxygen). A large, hemodynamically significant pneumothorax (tension pneumothorax) should be managed with high-flow supplemental oxygen and emergent needle thoracostomy, followed by thoracostomy tube placement and hospitalization. In contrast, observation alone has been shown to be safe for small pneumothoraces in patients with minimal symptoms (**Table 33** and **Table 34**). Patients presenting with SSP are at higher risk for persistent air leak or further expansion of the pneumothorax due to their underlying lung disease. As a result, SSPs are best managed with a small-bore (<14 Fr [4.7 mm]) pleural drain instead of simple aspiration.

TABLE 33. Management of Primary Spontaneous Pneumothorax

Size and Clinical Symptoms	Management
<2 cm on chest radiograph, minimal symptoms	Observation alone; may be managed as an outpatient if easy access to medical care is available if clinical symptoms change
>2 cm on chest radiograph, breathlessness, and chest pain	Needle aspiration; if reaccumulation then insertion of a small-bore (<14 Fr [4.7 mm]) thoracostomy tube
Clinical instability regardless of size	Emergent needle decompression followed by thoracostomy tube insertion[a]

[a]If persistent air leak (>3-5 days), refer to a thoracic surgeon for possible surgical pleurodesis and bleb resection.

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TABLE 34. Management of Secondary Spontaneous Pneumothorax

Size and Clinical Symptoms	Management
<2 cm on chest radiograph, minimal symptoms	Admit to hospital for observation and supplemental oxygen
>2 cm on chest radiograph, breathlessness, and chest pain	Insertion of a small-bore (<14 Fr [4.7 mm]) thoracostomy tube
Clinical instability regardless of size	Emergent needle decompression followed by thoracostomy tube insertion[a]

[a]If persistent air leak (>48 hours), refer to a thoracic surgeon for possible surgical bleb resection and pleurodesis; recurrence prevention (pleurodesis) should be offered to all patients after one event of secondary spontaneous pneumothorax.

CONT.

Recurrence is estimated at 23% to 50% over the first 5 years in PSP and close to 50% in SSP. Intervention to prevent recurrence includes both chemical and mechanical pleurodesis, which is recommended in all SSP and after the second occurrence of a PSP.

All patients should be counseled against air travel until complete resolution of the pneumothorax has been confirmed by chest radiograph. In addition, diving should be discouraged permanently unless a definitive prevention plan (such as surgical pleurectomy) has been performed.

KEY POINTS

- A large, hemodynamically significant pneumothorax (tension pneumothorax) should be managed by high-flow supplemental oxygen and emergent needle thoracostomy followed by thoracostomy tube placement and hospitalization.

HVC

- Observation alone has been shown to be safe for small pneumothoraces in patients with minimal symptoms.

Pulmonary Vascular Disease

Pulmonary Hypertension

The pulmonary vasculature is a system of low pressure and high compliance, such that in healthy individuals, pulmonary artery pressures remain relatively unchanged during states of stress and high flow, such as exercise. The normal mean pulmonary artery pressure is approximately 15 mm Hg. Pulmonary hypertension (PH) is defined by a resting mean pulmonary artery pressure of 25 mm Hg or greater. Unabated, PH eventually leads to right ventricular (RV) failure and may directly contribute to death; however, the rate of progression is highly variable and dependent upon the origin of disease and comorbidities.

The current classification system subdivides PH into five groups (**Table 35**), which are based on similarities in mechanisms,

TABLE 35. Classification of Pulmonary Hypertension

1. PAH
   - 1.1 Idiopathic PAH
   - 1.2 Heritable
     - 1.2.1 *BMPR2*
     - 1.2.2 *ALK1*, endoglin (with or without hereditary hemorrhagic telangiectasia)
     - 1.2.3 Unknown
   - 1.3 Drug- and toxin-induced
   - 1.4 Associated with
     - 1.4.1 Connective tissue diseases
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart diseases
     - 1.4.5 Schistosomiasis
     - 1.4.6 Chronic hemolytic anemia
   - 1.5 Persistent pulmonary hypertension of the newborn
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
2. Pulmonary hypertension due to left-sided heart disease
   - 2.1 Systolic dysfunction
   - 2.2 Diastolic dysfunction
   - 2.3 Valvular disease
3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 COPD
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear or multifactorial causes
   - 5.1 Hematologic disorders: myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic kidney failure on dialysis

ALK1 = activin receptor-like kinase type 1; *BMPR2* = bone morphogenetic protein receptor type II; PAH = pulmonary arterial hypertension.

Reprinted from Journal of the American College of Cardiology, 62(25 Suppl), Simonneau G, Gatzoulis MA, Adatia I, et al, Updated clinical classification of pulmonary hypertension, D34-41, 2014, with permission from Elsevier.

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clinical presentation, and approach to treatment. All five groups can be termed PH, but group 1 is distinguished by disease localized to small pulmonary arterioles resulting in high pulmonary vascular resistance and is referred to as pulmonary arterial hypertension (PAH). Groups 2 through 5 refer to important secondary causes of PH and include left-sided heart disease, respiratory disorders (COPD, interstitial lung disease, and sleep-disordered breathing), and chronic venous thromboembolic disease. Groups 1 (PAH) and 4 (chronic thromboembolic pulmonary hypertension [CTEPH]) are discussed separately from the other causes of PH (see Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension sections).

KEY POINT

- Pulmonary hypertension is defined by a resting mean pulmonary artery pressure of 25 mm Hg or greater.

Pathophysiology

The pathophysiology of PH is determined by the specific cause, with the vast majority of cases of PH attributed to left-sided heart disease (group 2) and hypoxic respiratory disorders (group 3). With group 2 disease, left ventricular (LV) dysfunction and valvular disease lead to PH by volume and pressure overload. In group 3, vasoconstriction brought on by alveolar hypoxia is an important mechanism in patients with chronic respiratory disorders, eventually leading to pulmonary vascular remodeling. With all causes of PH, RV hypertrophy and dilatation develop over time in response to pulmonary artery pressure overload, at which point mismatch of myocardial oxygen supply and demand can result in ischemia, arrhythmias, and RV failure.

KEY POINT

- The vast majority of cases of pulmonary hypertension are attributed to left-sided heart disease and hypoxic respiratory disorders.

Diagnosis

PH is easily overlooked because early signs and symptoms, such as exertional dyspnea and fatigue, are nonspecific. In patients with chronic LV dysfunction or lung disease, symptoms due to PH may be minimal and difficult to distinguish from the underlying condition. As the disorder progresses, RV impairment may be heralded by exertional chest pain, syncope, and peripheral edema. Findings on physical examination depend on the severity of disease. The cardiovascular examination may show jugular venous distention, a prominent jugular venous *a* wave, parasternal heave, a widened split S_2 with a prominent pulmonic component, or right-sided regurgitant murmurs as the RV dilates. As RV dysfunction progresses, hepatomegaly, ascites, and peripheral edema develop.

Echocardiography is a useful initial tool in the evaluation of suspected PH, as it allows an estimation of pulmonary artery pressures and right heart function as well as an assessment of the left heart. Because echocardiography may underestimate true pulmonary artery pressures, the evaluation should not end with an unrevealing echocardiogram if the index of suspicion for PH is high. In such cases, right heart catheterization may be confirmatory.

Once PH is confirmed, further testing, guided by clinical history, helps determine identifiable causes. Left heart catheterization can assess coronary flow and LV function. Diagnostic tests for respiratory diseases might include pulmonary function tests, chest imaging, ventilation perfusion (V/Q) scanning, and overnight pulse oximetry. Laboratory studies to explore group 1 disease may include HIV serology, liver chemistry studies, and autoantibody titers. Prior to treatment, exercise testing such as the 6 minute walk test should be performed to determine functional impairment and to serve as a baseline with which to compare therapeutic response. H

KEY POINTS

- Echocardiography is a useful initial tool in the evaluation of suspected pulmonary hypertension, as it provides a noninvasive estimation of pulmonary artery pressures and right heart function as well as an assessment of the left heart.
- Because echocardiography may underestimate true pulmonary artery pressures, right heart catheterization should be considered after a normal echocardiogram if the index of suspicion for pulmonary hypertension is high.

Treatment

H

Therapy for PH groups 2 through 5 is typically directed at the underlying condition. Strategies may include medical optimization of LV systolic and diastolic function, optimal inhaler therapy for COPD, supplemental oxygen for documented hypoxemia, and positive airway pressure therapy for sleep-disordered breathing. Anticoagulation and possible surgery is indicated for CTEPH (group 4). Advanced therapy (vasodilators) is generally reserved for PAH (group 1) and does not have a clear role in groups 2 through 5 PH. Advanced therapy may, in fact, be harmful in patients with PH due to LV dysfunction (group 2) or lung disease (group 3) because of the potential for pulmonary vasodilators to overload a compromised LV and to worsen V/Q mismatching, respectively. H

KEY POINTS

- Therapy for pulmonary hypertension groups 2 through 5 (disease resulting from left-sided heart disease, respiratory disorders, or chronic venous thromboembolic disease) is directed at the underlying condition.
- Advanced therapy for pulmonary hypertension with vasodilators should be reserved for patients with pulmonary arterial hypertension (group 1) as they have not been shown to be efficacious and may be harmful in this group. HVC

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Chronic Thromboembolic Pulmonary Hypertension

A small subset (<5%) of patients who experience an acute pulmonary embolism go on to develop CTEPH. For a discussion of pulmonary embolism, see MKSAP 17 Hematology and Oncology. In CTEPH, the organized thrombus incorporates into the pulmonary artery endothelium, thereby increasing pulmonary vascular resistance and pressures and eventually leading to right-sided heart failure. A hypercoagulable state is sometimes, but not always, proved by laboratory investigations in such patients, whose endogenous fibrinolytic system that would normally break down acute clot is overcome.

Diagnosis

CTEPH usually presents with progressive exertional dyspnea that correlates with the extent of hemodynamic derangement and RV involvement. Because this symptom is nonspecific and a substantial proportion of patients (>25%) do not report a history of pulmonary embolism, CTEPH remains an underappreciated cause of PH. There are two diagnostic criteria: (1) documentation of PH (pulmonary artery pressure ≥25 mm Hg) by right heart catheterization in the absence of left heart pressure overload and (2) compatible imaging evidence of chronic thromboembolism. CT pulmonary angiography (CT PA), a commonly utilized test in the evaluation of exertional dyspnea, may demonstrate proximally located abnormalities such as vascular webs, intimal irregularities, and luminal narrowing but has limited sensitivity in more distal lesions. V/Q scanning is a more sensitive indicator of CTEPH and is generally the preferred first imaging modality. Once CTEPH is suggested by V/Q scanning or possibly CT PA, conventional pulmonary angiography should be performed to best characterize the extent and distribution of organized thrombus and to determine suitability for surgical intervention.

KEY POINTS

- There are two diagnostic criteria for chronic thromboembolic pulmonary hypertension: (1) documentation of pulmonary hypertension (pulmonary artery pressure ≥25 mm Hg) by right heart catheterization in the absence of left heart pressure overload and (2) compatible imaging evidence of chronic thromboembolism.

HVC

- Ventilation-perfusion scanning is a sensitive indicator of chronic thromboembolic pulmonary hypertension and is generally the preferred first imaging modality.

Management

Anticoagulant therapy is indicated in all patients to help prevent further thromboembolism and, generally, duration of treatment is lifelong. In patients with coexisting clot in the lower extremities, inferior vena cava interruption can be considered to help prevent further thromboembolism; however, its role in long-term outcomes is not known. Surgery in the form of pulmonary thromboendarterectomy is the only definitive therapy for CTEPH. Because even mild disease may irreversibly progress, surgical evaluation at an experienced center is warranted in all patients with CTEPH regardless of disease severity. Pulmonary thromboendarterectomy can result in normalization of pulmonary hemodynamics in about one third of patients who undergo surgery; however, only about half of patients will be surgical candidates and fewer than that will opt for surgery.

KEY POINT

- Pulmonary thromboendarterectomy is the only definitive therapy for chronic thromboembolic pulmonary hypertension.

Pulmonary Arterial Hypertension

Group 1 PAH is defined by a proliferative vasculopathy originating in the pulmonary artery endothelium, driven by imbalances in substances that affect vascular tone and endothelial/smooth muscle cellular growth. These pathways (nitric oxide, prostacyclin, and endothelin) are targets for therapy. PAH is classified as (1) idiopathic (previously referred to as primary pulmonary hypertension), (2) heritable, or (3) associated with other conditions.

Heritable forms, which are autosomal dominant with incomplete penetrance, demonstrate mutations in the transforming growth factor β (TGF-β) signaling system, with most occurring in bone morphogenetic protein receptor type II (*BMPR2*). Because *BMPR2* is a gene that normally contributes to the apoptotic process, mutations might explain the propensity for cellular proliferation in PAH. Heritable disease comprises a minority of PAH cases but appears to confer a worse prognosis than sporadic disease.

PAH is most commonly encountered in association with other conditions, including connective tissue diseases, portal hypertension, HIV infection, illicit drug use, toxin exposure, and congenital heart disease.

Connective tissue diseases (classically systemic sclerosis) obliterate pulmonary arterioles and capillaries by direct proliferative effects on the vascular wall as well as by fibrosis of the surrounding lung interstitium. The association with PAH is stronger in limited cutaneous systemic sclerosis than in diffuse cutaneous disease. Rheumatoid arthritis can also affect the pulmonary vascular bed, as can systemic lupus erythematosus.

Patients with chronic liver disease and portosystemic shunting can develop a form of PAH referred to as portopulmonary hypertension (see MKSAP 17 Gastroenterology and Hepatology). The mechanism might relate to the diseased liver's inability to clear vasoactive substances that subsequently act on the pulmonary vasculature.

Patients with HIV infection have an approximately 10-fold higher risk of PAH compared with patients without HIV infection. The mechanism is not known but likely relates to both viral and host factors.

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CONT.

Drugs implicated in PAH include fenfluramine, phentermine, and dexfenfluramine. The association with anorectic drugs may also suggest a link between PAH and obesity. Reports exist of PAH associated with tyrosine kinase inhibitors (dasatinib and imatinib) as well as with interferon alfa. Illicit drugs linked to PAH include cocaine and amphetamines (smoked or injected).

PAH in patients with congenital heart disease is attributable to pulmonary vessel blood volume overload due to intracardiac shunting typical of ventricular or atrial septal defects.

Younger patients with PAH are more commonly female; gender distribution is similar in older age groups. Variables associated with worse outcomes include increasing age, advanced functional limitation, and elevated levels of cardiac biomarkers such as N-terminal pro B-type natriuretic peptide. Echocardiographic findings of pericardial effusion, right atrial enlargement, and poor RV contractile reserve during stress testing also portend a worse prognosis.

KEY POINT

- Pulmonary arterial hypertension is most commonly encountered in association with other conditions, including connective tissue diseases, portal hypertension, HIV infection, illicit drug use, toxin exposure, and congenital heart disease.

Diagnosis

The diagnostic evaluation of PAH usually includes testing similar to that described for other forms of PH, with the exception that right heart catheterization is required to confirm pulmonary hemodynamics as well as to determine whether there is a specific response to vasodilator infusion, which may help guide therapy. Although PAH is defined by typical pathology of the pulmonary arterial bed, lung biopsies in this population are risky and are generally not performed in practice. The role of genetic testing is not yet defined.

KEY POINT

- In pulmonary arterial hypertension, right heart catheterization is required to confirm pulmonary hemodynamics as well as to determine whether there is a specific response to vasodilator infusion, which may help guide therapy.

Treatment

There are no curative treatments for PAH, but the use of targeted vascular therapies has improved survival rates. The goals of therapy are to reduce vascular pressures, control symptoms, and improve or maintain quality of life. Supportive measures should be considered in all patients with PAH. Such interventions might include diuretic therapy to combat volume overload and supplemental oxygen for hypoxemia at rest or with exercise. Because PAH predisposes to in-situ pulmonary vascular thrombosis and embolism, anticoagulation is recommended. Digoxin appears to improve RV function in some patients with PAH and, owing to its vagal properties, may be a useful adjunct in managing supraventricular dysrhythmias that are common in this population. Exercise training has been shown to improve functional limitations.

Vascular-targeted treatments are directed at reducing vasoconstriction and/or interrupting the pathways mediating cellular proliferation. Calcium channel blockers, used for decades prior to the availability of current advanced therapy agents, are still prescribed but only for patients demonstrating a vasodilator response on right heart catheterization. Close follow-up is required because the effect may not be durable. Use of advanced agents (**Table 36**) may be guided by disease severity. Oral agents (phosphodiesterase-5 inhibitors, such as sildenafil or tadalafil, or endothelin-1 receptor antagonists, such as bosentan or ambrisentan) are reasonable initial therapies for mild to moderate disease. Iloprost, an inhaled prostanoid, can be used but requires frequent administration. A parenteral prostacyclin analogue such as epoprostenol, administered by a continuous central venous infusion, is first-line therapy for severe disease and for those in whom disease progresses despite oral therapy. Combining drugs with different mechanisms may enhance efficacy. Given the complexity of management and the steady increase in the number of drugs available to treat PAH, some of which can cost more than $100,000 per year, careful initiation and follow-up by an experienced specialist is warranted. Lung or heart-lung transplantation should be considered for patients in whom drug treatment is unsuccessful.

TABLE 36. Pharmacologic Therapy for Pulmonary Arterial Hypertension

Class	Comments
Calcium channel blockers	Only for patients with acute vasodilator response at catheterization; acute response does not assure chronic response
Prostanoids (epoprostenol, treprostinil, iloprost)	Supplements endogenous levels of prostacyclin (PGI_2), a vasodilator with anti-smooth muscle proliferative properties
Endothelin-1 receptor antagonists (bosentan, ambrisentan)	Blocks action of endogenous vasoconstrictor and smooth muscle mitogen endothelin; class-wide risk of liver injury and teratogenicity; liver chemistry testing and pregnancy testing for reproductive-aged women are required[a]
Phosphodiesterase-5 inhibitors (sildenafil, tadalafil)	Prolongs effect of intrinsic vasodilator cyclic GMP by inhibiting hydrolysis by phosphodiesterase-5

GMP = guanosine monophosphate.

[a]Although not required for ambrisentan, some experts suggest that it is prudent to perform liver chemistry tests at the outset of treatment for pulmonary arterial hypertension and at periodic intervals thereafter at the discretion of the managing physician.

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KEY POINTS

- There are no curative treatments for pulmonary arterial hypertension, but the use of targeted vascular therapies has improved survival rates.
- Supportive measures (diuretic therapy, supplemental oxygen), anticoagulation, digoxin, and exercise training should be considered in patients with pulmonary arterial hypertension.

Lung Tumors

Pulmonary Nodule Evaluation

A solitary pulmonary nodule (SPN) is defined as a lesion less than 3 cm in size surrounded by normal lung parenchyma. The causes of SPNs include malignancy (primary lung and metastatic cancer) as well as benign causes such as granulomata, hamartomas, or vascular malformations.

A SPN 8 mm or smaller is considered a subcentimeter pulmonary nodule and is managed differently than a larger nodule. The risk of malignancy in an individual patient's subcentimeter pulmonary nodule is divided into low and high risk based on the patient's age (older than 50 years of age confers higher risk), history of past or present smoking, and other risk factors for lung cancer, such as environmental or occupational exposures (for example, asbestos and radon), a diagnosis of COPD, a history of radiation therapy, and possibly a family history of lung cancer. The clinician should establish if prior imaging studies are available for comparison. If long-term stability cannot be established from prior imaging studies, serial interval imaging is recommended. The Fleischner criteria (**Table 37**) are commonly used to determine the timing and duration of imaging follow-up for subcentimeter nodules.

For nodules larger than 8 mm but less than 30 mm, the first step in management is also to assess the pretest probability of malignancy. Clinical prediction models, such as the Veterans Affairs Cooperative or the Mayo Clinic models, are available to categorize the risk as low (<5%), moderate (5% to 65%), and high (>65%). These models typically incorporate several risk factors for malignancy: older age, smoking history, nodule size, history of prior malignancy, upper lobe location, and the presence of spiculation; clinicians frequently add findings of nodule attenuation on CT to help determine the risk for malignancy. Low-attenuation nodules (subsolid) are less dense on imaging, allowing normal parenchymal structures to be visualized through them. Subsolid nodules are less common but are actually more likely to be malignant.

As with subcentimeter nodules, the availability of prior imaging of the chest to assess the stability or growth of these lesions is helpful. An enlarging pulmonary nodule warrants more aggressive evaluation with tissue diagnosis or excision depending on the nodule's pretest probability of malignancy. If prior imaging is not available or the nodule is stable in size, further management is based on the pretest probability (**Table 38**). Additionally, if imaging reveals multiple pulmonary nodules, guidelines recommend evaluating the risk of malignancy for each individual nodule to determine the best management strategy. If solid pulmonary nodules remain stable in size for 24 months, most clinicians no longer recommend surveillance imaging. However, given the higher probability of malignancy with ground-glass and partly solid nodules, these patients may warrant longer, if not lifelong, surveillance.

A pulmonary mass, defined as greater than 3 cm in diameter, is highly suspicious for malignancy in a patient with risk factors. Biopsy for tissue diagnosis (in the absence of suspected metastases) or surgical resection (if no evidence of metastatic disease is found) is typically the first step in the evaluation.

TABLE 37. Fleischner Criteria for Surveillance Imaging of Subcentimeter Solitary Solid Pulmonary Nodules

Nodule Size (mm)[a]	Low Pretest Probability[b]	High Pretest Probability[c]
≤4	No follow-up needed[d]	Follow-up CT at 12 months; if unchanged, no further follow-up[e]
>4 to 6	Follow-up CT at 12 months; if unchanged, no further follow-up[e]	Initial follow-up CT at 6 to 12 months then at 18 to 24 months if no change[e]
>6 to 8	Initial follow-up CT at 6 to 12 months then at 18 to 24 months if no change	Initial follow-up CT at 3 to 6 months then at 9 to 12 months and 24 months if no change
>8	Follow-up CT at around 3, 9, and 24 months; dynamic contrast-enhanced CT, PET, and/or biopsy	Same as for low-risk patient

[a]Average of length and width.

[b]Minimal or absent history of smoking and of other known risk factors.

[c]History of smoking or of other known risk factors.

[d]The risk of malignancy in this category (<1%) is substantially less than that in a baseline CT scan of an asymptomatic smoker.

[e]Nonsolid (ground glass) or partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma.

Reprinted from MacMahon H, Austin JH, Gamsu G, et al; Fleischner Society. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. Radiology. 2005 Nov;237(2):395-400. [PMID: 16244247], with permission from the Radiological Society of North America.

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TABLE 38. Management Recommendations for Solid Solitary Pulmonary Nodules Ranging from Greater than 8 mm to Less than 30 mm

Pretest Probability of Malignancy	Recommendation
Low (<5%)	Surveillance CT at 3 to 6, 9 to 12, and 18 to 24 months (re-evaluate for PET imaging, tissue diagnosis, or excision if evidence of growth)
Intermediate (5% to 65%)	PET/CT imaging: Tissue diagnosis or excision if the nodule demonstrates high metabolic activity, as defined by the concentration of uptake of the tracer (fluorodeoxyglucose) At least short-term surveillance if negative, but consider more aggressive evaluation depending on individual patient factors
High (>65%)	Surgical excision (consider PET/CT imaging for staging first)

Information from Alberts WM; American College of Chest Physicians. Diagnosis and management of lung cancer executive summary: ACCP evidence-based clinical practice guidelines (2nd Edition). Chest. 2007 Sep;132(3 Suppl):1S-19S. [PMID: 17873156]

KEY POINTS

- The first step in the management of a solitary pulmonary nodule is to assess the pretest probability of malignancy.
- HVC If prior imaging of the chest is available, it should be reviewed as a low-risk and inexpensive way to assess the stability or growth of the solitary pulmonary nodule.

Lung Cancer

Lung cancer is the second most common cancer diagnosed in the United States but is the leading cause of cancer deaths. Approximately 80% to 90% of lung cancers can be attributed to cigarette smoking or exposure to second-hand smoke. Therefore, smoking prevention and cessation may be the most important steps in preventing lung cancer. Additional risk factors for lung cancer include exposure to asbestos, ionizing radiation, radon, and arsenic. The relative risk for developing lung cancer significantly increases when a smoker is exposed to another carcinogen or risk factor, such as asbestos. The incidence of lung cancer is also increased in patients with a history of HIV infection, increasing age, and a history of comorbid lung conditions, including emphysema and idiopathic pulmonary fibrosis. Although still poorly understood, a familial predisposition of primary lung cancer has been observed as well.

KEY POINTS

- Lung cancer is the second most common cancer diagnosed in the United States but is the leading cause of cancer deaths.
- HVC Smoking prevention and cessation may be the most important steps in preventing lung cancer.

Lung Cancer Types

Lung cancers are classified by histologic type (**Table 39**). Most (80%) lung cancers are non–small cell lung cancers (NSCLC), with the most common type being adenocarcinoma of the lung. Adenocarcinoma typically presents in the periphery of the lung. Most squamous cell carcinomas, which represent the second most common form of NSCLC, are located in the central portions of the lung and are more common in patients with a smoking history. Current treatment options for both of these NSCLCs include surgical resection, radiation therapy, chemotherapy, and targeted therapies (see MKSAP 17 Hematology and Oncology). Small cell lung cancer (SCLC) tends to be more aggressive than NSCLC and is usually already disseminated at presentation but is usually more sensitive to chemotherapy and radiation therapy initially. It typically presents as a large hilar mass with bulky mediastinal lymphadenopathy.

Diagnosis and Staging

H

The evaluation of a patient with suspected lung cancer aims to confirm whether the patient indeed has lung cancer, to determine the pathology (NSCLC versus SCLC), and to assess the stage at presentation. Most patients typically undergo chest CT as the first imaging modality, either after an abnormal chest radiograph or as evaluation of a symptom. Initial chest CT imaging is used to determine the size and location of the primary tumor, the presence and location of regional lymph node involvement, and the presence of metastases, which include not only extrathoracic organs but also nodules within a contralateral lobe of the lung and pleural disease. The findings on the chest CT help determine whether a PET/CT is necessary. A PET/CT can help in staging and therefore also help guide where to biopsy. For example, if a patient has a solitary pulmonary nodule, a PET/CT may help determine if any lymph node involvement is present that was not visible on the chest CT.

TABLE 39. Histologic Classification of the Most Common Types of Lung Cancer

Histologic Type	Percentage of All Lung Cancers
Non-Small Cell Lung Cancer	
Adenocarcinoma	38%
Squamous cell carcinoma	20%
Large cell carcinoma	3%
Adenosquamous carcinoma	0. 6% to2.3%
Sarcomatoid carcinoma	0.3%
Neuroendocrine Tumors	
Small cell lung cancer	14%
Large cell lung cancer	3%
Typical carcinoid tumor	1% to 2%
Atypical carcinoid tumor	0. 1% to0. 2%

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CONT.

The next step is to obtain tissue diagnosis. The choice of initial diagnostic testing should be aimed first at identifying potential lymph node involvement or metastatic disease. Tissue diagnosis should then be targeted at the lesion that would result in the highest potential staging. For example, a patient presenting with a concerning pulmonary mass and a pleural effusion would require diagnostic thoracentesis to provide accurate staging. The thoracentesis, however, may also provide a diagnosis if cytology is positive. If the patient underwent tissue diagnosis of the mass, a thoracentesis would still be required to provide staging information. The prognosis and treatment change based on the pathology and stage of the lung cancer. Consideration of both of these at the time of diagnosis can ultimately result in fewer tests for the patient. Conversely, in a patient who presents with an isolated pulmonary nodule or mass suspicious for NSCLC, biopsy or resection of this primary lesion is indicated. If the pretest probability of NSCLC is high, surgical resection may be the best strategy because this may be curative. Although SCLC can present as a SPN, this is incredibly rare. However, tissue biopsy to confirm the diagnosis of a NSCLC should be obtained prior to surgical resection if SCLC is a significant possibility (for example, in a patient with a hilar mass). If the pretest probability for NSCLC is low, CT-guided transthoracic needle aspiration or bronchoscopy with transbronchial biopsy could be considered depending on the location of the nodule.

Lung Cancer Screening

The National Lung Cancer Screening Trial (NLST) demonstrated a 20% reduction in lung cancer deaths at 6.5 years of follow-up in a specific group of high-risk patients who completed 3 years of annual chest imaging with low-dose CT compared with chest radiograph. Based on these data, the United States Preventive Services Task Force (USPSTF) recommends screening patients between the ages of 55 and 79 years who have a 30-pack-year or more history of smoking and who are currently smoking or quit within the last 15 years. Annual low-dose CT imaging should continue until comorbidity limits survival or the ability to tolerate surgical resection, or the patient reaches the age of 80 years. The USPSTF guidelines also recommend that annual screening be discontinued in patients who have stopped smoking for 15 years. If nodules are identified, clinicians should follow established guidelines on how to manage solitary pulmonary nodules for patients at high risk for lung cancer.

The risks of screening, especially the risk of potentially false-positive findings on imaging, outweigh the benefit in patients at low risk for lung cancer. Therefore, lung cancer screening is not currently recommended for patients who do not meet the above criteria.

The Centers for Medicare and Medicaid Services (CMS) recently began reimbursing low-dose CT for lung cancer screening in patients aged 55 to 77 years who meet the above criteria.

KEY POINT

- The United States Preventive Services Task Force recommends low-dose CT screening for lung cancer in patients between the ages of 55 and 79 years who have a 30-pack-year or more history of smoking and who are currently smoking or quit within the last 15 years. HVC

Preinvasive Lung Lesions

Both categories of NSCLC and SCLC include preinvasive lesions that warrant, at a minimum, ongoing surveillance. A 2011 change in the pathologic classification of lung cancer eliminated the previous term of bronchoalveolar cell carcinoma, previously considered a type of NSCLC. This entity is now divided into three categories or subtypes of adenocarcinoma: atypical adenomatous hyperplasia, adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma. AIS most commonly presents as an incidental finding of ground-glass opacification on chest CT (**Figure 15**). Ground-glass opacifications appear as gray subsolid lesions within the parenchyma of the lung that do not obscure the underlying blood vessels or airways. A less common variant is mucinous AIS, which appears as a solid nodule on imaging. Minimally invasive adenocarcinoma presents similarly to AIS but has a small area of invasion on pathology (≤5 mm). For all three subtypes, the 5-year survival rate is 100% after surgical resection. Current Fleischner criteria recommend that solitary ground-glass nodules larger than 5 mm should be monitored with repeat chest imaging. Initial imaging is recommended at 3 months and then annually for at least 3 years. The guidelines are the same for multiple ground-glass nodules when at least one is larger than 5 mm, whereas multiple ground-glass nodules of 5 mm or smaller should be monitored with repeat imaging at 2 and 4 years. Surgical resection should be considered if a nodule increases in size or the density increases.

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia is a rare potential precursor of neuroendocrine tumors of the lung and is defined as the presence of multiple carcinoid tumorlets (<0.5 cm) or widespread neuroendocrine cell hyperplasia.

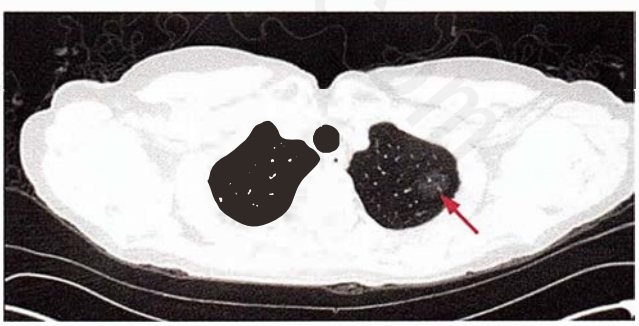

FIGURE 15. A large ground-glass opacification can be seen in the left lung apex on chest CT (*arrow*). It was later confirmed to be an adenocarcinoma in situ on surgical pathology.

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Other Pulmonary Neoplasms

Bronchial Carcinoid Tumors

Although bronchial carcinoid tumors represent only a small percentage of all lung cancers, they are the most common lung cancer to present in children and adolescents. Most lesions involve the proximal airways, so patients may present with symptoms related to endobronchial narrowing or obstruction, including postobstructive pneumonia (**Figure 16**). Patients with peripheral lesions may be asymptomatic at the time of diagnosis. Only approximately 1% to 5% of patients present with symptoms of carcinoid syndrome, which is characterized by the release of vasoactive substances, including serotonin, and causes flushing, bronchospasm, and diarrhea. Carcinoid syndrome is associated with larger tumor size and the presence of liver metastases.

A typical carcinoid is considered a low-grade tumor with an excellent 5-year survival rate of 92% to 100%. Atypical carcinoid tumors are characterized by a higher number of observed mitoses or the presence of necrosis on pathology and are considered intermediate-grade malignancies. They have a higher tendency to metastasize and are associated with a lower 5-year survival rate of 61% to 88%. Although invasion of lymph nodes by typical carcinoid tumors may not decrease survival, it is associated with a worse prognosis in patients with atypical carcinoid tumors. Once a diagnosis is made, surgical resection is recommended for both types of bronchial carcinoid tumors even when lymph node involvement is documented. It may be beneficial to surgically resect affected lymph nodes and other areas of metastases as well. Carcinoids tend to be resistant to chemotherapy and radiation therapy. The routine use of adjuvant therapy is controversial but should be considered if residual disease is documented after attempted surgical resection or if patients present with either lesions not amendable to resection or progressive disease. Somatostatin analogs are reserved for patients who present with carcinoid syndrome and some patients with metastatic disease. Patients with a history of bronchial carcinoids should be monitored for recurrence.

KEY POINTS

- Most bronchial carcinoid tumors involve the proximal airways, so patients may present with symptoms related to endobronchial narrowing or obstruction, including postobstructive pneumonia.
- A typical carcinoid is considered a low-grade tumor with an excellent 5-year survival rate of 92% to 100%.

Mesothelioma

Malignant pleural mesothelioma is a very aggressive tumor that arises from the mesothelial cells of the pleura. Exposure to airborne asbestos fibers is the most significant risk factor for the development of mesothelioma. Patients most commonly present with symptoms of a slowly enlarging pleural effusion. Chest imaging typically shows a unilateral pleural effusion, but patients can also present with pleural thickening, nodules, or masses. This is usually accompanied by the presence of pleural plaques or calcifications (**Figure 17**). Cytologic diagnosis can often be established by thoracentesis or closed pleural biopsy. Video thoracoscopy may be required if initial attempts with less invasive sampling are nondiagnostic or if larger tissue samples are required for subtype classification. Patients with resectable disease still require chemotherapy and radiation therapy. If surgery is not possible, systemic chemotherapy is combined with symptom-driven treatments.

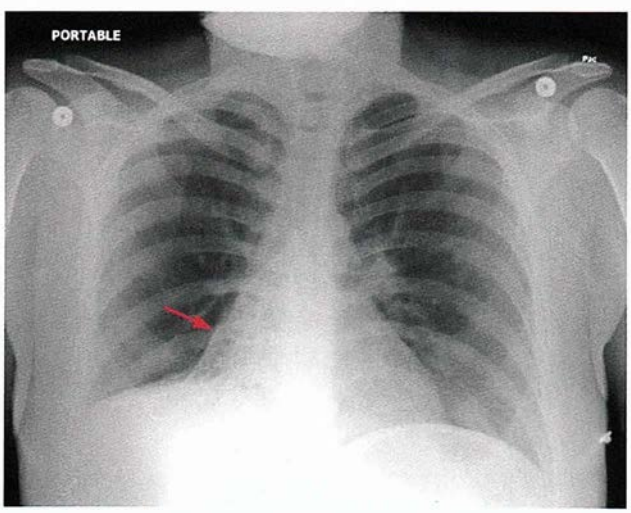

FIGURE 16. A chest radiograph confirmed a persistent right lower lobe consolidation (*arrow*) in a 20-year-old woman who presented with coughing and wheezing that persisted despite several courses of antibiotics. Bronchoscopy confirmed a typical bronchial carcinoid tumor obstructing the bronchus intermedius.

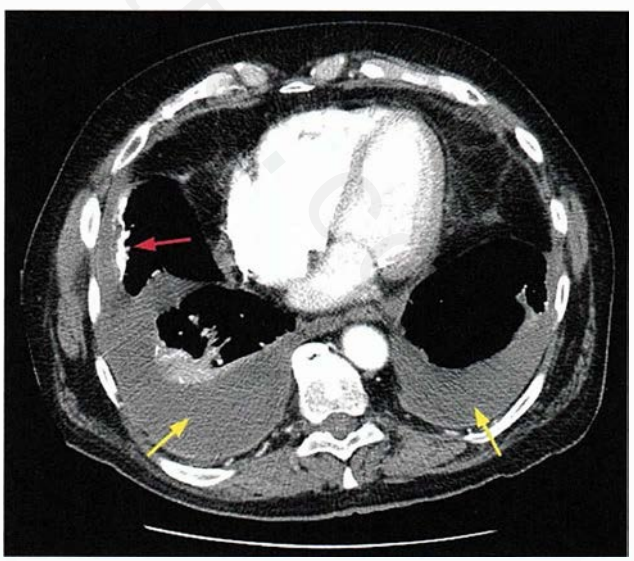

FIGURE 17. Chest CT shows bilateral pleural effusions (*yellow arrows*) with right-sided pleural plaques (*red arrow*).

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CONT. For a discussion of other types of asbestos-related lung disease, see Occupational Lung Disease.

KEY POINTS

- Exposure to airborne asbestos fibers is the most significant risk factor for the development of mesothelioma.
- Patients with mesothelioma most commonly present with symptoms of a slowly enlarging pleural effusion.

Pulmonary Metastases

Pulmonary metastases most commonly present as multiple, peripheral, or subpleural pulmonary nodules but can also present as solitary pulmonary nodules (**Figure 18**). Metastases are often identified on imaging obtained for staging of the primary cancer. Although many (80% in some reports) of the nodules identified during staging end up being benign, early detection and treatment of pulmonary metastases has improved survival in some patients, especially those with primary colon cancer or sarcomas. The most common primary malignancies to metastasize to the lung are carcinomas (colon, kidney, breast, testicle, and thyroid), sarcomas (bone), and melanoma. Endobronchial metastases are rare and are most commonly associated with renal cell carcinoma. Lymphangitic spread of tumor is most commonly associated with adenocarcinoma (lung, breast, and gastrointestinal tract), melanoma, lymphoma, and leukemia and should be considered if a peripheral interstitial abnormality is identified on high-resolution CT in a patient with one of these malignancies.

KEY POINT

- Pulmonary metastases most commonly present as multiple, peripheral, or subpleural pulmonary nodules but can also present as solitary pulmonary nodules.

Mediastinal Masses

The mediastinum can be divided into three separate compartments (**Figure 19**), which can help narrow the differential diagnosis of a mediastinal mass. Each compartment normally contains separate and distinct anatomic structures that can lead to development of a mass. Patients may be asymptomatic and are diagnosed after obtaining a chest radiograph for another reason, whereas others present with symptoms related to compression of adjacent structures. For example, they may present with dyspnea if the airway is compressed from a nearby mass or with upper extremity edema if vascular structures are compressed.

Anterior Mediastinal Masses

In adults, anterior mediastinal thymomas are the most common mediastinal lesions, accounting for up to 20% of mediastinal masses. Thymomas are more common in the superior portion of the anterior compartment. Patients usually present as middle-age adults and may develop paraneoplastic syndromes. For example, myasthenia gravis can develop in 35% to 40% of patients with a thymoma. Other less common paraneoplastic syndromes include pure red blood cell aplasia, nonthymic cancers, and acquired hypogammaglobulinemia. The second most common cause is lymphoma (**Figure 20**); patients are typically younger at the time of presentation. Hodgkin lymphoma is the most common lymphoma to involve the mediastinum, followed by lymphoblastic lymphoma and primary mediastinal diffuse large B-cell lymphoma. Teratomas are the most common type of mediastinal germ cell tumors, and they typically present in the anterior mediastinum. They can contain fat, fluid, and even bone.

KEY POINT

- The most common cause of an anterior mediastinal mass is thymoma; other causes include lymphoma and teratoma.



FIGURE 18. CT of the chest demonstrates two subcentimeter nodules (*arrows*) in the left upper lobe in a patient with known breast cancer.

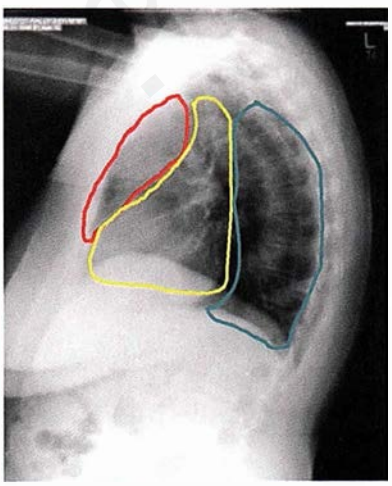

FIGURE 19. A lateral chest radiograph demonstrates the anterior (*red*), middle (*yellow*), and posterior (*blue*) mediastinal compartments.

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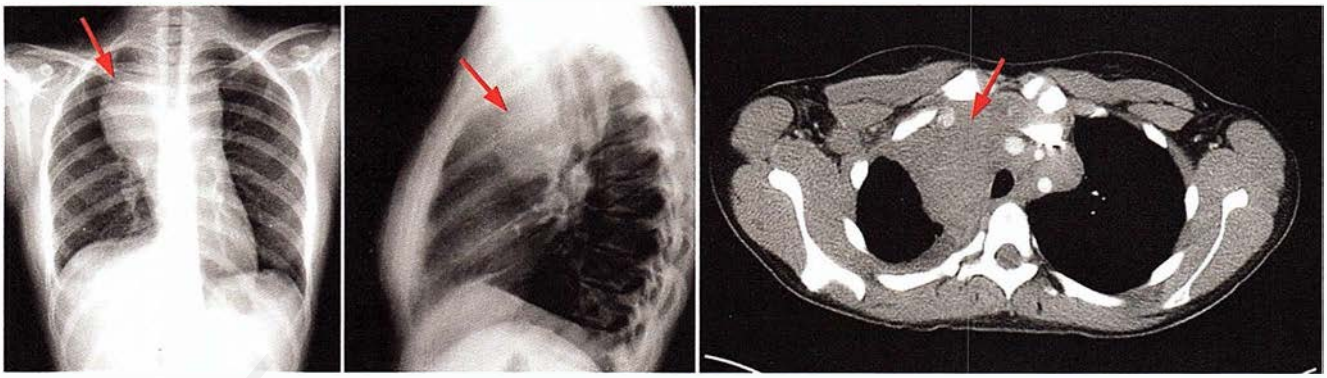

FIGURE 20. A 20-year-old woman presented with exertional dyspnea and was found to have an anterior mediastinal mass (*arrows*) on chest imaging. She was subsequently diagnosed with Hodgkin lymphoma.

Middle Mediastinal Masses

Lymphadenopathy is the most common cause of middle mediastinal masses. Several cystic structures can also develop in this compartment, including bronchogenic, pericardial, and esophageal duplication cysts. Although cysts can be followed, they may be resected if patients are symptomatic or the diagnosis is uncertain.

KEY POINT

- Lymphadenopathy is the most common cause of a middle mediastinal mass.

Posterior Mediastinal Masses

In children, posterior neurogenic tumors are the most common diagnosis of the mediastinum. These typically arise from the sympathetic ganglia (for example, neuroblastomas), whereas in adults, the neurogenic tumors tend to arise from the nerve sheaths (for example, schwannomas). Paraspinal extramedullary hematopoiesis may also involve this mediastinal compartment.

KEY POINT

- The most common cause of a posterior mediastinal mass is a neurogenic tumor.

Sleep Medicine

For a discussion of insomnia, see MKSAP 17 General Internal Medicine.

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS), also referred to as hypersomnia, refers to the struggle to remain awake and alert during daytime hours. Patients may use terms like "tiredness," "fatigue," and "sleepiness" interchangeably to describe their symptoms, but the distinctions are important. Fatigue is a lack of energy that prevents mental or physical activity at the intensity and/or pace desired and is rarely the result of a primary sleep disorder.

Causes of excessive sleepiness can be categorized as extrinsic (circumstantial) or intrinsic (disease-related) processes (**Table 40**).

The most common cause of EDS is the overall lack of time devoted to the sleep period, referred to clinically as insufficient sleep syndrome.

The first step in the evaluation of EDS should include a thorough history of the sleep-wake schedule, with the goal of ensuring nightly opportunities for adequate sleep time (7.5 to 8.0 hours for most people). Sleep diaries maintained over a 1- or 2-week period are simple tools to track hours spent awake and asleep. For a more objective assessment, a wrist actigraph measures movement and ambient light and allows an estimation of the sleep period over a 1- or 2-week period. Subjective questionnaires such as the Epworth Sleepiness Scale may be helpful in quantifying EDS.

Laboratory-based polysomnography is generally indicated if there is suspicion of primary sleep disorders such

TABLE 40. Extrinsic and Intrinsic Causes of Excessive Daytime Sleepiness

Extrinsic Causes
Insufficient sleep duration (or inadequate opportunity for sleep)
Circadian rhythm disturbance (shift work sleep disorder, jet lag)
Drug-, substance-, or medical condition–related hypersomnia
Environmental sleep disorder (ambient noise, pets)
Intrinsic Causes
Sleep-disordered breathing syndromes, such as obstructive sleep apnea and central sleep apnea
Narcolepsy
Idiopathic hypersomnia
Restless legs syndrome and periodic limb movement disorder
Circadian rhythm sleep disorders

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as sleep apnea, limb movement disorder, or a hypersomnia syndrome such as narcolepsy. Portable sleep monitoring devices can be used to diagnose obstructive sleep apnea (OSA). Occasionally, multiple sleep latency testing (MSLT) is used to provide an objective measure of sleepiness. MSLT requires a series of brief nap opportunities over the course of a full day in a sleep laboratory to determine the average time to fall asleep and is time and labor intensive; however, it is required to establish the diagnoses of narcolepsy and idiopathic hypersomnia. A mean sleep latency of less than 5 minutes is a clear indicator of pathologic sleepiness, whereas more than 15 minutes is considered normal.

Patients with EDS should be counseled to maintain a consistent sleep-wake schedule that allows for 8 hours of sleep and should be instructed about the dangers of driving or operating machinery while drowsy. Specific treatment depends on the underlying condition (for example, stimulant medications for narcolepsy). Strategic naps and/or caffeinated beverages may be helpful for short-term management of sleepiness.

KEY POINTS

- The most common cause of excessive daytime sleepiness is the overall lack of time devoted to the sleep period.
- Patients with excessive daytime sleepiness should be counseled to maintain a consistent sleep-wake schedule that allows for 8 hours of sleep.

Common Conditions that Disrupt Circadian Rhythm

Jet Lag

Jet lag is a syndrome resulting from desynchronization of the internal circadian clock with the local destination time following air travel across multiple (usually more than five) time zones. Disruption of body rhythms occurs proportionally to the distance traveled. Symptoms may include insomnia, daytime sleepiness, and neuropsychiatric impairment. Because resynchronization takes on average 1.0 to 1.5 days for every hour change in time zone, lingering symptoms can be disruptive to business travel and family vacations. Management includes avoiding sleep deprivation prior to travel. For highly motivated travelers, a gradual shift in the sleep period over several days prior to travel to synchronize with the destination can ease the transition. Although hypnotic medications in flight may promote sleep, they pose a risk of parasomnias such as sleepwalking. Once at the destination, exposure to sunlight during the waking hours is the most powerful environmental cue to help reset the internal clock. Over-the-counter melatonin supplements, the timing of which depends upon the direction travelled, can also help resynchronization.

Shift Work Sleep Disorder

As many as one third of shift workers suffer from shift work sleep disorder (SWSD), characterized by insomnia during the daytime sleep period and resultant sleepiness during the nighttime work period. The first step in management is to address sleep-related behaviors and the sleep environment, referred to as sleep hygiene. Those who routinely work night shifts and suffer from SWSD should control exposure to bright light, promoting it in the evening before the night shift and avoiding it in the morning in anticipation of the daytime sleep period. Caffeinated beverages during work hours may enhance alertness. Planned napping during work breaks may also be useful. Modafinil, a novel stimulant approved for use in SWSD, should be considered only after conservative measures such as sleep hygiene counseling are tried. The long-term efficacy of hypnotic medications in those with chronic insomnia has not been proved.

Obstructive Sleep Apnea

OSA is a common condition defined by narrowing or occlusion of the upper airway during sleep, resulting in repetitive interruption of the sleep cycle. These disordered breathing events are classified as apneas (characterized by complete cessation of airflow) or hypopneas (reductions in airflow). They are typically accompanied by oxyhemoglobin desaturations and are terminated by an awakening from sleep. They may be quantified during diagnostic sleep testing by the apnea-hypopnea index (AHI). The AHI refers to the number of disordered breathing events per hour of sleep. An AHI of 5 to 15 is indicative of mild OSA, and an AHI of more than 30 reflects severe OSA.

KEY POINT

- Obstructive sleep apnea is a common condition defined by narrowing or occlusion of the upper airway during sleep, resulting in repetitive interruption of the sleep cycle.

Pathophysiology

An unstable upper airway is the hallmark of OSA. Neuromuscular mechanisms that maintain airway patency during sleep are overcome by forces that promote collapse (see Risk Factors). The same mechanisms are responsible for snoring. The upper airway is more prone to collapse due to gravitational forces during sleep in the supine position, as well as during rapid eye movement (REM), a stage of sleep characterized by atonia of most muscles of the body other than extraocular muscles and the respiratory diaphragm. During upper airway collapse, efforts to breathe against the occlusion continue, resulting in wide swings in intrathoracic pressure. Termination of disordered breathing events typically occurs with a brief awakening from sleep (called a microarousal), in which upper airway patency is restored, ventilation resumes, and reoxygenation occurs; this is followed by resumption of sleep.

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Disruption of sleep architecture by repetitive microarousals is a primary contributor to the neurocognitive sequelae of OSA. Oxyhemoglobin desaturations can be pronounced, particularly in those who have coexistent cardiopulmonary disease. Disordered breathing events are associated with autonomic instability, increased vascular tone, and alterations in heart rate. Heart failure, cardiac arrhythmias, and diabetes mellitus are also associated with OSA, but because these conditions have similar underlying risk factors (such as obesity, aging, and male gender), cause and effect are difficult to establish.

Risk Factors

Obesity is the most important risk factor for OSA. Regional distribution of adipose tissue concentrated in the trunk and neck imparts the highest risk. Tonsillar hypertrophy, macroglossia, retrognathia/micrognathia, and upper airway mass lesions can cause upper airway narrowing. Cigarette smoking is a risk factor for OSA. OSA can be worsened by alcohol and sedative drugs. Endocrinopathies such as polycystic ovary syndrome and advanced hypothyroidism can increase the risk of OSA.

KEY POINT

- Obesity is the most important risk factor for obstructive sleep apnea.

Clinical Features and Diagnosis

Loud snoring, gasping, and breathing pauses observed by a bed partner are commonly the first indicators that bring patients with OSA to medical attention. Subjective symptoms include frequent awakenings, dry mouth, snorting, and nonrestorative sleep. Nocturia is common in men with OSA.

EDS is the classic result of OSA. EDS is not a universal symptom, but the absence of self-reporting may not reflect the degree of impairment, which may be detectable on objective testing of alertness (such as MSLT). Other neuropsychiatric symptoms are common and include mood alterations, difficulty concentrating, and problems completing tasks at school or the workplace.

Occasionally, OSA first presents immediately following a surgical procedure involving general anesthesia and/or narcotic analgesia, where repeated apneas, acute respiratory failure, and even death unexpectedly occur. Screening questionnaires (STOP-Bang) are available to help identify OSA during pre-anesthesia evaluation and may reduce the increased rate of postoperative complications in these patients.

Objective testing is required for the diagnosis of OSA. The traditional gold standard of in-laboratory, technician-attended polysomnography (PSG) is being replaced in some regions of the country by portable technology designed for use by the unaccompanied patient, referred to as out-of-center sleep testing (OCST). This portable testing is typically limited to measurement of oronasal airflow, chest wall excursion, body position, and pulse oximetry, whereas in-laboratory PSG additionally measures brain waves (electroencephalography), muscle activity (electromyography), and heart rhythm (electrocardiography), all attended by a technician in case of technical issues. OCST performs comparably to PSG in patients without comorbid cardiopulmonary disease who have a high pretest probability of moderate to severe OSA.

Determining whether objective testing is indicated can be challenging. In general, any patient with unexplained EDS should undergo OSA testing. For less obvious cases, screening tools are available to aid in decision-making. Examples include the Sleep Apnea Clinical Score (SACS) and the Berlin questionnaire.

Overnight pulse oximetry alone has a high rate of false-positive and false-negative results and has not been validated as a screening tool for OSA. A normal-appearing overnight pulse oximetry may allow for avoidance of further testing in patients with a low pretest probability, those with few symptoms, or in those whose preference is to avoid treatment.

KEY POINTS

- Out-of-center sleep testing performs comparably to polysomnography in patients without comorbid cardiopulmonary disease who have a high pretest probability of moderate to severe obstructive sleep apnea.
- Overnight pulse oximetry alone has a high rate of false-positive and false-negative results and has not been validated as a screening tool for obstructive sleep apnea; its use should be limited to patients with low pretest probability, few symptoms, or in patients who prefer to avoid treatment. HVC

Treatment

The primary goal of OSA management is to resolve attributable symptoms, particularly EDS or daytime neurocognitive impairment. Positive airway pressure (PAP) therapy is generally the preferred treatment. Those who perform mission-critical work (truck drivers, pilots) warrant particular attention even when symptoms are limited. The role of treatment in asymptomatic, otherwise healthy individuals is debatable. Furthermore, treatment of OSA as a means to adjunctively manage comorbid cardiovascular disease such as hypertension, cardiac arrhythmias, and heart failure is controversial.

Behavioral Modifications

All patients with OSA should be counseled on behavior modifications, particularly weight loss in those who are overweight or obese. A weight loss program may be the primary therapy for minimally symptomatic patients with mild OSA. Studies of bariatric surgery have shown improvements in OSA, but surgery rarely leads to complete resolution of OSA. Additional lifestyle or conservative measures include reducing alcohol

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intake before bedtime and avoiding a supine posture if OSA is dependent on position.

KEY POINT

- All patients with obstructive sleep apnea should be counseled on behavior modifications, particularly weight loss in those who are overweight or obese.

Positive Airway Pressure

PAP has proven efficacy in eliminating apneas and hypopneas, reducing symptoms, and enhancing quality of life. The mechanism by which PAP acts is primarily related to pressurization of the upper airway sufficient to overcome the collapsing forces of surrounding soft tissue, thereby eliminating upper airway collapse and airflow limitation.

There are a variety of modes by which PAP therapy is delivered (**Table 41**). Traditionally, PAP devices have been manually titrated by a trained technologist in the polysomnography laboratory to a fixed and constant pressure, referred to as continuous positive airway pressure (CPAP). However, the increasing use of OCST is coupled with autotitrating PAP (APAP), which uses a computer algorithm to detect and overcome upper airway resistance in real time, thereby eliminating the need for laboratory-based manual titration. Studies have shown APAP to be as effective as laboratory-derived CPAP at reducing the AHI and may have some advantages over CPAP in terms of patient comfort.

A variety of patient-device interfaces are available, including nasal pillows that sit at the nasal openings, nasal masks that cover the nose, and oronasal (full face) masks that cover the nose and mouth.

The effectiveness of PAP therapy is dependent on patient compliance, which can be compromised by lack of motivation or side effects such as rhinitis and nasal congestion. Data download from the machine provide objective measures of compliance (a minimum level of which is required for Medicare coverage) as well as information related to air leak that might indicate poor mask fit. Dedicated patient education programs can promote adherence. Proper mask fitting and a desensitization program (in which the patient gradually increases time wearing the mask while awake) can help manage claustrophobia. Nasal side effects can be alleviated with in-line heated humidification or anticholinergic or glucocorticoid nasal sprays.

KEY POINT

- Positive airway pressure is the preferred therapy for nearly all patients with symptomatic obstructive sleep apnea.

Oral Appliances

Oral appliances are an alternative to PAP therapy for mild to moderate OSA. They act by one of two mechanisms to increase upper airway caliber: (1) advancement of the mandible by traction or (2) preventing posterior displacement of the tongue by suction. Oral appliances generally do not reduce the AHI as reliably as PAP; however, if patients treated with appliances are adherent to therapy over a greater total sleep time compared with PAP, as some data suggest, the "treatment dose" may be comparable between the two.

Upper Airway Surgery

Except for obstructing mass lesions of the upper airway, surgery is not recommended as initial therapy for OSA and should generally be preceded by a trial (as long as 3 months) of PAP.

Uvulopalatopharyngoplasty (UPPP), a soft-palatal procedure, results in very modest reductions in the AHI. Maxillomandibular advancement, which may be performed in conjunction with a soft-palatal procedure, may be more effective at reducing the AHI. Tonsillectomy is not generally curative in adults.

TABLE 41. Positive Airway Pressure Modes

Mode	Description	Indication
CPAP (continuous positive airway pressure)	Fixed pressure derived from an in-lab titration attended by a technician	OSA Occasionally CSA
APAP (auto-titrating positive airway pressure)	Range of pressure delivered to maintain upper airway patency, determined by a proprietary computer algorithm	OSA
BPAP (bilevel positive airway pressure, bilevel assisted ventilation)	Inspiratory pressure support delivered over and above a minimum expiratory pressure, derived from an in-lab titration	Hypoventilation syndromes OSA when CPAP fails (including when patient intolerant)
Auto-BPAP	Range of bilevel pressures determined by a proprietary computer algorithm	Same as BPAP
ASV	Breath-by-breath adjustment of inspiratory pressure support and back-up rate determined by proprietary computer algorithm; expiratory pressure set by a technician	CSA (including mixed CSA and OSA)
Auto-ASV	Inspiratory and expiratory pressures determined by a proprietary algorithm	Same as ASV

ASV = adaptive servoventilation; CSA = central sleep apnea; OSA = obstructive sleep apnea.

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Central Sleep Apnea Syndromes

Classification and Pathophysiology

Central sleep apnea (CSA) syndromes share the common pathophysiologic mechanism of dysfunctional ventilatory control resulting in a tendency toward hyperventilation and hypocapnia.

CSA is defined by the loss of neural output originating from the respiratory centers in the central nervous system to the respiratory pump machinery, resulting in pauses in breathing. During sleep testing, CSA is manifested by the absence of respiratory effort associated with loss of airflow for at least 10 seconds.

Compared with wakefulness, ventilation normally decreases during sleep and is primarily determined by blood carbon dioxide tension (arterial P_{CO_2}), with a lesser influence from oxygen tension. There is a near-linear relationship between arterial P_{CO_2} and ventilation, particularly in non-REM sleep, when CSA is typically encountered. The stimulus to breathe decreases along with arterial P_{CO_2} until the apneic threshold is reached, at which point ventilation ceases. Common to all CSA syndromes is the propensity to intermittently cross the apneic threshold, which causes a pause in breathing that destabilizes further ventilation.

KEY POINT

- Central sleep apnea is manifested on sleep testing by the absence of respiratory effort associated with loss of airflow for at least 10 seconds.

Risk Factors

Comorbid illnesses that predispose to instability of the ventilatory control system are the most common risk factors for CSA. The most important and prevalent association is between CSA and heart failure, which classically manifests as the Cheyne-Stokes breathing pattern, characterized by a pattern of ventilation with periods of waxing and waning tidal volumes.

The association between opioid analgesics and CSA is increasingly recognized. Opioids are known for their respiratory depressant effects in high doses, but they also destabilize ventilation, resulting in CSA and a chaotic breathing rhythm.

Other risk factors for CSA include atrial fibrillation, stroke, brainstem lesions, and possibly kidney failure; high-altitude periodic breathing is a form of CSA. Primary or idiopathic CSA, in which no risk factors are identified, occurs in a small proportion of patients.

Symptoms and Diagnosis

Because symptoms of CSA may be difficult to distinguish from OSA (frequent awakenings, nonrestorative sleep, EDS), a high index of suspicion is needed, particularly in the clinical context of comorbid disease. In-laboratory polysomnography is required to accurately diagnose CSA; OCST is not indicated for non-OSA sleep disorders. Overnight pulse oximetry alone does not reliably distinguish between OSA and CSA.

Treatment

The strongest indication for treatment of CSA is the presence of sleep-related symptoms, and therapy should first target management of modifiable comorbid conditions or risk factors. For example, reduction or withdrawal of opioids improves CSA. Medical optimization of heart failure (with drugs, devices, or surgery such as valve repair or heart transplantation) has been shown to improve CSA and Cheyne-Stokes breathing.

CPAP may occasionally be useful, especially in patients with overlapping OSA; however, CSA may be exacerbated by CPAP (known as "complex sleep apnea" or "treatment-emergent CSA"). Adaptive servoventilation, a novel form of PAP therapy, often suppresses CSA during polysomnography, but has not yet been shown to improve important outcomes in those with heart failure. Consultation with a sleep specialist is recommended.

KEY POINT

- The strongest indication for treatment of central sleep apnea is the presence of sleep-related symptoms, and therapy should first target management of modifiable comorbid conditions or risk factors.

Sleep-Related Hypoventilation Syndromes

The sleep-related hypoventilation syndromes result from exacerbation of an underlying condition that impairs daytime gas exchange by the decreased ventilatory drive normally associated with sleep. The most common sleep-related hypoventilation syndromes are those associated with COPD, obesity, and restrictive lung diseases related to kyphoscoliosis or neuromuscular disorders (**Table 42**). Hypoventilation

TABLE 42. Sleep-Related Hypoventilation Syndromes

COPD
Obesity hypoventilation syndrome
Myxedema
Neuromuscular disease
Muscular dystrophy
Amyotrophic lateral sclerosis
Myasthenia gravis
Guillain-Barré syndrome
Phrenic nerve injury
Poliomyelitis, post-polio syndrome
Cervical spine injury
Kyphoscoliosis

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is most marked during REM sleep, during which muscle atonia can result in severe oxyhemoglobin desaturations. Hypoventilation syndromes are diagnosed when there are sustained reductions in oxyhemoglobin saturations (<90% for at least 5 minutes or more than 30% total sleep time by pulse oximetry or polysomnography) in the context of a compatible medical condition. Obstructive disordered breathing events may or may not be an associated feature, and it is the sustained reductions in oxyhemoglobin saturations that distinguish hypoventilation syndromes from the brief, repetitive deoxygenation-reoxygenation cycles typical of OSA.

KEY POINT

- The most common sleep-related hypoventilation syndromes are those associated with COPD, obesity, and restrictive lung diseases related to kyphoscoliosis or neuromuscular disorders.

Chronic Obstructive Pulmonary Disease

Hypoventilation in COPD typically results from severe airflow obstruction. Treatment should include optimization of COPD therapy. Supplemental oxygen has been a mainstay of treatment for hypoxemia due to COPD. Nocturnal bilevel positive airway pressure (BPAP) can be used for hypercapnic respiratory failure due to COPD. OSA may be superimposed on these gas exchange abnormalities; this is referred to as the overlap syndrome. PAP has been found to improve important outcomes in the overlap syndrome, such as mortality and hospitalization rates.

Obesity Hypoventilation Syndrome

Daytime hypercapnia (arterial P_{CO_2} >45 mm Hg [6.0 kPa]) is a cardinal sign of obesity hypoventilation syndrome (OHS), reflecting reduced ventilation during wakefulness and sleep that is not attributed to another cause. It likely results from a combination of mechanical load owing to obesity and attenuation of both hypoxic and hypercapnic ventilatory drive. Cardiopulmonary morbidity in OHS is prevalent, with high rates of biventricular failure and pulmonary hypertension.

First-line therapy for OHS is PAP. Because OSA often coexists with OHS, patients with OHS have historically been treated with CPAP, with or without supplemental oxygen. However, because hypoventilation and hypoxemia often persist on CPAP, the paradigm is shifting towards BPAP devices. Weight loss (and possibly bariatric surgery) should be recommended.

KEY POINT

- Daytime hypercapnia is a cardinal sign of obesity hypoventilation syndrome, reflecting reduced ventilation during wakefulness and sleep that is not attributed to another cause.

Neuromuscular Diseases

Assisted breathing devices are often prescribed to alleviate sleep-related symptoms and support blood oxygen levels in patients with neuromuscular disorders (see Table 42). BPAP or volume-cycled devices with or without supplemental oxygen may be useful, particularly if the patient has associated pulmonary hypertension, right-sided heart failure, or polycythemia. Tracheostomy and home mechanical ventilation are effective and may be appropriate for some patients. Supplemental oxygen should generally not be prescribed without adjunctive ventilatory support because supplemental oxygen may further depress ventilation in patients with respiratory muscle weakness.

KEY POINT

- Assisted breathing devices are often prescribed to alleviate sleep-related symptoms and support blood oxygen levels in patients with neuromuscular disorders.

High-Altitude-Related Illnesses

Sleep Disturbances and Periodic Breathing

High-altitude illness (HAI) encompasses a number of disorders that can occur when a person residing at low altitude ascends to higher elevation. Although the proportion of air comprised of oxygen remains constant at 21% as altitude increases, diminishing barometric pressure reduces the amount of oxygen available for gas exchange, resulting in a condition known as hypobaric hypoxia. The response to hypobaric hypoxia is a common pathophysiologic mechanism underlying HAI.

In general, HAI is more common at elevations of 2500 meters (approximately 8200 feet) and above. Susceptibility to HAI is individualized and difficult to predict but is likely to recur in those who have experienced it previously. Young age and the level of physical fitness have not been shown to be protective. Two key risk factors are the destination altitude and the rate of ascent, with gradual ascension allowing acclimatization and a decreased risk for HAI.

One of the first responses to hypoxic stress associated with hypobaric hypoxia is an increase in ventilation, which is a key pathophysiologic mechanism in high-altitude periodic breathing (HAPB). Hypoxia-induced hyperventilation drives the arterial P_{CO_2} toward the apneic threshold, with a decrease in respiratory rate and eventual rise in arterial P_{CO_2}; this results in increased respiratory drive and recurrent hyperventilation. These cyclic apneas and hyperpneas are associated with repetitive arousals from sleep, often with paroxysms of dyspnea and usually occurring the first night at elevation.

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HAPB and other HAIs can be prevented by gradually ascending, which can generally be accomplished by spending one night at an intermediate altitude to allow acclimatization. Acetazolamide accelerates the acclimatization process by inducing a slight metabolic acidosis to stimulate ventilation and enhance gas exchange; it can be used prophylactically in patients with a history of altitude illness. Supplemental oxygen can relieve symptoms of disrupted sleep and paroxysmal nocturnal dyspnea, but because most cases of HAPB are self-limited after a few nights, this is generally not indicated in otherwise healthy individuals.

KEY POINTS

- Gradual ascent allows acclimatization and attenuates symptoms of high-altitude illness.
- Acetazolamide accelerates the acclimatization process to high altitude by inducing a slight metabolic acidosis to stimulate ventilation and enhance gas exchange.

Acute Mountain Sickness and High-Altitude Cerebral Edema

Hypoxia and hypocapnia associated with altitude alter cerebral blood flow and oxygen delivery to the brain. When autoregulatory mechanisms are overcome, symptoms may be mild, as with acute mountain sickness (AMS), or severe, as with life-threatening cerebral edema. AMS, the most common HAI, is characterized by nonspecific symptoms such as headache, fatigue, nausea, and vomiting, in addition to disturbed sleep related to HAPB. Approximately 25% of unacclimatized visitors to an altitude of 2000 meters (approximately 6500 feet), the elevation at most major U.S. ski areas, will experience AMS. Heavy exertion and dehydration tend to amplify the symptoms, which are typically delayed for 6 to 12 hours after ascent and usually resolve within 24 to 48 hours, provided no further ascent occurs. As in HAPB, slow ascent helps prevent the syndrome. For mild symptoms, conservative treatment may include aspirin, NSAIDs, or antiemetics. Acetazolamide is best proven as a prophylactic for AMS but may be effective as a treatment by accelerating acclimatization. Dexamethasone reduces symptoms of AMS. Supplemental oxygen or hyperbaric therapies, when available, are also used to treat AMS.

High-altitude cerebral edema is a more extreme manifestation of AMS that tends to occur at elevations above 3000 to 4000 meters (approximately 9800 to 13,000 feet); prophylactic acetazolamide should be considered in patients planning to ascend to this level to decrease the risk of this significant complication. Vascular leak leads to brain swelling, resulting in manifestations that range from confusion and irritability to ataxic gait to coma and death. Recognition of cerebral edema mandates immediate intervention. Definitive treatment is immediate descent from altitude, particularly when the patient is still ambulatory, because evacuation is exponentially more complicated, if not impossible, when the patient is incapacitated. Dexamethasone, supplemental oxygen, and hyperbaric therapy may be used in addition to descent from altitude.

KEY POINTS

- Acute mountain sickness is the most common high-altitude illness and is characterized by headache, fatigue, nausea, vomiting, and disturbed sleep; acetazolamide may be used to prevent acute mountain sickness.
- High-altitude cerebral edema is a medical emergency resulting from vasogenic brain swelling and should prompt urgent descent from altitude.

High-Altitude Pulmonary Edema

As in cerebral edema, vascular leak driven by hypoxia appears to play a role in high-altitude pulmonary edema; the two conditions can coexist. The cascade of events seems to begin with a rise in pulmonary arterial pressures within 2 to 4 days of ascent to altitudes generally greater than 2500 meters (approximately 8200 feet). Symptoms of cough, dyspnea, and exertional intolerance are usually insidious but occasionally may occur abruptly and awaken a patient from sleep. Other features of AMS may or may not be present. A key feature of high-altitude pulmonary edema is dyspnea at rest. Tachypnea and tachycardia are typical, and crackles or wheezing can be auscultated. Pink frothy sputum or frank hemoptysis may occur, followed by worsening gas exchange and respiratory failure. The treatment of choice is supplemental oxygen along with rest, both of which will acutely reduce pulmonary arterial pressures. Descent should be considered, particularly if oxygen is not available. Salvage therapies in the absence of supplemental oxygen and descent include vasodilators such as nifedipine or phosphodiesterase-5 inhibitors (sildenafil or tadalafil). Conventional treatments for pulmonary edema in the setting of heart failure, such as diuretics and nitrates, are not recommended in this setting.

Air Travel in Pulmonary Disease

The principles of hypobaric hypoxia also apply to commercial airline travel, where cabins are pressurized to the equivalent of 1500 to 2500 meters (approximately 5000 to 8200 feet) in altitude, resulting in an inspired oxygen tension between 110 and 120 mm Hg (about 70% of the levels encountered at sea level). Although in healthy individuals this correlates with an arterial Po_2 of approximately 60 mm Hg (8.0 kPa), those with underlying pulmonary disease are at risk for significant hypoxemia during flight. For such patients, pulse oximetry is a useful screening tool. An oxyhemoglobin saturation of less than 92% at sea level indicates a likely need for in-flight supplemental oxygen. Two to three liters per minute of supplemental oxygen by nasal cannula is typically adequate. In those with sea-level oxyhemoglobin saturation between 92% and 95%, hypoxia altitude simulation testing, available at some centers, can be

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used to determine the need for oxygen supplementation. Patients considered high-risk for in-flight hypoxia and its complications include those with COPD with hypercapnia, a recent exacerbation of chronic lung disease, pulmonary hypertension, and restrictive lung disease, in addition to patients who have had previous in-flight symptoms. In patients who are already on long-term supplemental oxygen, doubling of the flow rate during flight is typically adequate.

Trapped air in any noncommunicating body cavity (lung bullae, blebs, or cysts) will expand under hypobaric conditions. However, the risk of pneumothorax associated with rupture of these cavities during flight is believed to be low, owing to the partial pressurization of airline cabins. Acute exacerbations of obstructive airways disease such as asthma or COPD, in which air trapping can be pronounced, might present a particular risk for pneumothorax and should prompt a delay in planned air travel. An existing pneumothorax has traditionally been considered a contraindication to flight owing to the potential risk of expansion and tension physiology; however, there is some evidence that travel may be safe in the presence of a small pneumothorax that has been radiographically stable.

KEY POINTS

- An oxyhemoglobin saturation of less than 92% at sea level indicates a likely need for in-flight supplemental oxygen to prevent hypoxia.
- In patients who are already on long-term supplemental oxygen, doubling of the flow rate during flight is typically adequate to prevent hypoxia.

Critical Care Medicine

Recognizing the Critically Ill Patient

Timely and directed care for critically ill patients is important for their recovery. Identifying critically ill patients can be challenging because disease presentations may be subtle and progressive. The initial history, vital signs, physical examination, and other supportive information, such as the oxygen saturation breathing ambient air and basic laboratory tests, establish a baseline for later comparison. General criteria for ICU admission vary among institutions depending on the type of specialty ICU, intermediate units, or support staff that are available. Indications for ICU admission include an unstable airway, unstable blood pressure, unstable mental status, life-threatening cardiac arrhythmias, respiratory failure, severe metabolic derangements, or the need for frequent (more than every 2 hours) measurement of vital signs.

In patients not initially admitted to the ICU, several parameters have been identified to assist in the identification of patients at risk for instability. The different scoring systems use different parameters and have variable sensitivities and specificities. The common parameters used in all scoring systems include changes in respiration rate, heart rate, systolic blood pressure, temperature, alertness, and oxygen saturation (with and without oxygen use). Patient age is an independent risk factor for increased risk of adverse events.

Rapid response teams (RRTs) were created to improve the care of hospitalized patients with deteriorating status; the goal is to reduce the incidence of cardiopulmonary arrest and hospital mortality. Unfortunately, clear criteria do not exist for activating RRTs. However, a number of indicators have been identified that are associated with increased risk of decompensation; when these indicators are present, rapid response intervention may be effective. These indicators include changes in vital signs (heart rate of <30/min or ≥139/min; systolic blood pressure <70 mm Hg or ≥200 mm Hg; respiration rate <9/min or >35/min, temperature <34.0 °C [93.2 °F] or ≥39.0 °C [102.2 °F]), oxygen saturation less than 85%, and development of altered mental status or coma.

Rapid response systems (RRSs) involve mechanisms to identify clinical criteria suggesting potential deterioration or instability in patients, along with methods for notifying and activating the RRT of this change in status. RRSs also provide analysis of the event data, feedback, quality review, and recommendations for improvement and periodic reassessment of the system. Whether electronic alerts (by prompts in the electronic medical record or by direct paging of different types of systems) will add to outcome improvement has not been determined. The effectiveness of RRSs is debated, but most RRSs are associated with reduced rates of cardiopulmonary arrest outside of the ICU. Delay in activation of the system is associated with higher mortality. The overall impact of RRSs on mortality of hospitalized adult patients depends on the individual hospital and its resources for recognizing and rescuing deteriorating patients. Several large studies have shown that the introduction of RRSs does not reduce mortality at hospital discharge in adult patients.

Telemedicine is a strategy that uses remote monitoring of patients in the ICU to improve the quality of health care. The information collected includes patient vital signs, electrocardiogram, other types of electrical data, and remote visualization of the patient by camera. Although this technology has been available for over 25 years, study results on patient outcomes are variable, ranging from no demonstrable clinical benefit or improvement in hospital mortality to reduced hospital mortality, reduced ICU length of stay, and reduced duration of mechanical ventilation. Differences between studies have been attributed to the uneven access of the patient to the different telemedicine teams, with some teams having primary versus consultant roles. Patients of telemedicine programs are more likely to receive evidence-based care to prevent ICU complications. Although interest in the use of this technology is growing, the cost of implementation and maintenance can be substantial. More data are needed to optimize the use and appropriate circumstances for implementation of this strategy (for example, rural versus suburban, small ICU versus large ICU, degree of illness).

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Methods for assessing severity of illness in patients admitted to the ICU include the Acute Physiology and Chronic Health Evaluation (APACHE), the Mortality Probability Model (MPM), and the Simplified Acute Physiology Score (SAPS). However, severity scoring has limited usefulness in predicting individual patient outcomes. Therefore, their use is more commonly limited to assessing ICU performance and quality benchmarking.

KEY POINT

- Indications for ICU admission include an unstable airway, unstable blood pressure, unstable mental status, life-threatening cardiac arrhythmias, respiratory failure, severe metabolic derangements, or the need for frequent (more than every 2 hours) measurement of vital signs.

Principles of Critical Care

General Ventilator Principles

Noninvasive (usually via face mask) and invasive (via endotracheal or cuffed tracheostomy tube) ventilators are available to support patients with respiratory failure. Before any ventilator is used, the purpose and goals of using the device should be identified; this is helpful in deciding which therapy is appropriate and the initial device settings to use (Table 43).

TABLE 43. Determination of the Purpose and Goals of Invasive or Noninvasive Ventilation in a Patient with Respiratory Failure

Considerations	Potential Answers
What is the cause of the failure?	Hypoxia, hypercapnia, or both
How quickly will the patient recover?	Noninvasive ventilation can be considered if recovery is quick (as long as there are no contraindications); otherwise use invasive ventilation
What is the best tidal volume for this patient?	6-8 mL/kg of ideal body weight is a safe starting point for most forms of respiratory failure (≤6 mL/kg for most patients with ARDS)
What should the minute ventilation be for this patient?	Minute ventilation equals tidal volume times the respiration rate; setting a normal minute ventilation of 6-8 L/min is a starting point; it may need to be higher for metabolic acidosis or catabolic states or in situations where dead space is increased; it may need to be higher when lung-protective strategies are used
How much oxygen is needed?	Start with an FIO_2 of 1.0 and quickly decrease while following pulse oximetry to target oxygen saturation at 92% to 95% for most patients; use PEEP at an initial setting of 5 cm H_2O; increase PEEP to decrease high FIO_2 need via alveolar recruitment and optimal airway pressures

ARDS = acute respiratory distress syndrome; PEEP = positive end-expiratory pressure.

Noninvasive Ventilation

Fundamental Concepts

Noninvasive ventilation (NIV) is the delivery of positive airway pressure using a cushioned face mask without the use of an invasive connection directly in a patient's airway, such as an endotracheal tube or tracheostomy. Similar to invasive mechanical ventilation, different ventilation modes can be used (see Invasive Mechanical Ventilation, Fundamental Concepts). Pressure is the most common means through which the primary breath is supported, with all breaths initiated by the patient. Similar to invasive mechanical ventilation, the inspiratory phase of respiration can be supported by delivering air pressure and the expiratory phase can occur with exhalation against positive end-expiratory pressure (PEEP). Physiologically, the positive inspiratory pressure (also known as pressure support) assists with the inspiratory effort to offset the work of breathing. PEEP slightly expands the airways; this recruits atelectatic or flooded alveoli and counters the increased workload of breathing associated with increased airway resistance. Continuous positive airway pressure (CPAP) uses a continuous pressure during inhalation and exhalation with the primary goal of providing PEEP on exhalation. Although there is positive pressure during the inspiratory phase of respiration with CPAP, this pressure is continuous during inspiration and expiration. Bilevel support is the term used when positive pressure is changed with the inspiratory and expiratory phase of respiration in NIV. Bilevel support allows for increased support of inspiration with PEEP and potentially results in higher total volume of ventilation, CO_2 clearance, and decreased work of breathing.

Indications and Patient Selection

NIV in critically ill patients can prevent use of intubation in several disease states. For example, NIV decreases the need for intubation in patients with moderate to severe exacerbations of COPD (see Chronic Obstructive Pulmonary Disease). Careful monitoring of response to NIV after 1 to 2 hours is important to avoid deterioration to respiratory arrest. Intubation is indicated if there is no clinical response or if arterial blood gases worsen after the start of NIV.

In cardiogenic pulmonary edema, NIV reduces the risk of intubation (using either CPAP or inspiratory pressure support with PEEP) and is associated with a faster resolution of respiratory distress and metabolic derangements. Mortality data for NIV in cardiogenic pulmonary edema vary, but all studies reveal some benefit, such as more rapid relief of respiratory distress, decreased mortality, or reduced intubation rate. CPAP is recommended initially; however, if the patient has evidence of hypercapnia or remains dyspneic, a switch to inspiratory pressure support with PEEP is indicated. Intubation is the next step if improvement is not seen on close monitoring.

NIV can be used to support patients in acute respiratory failure due to obesity hypoventilation syndrome (OHS). NIV

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CONT. for OHS respiratory failure is associated with similar efficacy and better outcomes as compared with NIV for patients with COPD exacerbation.

In patients with hypoxic respiratory failure, such as severe pneumonia or acute respiratory distress syndrome (ARDS), the use of NIV is controversial. Select patients may benefit from short-duration NIV to avoid intubation, ventilation, and associated complications. These patients should be monitored closely in an ICU so that intubation can be performed if they do not improve or begin to deteriorate.

NIV is associated with decreased ICU mortality, intubation rates, and ICU length of stay in immunocompromised patients. Factors associated with failure of NIV include the need for vasopressors or kidney replacement therapy or the presence of ARDS.

The use of NIV after extubation to facilitate weaning from invasive mechanical ventilation for patients with COPD has yielded mixed results. A trial of NIV can be done if the reason for respiratory failure is quickly reversible; however, the threshold for reintubation should be low if the patient is not quickly improving.

NIV can be used after planned extubation for patients with a high risk of deterioration (>65 years of age, cardiac failure as a cause of intubation, COPD exacerbation, hypercapnia during a spontaneous breathing trial, or any combination of failure of weaning, heart failure, arterial Pco_2 of >45 mm Hg [6.0 kPa] after extubation, multiple comorbidities, or weak cough or stridor after extubation). In most patient populations, data suggest that NIV is not helpful in preventing reintubation in those with established respiratory failure after extubation.

Application

Starting NIV promptly is important for patients with respiratory failure who do not have contraindications to NIV use (**Table 44**). Waiting to start NIV until after the failure of medical treatment reduces its benefits. Patient selection is important, as the patient needs to have a level of mentation that will allow for both the placement of a tight mask and some ability to interact with the staff. The application of NIV requires trained personnel familiar with proper mask fitting and how to make adjustments of the pressure depending on the patient's condition and tolerance. Patients should be assessed for improvement of respiration rate, pH, Pco_2, oxygen saturation, and mental status after an hour of NIV. If improvement is seen, NIV should be continued, and the patient should be subsequently weaned as tolerated. If there is no improvement but the patient is clinically stable, titration of NIV can be made with reassessment. Intubation is indicated when the patient's condition is unstable or deteriorating. Complications of NIV include mask pressure skin breakdown, sinus congestion, gastric distention, and eye irritation. Patients should be monitored in an ICU or an area equipped to respond to potential deterioration.

TABLE 44. Potential Contraindications to Noninvasive Ventilation

Medical Instability
Respiratory or cardiac arrest
Severe acidosis (initial pH <7.25; failure to improve after 1-2 h)
Hemodynamic instability/severe cardiac arrhythmia
Active upper gastrointestinal bleeding
Inability to Protect Airway
Excessive secretions/inability to clear secretions
Severe bulbar dysfunction
Encephalopathy or agitated delirium
Mechanical Issues
Large air leak due to inability to fit mask
Recent facial trauma or surgery
Recent transsphenoidal surgery or high esophageal anastomosis
Upper airway obstruction
Intolerance to delivered pressure

KEY POINTS

- Noninvasive ventilation in critically ill patients can prevent intubation in those with respiratory failure associated with several disease states, including COPD exacerbation, heart failure, and obesity hypoventilation syndrome.
- Noninvasive ventilation is associated with decreased ICU mortality, intubation rate, and ICU length of stay in immunocompromised patients. HVC

Invasive Mechanical Ventilation

Fundamental Concepts

Invasive mechanical ventilation refers to the administration of ventilation directly in the trachea via an endotracheal tube or tracheostomy. Indications for intubation include the failure to oxygenate despite supplemental oxygenation and/or the inability to maintain carbon dioxide levels in an appropriate range for a specific patient.

The ventilator uses a mode to define the interaction with the patient. There are numerous mode names (nearly 300 according to a recent review), and the same mode may have different labels depending on the ventilator manufacturer. Mode taxonomy has been described in the literature but has not been universally adopted.

Despite variable nomenclature, the different modes of mechanical ventilation consist of three basic components that may serve as a useful basis for classification:

1. Breath control: This refers to the method by which the mechanical breath is delivered. If the tidal volume and inspiratory flow are designated, the breath is classified as volume controlled (VC). Conversely, if the breath is delivered based on a preset inspiratory pressure, the breath is pressure controlled (PC).

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2. Breath sequence: Spontaneous and mandatory are the two types of breaths. A mandatory breath is started (triggered) or ended (cycled) by the machine; ventilators may also be set to allow triggering of a mandatory breath coordinated with patient inspiratory effort. If the breath is both triggered and cycled by the patient, it is a spontaneous breath. By definition, a mandatory breath is always assisted (that is, the machine does some portion of the work of breathing), but a spontaneous breath may or may not be assisted. Therefore, there are three breath sequences:
   - Continuous mandatory ventilation (CMV): All breaths are mandatory. A preset frequency represents the minimum number of mandatory breaths per minute; the patient may trigger breaths at a higher frequency.
   - Intermittent mandatory ventilation (IMV): Spontaneous breaths are allowed between or during mandatory breaths. A preset frequency represents the maximum number of mandatory breaths per minute.
   - Continuous spontaneous ventilation (CSV): All breaths are spontaneous.
3. Targeting scheme: This refers to a variety of ventilator algorithms that can be used to tailor mechanical ventilation to the patient's continuously changing lung characteristics and respiratory effort. These options are often proprietary, vary between ventilators, and range from simply maintaining a constant airway pressure during a pressure-controlled breath to use of artificial intelligence–based algorithms to achieve specific treatment goals.

Based on these variables, a ventilator mode may be classified by indicating the method of breath control followed by the breath sequence. For example, VC-IMV indicates volume-controlled, intermittent mandatory ventilation. The targeting scheme is then defined by a small letter at the end of the acronym. Because IMV may have two types of breaths, the two letters indicating the targeting scheme are separated by a comma. The most commonly used modes of mechanical ventilation are described in **Table 45**.

TABLE 45. Most Frequently Used Ventilator Modes

Common Name	Mode Classification	Breath Control Variable	Breath Sequence	Targeting Scheme
Volume control and assist/control	VC-CMVs	VC: The ventilator controls the flow (volume) during the mandatory breath. If the patient's effort, lung compliance, or resistance changes, the ventilator will still deliver the set tidal volume (but the pressure will change).	CMV: All breaths are mandatory. The patient may or may not trigger the breath, but the ventilator always ends the breath when the tidal volume is delivered. The name "assist/control" is a misnomer from the past.	Set-point, s: The operator sets all the parameters of the breath (flow waveform, flow rate, and volume). The ventilator only delivers the breath and does not adjust anything to the patient effort or change in lung characteristics.
Pressure control and assist/control	PC-CMVs	PC: The ventilator controls the pressure during the mandatory breath. If the patient's effort, lung compliance, or resistance changes, the ventilator will still deliver the set inspiratory pressure (but the tidal volume delivered will change).	CMV: All breaths are mandatory. The patient may or may not trigger the breath, but the ventilator always ends the breath when the preset inspiratory time elapses.	Set-point, s: The operator sets all the parameters of the breath (inspiratory pressure and inspiratory time). The ventilator only delivers the breath and does not adjust to the patient effort or change in lung characteristics.
Pressure support, continuous positive airway pressure	PC-CSVs	PC: The ventilator controls the pressure during the breath.	CSV: All breaths are spontaneous. The patient triggers and cycles the breath.	Set-point, s: The operator sets all the parameters of the breath (inspiratory pressure). The ventilator delivers the breath and does not adjust to the patient effort or change in lung characteristics.
Synchronized intermittent mandatory ventilation	PC-IMVs,s or VC-IMVs,s	PC or VC: The mandatory breaths can be set to be volume or pressure controlled, not both. The breath may be volume or pressure controlled.	IMV: Preset mandatory breaths are given at a minimum set rate. Spontaneous breaths are permitted in between mandatory breaths. The triggering of the mandatory breath will be coordinated with the patient if the inspiratory effort occurs close to the scheduled time trigger (determined by the set frequency).	Set-point, s: One "s" refers to the mandatory breath and the other to the spontaneous breath. Generally, all spontaneous breaths in IMV are pressure supported (PC-CSVs).

CMV = continuous mandatory ventilation; CSV = continuous spontaneous ventilation; IMV = intermittent mandatory ventilation; PC = pressure controlled; VC = volume controlled.

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CONT.

VC-CMV is commonly used in patients with ARDS, where the goal is to limit tidal volume. PC-CMV can also be used to ventilate in patients with ARDS, but close monitoring of the tidal volume should be maintained and adjustments of pressure should be performed as compliance improves.

The synchronized IMV mode was originally designed to gradually reduce support over time; however, clinical trials show it to be an inferior mode for weaning. Several modes that incorporate newer technology rely on the IMV breath sequence. This allows the patient to breathe spontaneously when able but to have the safety of a backup mandatory breath rate when needed. These modes require more sophisticated targeting schemes such as using artificial intelligence to run the ventilator.

Weaning

Weaning from mechanical ventilation can start when the precipitating event or underlying condition that caused respiratory failure has resolved or is resolving. Patients should be assessed daily for their readiness to be removed from mechanical ventilation by performing a spontaneous breathing trial (SBT). Protocol-driven methods of assessing weaning readiness may reduce the duration of mechanical ventilation and the complications associated with longer ventilator stays. Sedation reduction or removal allows for a more accurate SBT. There are several methods used to assess if an SBT will be successful. The respiration rate to tidal volume ratio, or rapid shallow breathing index (RSBI), is the most familiar. A patient with an RSBI of less than 105 has an approximately 80% chance of being successfully extubated, whereas an RSBI of greater than 105 virtually guarantees weaning failure.

Other criteria that have been suggested for a successful weaning trial include (1) the ability to tolerate a weaning trial for 30 minutes (in most patients, SBT failure will occur within approximately 20 minutes), (2) maintain a respiration rate of less than 35/min, and (3) keep an oxygen saturation of 90% without arrhythmias; sudden increases in heart rate and blood pressure; or development of respiratory distress, diaphoresis, or anxiety. Once the SBT is tolerated, the ability to clear secretions, a decreasing secretion burden, and a patent upper airway are other criteria that should be met to increase extubation success.

KEY POINT

- Patients should be assessed daily for their readiness to be weaned from mechanical ventilation by withdrawing sedation and performing a spontaneous breathing trial.

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs at least 48 hours after endotracheal intubation. VAP is a serious, costly, and preventable condition associated with an increased mortality and length of ICU and hospital stay. VAP is difficult to diagnose but potential clues to its presence include temperature greater than 38.0 °C (100.4 °F), leukocytosis or leukopenia, increased purulent secretions, new or progressive pulmonary infiltrates, and worsening ventilation parameters, particularly after a period of improvement. Patients suspected of having VAP should undergo lower respiratory tract sampling, followed by microscopic analysis and culture of the specimen. Nonbronchoscopic sampling methods are simple suctioning of the endotracheal tube and mini-bronchoalveolar lavage, which involves use of a telescoping catheter (instead of a bronchoscope) to instill and aspirate physiologic saline for microbiologic analysis. Bronchoscopic methods use standard bronchoalveolar lavage and a protected specimen brush. Deep sampling methods may allow for narrower antibiotic choices and more rapid de-escalation of antibiotics. For further discussion of VAP, see MKSAP 17 Infectious Disease.

Invasive Monitoring

Invasive monitoring using a pulmonary artery catheter (PAC) to determine the stroke volume and cardiac output (CO) by thermodilution was a common method to determine volume status in critically ill patients and is the standard to which current noninvasive CO devices are compared. Owing to the lack of benefit in many studies using PACs, indications for the use of a PAC are now more selective. These indications now focus on cardiac conditions, such as cardiogenic shock requiring supportive therapy, severe heart failure requiring vasoactive therapy, differentiating high-output heart failure from sepsis, and differentiating and/or treating causes of pulmonary hypertension. Because of the potential harms and difficulty in interpretation associated with invasive CO measurement, noninvasive devices are more attractive for use in unstable patients. In resuscitating hemodynamically unstable patients, the ability to predict intravascular volume status and responsiveness to fluids (defined as an increase of cardiac output ≥15% following an adequate fluid challenge) is important. Bedside ultrasound to assess vena caval dimensions induced by positive pressure ventilation appears to be highly predictive of volume responsiveness and is a noninvasive alternative to PAC. Likewise, the use of bedside ultrasound to assess global cardiac function has gained acceptance. However, like PACs, there are limited data showing that any of the noninvasive monitoring devices improve patient outcomes, and all have limitations. The accurate prediction of intravascular volume status and subsequent fluid response remains clinically difficult and lacks an accepted standard testing methodology.

Blood Pressure Support

Blood pressure support is important for all forms of shock (see Shock), with a goal mean arterial pressure of

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CONT. approximately 65 mm Hg. Lower values may be tolerated as long as kidney perfusion is maintained. Fluid resuscitation to ensure adequate intravascular volume is a necessary initial intervention (see Sepsis, Management, Initial Resuscitation), with timely addition of vasopressors through central access if hypotension persists despite volume challenge. Multiple comparative studies of vasopressors in septic shock suggest norepinephrine as a first-line agent, followed by epinephrine. Dopamine should be reserved for select patients; tachycardia is a major side effect, making this agent useful to increase cardiac output in the presence of a relative bradycardia. Vasopressin is considered a second-line agent (although it has been shown to be effective in less severe sepsis) that can be added to decrease the dose and side effects of norepinephrine. Indications, physiologic actions, side effects, and contraindications of vasopressors are described in **Table 46**.

Intravenous Access

A large-caliber intravenous (IV) peripheral access is standard for administering resuscitation fluids and remains the preferred initial IV route in resuscitation. When blood pressure remains low and infusion of vasoconstricting agents is needed to improve the mean arterial pressure, central access is required. The four broad categories of central access are (1) peripherally inserted central catheter (PICC), (2) temporary nontunneled, (3) long-term tunneled, and (4) implanted port (**Table 47**). However, when IV access cannot rapidly be obtained, intraosseous (I/O) access is an immediate alternative. Sites for I/O access in adults include 1 to 2 cm below the tibial tuberosity and the humeral head. Alternative access should replace the I/O within approximately 24 hours of placement to minimize complications.

Ultrasound-guided central line insertion is recommended for the placement of central lines to reduce failure of catheter placement and vessel injury, as well as prevention of pneumothorax for approaches above the diaphragm.

KEY POINTS

- Bedside ultrasound to assess vena caval dimensions induced by positive-pressure ventilation appears to be highly predictive of volume responsiveness and is a noninvasive alternative to a pulmonary artery catheter. HVC
- A large-caliber intravenous peripheral access is standard for administering resuscitation fluids and remains the preferred initial intravenous route in resuscitation.
- Ultrasound-guided central line insertion is associated with a reduction in failure of catheter placement and vessel injury, as well as prevention of pneumothorax. HVC

Comprehensive Management of Critically Ill Patients

Once a patient in the ICU has been stabilized, comprehensive management includes identifying goals of care, preferably with the patient's input. However, most critically ill patients are unable to participate in decisions regarding their care, so the person best able to represent the patient's interests must be identified. If there is a health care power of attorney (POA), any and all decisions regarding the patient can be made by the appointee once the patient is unable to make decisions on his or her own. In the absence of a POA, a health care representative should be identified. Each state differs in the defined hierarchy to be followed in identifying the health care representative. The decisions that can be made by the health care representative are more restricted than those of a POA, and regulations vary from state to state. Ultimately, clear communication with all participants involved in the care of the patient is needed for optimal care decisions.

TABLE 46. Vasopressor Agents and Their Physiologic Effects

Agent (Dose)	Receptors	Clinical Use	Common Side Effects or Contraindications
Norepinephrine	$\alpha_1 > \beta_1$	First-line in septic shock, other refractory shock	Some arrhythmias, digital ischemia
Dopamine (low)	DA > β_1	Historically used for kidney failure, but no evidence of effectiveness for this indication	Arrhythmias, ischemia
Dopamine (medium)	$\beta_1 > \beta_2$	Septic or cardiogenic shock	Arrhythmias, ischemia
Dopamine (high)	$\alpha_1 > \beta_1$	First-line for septic shock, other refractory shock	Arrhythmias, ischemia
Epinephrine (low)	$\beta_1 > \beta_2$	Second-line for septic or cardiogenic shock	Arrhythmias, ischemia
Epinephrine (high)	$\alpha_1 = \beta_1$	Second-line for septic shock, other refractory shock	Arrhythmias, ischemia
Phenylephrine	α_1	Milder shock states, least risky through peripheral IV line	Lowest arrhythmia risk, not as powerful as other vasopressors
Vasopressin	Vasopressin receptors	Second vasopressor for septic shock only, add to catecholamine vasopressor	Splanchnic, mesenteric, and digital ischemia

α_1 = α_1 adrenergic receptor; β_1 = β_1 adrenergic receptor; β_2 = β_2 adrenergic receptor; DA = dopaminergic receptor; IV = intravenous.

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TABLE 47. Types of Central Access

Type	Indications	Duration	Potential Complications	Contraindications
Peripheral IV central catheter	Delivery of potentially caustic medications such as vasoactive agents, sedatives or antibiotics; central venous access	Few days up to 1 year	Low risk overall, avoiding pneumothorax and fewer infections; clot formation or occlusion due to smaller vessel diameter	Current or pending dialysis; not for rapid infusion of blood products
Temporary nontunneled central venous access	Same as above; short-term dialysis; central venous pressure monitoring	Usually not more than 6 weeks	Infection; site-specific complications such as pneumothorax for subclavian or low intrajugular approach	Not for rapid infusion of blood products owing to small diameter of catheter
Long-term tunneled central venous access (valved tip and nonvalved tip)	Long-term TPN; chemotherapy; long-term antibiotic; dialysis	More than 6 weeks	Infection; valves prevent back bleeding but have an increased risk of catheter malfunction	Not for rapid infusion of blood products owing to small diameter of catheter
Ports or totally implanted central venous access	Long-term intermittent access such as chemotherapy	More than 6 weeks	Lowest risk of infection but more difficult to implant with more costs; hidden extravasation beneath skin	Not for rapid infusion of blood products owing to small diameter of catheter
Intraosseous (tibia or humeral head [adults])	When IV access otherwise not obtained and need for emergency fluids and/or medications	About 24 hours	Low risk of infection; flow rates may be slower; if pain with infusion can use 2% preservative-free lidocaine injected slowly to control it	Do not place in a bone with a fracture or recent (24-48 h) intraosseous access attempt

IV = intravenous; TPN = total parenteral nutrition.

Sedation and Sedation Interruption

CONT.

Pain, agitation, and delirium are interrelated, and current recommendations suggest a comprehensive view of all three for critically ill patients. For a discussion of delirium, see MKSAP 17 Neurology. Light sedation (defined as a drowsy or calm and cooperative patient), rather than deep sedation (where the patient is barely awake or unarousable) is recommended unless contraindicated (severe ARDS, ventilator dyssynchrony). Either daily sedation interruption or light sedation targeted titration should be used routinely in mechanically ventilated adult patients in the ICU. Using a lighter sedation goal reduces ICU-related posttraumatic stress disorder, time on the ventilator, and mortality.

Strategies using nonbenzodiazepine-based sedatives are preferred owing to the increased ICU delirium associated with benzodiazepine use. Analgesia-based sedation is an alternative method to benzodiazepine-based sedation that does not result in an increase in days on the ventilator or in the ICU. Opioids are considered the drug class of choice for treatment of nonneuropathic pain in critically ill patients, including mechanically ventilated adult patients in the ICU. An opioid analgesic should be given as an interrupted infusion.

KEY POINT

HVC

- When compared with deep sedation, light sedation (a drowsy and cooperative patient) reduces ICU-related posttraumatic stress disorder, time on the ventilator, and mortality.

Early Mobilization

Early mobilization strategies range from simple range of motion of extremities to standing and walking. Mobilization is recommended within 48 hours of admission to the ICU and improves physical function of ICU survivors. Early mobilization, along with careful attention to pain, agitation, and delirium management, has been shown to reduce ICU and hospital length of stay, shorten return to independent functional status, and improve survival.

KEY POINT

- Mobilization within 48 hours of admission, along with careful attention to pain, agitation, and delirium management, reduces ICU and hospital length of stay, shortens return to independence, and improves survival.

ICU-Acquired Weakness

ICU-acquired weakness includes critical illness polyneuropathy (with axonal nerve degeneration) and critical illness myopathy (with muscle myosin loss), resulting in profound weakness. The pathophysiologic mechanisms are postulated to be multifactorial; they include dysfunctional microcirculation that leads to neuronal and axonal injury, inactivation of sodium channels, myonecrosis secondary to the catabolic state, acute muscle wasting of critical illness, and mitochondrial dysfunction of skeletal muscles. ICU-acquired weakness is associated with long-term functional disability, prolonged ventilation, and in-hospital mortality. Cited risk factors include hyperglycemia, sepsis, multiple organ dysfunction, and systemic inflammatory response. Exposure to glucocorticoids and neuromuscular blocking agents was not found to be consistently associated with ICU-acquired weakness; however, limited use is recommended if these medications are required in the care of critically ill patients.

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Long-Term Cognitive Impairment

Long-term cognitive impairment is now recognized in patients recovering from critical illness. Delirium is frequently seen in patients in the ICU, and longer durations of delirium are associated with worse executive function and global cognition at 3 and 12 months. A strong association is also noted with ICU hypoxemia when cognition is assessed at 1 year. Hypoglycemic periods have also been associated with mood disorders after discharge. These findings have raised interest in understanding longer-term outcomes in patients in the ICU, and they are considered part of the postintensive care syndrome.

Postintensive Care Syndrome

Postintensive care syndrome is a term used to describe new or worsening physical, cognitive, or mental health problems arising after a critical illness that persist beyond the initial hospital discharge. This term can be applied to either the patient or family member, as both report a wide range of impairment after hospital discharge. There is a paucity of data available to provide direction on the most effective interventions for the patient and family. The use of ICU diaries and clear communication by the ICU team with the family appear to have a beneficial effect on the family.

KEY POINT

- ICU-acquired weakness (polyneuropathy and myopathy) is associated with long-term functional disability, prolonged ventilation, and in-hospital mortality; risk factors include hyperglycemia, sepsis, multiple organ dysfunction, and systemic inflammatory response.

Nutrition

Nutrition is an essential part of management for patients in the ICU and can be given enterally or parenterally, with the enteral route preferred. Initiation of enteral nutrition is recommended at 24 to 48 hours following admission if the patient is hemodynamically stable, with advancement to goal by 48 to 72 hours. The presence of abdominal distention, decreased passage of stool or flatus, or vomiting indicates that the patient may have gut ischemia or another gastrointestinal problem, and tube feeds should be discontinued or slowed. Studies examining gastric residual volumes suggest that volumes of 200 to 500 mL are safe; however, increasing residual volumes may signal a need to hold or reduce the feeding volume. The caloric goals of nutrition should be clearly identified and determined by the energy requirement of the patient. The energy requirement can be calculated by any of a number of predictive equations or more accurately by indirect calorimetry, although this may not be widely available. The simple formula of 25 to 35 kcal/kg/d, based on actual body weight, can also be used to estimate caloric need in patients in the ICU (or approximately 30 mL/kg/d of a 1 kcal/mL formula). If less volume is needed, more concentrated formulas can be used. Medications such as propofol add fat calories and should be considered in the calculation of total calories. Providing enteral calories and protein close to goals improves outcomes. For patients who cannot tolerate enteral feeding, parenteral nutrition in the form of total parenteral nutrition should not be started before day 7 of an acute illness; studies show that late feeding (after 7 days) is associated with faster recovery and fewer complications as compared with early feeding (within 48 hours).

KEY POINT

- Initiation of enteral nutrition is recommended at 24 to 48 hours following ICU admission if the patient is hemodynamically stable, with advancement to goal by 48 to 72 hours.

ICU Care Bundles

ICU care bundles are a set of treatment goals that, when grouped together, should promote optimal outcomes for a patient in the ICU. The Institute for Healthcare Improvement supports the use of bundles to ensure the minimal standard of care for each patient. Unfortunately, not all care bundles consist of the same components, and the effectiveness of all aspects of the bundle and the overall benefits of bundles in ICU care have not yet been established.

High-Value Care in the ICU

The cost of care in the ICU is often extremely high. Despite the level of severity of illness in the ICU, providing high-value care should remain a primary consideration in managing patients in this setting. Several critical care organizations have joined with the American Board of Internal Medicine Foundation to provide five tests or procedures whose necessity should be questioned or discussed. The five selected for patients in the ICU are listed in Table 48.

Common ICU Conditions

Upper Airway Emergencies

Delayed recognition and management of severe upper airway obstruction is often catastrophic given the difficulty of

TABLE 48. ICU Choosing Wisely Top Five

Don't order diagnostic tests at regular intervals (such as every day), but rather in response to specific clinical questions.
Don't transfuse erythrocytes in hemodynamically stable, nonbleeding patients in the ICU who have a hemoglobin concentration greater than 7 g/dL (70 g/L).
Don't use parenteral nutrition in adequately nourished critically ill patients within the first 7 days of an ICU stay.
Don't deeply sedate mechanically ventilated patients without a specific indication and without daily attempts to lighten sedation.
Don't continue life support for patients at high risk for death or severely impaired functional recovery without offering patients and their families the alternative of care focused entirely on comfort.

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endotracheal intubation in this setting and the risks associated with emergent surgical cricothyrotomy. Maintaining a low threshold to secure a safe airway with early intubation, as well as close respiratory monitoring of at-risk patients not undergoing immediate intubation, is vital. The presence of drooling, stridor, and voice change helps identify patients with significant airway compromise. Endoscopic visualization of the upper airway is helpful for identifying the cause, severity, and progression over time. Epiglottitis is an important infectious cause of obstruction and is associated with sore throat and odynophagia in nearly all patients. The diagnosis is confirmed by direct visualization of the epiglottis or by the presence of epiglottal edema on lateral neck radiographs. Abscesses in the peritonsillar, retropharyngeal, and parapharyngeal space, as well as Ludwig angina (bilateral infection of the submandibular space), can present with similar symptoms and cause life-threatening upper airway obstruction. In addition to ensuring airway patency, treatment consists of antibiotics along with surgical drainage of abscesses when present. Noninfectious causes of upper airway obstruction include trauma, foreign body, external compression from tumor or thyroid disease, inhalational injuries (see Acute Inhalational Injuries), and angioedema (see Anaphylaxis).

Shock

Shock is defined as a general deficiency in vascular perfusion, leading to tissue ischemia and dysfunction. The term shock is generic and denotes a condition that can arise from a wide range of causes and manifest in a variety of ways clinically, depending on the duration and severity of ischemia and the sensitivity to hypoxia of affected organs. Signs of shock relate to hypoperfusion, such as low blood pressure and prolonged capillary refill time, and other signs and symptoms relate to organ dysfunction due to oxygen deprivation (**Table 49**).

Blood pressure measurements and responses may be variable in shock. Not all hypotension is shock, and not all shock states may present initially with hypotension. The blood pressure of a patient in shock may be within normal parameters, but it may be relatively low compared with baseline pressure for that individual. Such a situation will sometimes lead to organ dysfunction, in which case the organ-specific manifestations may be the key to early diagnosis of the shock state. Nonetheless, blood pressure and its physiologic components are essential to understanding and managing shock (**Figure 21**).

Shock can be classified into three basic types depending on the principal reason for decreased tissue perfusion. Hypovolemic shock is due to inadequate perfusion in the setting of decreased blood volume (for example, from hemorrhage or dehydration). Cardiogenic shock refers to poor perfusion from decreased cardiac function, such as from an exacerbation of heart failure or from acute heart failure following a coronary event. Distributive shock results from a loss of vascular tone, as in sepsis or anaphylaxis, leading to redistribution of the blood volume and poor circulation. Obstructive shock is a subset of cardiogenic shock in which there is mechanical blockage in the central circulation, as can occur with massive pulmonary embolism or tension pneumothorax.

The basic goals of management in shock, regardless of type, are to restore perfusion as quickly as possible and to reverse the disease process leading to the shock state. Understanding which type of shock a patient has is critically important, as interventions may differ dramatically for one type versus another. The mainstays of shock treatment include fluid administration, vasopressors (see Blood Pressure Support), inotropes, and blood transfusion. Each of these therapies may have a role in any kind of shock, but they should be used carefully in each specific patient to avoid creating

TABLE 49. Signs and Symptoms of Shock

Evidence of Hypoperfusion	Evidence of Organ Dysfunction
Low blood pressure	Lightheadedness
SBP <90 mm Hg	Altered mental status
MAP <65 mm Hg	Diaphoresis
Decrease in SBP >40 mm Hg	Decreased urine output
Lack of BP response to fluid bolus	Increased serum creatinine level
Prolonged capillary refill time	Chest pain or other ischemic pain

BP = blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure.

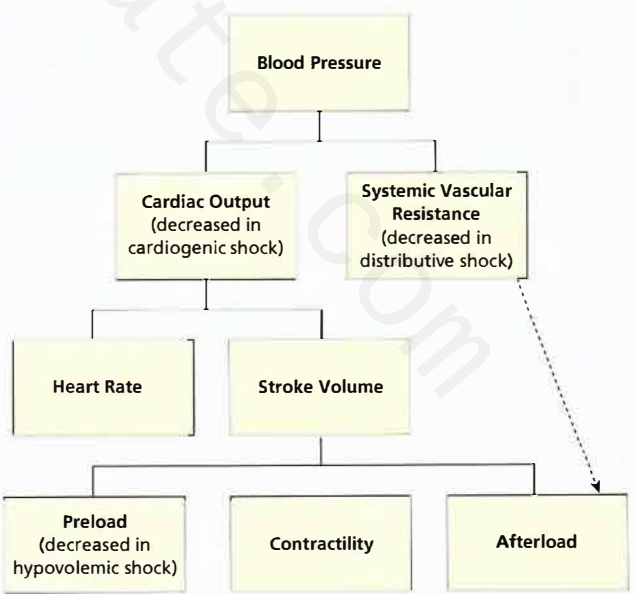

FIGURE 21. Key hemodynamic parameters of shock.

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CONT. iatrogenic harm. Although these measures mitigate the effects of poor perfusion in a patient experiencing shock, diagnosing and reversing the underlying cause of shock is just as important and may involve a variety of interventions specific to the situation (**Table 50**).

KEY POINTS

- Shock is classified into three types: (1) hypovolemic (due to inadequate perfusion in the setting of decreased blood volume), (2) cardiogenic (due to poor perfusion from decreased cardiac function), and (3) distributive (due to loss of vascular tone).
- The basic goals of management in shock, regardless of its type, are to restore perfusion as quickly as possible and to reverse the disease process leading to the shock state.
- The mainstays of shock treatment include fluid administration, vasopressors, inotropes, and blood transfusion; however, diagnosing and reversing the underlying cause of shock is as important as restoring perfusion.

Hypoxemic Respiratory Failure

Hypoxemic respiratory failure is one of the major types of respiratory insufficiency and results from a disease process leading to inadequate oxygenation of arterial blood. Severe hypoxemia is generally defined as an arterial Po_2 of 60 mm Hg (8.0 kPa) or less or an oxygen saturation of 89% or less while breathing ambient air, and/or an arterial Po_2/Fio_2 ratio of 200 mm Hg (26.6 kPa) or less. When hypoxia does not immediately respond to supplemental oxygen, there is risk of ischemic organ damage, and aggressive measures to improve oxygenation of the blood and the organs it perfuses may be needed.

The most common causes of hypoxemic respiratory failure are conditions that lead to mismatch of the ventilation (V) by inspired air in the alveoli and perfusion (Q) of adjacent alveolar capillaries by blood with the capacity to carry and circulate the oxygen to body tissues (called V/Q mismatch, in which the ratio of V to Q may be "high" if the unbalance is toward more ventilation than perfusion, or "low" if unbalanced toward more perfusion and less ventilation). Conditions such as pulmonary embolism lead to high V/Q mismatch, where ventilation is normal and perfusion is impaired in the lungs. More common are low V/Q conditions (also called intrapulmonary shunt) such as pneumonia or atelectasis, in which blood flows through capillaries adjacent to alveoli that are not ventilated, so the blood does not pick up any oxygen. Hypoxia due to low V/Q (shunt) will not improve with supplemental oxygen because inspired gas does not interface with the shunted blood in the lungs. In contrast, high V/Q is generally more responsive to oxygen therapy.

KEY POINTS

- Hypoxemic respiratory failure is usually characterized by an arterial Po_2 of 60 mm Hg (8.0 kPa) or less or an oxygen saturation of 89% or less while breathing ambient air, and/or an arterial Po_2/Fio_2 ratio of 200 mm Hg (26.6 kPa) or less.
- Hypoxemic respiratory failure is commonly caused by low ventilation-perfusion (V/Q) mismatch conditions (also called intrapulmonary shunt), in which blood flows through capillaries adjacent to alveoli that are not ventilated.

Acute Respiratory Distress Syndrome

ARDS is a clinical syndrome that can result from a variety of insults to the lungs, leading to alveolar and interstitial inflammation and edema, with a complex milieu of inflammatory cells and protein. There is heterogeneous but often widespread damage to the alveolar epithelium and vascular endothelium, as well as surfactant dysfunction leading to alveolar instability and collapse. The pathologic description of this process is diffuse alveolar damage (**Figure 22**). All of these features worsen gas exchange, and the result can be profound hypoxia due to

TABLE 50. Characteristics of the Types of Shock

Type of Shock	Pathophysiology	Measures to Restore Perfusion	Measures to Reverse the Cause of Shock
Hypovolemic shock	Decreased effective circulating volume diminishes preload and the heart is unable to maintain adequate output	IV fluids Blood transfusion	Control sites of bleeding Control other fluid loss (e.g., diarrhea)
Cardiogenic shock	Cardiac function is impaired, either because of damage or disease to the heart muscle, arrhythmia, or obstruction of the central circulation or heart valves	IV fluids or diuresis to optimize preload Inotropic medications Maintenance of an appropriate heart rate	Coronary revascularization Thrombolysis Treatment of underlying rhythm disturbance Relief of obstruction
Distributive shock	Loss of vascular tone leads to pooling of blood in capacitance spaces, decreasing the circulating volume	IV fluids Vasopressors	Antibiotics Control of infectious source

IV = intravenous.

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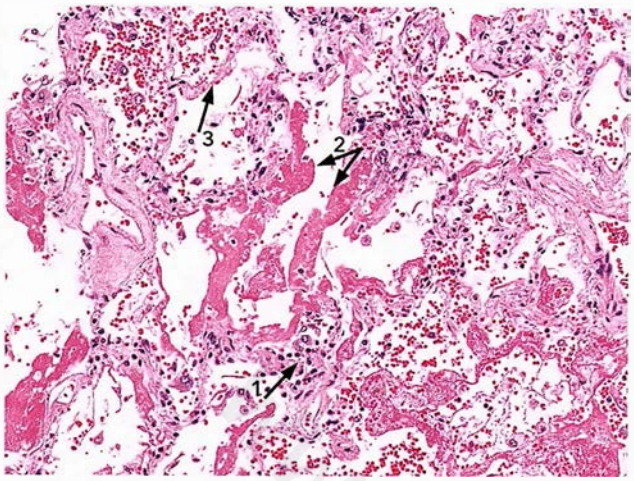

FIGURE 22. Diffuse alveolar damage. 1 = interstitial edema (thickened cellular space between airspace and vasculature); 2 = hyaline membranes (proteinaceous alveolar exudates that accumulate along the alveolar surfaces and impair gas exchange); 3 = denuded epithelium (usually numerous type 1 alveolar cells have undergone apoptosis and been replaced by hyaline membrane or fibrosis).

CONT.

low V/Q mismatch. The changes can severely reduce lung compliance, making adequate ventilation difficult and further worsening hypoxia. Pulmonary artery pressure is also increased, which can worsen oxygen delivery by decreasing overall cardiac output.

ARDS is diagnosed when the following Berlin definition criteria are met:

- Presentation within 1 week of known insult, or with worsening respiratory symptoms
- Pao_2/Fio_2 ≤300 mm Hg (40.0 kPa) with PEEP ≥5 cm H_2O
- Bilateral otherwise unexplained opacities seen on frontal chest imaging

In 2012, the classification scheme for ARDS was modified to include three severity levels based on oxygenation:

- Mild: Pao_2/Fio_2 ≤300 mm Hg (40.0 kPa) but >200 mm Hg (26.6 kPa)
- Moderate: Pao_2/Fio_2 ≤200 mm Hg (26.6 kPa) but >100 mm Hg (13.3 kPa)
- Severe: Pao_2/Fio_2 ≤100 mm Hg (13.3 kPa)

In addition, the term acute lung injury for milder cases of ARDS was eliminated, and pulmonary artery occlusion pressure was no longer included as part of the diagnostic criteria.

ARDS may be caused by a wide variety of diseases, conditions, or insults, some of which lead to direct injury to the lung and some of which cause indirect injury. Pulmonary causes include pneumonia, aspiration, inhalational injury, near drowning, and drugs. Nonpulmonary causes include sepsis, pancreatitis, and transfusion reactions. In some cases, different causes are associated with different prognoses for recovery; however, after treatment for the underlying cause, the management of all forms of ARDS is the same. Importantly, some cases of ARDS may be caused or made worse by mechanical ventilation, especially if lung-protective strategies are not used.

Ventilatory Management

Ventilator management (see Invasive Mechanical Ventilation) is required for most patients with ARDS; however, mechanical ventilation has the potential to cause and/or worsen the condition. When this happens, it is known as ventilator-induced lung injury (VILI) and is especially likely if the mode or settings lead to overdistention of alveoli (volutrauma), repeated opening and closing of alveoli (atelectrauma), or release of inflammatory mediators in the lung or systemic circulation (biotrauma). Even patients who had no evidence of lung injury at the time of intubation can develop ARDS quickly if the ventilator settings are injurious. Those whose lungs are already injured or who have risk factors for developing injury are even more likely to have damage from VILI.

Because of this, lung-protective ventilator strategies have been developed and have led to improved outcomes for patients with ARDS. These parameters generally include limiting the tidal volume given in mechanical ventilation to 6 mL/kg of ideal body weight, limiting the plateau pressure in the respiratory cycle to no more than 30 cm H_2O, and use of adequate PEEP to prevent the collapse of unstable alveolar units in the expiratory phase of the cycle. There is evidence that even lower tidal volumes may be better for the lungs and that higher levels of PEEP than those previously recommended may be more protective. Current recommendations are to use a PEEP level that achieves adequate oxygenation with an Fio_2 of less than 0.6 and does not cause hypotension. With emphasis on minimizing the mechanical stress to injured lung tissue, the currently recommended approach is to limit volume and pressure as much as patients can tolerate, even allowing blood levels of CO_2 to rise somewhat in exchange for more protective volumes and pressures; this is known as permissive hypercapnia. In the absence of evidence-based guidelines, a pH of 7.25 or even lower may be acceptable in order to ventilate the lungs as gently as possible.

KEY POINT

- Patients with acute respiratory distress syndrome should be ventilated using lung-protective ventilator strategies, which consist of limiting the tidal volume to 6 mL/kg of ideal body weight, limiting the plateau pressure to no more than 30 cm H_2O, and using adequate positive end-expiratory pressure to prevent the collapse of unstable alveolar units in the expiratory phase.

Nonventilatory Management

Decades of research on potential treatments for ARDS have produced no approved pharmacologic therapies, although some molecular targets are still under investigation and may lead to effective interventions. Some controversy still exists regarding the use of glucocorticoids, but trial results have been

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inconsistent and mostly negative, and published guidelines do not recommend them for use in ARDS.

Although there is some evidence that neuromuscular blockade may be helpful in decreasing mortality associated with ARDS, it is not an established therapy in treating ARDS.

Conservative fluid management has been shown to affect clinical outcomes in ARDS; the goal is to keep the lungs as dry as possible during the period of injury and susceptibility to additional damage. Limiting intravenous fluids and using diuretics to keep central venous pressures at lower targets has been associated with a more rapid improvement in lung function, shorter duration of mechanical ventilation, and shorter ICU length of stay, but no effect on mortality.

Studies of other adjunct therapies such as inhaled vasodilators (nitric oxide or prostacyclin) and glucocorticoids have generally shown improved oxygenation but no survival benefit.

In 2013 a randomized controlled trial of prone positioning showed an impressive mortality benefit for patients placed in the prone position for 16 hours per day until their oxygenation improved to an arterial Po_2/Fio_2 ratio of at least 150 mm Hg (20.0 kPa). Based on this evidence, prone positioning is recommended for all patients with severe ARDS for whom the risk/benefit ratio of such positioning is low. Some patients cannot be placed prone owing to their weight or other comorbid conditions. The process of placing critically ill patients prone may be technically challenging; it can be done manually or in specialized beds that rotate the patient between the prone and supine positions.

In patients with refractory hypoxemia, extracorporeal membrane oxygenation (ECMO) is a rescue therapy that can be considered to improve oxygenation while the lungs heal. The ability to oxygenate selected patients with this technology has improved markedly, but still only a relatively small number of patients with ARDS are candidates for ECMO (usually those with no other organ systems in failure and a reasonably good prognosis for lung recovery with time and treatment). Additionally, only a few large medical centers offer ECMO. If this therapy is to be considered, patients should be transferred to such a center as early as possible in their illness.

KEY POINTS

- Patients with acute respiratory distress syndrome should receive conservative fluid management, which consists of limited intravenous boluses and using diuretics to keep central venous pressures at lower targets.
- Prone positioning may result in a mortality benefit for selected patients with acute respiratory distress syndrome on mechanical ventilation.

Heart Failure

Heart failure is a common cause of hypoxemic respiratory failure. Unlike in ARDS, in which the edema is part of a complex process with tissue damage, inflammatory cells, and other changes, pulmonary edema from heart failure is usually transudative fluid in the pulmonary interstitium and alveolar spaces. Fluid can accumulate in the lungs as a result of acute or chronic impairment of either systolic or diastolic heart function. It can interfere with gas exchange dramatically, but it usually improves with noninvasive positive airway pressure ventilation and diuresis. Cardiogenic pulmonary edema can appear identical to ARDS on imaging, so diagnostic measures to distinguish the two entities are essential and should be considered in a timely fashion; these measures include clinical presentation, electrocardiography, echocardiography, and measurement of biomarkers for cardiac ischemia or strain (troponin, creatine kinase, B-type natriuretic peptide).

KEY POINT

- Heart failure can cause pulmonary edema and interfere with gas exchange; however, it usually improves with noninvasive positive airway pressure ventilation and diuresis.

Atelectasis

Atelectasis is collapse of alveolar units, leading to low V/Q, or shunt, physiology. It occurs in ARDS owing to the disruption of surfactant but can occur in less severely injured or even normal lungs without the loss of surfactant function. It is common after anesthesia and in situations where patients cannot or do not take full breaths owing to inactivity, pain, sedation, chest wall abnormalities (including obesity), chest trauma, or muscle weakness. In ventilated patients, atelectasis commonly occurs when patients are receiving low tidal volume ventilation or have airway obstructions such as mucus plugging or a misplaced endotracheal tube. Atelectasis is treated with chest physiotherapy, incentive spirometry, ambulation (including early mobilization after surgery), and sometimes positive airway pressure, such as PEEP on a ventilator or noninvasive CPAP.

KEY POINT

- Atelectasis is treated with chest physiotherapy, incentive spirometry, ambulation (including early mobilization after surgery), and sometimes positive airway pressure.

Pneumonia

Pneumonia is infection filling the alveolar space, and it often causes consolidation on lung imaging studies. Because infected alveoli are not aerated, this creates shunt, which can lead to hypoxemia if widespread. Pneumonia is also a common cause of ARDS. The two processes may coexist and can be difficult to differentiate from each other. When pneumonia or any other alveolar filling process in the lung is heterogeneous, the affected areas can be difficult to recruit using PEEP, since added pressure will expand the unaffected, more compliant areas of the lungs much more easily and can lead to injury (volutrauma) to these healthier segments before the diseased segments improve.

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Hypercapnic (Ventilatory) Respiratory Failure

Hypercapnic, or ventilatory, respiratory failure occurs when alveolar ventilation is inadequate to clear the CO_2 produced by cellular metabolism, and the level of CO_2 increases in the blood. The imbalance can be due to increased CO_2 production associated with an increased metabolic rate or due to decreased alveolar ventilation. Unlike hypoxemic respiratory failure, ventilatory failure is not usually due to gas exchange abnormalities, since CO_2 is more soluble than oxygen and therefore diffuses more readily between the alveolar air space and pulmonary capillary blood. Because oxygenation also depends on ventilation of the alveoli with fresh inspired gas, patients in ventilatory failure are often hypoxic as well. However, these patients' hypoxia will improve with supplemental oxygen more readily than those with V/Q mismatch.

Decreased alveolar ventilation is caused by one or more of three abnormalities: (1) decreased respiratory drive; (2) restrictive defects of the lung, chest wall, or respiratory muscles; or (3) conditions that increase dead space in the lungs so that much of the inspired air does not reach areas of gas exchange with the blood.

Decreased Respiratory Drive

Decreased respiratory drive is most often due to sedative and analgesic drugs that suppress the respiratory center in the brainstem. Overdoses of both medicinal and recreational agents can be lethal by this mechanism. Opiates are especially potent inhibitors of respiratory drive, but benzodiazepines, barbiturates, and any other sedating medication can have the same effect if taken in sufficient doses (see Toxicology, Toxicity of Drugs of Abuse). Strokes do not usually suppress respiratory drive unless they increase intracranial pressure, which can lead to brainstem herniation. Metabolic conditions such as hypoglycemia and hypothyroidism can also sometimes suppress respiratory drive. Whenever respiratory drive is impaired, the respiration rate is decreased, often with decreased tidal volume as well. Interventions include ventilatory support and reversal of effects of any known or suspected suppressive agents.

KEY POINT

- In patients with hypercapnic respiratory failure due to decreased respiratory drive, interventions consist of ventilatory support and reversal of effects of any known or suspected suppressive agents.

Restrictive Lung Disease

Restrictive ventilatory defects are defined by a decrease in the total lung capacity or the vital capacity. Such limitation may be seen in three types of disease: (1) parenchymal lung disease, in which fibrotic or infiltrated lung tissue loses its mechanical compliance; (2) extrapulmonary restriction due to chest wall disease, in which the spine, ribs, or other thoracic structures limit lung expansion; and (3) neuromuscular weakness, in which the lungs can be passively expanded to normal volume but the patient's ability to take a full breath is limited by weakness of the respiratory muscles.

Diffuse Parenchymal Lung Disease

Diffuse parenchymal lung disease is discussed in the Diffuse Parenchymal Lung Disease chapter. It may be distinguished from the other two types of restrictive disease by the presence of fibrotic changes on high-resolution CT, reduced lung volumes, and a reduction in the diffusing capacity of the lungs, which is usually normal in chest wall disease and muscular weakness. Because of the diffusion abnormality, hypoxia is often more severe than hypercapnia in these patients, but they may develop ventilatory failure, especially in the setting of an exacerbation or other superimposed acute process such as infection or aspiration.

Extrapulmonary Restriction

Extrapulmonary restriction may be caused by deformities or diseases of the chest wall, spine, or abdomen. These conditions increase the work of breathing by placing the respiratory muscles at a mechanical disadvantage or by physically limiting the extent to which the lungs can expand with inhalation. In the ICU setting, chronic conditions of this type are usually only significant when combined with another acute condition that impairs breathing. Positive-pressure ventilation, either invasive or noninvasive, can be helpful in supporting patients through the acute condition that led to ventilatory failure. When extrapulmonary restriction is severe, patients have very limited ventilatory reserve, and they may go into respiratory failure frequently and after minimal provocation.

KEY POINT

- Hypercapnic respiratory failure due to extrapulmonary restriction may be caused by deformities or diseases of the chest wall, spine, or abdomen, which increase the work of breathing.

Neuromuscular Weakness

Neuromuscular weakness is a special case of extrapulmonary restriction, in which the lungs are usually normal, capable of normal gas exchange and expansion, but are limited by the patient's inability to fill them without assistance during inspiration. In patients with generalized weakness syndromes, pulmonary function tests show restriction on spirometry and lung volume measurement but normal diffusing capacity. Symptoms of dyspnea and especially orthopnea are common because the supine position impairs accessory respiratory muscles and leaves the weakened diaphragm with most of the work of breathing. Signs on physical examination may include paradoxical inward motion of the abdomen with inspiration and other signs of accessory muscle use for breathing. Some neuromuscular weakness syndromes (for example, amyotrophic lateral sclerosis) also affect bulbar function, resulting in slurred speech, trouble swallowing liquids, choking, and coughing. It is often complications from these related

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difficulties that result in acute respiratory failure and ICU admission for these patients. Aspiration pneumonia is common and poorly tolerated.

Patients with spinal cord injury may have respiratory muscle weakness as a result of their injury. The phrenic nerves originate from cervical spinal roots C3, C4, and C5. Patients with complete injury above the level of C3 will require lifelong mechanical ventilation assistance. Other patients with incomplete or lower injury may recover some function with time. Injuries below C5 will not directly impair muscles of inspiration but may impair forceful expiration and cough, making secretion management difficult and increasing the risk of atelectasis and infection.

One of the challenges of caring for patients with neuromuscular weakness, especially those with progressive syndromes, is in knowing when to recommend mechanical ventilation and/or tracheostomy placement. Considerations include risk of aspiration and other complications, based on patients' respiratory muscle strength, but also on bulbar function and other impairments. Other factors affecting the quality of life include speech, mobility, and the ability to eat and drink. Patients with altered mental status, severe respiratory distress, or profound hypoxia or hypercapnia clearly need immediate ventilatory support. In patients with less dramatic presentation, pulmonary function testing and arterial blood gas analysis can help determine when ventilatory support is needed (**Table 51**). However, no single test can predict the ideal time to initiate ventilatory support for a given patient, so the decision should be made based on all available data, patient values and preferences, and clinical judgment. In patients requiring ventilator support, noninvasive positive pressure ventilation is the usual initial method used, typically on an intermittent, nocturnal basis.

KEY POINT

- In patients with generalized neuromuscular weakness syndromes, pulmonary function tests show restriction on spirometry and lung volume measurement but normal diffusing capacity.

Obstructive Lung Disease

Obstructive lung disease is defined by increased resistance to airflow, usually of small airways during expiration. This may be transient and reversible, as in asthma, or fixed, as in advanced COPD. Less commonly, obstruction may be caused by obstruction of the large airways due to tumors, abscesses, trauma, angioedema, or inhalational injury. Obstructive conditions can lead to ventilatory failure as the resistance to expiratory flow causes air trapping. This occurs when airway resistance to flow causes incomplete exhalation before the next breath is initiated by the mechanical ventilator. This "trapped" volume of air may be small with each breath, but it can build up over many breaths to a significant volume of unexpired air in the chest. This leads to elevated intrathoracic pressure, also called auto-PEEP or intrinsic PEEP, which hyperinflates the chest and reduces fresh gas entry into the alveoli. This converts normally functional alveolar units to dead space, which increases the work of breathing and decreases the effective alveolar ventilation, leading to a rise in CO_2. These patients may also be hypoxic but usually respond readily to supplemental oxygen. If hypoxia is profound or refractory to oxygen therapy, it is reasonable to consider another concurrent disease process.

KEY POINTS

- Obstructive lung disease can cause ventilatory failure as the resistance to expiratory flow causes air trapping, leading to elevated intrathoracic pressure known as auto-positive end-expiratory pressure (auto-PEEP) or intrinsic PEEP.
- Patients with ventilatory failure from obstructive lung disease may be hypoxic but usually respond readily to supplemental oxygen; if hypoxia is profound or refractory to oxygen therapy, alternative diagnoses should be considered.

Critical Care Management of Severe Asthma Exacerbation

Patients with severe asthma exacerbation may present with tachypnea, inability to speak in full sentences, accessory respiratory muscle use, and diminished air entry with pulsus paradoxus due to hyperinflation; however, not all patients presenting with serious exacerbation initially appear ill. Arterial blood gas analysis often shows hypocapnia, but a normal or mildly elevated CO_2 level can be a sign of respiratory

TABLE 51. Signs of Respiratory Failure in Patients with Neuromuscular Weakness

Test	Findings Indicating Respiratory Failure	Comments
Vital capacity	<50% of predicted	Lower values predict higher risk of respiratory failure
Maximal inspiratory pressure	−60 cm H_2O	If less negative, indicates diaphragm weakness and inadequate accessory muscle compensation leading to high risk of respiratory failure; this is the qualifying threshold for noninvasive ventilation
Maximal expiratory pressure	+40 cm H_2O	If less positive, indicates inadequate expiratory muscles, including abdominal muscles; may lead to impaired cough and secretion management
Arterial P_{CO_2}	>45 mm Hg (6.0 kPa)	Most useful in initial assessment, less useful for following trends toward needing mechanical ventilation

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muscle fatigue and impending failure. FEV_1 or peak expiratory flow (PEF) may be measured if the patient can tolerate the maneuvers. If the FEV_1 and PEF do not increase to above 40% of predicted in response to aggressive bronchodilator and glucocorticoid therapy, the patient should be admitted to the ICU for close monitoring and continued aggressive therapy. If the patient is unable to perform FEV_1 or PEF maneuvers or has altered mental status, increasing work of breathing, or agonal respiration, immediate intubation is usually indicated.

Patients with severe asthma requiring admission to the ICU can be among the most challenging to manage, even with invasive mechanical ventilation. The problems of air trapping or auto-PEEP may be even worse while ventilated compared with when the patient was breathing spontaneously. If auto-PEEP is not recognized, pressure within the chest can build, mimicking the physiology of tension pneumothorax, with diminished air entry as well as decreased venous return to the heart, resulting in cardiovascular instability. If this is observed in a patient with asthma on mechanical ventilation, the immediate response is to disconnect the ventilator circuit from the patient's endotracheal tube to allow for a prolonged exhalation to release auto-PEEP. The ventilator settings should then be adjusted to allow for more effective exhalation to avoid further air trapping. Slowing the respiration rate, decreasing the tidal volume, and increasing the inspiratory flow rate while tolerating respiratory acidosis are ways to increase the exhaled volume with each cycle.

Glucocorticoids and bronchodilators remain the mainstay of pharmacologic therapy. Empiric antibiotics are recommended only when suspicion for a specific infection is high. Various adjunctive therapies exist for very severe asthma and may contribute to effective ventilation and resolution of the exacerbation; however, most of these lack strong evidence to recommend their use. These include high-dose magnesium sulfate, helium-oxygen mixtures (heliox, often in a ratio of 80:20 or 60:40), sedation with ketamine, and general anesthesia.

KEY POINTS

- Arterial blood gas analysis often shows hypocapnia in patients with severe asthma exacerbation, but a normal or mildly elevated CO_2 level can be a sign of respiratory muscle fatigue and impending failure.
- If the FEV_1 and peak expiratory flow do not respond to aggressive bronchodilator and glucocorticoid therapy to above 40% of predicted, patients with severe asthma exacerbation should be admitted to the ICU for close monitoring and aggressive therapy.

Critical Care Management of COPD Exacerbation

Patients with severe COPD exacerbation present similarly to patients with asthma, with respiratory muscle fatigue from increased work of breathing. Their CO_2 levels are usually high, with a pH indicating an acute respiratory acidosis. If hypoxic, they should be given supplemental oxygen even if CO_2 is elevated at baseline. Some of these patients rely on arterial Po_2 for respiratory drive; in these individuals, a reasonable oxygen saturation goal is 90% to 92%. If patients display signs of respiratory failure, ventilatory support is needed; noninvasive support is often effective in this situation. If a trial of noninvasive ventilation with bilevel PAP is not effective in reducing the work of breathing or the patient develops significant hypercapnia (usually meaning a level of CO_2 higher than the patient's normal level, which is worsening or not improving with therapy), the patient should be intubated and mechanically ventilated. Patients with COPD exacerbation have the same risk for air trapping and auto-PEEP as patients with asthma; therefore, the same ventilatory strategies should be used to avoid these issues. Patients intubated for COPD are unique in that when their respiratory parameters are improved, they are often extubated directly to bilevel noninvasive PAP, which is not usually done for other intubated patients. The same pharmacologic strategies that are used in less severe COPD exacerbations, including glucocorticoids, bronchodilators, and empiric antibiotics, should be continued (see Airways Disease, Chronic Obstructive Pulmonary Disease).

KEY POINTS

- If patients with a COPD exacerbation display signs of respiratory failure, ventilatory support is needed; noninvasive support is often effective in this situation.
- If a trial of noninvasive ventilation is not effective to reduce the work of breathing in patients with COPD exacerbation, the patient should be intubated and mechanically ventilated.

Sepsis

Definition, Pathophysiology, and Clinical Presentation

Sepsis is an intense host inflammatory response to a known or suspected infection that causes systemic manifestations remote from the site of infection. The sepsis response causes generalized vasodilation, increased microvascular permeability, and widespread cellular injury that result in multiorgan dysfunction. Severe sepsis is defined as sepsis that causes inadequate organ perfusion or outright organ dysfunction, and the term septic shock refers to sepsis-related hypotension that persists despite fluid resuscitation. In addition to demonstrating evidence of infection, patients with these advanced forms of sepsis present with characteristic derangements in their vital signs, physical examination findings, and laboratory studies (**Table 52**).

Early recognition of sepsis is based on signs of developing end-organ failure. However, signs and symptoms in early sepsis may be subtle and nonspecific, and timely diagnosis can be confounded by baseline comorbidities (for example, dementia) and medications (for example, β-blockers). Therefore, evidence of organ dysfunction in suspected sepsis should be actively sought (for example, evaluation for mild cognitive impairment or low urine output) since delays in treatment of

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TABLE 52. Diagnostic Criteria for Sepsis[a]

Infection, documented or suspected, and some of the following:

General variables
Fever (>38.3 °C [100.9 °F]
Hypothermia (core temperature <36.0 °C [96.8 °F])
Heart rate >90/min or >2 SD above normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 h)
Hyperglycemia (plasma glucose >140 mg/dL [7.8 mmol/L]) in absence of diabetes
Inflammatory variables
Leukocytosis (leukocyte count >12,000/μL [12 × 10^9/L])
Leukopenia (leukocyte count <4000/μL [4 × 10^9/L])
Normal leukocyte count with >10% immature forms
Plasma C-reactive protein >2 SD above normal value
Plasma procalcitonin >2 SD above normal value
Hemodynamic variables
Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg, or SBP decrease >40 mm Hg in adults or <2 SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (Po_2/Fio_2 <300 mm Hg [39.9 kPa])
Acute oliguria (urine output <0.5 mL/kg/h for >2 h despite adequate fluid resuscitation)
Serum creatinine increase >0.5 mg/dL (44.2 μmol/L)
Coagulation abnormalities (INR >1.5 or aPTT >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000/μL [100 × 10^9/L])
Hyperbilirubinemia (plasma total bilirubin >4 mg/dL [68.4 μmol/L])
Tissue perfusion variables
Hyperlactatemia (>1 mEq/L [1 mmol/L])
Decreased capillary refill or mottling

aPTT = activated partial thromboplastin time; INR = international normalized ratio; MAP = mean arterial pressure; SBP = systolic blood pressure; SD = standard deviation.

[a]Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5 °C [101.3 °F] or <35.0 °C [95.0 °F]), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

Springer and Intensive Care Medicine, Volume 39, 2013, 165-228, 2012 Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock 2012, Dellinger RP, Levy MM, Rhodes A, et al, Table 1, with kind permission from Springer Science and Business Media.

CONT. early sepsis are associated with higher mortality. Unlike most shock states, early sepsis typically produces bounding pulses and warm rather than cool extremities. Measurement of plasma lactate may identify early sepsis in normotensive patients in need of aggressive fluid resuscitation despite having a normal blood pressure. H

KEY POINTS

- Early recognition of sepsis is based on signs of developing end-organ failure.
- Delays in treatment of early sepsis are associated with higher mortality.

Epidemiology

Not only is the annual incidence of sepsis increasing worldwide, but severe sepsis and septic shock account for a growing proportion of all cases. These more severe forms carry a 25% mortality risk. Absence of baseline comorbidities, urinary tract site of infection, community-acquired infection, early administration of appropriate antibiotics, and aggressive hemodynamic support predict lower mortality.

Management

Successful treatment of severe sepsis and septic shock depends on the rapid institution of hemodynamic support, empiric treatment of infection, and diagnostic studies. To that end, the following interventions should be performed concomitantly rather than sequentially.

KEY POINT

- Successful treatment of severe sepsis and septic shock depends on the rapid institution of hemodynamic support, empiric treatment of infection, and diagnostic studies.

Initial Resuscitation

H Morbidity and mortality in patients with sepsis are heavily influenced by the care delivered during the first several hours after sepsis onset. Multiple clinical trials have established the critical role of timely recognition of sepsis and early goal-directed therapy (EGDT), defined as aggressive management of specific clinical parameters to specified targets, in improving clinical outcomes. Once sepsis is recognized, EGDT interventions focus on adequate fluid resuscitation with intravenous fluid and vasopressors to support blood pressure and avoid organ hypoperfusion and multiorgan injury, as well as early treatment of infection.

Patients with severe sepsis and septic shock usually have clinically apparent evidence of end-organ injury due to hypoperfusion. Hypotension is often the most evident manifestation of hypoperfusion and has been defined as serial systolic blood pressure readings less than 90 mm Hg or mean arterial pressure less than 70 mm Hg. Lactic acidosis also supports organ injury due to hypoperfusion and is used to identify patients with severe sepsis and septic shock.

Crystalloid infusion (normal [0.9%] saline or lactated Ringer solution) to support circulating intravascular volume should be administered to all patients with severe sepsis and septic shock. Crystalloid is recommended at a volume of 30 mL/kg body weight, with most patients receiving between 2 to 4 L as the initial intervention to treat shock due to sepsis.

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Recent evidence has shown that chloride-rich fluids increase the risk of acute kidney injury in sepsis, and switching from normal saline to lower chloride alternatives such as lactated Ringer solution may reduce the risk of kidney failure in patients requiring large-volume resuscitation. Multiple trials indicate albumin and crystalloids are equally effective for fluid resuscitation in patients with sepsis, although albumin may be advantageous in the subset of patients with low oncotic pressure and persistently low intravascular filling pressures. Crystalloids are less expensive and considered first-line therapy. The synthetic colloid hydroxyethyl starch increases the risk of kidney failure in patients with sepsis and is not recommended.

The optimal targets to measure adequacy of resuscitation are not clear. A commonly used measure is central venous pressure (CVP) with a goal of 8 to 12 mm Hg. Although CVP does not consistently reflect volume status, a low CVP generally can be relied on as a marker of fluid responsiveness. Urine output of 0.5 mL/kg/h or greater is also indicative of adequate fluid resuscitation, but this marker may not be feasible in patients with acute kidney injury associated with hypoperfusion. Central venous oxygen saturation ($Scvo_2$) is used as an indicator of adequacy of oxygenation, reflecting the balance between oxygen delivery and consumption. A $Scvo_2$ greater than or equal to 70% has been recommended as a target for adequacy of resuscitation.

The current Surviving Sepsis Campaign guidelines recommend measurement of CVP and serial measurement of $Scvo_2$ to assess the adequacy of resuscitation, with failure to achieve the target $Scvo_2$ during the first 6 hours of resuscitation being an indication for initiation of inotropes and blood transfusion. However, several recent studies that did not use CVP or $Scvo_2$ monitoring to guide resuscitation had similar outcomes compared with patients managed with EGDT using these endpoints. Therefore, the utility of CVP and $Scvo_2$ monitoring compared with clinical judgment and other measures of fluid responsiveness is unclear, and further study of methods for assessing adequacy of resuscitation are ongoing.

Current Surviving Sepsis Campaign guidelines also recommend serial plasma lactate measurements to assess the adequacy of resuscitation. Among patients with elevated lactate levels, resuscitation is targeted to reduce levels by 10% to 20% over the first 6 hours. While aggressive fluid resuscitation is efficacious in the first several hours of sepsis management, judicious fluid administration is warranted thereafter, as intravascular volume overload can contribute to pulmonary edema and pleural effusions.

If hypotension does not rapidly correct with fluids, vasopressors should be titrated to maintain a mean arterial pressure of 65 mm Hg or greater. Norepinephrine is considered first-line therapy. Dopamine is known to cause tachyarrhythmia and should be reserved for selected patients with hypoperfusion and relative bradycardia. Vasopressin, epinephrine, and phenylephrine typically are added when norepinephrine alone is insufficient.

KEY POINT

- Early fluid resuscitation in sepsis warrants close monitoring and often entails serial measurements of blood pressure, central venous pressure, urine output, central venous oxygen saturation, serial plasma lactate measurements, and a variety of noninvasive assessments of fluid responsiveness.

Antibiotic Therapy

In septic shock, mortality increases with each hour that appropriate antibiotic therapy is delayed. Two sets of blood cultures should be obtained before antibiotic infusion, in addition to cultures from the suspected infection site. However, antibiotics should ideally be administered within 1 hour of diagnosis, even if full cultures have not been obtained. Empiric antimicrobial treatment should cover all suspected pathogens, with special attention to risk factors for resistant or opportunistic organisms, including methicillin-resistant *Staphylococcus aureus* and *Pseudomonas* species. The latter organisms merit empiric combination antibiotic therapy. Indications for empiric coverage of *Candida* species include recent antibiotic exposure, use of total parenteral nutrition, colonization in multiple sites, and impaired immune function. Allowable speed of administration, penetration into the infected site, drug-drug interactions, recent antibiotic exposure, local antiinfective resistance patterns, allergies, and comorbidities such as hepatic failure and acute kidney injury are important considerations in antimicrobial selection. De-escalation of empiric coverage should be considered daily depending on culture results and clinical course. Treatment should be narrowed to coverage of the causative organism alone if identified.

KEY POINT

- Broad, empiric antimicrobial coverage should be initiated within 1 hour of diagnosis of sepsis, even if obtaining cultures is incomplete.

Source Control

Identification and control of the source of infection are critical steps in managing sepsis; this ideally should be achieved within 12 hours using the highest yield and lowest risk diagnostic intervention available. Respiratory and skin sources of sepsis are usually readily identified by history, examination, and chest radiography. In contrast, the diagnosis of abdominal sepsis can be challenging, particularly in obtunded or sedated patients (see Acute Abdominal Surgical Emergencies). Antibiotics alone may be insufficient to control infection in a variety of scenarios, such as severe colitis, necrotizing fasciitis, and ascending cholangitis.

Adjunctive Therapies

Although hydrocortisone improves hypotension in septic shock, the bulk of evidence suggests no mortality reduction. Patients with persistent shock despite fluids and vasopressors may be an exception, and the current Surviving Sepsis

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Campaign guidelines recommend a daily total dose of 200 mg of intravenous hydrocortisone in this setting. Addition of a mineralocorticoid is unnecessary, and cortisol stimulation testing to identify patients with relative adrenal insufficiency is not recommended. However, stress-dose hydrocortisone is indicated for persistently hypotensive patients with baseline adrenal insufficiency, as well as in at-risk patients, such as those on chronic, low-dose systemic glucocorticoids.

Hyperglycemia is common in critically ill patients and is associated with increased morbidity and mortality. A study of intensive insulin therapy, which targeted plasma glucose levels between 80 and 110 mg/dL (4.4 and 6.1 mmol/L), found reduced mortality in postsurgical patients. However, in the subsequent landmark NICE-SUGAR trial, intensive insulin therapy resulted in higher mortality among patients in the medical and surgical ICU compared with maintaining plasma glucose levels between 144 and 180 mg/dL (8.0 and 10.0 mmol/L). The American College of Physicians guideline recommends that, following initial stabilization, patients with severe sepsis and hyperglycemia who are admitted to the ICU should receive insulin therapy to achieve a plasma glucose level between 140 and 200 mg/dL (7.8 and 11.1 mmol/L). Some guidelines use a threshold of two consecutive plasma glucose levels greater than 180 mg/dL (10.0 mmol/L) for initiating intravenous insulin.

Indications for invasive mechanical ventilation in patients with sepsis include hypoxemia, increased work of breathing, and encephalopathy with compromised airway protection. A lung-protective ventilator strategy that utilizes low tidal volumes is recommended when ARDS is present. The role of noninvasive ventilation in ARDS is limited, given a lack of efficacy in clinical trials and the high prevalence of concomitant encephalopathy.

Thrombocytopenia often complicates septic shock. In the absence of active bleeding, the Surviving Sepsis Campaign guidelines recommend a threshold of less than 10,000/μL (10×10^9/L) for platelet transfusion but a threshold of less than 20,000/μL (20×10^9/L) in the presence of risk factors, which include fever, recent minor hemorrhage, rapid decline in platelet count, and concomitant coagulation abnormalities. The 2012 American College of Chest Physicians guidelines on thrombosis prevention recommend mechanical, rather than pharmacologic, deep venous thrombosis prophylaxis in critically ill patients with platelet counts less than 50,000/μL (50×10^9/L).

Acute Inhalational Injuries

Smoke Inhalation

Smoke inhalation is the leading cause of fire-related deaths, with mortality and morbidity occurring through three distinct pathways: thermal injury to the upper airway, irritant-mediated injury to the tracheobronchial tree, and poisoning from carbon monoxide and hydrogen cyanide (see Carbon Monoxide Poisoning and Cyanide Poisoning). Ensuring upper airway patency is the first priority in patients with significant smoke exposure. Intense heat can cause edema and blistering from the mouth to the larynx; subglottic thermal injury is uncommon. Patients with a visibly damaged airway or stridor are at high risk of complete upper airway obstruction due to swelling and require immediate intubation. In less severe cases, fiberoptic laryngoscopy can identify laryngeal edema that may warrant prophylactic intubation. Patients who are not immediately intubated should be monitored closely, especially those requiring massive fluid resuscitation that may result in increased soft tissue edema surrounding the injured airway. Treatment is supportive but requires confirmation that upper airway patency has been restored before extubation. This typically entails assessing for the presence of a cuff leak when the endotracheal tube cuff is deflated, but direct endoscopic visualization of the vocal cords also may be helpful in ambiguous cases.

Patients with inhalational injury involving the lower airways typically present with a normal chest radiograph. Wheezing, cough, and dyspnea are early signs of tracheobronchial injury, generally manifesting 12 to 36 hours after exposure. Patients are at risk of subsequent airway necrosis, mucosal sloughing, bleeding, copious secretions, atelectasis, pneumonia, and ARDS. Fiberoptic bronchoscopy can reveal the extent of injury and facilitate clearance of airway debris and secretions. In patients requiring intubation owing to inhalational injury–associated ARDS, a low tidal volume strategy is appropriate. Bronchospasm is treated with bronchodilators. Limited data support the use of nebulized heparin and nebulized *N*-acetylcysteine to promote clearance of blood clots and secretions. Long-term respiratory outcomes are generally favorable among survivors.

KEY POINTS

- Ensuring upper airway patency is the first priority in patients with significant smoke inhalation.
- Patients with tracheobronchial injury are at risk of subsequent airway necrosis, mucosal sloughing, bleeding, copious secretions, atelectasis, pneumonia, and acute respiratory distress syndrome.

Other Forms of Inhalational Injury

Upper airway and lung injury occur in a variety of settings, including occupational exposures (see Airways Disease, Asthma), use of recreational drugs, and exposure to chemical terrorism agents. Cocaine inhalation commonly causes bronchospasm and sputum production, but it can also precipitate pulmonary edema, pulmonary hemorrhage, pneumothorax, and thermal upper airway injury (in the case of free-basing cocaine and use of crack cocaine pipes). Inhalation of chlorine, ammonia, and riot-control agents causes rapid onset of upper airway irritation and respiratory distress. Phosgene gas can also cause life-threatening ARDS, but this typically manifests several hours after exposure.

Anaphylaxis

Anaphylaxis is defined as a severe, potentially life-threatening allergic or hypersensitivity reaction that occurs within

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seconds to a few hours of allergen exposure, most commonly food, medication, or an insect sting. Classically, anaphylaxis occurs when allergen-specific IgE coating the surface of mast cells and basophils comes in contact with the triggering allergen, thereby precipitating cellular degranulation. The resulting abrupt systemic release of a host of mediators has a variety of effects including vasoconstriction, vasodilatation, increased vascular permeability, and bronchoconstriction. The presentation is variable, and predicting the ultimate severity of the episode is difficult. Therefore, optimal management is contingent on prompt recognition and treatment. The diagnosis of anaphylaxis is dependent on the presence of multiorgan system involvement and/or exposure to a known or suspected allergen. Signs and symptoms according to organ system are summarized in **Table 53**. The nonspecific presentation makes recognition particularly difficult in critically ill patients already experiencing respiratory distress, hypotension, or anxiety.

In addition to eliminating exposure to the inciting agent, treatment entails early administration of epinephrine, either intramuscularly or as a continuous intravenous infusion. H_1 antihistamines relieve skin symptoms, whereas systemic glucocorticoids reduce the risk of recurrent or persistent symptoms. Repeat epinephrine administration may be needed until antihistamines or glucocorticoids become effective. Severely affected patients may require fluid resuscitation, vasopressors, and intubation due to upper airway edema. Following recovery, patients should maintain home access to an epinephrine autoinjector and may benefit from evaluation for anaphylactic triggers.

It is important to differentiate anaphylactic from nonallergic causes of upper airway edema, as the treatment differs substantially. Compared with anaphylaxis, nonallergic angioedema generally is not associated with pruritus or urticaria and usually has a more gradual onset. Medications, most commonly ACE inhibitors, can trigger angioedema via elevation of bradykinin levels. In these patients, management is primarily supportive and includes discontinuation of the offending medication and prompt intubation if the airway becomes compromised. The treatment of hereditary and acquired causes of angioedema, such as C1 inhibitor deficiency, centers on therapies to counter aberrant bradykinin and complement activation.

KEY POINTS

- The diagnosis of anaphylaxis is dependent on the presence of multiorgan system involvement and/or exposure to a known or suspected allergen; skin or mucosal involvement is present in 85% of affected patients.
- In addition to eliminating exposure to the inciting agent, treatment of anaphylaxis entails early administration of epinephrine, either intramuscularly or as a continuous intravenous infusion.

Hypertensive Emergencies

Hypertensive emergency refers to elevation of systolic blood pressure greater than 180 mm Hg and/or diastolic blood pressure greater than 120 mm Hg that is associated with end-organ damage; however, in some conditions such as pregnancy, more modest blood pressure elevation can constitute an emergency. An equal degree of hypertension but without end-organ damage constitutes a hypertensive urgency, the treatment of which requires gradual blood pressure reduction over several hours. Patients with hypertensive emergency require rapid, tightly controlled reductions in blood pressure that avoid overcorrection. Management typically occurs in an ICU with continuous arterial blood pressure monitoring and continuous infusion of antihypertensive agents. An expedited evaluation for the cause of hypertension as well as assessing for the presence of end-organ failure, including encephalopathy, focal neurologic deficits (including vision changes), myocardial ischemia, heart failure, and acute kidney injury, should be performed. Diagnostic studies should be driven by clinical suspicion (**Table 54**).

A paucity of treatment trials exists for hypertensive emergencies. However, the choice of antihypertensive medication and the degree of acute blood pressure reduction are guided by a strong pathophysiologic rationale for any given clinical scenario (see Table 54).

TABLE 53. Organ System Involvement in Anaphylaxis

Organ System	Symptoms	Signs	% of Patients with Organ Involved
Skin and mucosa	Pruritus of skin, oropharynx, genitals, palms, soles	Flushing, urticaria, angioedema	85%
Respiratory	Dyspnea, chest and throat tightness, stridor, cough, hoarseness, sneezing, rhinorrhea	Wheeze, stridor, respiratory distress	70%
Cardiovascular	Lightheadedness, chest pain, palpitations	Hypotension, tachycardia > bradycardia	45%
Gastrointestinal	Pain, nausea, vomiting, diarrhea		45%
Neurologic	Sense of impending doom, headache	Encephalopathy	15%

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TABLE 54. Presentation and Treatment of Hypertensive Emergencies

Emergency	Presentation	Initial Diagnostic Studies	Target Blood Pressure (mm Hg)	First-Line Agents	Notes
Hypertensive encephalopathy	Confusion, headache, vision changes	Head CT to exclude stroke and hemorrhage	↓ by 15%-20% or DBP to 100-110	Nicardipine Labetalol Nitroprusside	Risk of cyanide toxicity with nitroprusside
Ischemic stroke	Focal deficit, CNS depression, seizure	Head CT	Treat if SBP >220 or DBP >120; ↓ by 15%	Nicardipine Labetalol Nitroprusside	Target BP <185/110 mm Hg if a candidate for thrombolytic therapy
Hemorrhagic stroke	Focal neurologic deficit, CNS depression, seizure	Head CT	BP 160/90 or MAP 110	Nicardipine Labetalol	+/- intracranial pressure monitor to target BP
Aortic dissection	Chest, back pain; asymmetric BP; acute aortic regurgitation	Chest radiograph with wide mediastinum CT angiogram	SBP 100-120	Esmolol or labetalol first, add nitroprusside as needed	Target HR <65/min
Myocardial infarction	Chest pain, dyspnea, nausea	Electrocardiogram Troponin	MAP 60-100	Nitroglycerin β-Blocker	Avoid hydralazine
Acute left-sided heart failure	Dyspnea, crackles	Chest radiograph	MAP 60-100	Nitroglycerin and/or nitroprusside	Caution with calcium and β-blockers, hydralazine
Acute kidney injury	Usually no symptoms	↑ Cr, proteinuria	↓ by 20%-25%	Fenoldopam Nicardipine β-Blocker	ACE if scleroderma renal crisis
Preeclampsia, eclampsia	SBP >160 mm Hg or DBP >110 mm Hg, edema, seizure	Proteinuria ↑ liver chemistry studies, ↑Cr ↓ platelets	SBP 130-150 DBP 80-100	Labetalol Hydralazine	Avoid ACE inhibitor and nitroprusside Delivery = "cure"
Sympathomimetic drug use	Diaphoresis, mydriasis, ↑ BP	History Urine drug screen	↓ by 20%-25%	Nicardipine Nitroprusside	Benzodiazepine first Avoid β-blocker
Pheochromocytoma	↑ HR, diaphoresis, headache	Urine and plasma metanephrines	↓ by 20%-25%	Phentolamine Nitroprusside	Avoid β-blocker

ACE = angiotensin-converting enzyme; BNP = B-type natriuretic peptide; BP = blood pressure; CNS = central nervous system; Cr = serum creatinine; DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; SBP = systolic blood pressure.

KEY POINTS

- Hypertensive emergency refers to elevation of systolic blood pressure greater than 180 mm Hg and/or diastolic blood pressure greater than 120 mm Hg that is associated with end-organ damage.
- Patients with hypertensive emergency require rapid, tightly controlled reductions in blood pressure that avoid overcorrection.

Hyperthermic Emergencies

Severe hyperthermia is a life-threatening elevation of core body temperature to greater than 40.0 °C (104.0 °F). Unlike fever, which stems from an inflammatory response, hyperthermia is due to a failure of normal thermoregulation.

Heat Stroke

Heat stroke occurs with high ambient temperature and humidity and is defined by the presence of temperature greater than 40.0 °C (104.0 °F) and encephalopathy. It is often associated with hypotension, gastrointestinal distress, and weakness. Patients with advanced heat stroke exhibit shock, multiorgan failure, rhabdomyolysis, and myocardial ischemia. Exertional heat stroke typically occurs in healthy individuals undergoing vigorous physical activity in warm conditions. In contrast, the majority of patients with nonexertional heat stroke are older than 70 years or have chronic medical conditions that impair thermal regulation. Medications and recreational drugs with anticholinergic, sympathomimetic, and diuretic effects, including alcohol, pose added risk.

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The diagnosis typically is made based on the clinical context and physical examination. The differential diagnosis includes other causes of hyperthermia (**Table 55**), infection, stroke, seizures, and toxin ingestions. Rapid, sustained improvement in temperature with cooling interventions strongly suggests heat stroke. The primary treatment for nonexertional heat stroke is evaporative, external cooling. This involves removing all clothing and spraying the patient with a mist of lukewarm water while continuously blowing fans on the patient. Ice packs on the neck, axillae, and groin augment cooling. Ice water immersion is recommended for exertional heat stroke in young patients if intubation or close monitoring is unnecessary. Cooling should be continued until the rectal temperature falls to approximately 38.5 °C (101.3 °F). The usual response is sufficiently rapid enough that invasive interventions are largely unneeded. Antipyretic agents and dantrolene are not effective.

KEY POINTS

- Rapid, sustained improvement in temperature with cooling interventions strongly suggests heat stroke.
- Exertional heat stroke is often treated with ice water immersion, whereas nonexertional heat stroke is typically managed with evaporative external cooling.

Malignant Hyperthermia

Malignant hyperthermia is an uncommon cause of severe hyperthermia that occurs in genetically susceptible individuals upon exposure to a volatile anesthetic such as halothane or isoflurane. Features include mixed respiratory and metabolic acidosis, muscle rigidity, hyperkalemia, and rhabdomyolysis. Treatment includes prompt discontinuation of the triggering agent, increase in minute ventilation, bicarbonate infusion, correction of hyperkalemia, and dantrolene.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is associated with the use of neuroleptic medications and is characterized by the presence of encephalopathy, muscle rigidity, autonomic instability, and fever. Although most frequently described with older agents such as haloperidol, NMS can occur with atypical neuroleptics, including olanzapine, quetiapine, and risperidone. Antiemetic medications (including metoclopramide) and dose reduction of antiparkinson medications are also associated with NMS. The features of NMS overlap substantially with severe serotonin syndrome (see Table 55). Serotonin syndrome can be distinguished from NMS by the presence of hyperreflexia and myoclonus.

Accidental Hypothermia

Accidental hypothermia stereotypically affects young outdoor enthusiasts in cold climates, but in reality it occurs worldwide, in all seasons, often without outdoor exposure, and disproportionately among the elderly. Risk factors in addition to advanced age include chronic medical conditions, malnutrition, psychiatric illness, homelessness, and chemical dependency. The clinical manifestations of hypothermia vary depending on the severity (**Table 56**). Osborne or J waves (**Figure 23**) appear at temperatures less than 33.0 °C (91.4 °F) and should not be confused with myocardial ischemia. J waves can be present in the absence of known disease.

A critical first step in management is initiating passive external rewarming, which entails removing wet clothing and covering the patient with insulating material, especially the head and neck. Owing to a paucity of rewarming trials in accidental hypothermia, institutional resources and expertise play a major role in treatment selection. However, for mildly hypothermic, healthy individuals capable of shivering, passive external rewarming alone suffices. Active external rewarming using warm blankets or a forced heated air blanket is commonly used in hemodynamically stable patients with moderate hypothermia, when passive external rewarming proves

TABLE 55. Causes of Severe Hyperthermia

Diagnosis	Suggestive History	Key Examination Findings	Treatment	Notes
Heat stroke	Environmental exposure	Encephalopathy and fever	Evaporative cooling Ice water immersion	Avoid ice water immersion if nonexertional heat stroke
Malignant hyperthermia	Exposure to volatile anesthetic	Masseter muscle rigidity; ↑ arterial Pco_2	Stop inciting drug Dantrolene	Monitor and treat ↑ K^+ and ↑ arterial Pco_2
Neuroleptic malignant syndrome	Typical > atypical antipsychotic agent; onset over days to weeks	Altered mentation, severe rigidity, ↑ HR, ↑ BP, no clonus, hyporeflexia	Stop the inciting drug Dantrolene Bromocriptine	Resolves over days to weeks Mentation change first
Severe serotonin syndrome[a]	Onset within 24 h of initiation or increasing drug dose, gastrointestinal prodrome	Agitation, clonus, ↑ reflexes, rigidity	Stop inciting drug Benzodiazepines Cyproheptadine	Resolves in 24 h

BP = blood pressure; HR = heart rate; K^+ = potassium.

[a]Not routinely considered a cause of severe hyperthermia but commonly confused with neuroleptic malignant syndrome.

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TABLE 56. Presentation of Hypothermia by Severity

Severity	Temperature	Findings
Mild	32.0-35.0 °C (89.6-95.0 °F)	↑ HR, ↑ BP, ↑ RR, shivering, alert, poor judgment
Moderate	28.0-32.0 °C (82.4-89.6 °F)	↓ HR, ↓ BP, ↓ RR, ↓ CO, ↓O_2 consumption, ↓ kidney function, somnolence, no shivering, supraventricular arrhythmia
Severe	<28.0 °C (82.4 °F)	Coma, absent reflexes, ventricular arrhythmia, asystole, apnea

BP = blood pressure; CO = cardiac output; HR = heart rate; RR = respiration rate.

CONT.

inadequate in mild hypothermia, or as an adjunct in severe hypothermia. Administering warmed intravenous fluids (42.0 °C [107.6 °F]) transfers only a modest amount of heat but at least prevents further temperature declines associated with infusing large volumes of room-temperature fluids. Body cavity lavage with warm fluids is an option for patients with hypothermia that is severe or does not respond to external warming, particularly if there is no access to intravascular rewarming devices. The colon, bladder, and stomach are readily accessible for irrigation but have a small surface area for heat exchange. Rewarming by peritoneal or pleural space irrigation is supported by case reports. Although reported experience is limited, endovascular warming devices, which are routinely used for therapeutic hypothermia, are an attractive option for severely affected but hemodynamically stable patients. Extracorporeal support, including cardiopulmonary bypass, is recommended for patients in cardiac arrest because it maximizes the rewarming rate and can provide hemodynamic support. Conventional treatment of ventricular arrhythmias and asystole is often ineffective until the temperature is raised to greater than 30.0 °C (86.0 °F). Because severe hypothermia may appear clinically similar to death, aggressive rewarming is appropriate in all patients in a suggestive clinical situation in the absence of obvious irreversible signs of death.

KEY POINT

- Mild cases of hypothermia in healthy patients generally respond to passive external rewarming, whereas unstable patients with severe hypothermia are best treated with invasive measures, including cardiopulmonary bypass.

Toxicology

Treatment of patients with poisoning may require aggressive measures to stabilize extremes of blood pressure, in addition to endotracheal intubation for inadequate ventilation or airway protection, particularly if vomiting is present. Initial empiric treatment of patients with encephalopathy includes thiamine to prevent Wernicke encephalopathy and dextrose for hypoglycemia unless these diagnoses can be rapidly excluded. In addition to fingerstick glucose testing, the initial evaluation generally includes measurement of the acetaminophen level and salicylate level, analysis of QRS and QT intervals on electrocardiogram, and pregnancy testing in women of childbearing age. Urine toxicology screen is warranted in patients with severe symptoms or when the cause remains unclear after initial evaluation. Early consultation with a regional poison control center should be done in the case of severe or unfamiliar poisonings.



FIGURE 23. Electrocardiogram showing Osborne waves (*arrows*). Hypothermia may be associated with sinus bradycardia or with atrial fibrillation, and the appearance of the classic Osborne waves at the QT interval. They are best seen in the inferior and lateral chest leads. Osborne waves are defined by the shoulder or "hump" between QRS and ST segments.

Alcohol Poisoning

A key early step in suspected alcohol toxicity is determining whether alcohol ingestion entirely accounts for the patient's presentation. The initial evaluation should consider infectious, neurologic, metabolic, and endocrinologic causes of central nervous system depression, as well as coingestion of other substances. Determination of the specific alcohol consumed is also a priority, as toxicity and treatment vary substantially between ethanol, isopropyl alcohol, ethylene glycol, and methanol poisoning (**Table 57**). In addition to venous or arterial blood gas measurement, initial laboratory evaluation includes measurement of the serum ethanol level, glucose, electrolytes, ketones, kidney function, and osmolality. Calculation of the anion and plasma osmolal gaps aids in the diagnosis (see Table 57).

Anion gap elevation can be more severe in methanol and ethylene glycol poisoning than is typically seen with salicylate poisoning, lactic acidosis, and ketosis. Ethanol and isopropyl alcohol do not directly increase the anion gap.

A plasma osmolal gap greater than 10 is abnormal and is characteristic of all alcohols, but it lacks sensitivity and specificity. For example, an osmolal gap greater than 25 is highly compatible with early severe methanol or ethylene glycol poisoning, but the gap may normalize with delayed presentation.

Early administration of the alcohol dehydrogenase inhibitor fomepizole prevents breakdown of methanol and ethylene glycol into toxic metabolites. This may require empiric therapy while awaiting laboratory confirmation. Ethanol can be used to compete for alcohol dehydrogenase activity when fomepizole is unavailable, but titration can be difficult.

For information on alcohol withdrawal, see MKSAP 17 General Internal Medicine.

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TABLE 57. Presentation and Treatment of Alcohol Poisoning

Alcohol	Common Sources	Major Findings	Anion Gap	Osmolal Gap[a]	Treatment
Ethanol	Alcoholic beverages	CNS depression Nausea, emesis	No	NA	Supportive care
Isopropyl alcohol	Rubbing alcohol Disinfectants Antifreeze	CNS depression Ketone elevation	No	Yes	Supportive care
Methanol	Windshield wiper fluid De-icing solutions Solvents "Moonshine"	CNS depression Vision loss Hypotension	Yes	Yes	Fomepizole Ethanol (second-line) Dialysis (if severe) Folic acid
Ethylene glycol	Antifreeze De-icing solutions Solvents	CNS depression Acute kidney injury Hypocalcemia Hypotension	Yes	Yes	Fomepizole Ethanol (second-line) Dialysis (if severe)

BUN = blood urea nitrogen; CNS = central nervous system; Na = sodium; NA = not applicable.

[a]The osmolal gap represents the difference between the measured osmolality and calculated osmolality. The calculated osmolality = (2 × [Na]) + [glucose (mg/dL)]/18 + [BUN (mg/dL)]/2.8.

KEY POINT

- Ethylene glycol and methanol poisoning cause an elevated anion gap and an elevated osmolal gap; treatment is with fomepizole.

Carbon Monoxide Poisoning

Carbon monoxide poisoning causes thousands of deaths annually in the United States, with smoke inhalation as the leading cause of inadvertent exposure. Inhaled carbon monoxide has a much higher affinity for hemoglobin binding sites than oxygen and readily forms carboxyhemoglobin, which is an ineffective oxygen transporter and results in reduced tissue oxygen content. Symptoms of carbon monoxide poisoning vary and include headache, confusion, nausea, vomiting, and, in severe cases, loss of consciousness. It is important to understand that carboxyhemoglobin does not lower oxygen saturation measured by standard pulse oximetry or reduce arterial Po_2 determined by blood gas analysis. Co-oximetry, which measures carboxyhemoglobin levels, is used to make the diagnosis. Carboxyhemoglobin levels normally are less than 3% but can be 10% to 15% in heavy smokers. Myocardial ischemia is common in patients with carbon monoxide poisoning, and delayed onset of cognitive dysfunction, focal neurologic deficits, and movement disorders can arise even months after exposure.

Carbon monoxide is removed by competitive binding of oxygen to hemoglobin. The initial treatment is administration of 100% oxygen, which reduces the half-life of carboxyhemoglobin from 5 hours to 90 minutes. Hyperbaric oxygen therapy yields an even higher alveolar partial pressure of oxygen, thereby reducing the half-life to 30 minutes while substantially increasing the amount of oxygen directly dissolved in blood. Consensus is lacking on the use of hyperbaric therapy in carbon monoxide poisoning, but commonly cited indications include carboxyhemoglobin levels greater than 25% (or >20% in pregnant patients), persistent organ ischemia, and loss of consciousness. Carbon monoxide poisoning resulting from smoke inhalation should prompt consideration of concomitant cyanide poisoning.

KEY POINT

- Carbon monoxide poisoning presents with normal oxygen saturation as measured by standard pulse oximetry, is diagnosed with co-oximetry, and is treated with 100% oxygen and/or hyperbaric oxygen therapy.

Cyanide Poisoning

Acute cyanide poisoning primarily occurs through fire and occupational exposures and rarely from medications such as sodium nitroprusside. Cyanide disrupts oxidative phosphorylation, forcing cells to convert to anaerobic metabolism despite adequate oxygen supply. The result in severe cases is multiorgan failure with coma, seizures, and cardiovascular symptoms, including hypotension, bradycardia, heart block, and ventricular arrhythmias. Early manifestations are nonspecific. Diagnostic clues include lactic acidosis and inappropriately elevated Svo_2, which manifests as bright red venous blood. Cherry-red skin color, a classic finding, is infrequently encountered. Cyanide levels are not readily available and since toxicity is rapidly fatal, prompt empiric treatment is imperative in suspected cases. Recommended treatment includes sodium thiosulfate in combination with either hydroxocobalamin or nitrites.

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depending on availability. Hydroxocobalamin effectively binds intracellular cyanide to form cyanocobalamin, which poses no harm. Nitrites induce production of methemoglobin, which then avidly binds cyanide to form the much less toxic cyanomethemoglobin. Finally, sodium thiosulfate is a sulfur donor that promotes conversion of cyanide to thiocyanate, which is well tolerated in the absence of acute kidney injury. When concomitant carbon monoxide poisoning is suspected, nitrites should be avoided because methemoglobinemia can further impair oxygen delivery.

Toxicity of Drugs of Abuse

The clinical presentation and toxic effects of commonly used sympathomimetic, opioid, sedative, and hallucinogenic drugs are described in **Table 58**. Coingestion of more than one psychoactive drug or alcohol is common, and such patients often have overlapping or indistinct toxicologic syndromes. Obtaining a history of ingestion and chronic medical issues helps narrow an exceedingly broad differential diagnosis that includes therapeutic drug toxicity, infection, extremes of temperature, benzodiazepine or ethanol withdrawal, and a myriad of brain disorders and metabolic disturbances. **Table 59** summarizes distinguishing features of opioid, sympathomimetic, anticholinergic, and cholinergic toxicologic syndromes.

Initial stabilization includes endotracheal intubation for airway protection in patients with a depressed level of consciousness. However, an early empiric trial of the opioid antagonist naloxone is warranted when opioid overdose is suspected. Serial escalating doses may be necessary, and patients who respond may require a continuous naloxone infusion. Chronic opioid users require close monitoring for withdrawal. In contrast, the use of flumazenil, a γ-aminobutyric acid (GABA)–receptor antagonist for benzodiazepine overdose is controversial. Although a response can be helpful in confirming the diagnosis and can obviate the need for additional diagnostic studies, flumazenil can precipitate seizures in chronic benzodiazepine users. Its short half-life makes it challenging to use in patients requiring sustained reversal of long-acting benzodiazepines, and given the overall low risk of benzodiazepine overdose, only selective use under the guidance of a toxicologist is recommended. Intubation is appropriate for patients with inadequate ventilation or an inability to handle their secretions. In general, treatment of benzodiazepine overdose is supportive with assurance of adequate ventilation.

Management of sympathomimetic overdose centers on controlling agitation with benzodiazepines, evaluating for end-organ injury, and treating persistent hypertension. Cocaine and other stimulants have β-adrenergic activity that produces

TABLE 58. Presentation and Toxicity of Drugs of Abuse

Drug Class	Examples	Examination Findings	Antidote
Opioids	Heroin, oxycodone, fentanyl analogs	↓ HR, ↓ temp, ↓ BP, ↓ RR, miosis	Naloxone
Benzodiazepines	Lorazepam	CNS depression, usually normal vital signs and eye examination	Flumazenil
Sympathomimetics		Shared findings: ↑ HR, ↑ BP, ↑ temp, diaphoresis, mydriasis, agitation, seizure, ↑ CK, ↑ liver chemistry studies, ↑ Cr	Benzodiazepines are first line for agitation Avoid β-blockers for hypertension Haloperidol may worsen hyperthermia
	Cocaine	30-minute duration, myocardial infarction prominent	
	Methamphetamine	Violent agitation prominent, duration 20 h	
	MDMA ("ecstasy")	↓ Na, serotonin syndrome	
	Bath salts ("plant food")	Hallucinations, violent agitation common, duration up to 48 h, negative urine drug screen	
Hallucinogens	Dextromethorphan	↑ HR, ↑ BP, agitation, coma	Benzodiazepines are first line for agitation Haloperidol is second line
	LSD	Mild ↑ HR, ↑ BP; rare ↑ temp and hemodynamic instability	
	PCP	Variable mental status: agitation > CNS depression, nystagmus	
	Synthetic cannabinoids ("Spice", "K-2")	↑ HR, agitation > marijuana, ↑Cr, negative urine drug screen	

BP = blood pressure; CK = creatine kinase; CNS = central nervous system; Cr = creatinine; ECG = electrocardiogram; HR = heart rate; LSD = lysergic acid diethylamide; MDMA = 3,4-methylenedioxymethamphetamine; Na = sodium; PCP = phencyclidine; RR = respiration rate; temp = temperature.

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TABLE 59. Toxic Drug Syndromes and Their Manifestations

Syndrome	Manifestations	Representative Drugs
Sympathomimetic	Tachycardia Hypertension Diaphoresis Agitation Seizures Mydriasis	Cocaine Amphetamines Ephedrine Caffeine
Cholinergic	"SLUDGE" Confusion Bronchorrhea Bradycardia Miosis	Organophosphates (insecticides, sarin) Carbamates Physostigmine Edrophonium Nicotine
Anticholinergic	Hyperthermia Dry skin and mucous membranes Agitation, delirium Tachycardia, tachypnea Hypertension Mydriasis	Antihistamines Tricyclic antidepressants Antiparkinson agents Atropine Scopolamine
Opioids	Miosis Respiratory depression Lethargy, confusion Hypothermia Bradycardia Hypotension	Morphine and related drugs Heroin

SLUDGE = Salivation, Lacrimation, increased Urination and Defecation, Gastrointestinal upset, and Emesis.

CONT. vascular smooth muscle relaxation. Use of β-blockers in this setting therefore may exacerbate hypertension and should be avoided, although the actual risk is not well characterized.

Management of hallucinogenic overdose is supportive, as there are no antagonists to reverse the effects of these drugs. Patients with overdose of hallucinogens may be violent and combative and may require chemical and/or physical restraint while providing respiratory and hemodynamic support.

Therapeutic Drug Overdose

Critical illness can result from intentional or inadvertent overdose of a myriad of medications. Coingestion of medications or alcohol is particularly common with intended self-harm. Eliciting a detailed history from the patient, bystanders, first responders, and the patient's pharmacist, as well as retrieval of pill bottles, substantially enhances providers' ability to institute optimal early treatment and anticipate problems. The physical examination is useful for ascertaining the class of drugs involved (**Table 60**) and identifying alternative causes of illness such as infection. Cholinergic syndromes most often occur with accidental exposure to organophosphate insecticides rather than ingestion of medications with cholinergic properties. Early treatment focuses on preventing absorption of additional medication, administration of antidotes, and measures to accelerate drug elimination such as hemodialysis. For most medications, administering activated charcoal may reduce drug levels, but it should be withheld if the patient is at risk of aspirating or more than 1 to 2 hours have elapsed since the time of ingestion.

For a discussion of acetaminophen toxicity, see MKSAP 17 Gastroenterology and Hepatology. For a discussion of salicylate toxicity, see MKSAP 17 Nephrology. H

KEY POINT

- Coingestion commonly complicates the presentation and management of recreational and therapeutic drug toxicities.

Acute Abdominal Surgical Emergencies H

Advanced age, immunosuppression, and use of systemic glucocorticoids are not only risk factors for severe abdominal disease but are associated with atypical clinical presentation. A host of relatively common (for example, acute myocardial infarction, diabetic ketoacidosis) and uncommon (for example, sickle cell disease, vasculitides) diseases that do not require surgical intervention may present with abdominal pain. Despite the large number of possible causes, it is important to achieve early differentiation of medically managed conditions from surgical emergencies. Early surgical intervention can be lifesaving (**Table 61**), and prompt surgical consultation is imperative. Abdominal imaging is not always necessary in determining the need for surgery, and CT scans in particular may cause harmful delays.

For a discussion of abdominal compartment syndrome, see MKSAP 17 Nephrology. H

KEY POINT

- Early surgical consultation can be life-saving in patients with possible acute surgical abdomen.

Anoxic Brain Injury H

Temperature management and therapeutic hypothermia are the standard of care for improving neurologic outcomes in resuscitated individuals who remain unresponsive following cardiac arrest. Benefit appears to be greatest in patients who are not responding appropriately to verbal commands after return of spontaneous circulation following ventricular fibrillation or pulseless ventricular tachycardia. Arrest due to asystole and pulseless electrical activity is associated with poor neurologic outcomes and the benefit of cooling in

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TABLE 60. Presentation and Treatment of Therapeutic Drug Toxicities

Medication	Key Clinical Findings	Treatment	Notes
Nonopioid analgesics			
Acetaminophen	↑ liver chemistry studies, ↑Cr, ↑ INR, cerebral edema, vomiting	*N*-acetylcysteine	Transfer to liver transplant center if severe
Salicylates	Mixed respiratory alkalosis/anion gap metabolic acidosis, tinnitus, agitation, confusion	Bicarbonate infusion, dextrose	Target urine pH 7.5 to 8.0; hemodialysis if acute kidney injury or severe toxicity
Cardiovascular			
β-Blocker, calcium channel blocker	↓HR, ↓ BP, heart block, altered mental status if β-blocker	Atropine 1 mg IV up to 3 doses, glucagon, calcium chloride, vasopressors, cardiac pacemaker (if indicated), high-dose insulin and glucose, IV lipid emulsion	Treatments may be added sequentially or initiated simultaneously depending on severity of case and response to treatment
Digoxin	↓ HR, arrhythmia, nausea, emesis, abdominal pain, confusion, weakness	Digoxin-specific antibody	Use of antibody lowers K^+; hemodialysis not effective
Anticholinergics			
Tricyclic antidepressants	↓ BP, sedation, seizure, anticholinergic signs, arrhythmia	Bicarbonate infusion titrated to QRS duration; benzodiazepines for seizure	Physostigmine contraindicated
Antihistamines	Anticholinergic signs including agitation and seizures	Benzodiazepines; physostigmine if isolated anticholinergic overdose	Physostigmine use requires continuous cardiac monitor and bedside atropine
Hypoglycemic			
Sulfonylurea	↓ glucose, confusion, seizure, anxiety, diaphoresis, tremor	Dextrose + octreotide, glucagon IM = temporizing	Monitor for ↓ glucose for 48 hours if large ingestion
Metformin	↑ lactate, abdominal pain	Hemodialysis for severe ↓ pH or acute kidney injury	Glucose usually normal if isolated metformin ingestion
Others			
Lithium	GI distress, confusion, ataxia, tremor, myoclonic jerks, diabetes insipidus	Hemodialysis if lithium level >4 mEq/L or severe symptoms	Serum level can guide need for hemodialysis, confirm diagnosis
SSRI/SNRI	Agitation, clonus, ↑ reflexes, rigidity, fever, ↑ HR	Benzodiazepines, cyproheptadine if severe	Venlafaxine has ↑ cardiac toxicity

BP = blood pressure; Cr = creatinine; GI = gastrointestinal; HR = heart rate; IM = intramuscular; IV = intravenous; K+ = potassium; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

CONT.

these settings is unclear. However, temperature management is widely implemented regardless of the type of arrhythmia or whether the event was primarily cardiac or respiratory in origin.

Aside from advance directives limiting the aggressiveness of care, there are no absolute contraindications, and therapy should be initiated as soon as possible following arrival to the hospital. Intravascular cooling catheters, cooling blankets, cooling vests, and ice packs are commonly used to lower the temperature. Initial trials showing benefit cooled patients to 32.0 to 34.0 °C (89.6 to 93.2 °F) for 12 to 24 hours followed by gradual rewarming at 0.25 to 0.5 °C/hour (0.45 to 0.9 °F/hour). A recent, larger trial that compared cooling to 33.0 °C (91.4 °F) versus 36.0 °C (96.8 °F) for 28 hours found equivalent outcomes. In this study, temperatures were maintained below 37.5 °C (99.5 °F) until 72 hours post-arrest in both groups. Patients with ventricular fibrillation or ventricular tachycardia, immediate high-quality cardiopulmonary resuscitation, and limited arrest time have the best opportunity for neurologic recovery. Cooling these patients to between 36.0 and 32.0 °C (96.8 to 89.6 °F) for 24 hours appears to benefit neurologic recovery and should be utilized in conjunction with comprehensive care and support. Avoidance of fever (<37.5 °C [99.5 °F]) for several days post-arrest is a reasonable strategy.

Prognosis in patients who do not awaken following rewarming is best determined by serial neurologic examinations combined with ancillary tests, including somatosensory evoked potentials.

KEY POINT

- Temperature management and therapeutic hypothermia are the standard of care for improving neurologic outcomes in resuscitated individuals who remain unresponsive following cardiac arrest.

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TABLE 61. Causes and Presentation of Acute Abdominal Emergencies

Diagnosis	Presentation	Diagnostic Imaging	Notes
Acute cholecystitis and cholangitis	Persistent peritoneal RUQ or epigastric pain, fever, emesis, positive Murphy sign	Ultrasound EUS and ERCP for diagnosis and treatment of cholangitis	↑ alkaline phosphatase, ↑ bilirubin suggests cholangitis but typically not cholecystitis
Bowel obstruction	Cramping pain, emesis, distention, obstipation, dehydration	Radiograph: dilated loops of bowel with air-fluid levels CT scan: identifies cause, complications	Top causes: incarcerated hernia, adhesions, volvulus, intussusception
Acute appendicitis	Classic: periumbilical then RLQ pain, emesis, ↑ leukocyte count	Often unnecessary CT or ultrasound if unclear	Pain quality and location vary with appendix location
Peptic ulcer perforation	Abrupt peritoneal pain, later distention and hypovolemia	Radiograph: free air CT scan if unclear	Surgery necessary in majority of cases
Acute mesenteric ischemia	Pain > than examination findings, vomiting, hypotension, risk factors for clotting, embolism	CT angiography or conventional arteriography	Standard CT and serum lactate can be normal early in course
Toxic megacolon	Pain, diarrhea, ↑ temp, ↑ HR, ↑ BP, confusion	Radiograph: dilated colon, air-fluid levels in colon CT scan if unclear	Causes: inflammatory bowel disease, *Clostridium difficile* infection
Ruptured abdominal aortic aneurysm	↑ BP, abdominal and/or flank pain, pulsatile mass	Unnecessary if high suspicion and unstable CT or ultrasound if unclear	Risk factors: older age, male, smoking, hypertension, family history of aneurysm
Ectopic pregnancy with tubal rupture	↑ BP, ↑ Hb, ↑ hCG, abdominal pain, vaginal bleeding	Transvaginal ultrasound	High mortality without early surgery

BP = blood pressure; ERCP = endoscopic retrograde cholangiopancreatography; EUS = endoscopic ultrasound; Hb = hemoglobin; hCG = human chorionic gonadotropin; HR = heart rate; RLQ = right lower quadrant; RUQ = right upper quadrant; temp = temperature.

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 55-year-old man is evaluated in the emergency department after being rescued from his burning home by firefighters. His medical history is notable for COPD, and his only medication is an albuterol-ipratropium metered-dose inhaler.

On physical examination, he is alert and in pain. Temperature is 37.8 °C (100.0 °F), blood pressure is 124/60 mm Hg, pulse rate is 116/min, and respiration rate is 22/min; BMI is 31. Oxygen saturation is 98% breathing 3 L/min oxygen by nasal cannula. Soot is noted in the nares and throughout the oral pharynx. The oral mucosa is edematous. Burns are noted on the right upper extremity and lower chest. Cardiac examination reveals a regular rhythm. Pulmonary examination reveals a monophonic wheeze over the anterior chest, diffuse expiratory wheezes, and increased work of breathing.

Arterial blood gas studies breathing 30% oxygen reveal a pH of 7.32, a Pco_2 of 50 mm Hg (6.7 kPa), and a Po_2 of 78 mm Hg (10.4 kPa).

A chest radiograph shows increased lung volumes consistent with hyperinflation but no infiltrates.

Which of the following is the most appropriate next step in treating this patient's respiratory findings?

(A) Administer a helium-oxygen mixture
(B) Administer methylprednisolone
(C) Perform endotracheal intubation
(D) Start nebulized epinephrine
(E) Start noninvasive ventilation

Item 2

A 72-year-old man is admitted to the ICU for severe community-acquired pneumonia. He was admitted to the hospital 2 days ago with cough and dyspnea. Despite appropriate intravenous antibiotics, his respiratory status declined and he was transferred to the ICU, was intubated, and was placed on mechanical ventilation. A vasopressor was needed for persistent hypotension. Since ICU admission 36 hours ago, he has had stable oxygenation and blood pressure and his oxygen and vasopressor dose are being decreased. Medical history is otherwise unremarkable. Medications are ceftriaxone, azithromycin, norepinephrine, and low-molecular-weight heparin prophylaxis.

On physical examination, the patient is intubated but responsive. Temperature is 38.3 °C (100.9 °F), blood pressure is 95/58 mm Hg, and pulse rate is 110/min; BMI is 27. Chest examination shows decreased breath sounds at the left lung base. Cardiac examination reveals a grade 2/6 systolic flow murmur. The remainder of the examination is unremarkable.

Laboratory studies are significant for a leukocyte count of 15,000/μL (15×10^9/L); the complete blood count is otherwise normal. Complete metabolic profile is normal. Blood and sputum cultures are negative since admission.

A chest radiograph is significant for left lower lobe consolidation but is otherwise unremarkable.

Which of the following is most likely to prevent deconditioning in the ICU?

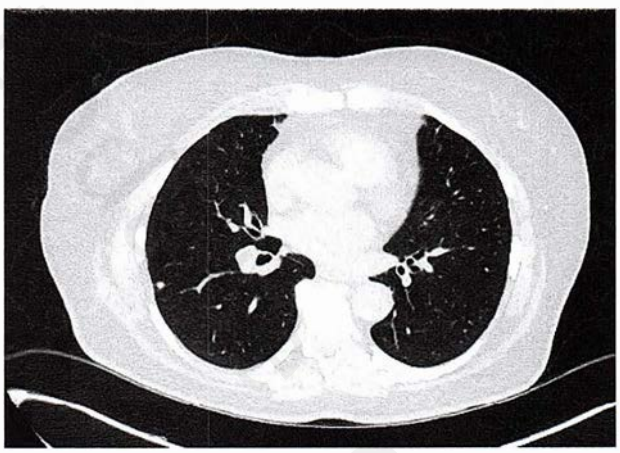
(A) Passive range of motion exercises only while in the ICU
(B) Progressive physical activity as tolerated starting now
(C) Progressive physical activity as tolerated following discontinuation of vasopressors
(D) Progressive physical activity as tolerated following extubation

Item 3

A 58-year-old woman is evaluated for a right pulmonary nodule that was discovered incidentally 3 weeks ago. She is currently asymptomatic and has not had shortness of breath, fever, chills, weight loss, or night sweats. Medical history is otherwise unremarkable, and she takes no medications. She is a life-long nonsmoker.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 126/82 mm Hg, pulse rate is 68/min, and respiration rate is 10/min; BMI is 30. There is no cervical or supraclavicular lymphadenopathy. The lungs are clear to auscultation. No clubbing is noted.

The 5-mm nodule seen on CT is shown.



Which of the following is the most appropriate next step in management?

(A) Bronchoalveolar lavage
(B) PET/CT scan
(C) Review any previous chest imaging
(D) Transthoracic needle biopsy

Item 4

A 62-year-old man is evaluated for declining exercise capacity over the past year. He was diagnosed with moderate COPD 3 years ago. His symptoms had previously been well controlled with tiotropium and as-needed albuterol. He has

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not had any hospitalizations. He is adherent to his medication regimen, and his inhaler technique is good. He quit smoking 2 years ago. All immunizations are up to date, including influenza and pneumococcal vaccination. A chest radiograph performed 3 months ago for increased cough and sputum production was normal. Pulmonary function testing performed 3 years ago showed an FEV_1 of 58% of predicted, an FEV_1/FVC ratio of 60%, and a DLCO of 85% of predicted.

On physical examination, vital signs are normal. Oxygen saturation is 93% breathing ambient air. No jugular venous distention is noted. The lungs are clear. Cardiac examination reveals normal heart sounds. There are no murmurs. No edema is noted.

Which of the following is the most appropriate management?

(A) Add roflumilast
(B) Obtain complete pulmonary function tests
(C) Perform chest CT
(D) Repeat spirometry
(E) Start oxygen therapy

Item 5

A 56-year-old woman is evaluated for a 4-week history of slowly progressive shortness of breath. She has a nonproductive cough that started around the same time and did not improve after a course of azithromycin. She has not had fever, chills, chest pain, wheezing, orthopnea, or lower extremity edema. Her medical history is notable for hormone receptor–negative infiltrating ductal carcinoma of the left breast diagnosed 8 months ago and treated with lumpectomy, radiation therapy, and adjuvant chemotherapy. She currently takes no medications.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 124/76 mm Hg, pulse rate is 110/min, respiration rate is 14/min, and oxygen saturation is 91% breathing ambient air; BMI is 26. Crackles are noted at the left lung base. The left breast shows a well-healed lumpectomy scar and mild radiation skin changes, but no masses. There is no cervical, supraclavicular, or axillary lymphadenopathy. No clubbing is observed.

A complete blood count is normal.

A chest CT with pulmonary embolism protocol was compared with a CT obtained 6 months ago. It shows left hilar and mediastinal lymphadenopathy with new interstitial thickening and beading at the left lung base and no ground-glass opacification. There is no evidence of pulmonary embolism.

Which of the following is the most likely diagnosis?

(A) Atypical pneumonia
(B) Bronchiolitis obliterans organizing pneumonia
(C) Idiopathic pulmonary fibrosis
(D) Lymphangitic carcinomatosis
(E) Radiation fibrosis

Item 6

A 60-year-old woman is evaluated for a 6-month history of worsening dyspnea, especially with exertion. She was diagnosed with COPD 4 years ago, and pulmonary function tests performed 3 months ago showed an FEV_1 of 32% of predicted and an FEV_1/FVC ratio of 55%. She has had three exacerbations in the last year. She completed pulmonary rehabilitation twice within the last 2 years and quit smoking 1 year ago. Medications are combination long-acting β_2-agonist and inhaled glucocorticoid, roflumilast, and albuterol as needed.

On physical examination, she is afebrile. Blood pressure is 120/74 mm Hg, pulse rate is 94/min, and respiration rate is 20/min. BMI is 28. Oxygen saturation breathing ambient air is 89%. There is no jugular venous distention. Pulmonary examination reveals decreased breath sounds. Cardiovascular examination reveals a loud pulmonic component of S_2. Bilateral lower extremity edema is noted to a level above the ankles.

Chest radiograph shows no infiltrate or mass. Arterial P_{O_2} is 57 mm Hg (7.6 kPa) breathing ambient air. Echocardiogram reveals an ejection fraction of 60% and no valvular or wall motion abnormalities. The estimated mean pulmonary artery pressure is 52 mm Hg.

Which of the following is the most appropriate treatment?

(A) Daily prednisone
(B) Long-term oxygen therapy
(C) Overnight pulse oximetry
(D) Repeat pulmonary rehabilitation

Item 7

A 62-year-old man is evaluated for 2-year history of increasing shortness of breath. His symptoms are worse when he walks up steps or lifts heavy objects. He also has an occasional nonproductive cough. His medical history is significant for hypertension, and his only medication is chlorthalidone. He is an active smoker with a 56-pack-year smoking history. He is a former construction worker and worked in a steel mill when he was in high school.

On physical examination, the patient is afebrile, blood pressure is 125/78 mm Hg, pulse rate is 90/min, and respiration rate is 18/min; BMI is 31. Oxygen saturation at rest breathing ambient air is 94%. Pulmonary examination reveals a mildly prolonged expiratory phase but is otherwise normal; no wheezes or crackles are noted. The remainder of the examination is unremarkable.

Chest radiograph shows mildly increased lung markings but no focal findings.

Spirometry shows an FEV_1/FVC ratio of 65%, an FEV_1 of 52% of predicted, and an FVC of 80% of predicted. Lung volumes show a total lung capacity of 120% of predicted, a residual volume of 125% of predicted, and a DLCO of 65% of predicted.

Based on this patient's clinical findings, which of the following is the most likely diagnosis?

(A) Bronchiectasis
(B) COPD
(C) Idiopathic pulmonary fibrosis
(D) Obesity hypoventilation syndrome

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Item 8

A 57-year-old woman is evaluated in the emergency department for an episode of hematemesis that occurred 1 hour ago. She had previously felt well except for a recent knee injury, for which she has been taking ibuprofen. She currently is experiencing lightheadedness and weakness. Medical history is otherwise unremarkable. She does not smoke or drink alcohol. She takes no other medications.

On physical examination, she appears ill and pale. Temperature is 36.5 °C (97.7 °F). Blood pressure and pulse rate in the supine position are 90/60 mm Hg and 105/min. When sitting, her blood pressure and pulse rate are 70/35 mm Hg and 128/min. Respiration rate is 14/min; BMI is 26. Mild diaphoresis is noted. Abdominal examination reveals no tenderness and no hepatosplenomegaly. No ecchymoses, rashes, or petechiae are noted.

Laboratory studies are pending and blood typing and cross-match are sent.

Which of the following is the most appropriate form of access for this patient?

(A) Intraosseous catheter
(B) Large-caliber peripheral intravenous catheter
(C) Single-lumen peripherally inserted central venous catheter
(D) Triple-lumen internal jugular venous catheter

Item 9

A 62-year-old man is admitted to the hospital for a 6-week history of progressive cough, hemoptysis, and shortness of breath. Prior to the onset of symptoms, he reports feeling well except for some difficulty rising out of a chair and walking up a flight of stairs because of lower extremity weakness. He has a 50-pack-year history of cigarette smoking. He has no other medical problems and takes no medications.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 140/84 mm Hg, pulse rate is 102/min, respiration rate is 14/min, and oxygen saturation is 90% breathing ambient air; BMI is 30. Cardiovascular and pulmonary examination findings are unremarkable. On neurologic examination, he has symmetric proximal muscle weakness in both his upper and lower extremities. There is no palpable peripheral lymphadenopathy.

Chest radiograph shows a right hilar mass. Chest CT confirms an 8-cm right hilar mass adjacent to the mediastinum with bulky bilateral mediastinal lymphadenopathy.

Which of the following is the most likely diagnosis?

(A) Adenocarcinoma of the lung
(B) Atypical bronchial carcinoid tumor
(C) Small cell lung cancer
(D) Squamous cell carcinoma of the lung

Item 10

A 60-year-old man is evaluated for a history of advanced COPD. He has fatigue and dyspnea with mild exertion, which significantly impairs his ability to perform routine activities. He is adherent to his medication regimen, and his inhaler technique is good. He has a history of multiple exacerbations, which have required hospitalization over the past year. He participated in pulmonary rehabilitation after his last hospitalization. Medical history is otherwise unremarkable. He quit smoking 3 years ago. Medications are roflumilast, tiotropium, mometasone/formoterol, as-needed albuterol, and 2 L of oxygen via nasal cannula.

On physical examination, respiration rate is 22/min; other vital signs are normal. BMI is 20. Pulmonary examination reveals decreased breath sounds bilaterally with no wheezing or crackles. The remainder of the examination is unremarkable.

Chest radiograph shows changes consistent with COPD, and chest CT shows bilateral homogeneous emphysema. Pulmonary function testing shows an FEV_1 of 18% of predicted, an FEV_1/FVC ratio of 33%, and a DLCO of 52% of predicted. Arterial blood gases on 2 L of oxygen reveal a pH of 7.37, a P_{CO_2} of 64 mm Hg (8.5 kPa), a P_{O_2} of 62 mm Hg (8.2 kPa), and an oxygen saturation of 91%.

Which of the following is the most appropriate next step in management?

(A) Daily oral glucocorticoid therapy
(B) Hospice care
(C) Lung transplantation
(D) Lung volume reduction surgery

Item 11

A 64-year-old man is evaluated for a 2-year history of shortness of breath with exertion and a chronic cough. His symptoms began approximately 1 year ago when he began having mild dyspnea with vigorous exercise; he also noted development of a mild, intermittent, nonproductive cough. Since that time he has had worsening shortness of breath with minimal physical activity, and the cough has become more frequent. He otherwise feels well. Medical history is otherwise unremarkable, and he takes no medications. He is a life-long nonsmoker.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 128/76 mm Hg, pulse rate is 88/min, and respiration rate is 14/min; BMI is 28. Oxygen saturation is 91% breathing ambient air. There is no jugular venous distention or supraclavicular lymphadenopathy. Lung examination reveals dry crackles at the bases bilaterally. Cardiac examination is unremarkable. Mild clubbing of the fingers is noted. There is no peripheral edema.

Results of a basic metabolic panel are normal.

Chest radiograph shows interstitial thickening at the bases bilaterally.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Chest CT with contrast
(B) Chest CT without contrast
(C) CT pulmonary angiography
(D) High-resolution chest CT

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Item 12

A 72-year-old man is evaluated for a 1-year history of cough and shortness of breath. He walks approximately 1 mile per day, but it now takes him twice as long as it did last year. He has noted no clear aggravating or ameliorating factors, and he believes his symptoms have steadily increased over the past year. He has not had chest pain, orthopnea, or paroxysmal nocturnal dyspnea.

On physical examination, vital signs are normal; oxygen saturation is 90% breathing ambient air. No jugular venous distention is noted. Pulmonary examination reveals inspiratory crackles at the bases. Cardiac examination is unremarkable.

Chest radiograph is normal. Pulmonary function testing reveals an FEV_1 of 68% of predicted, an FVC of 75% of predicted, an FEV_1/FVC ratio of 82%, and a D_{LCO} of 83% of predicted. Total lung capacity is 65% of predicted.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bronchoscopy, biopsy, and bronchoalveolar lavage
(B) Cardiopulmonary exercise testing
(C) High-resolution chest CT
(D) Ventilation-perfusion lung scan

Item 13

A 61-year-old woman is evaluated for a 4-month history of progressive dyspnea and fatigue without chest pain. Eighteen months ago, she was diagnosed with liver cirrhosis due to nonalcoholic steatohepatitis (NASH). Medical history is also significant for obesity. Medications are propranolol, spironolactone, and lactulose.

On physical examination, temperature is 36.4 °C (97.5 °F), blood pressure is 112/64 mm Hg, pulse rate is 60/min, and respiration rate is 16/min; BMI is 36. Mild scleral icterus is noted. Cardiac examination reveals a prominent S_2. The lungs are clear. Dilated veins are visible on the trunk and abdomen, and there is no appreciable ascites. Trace symmetric ankle edema is noted.

Chest radiograph shows cardiomegaly and clear lung fields. Pulmonary function tests show normal spirometry but reduced diffusing capacity (42% of predicted). A resting echocardiogram shows a left ventricular ejection fraction of 70% and an estimated right ventricular systolic pressure of 58 mm Hg. No shunt is seen with contrast enhancement. A dobutamine stress echocardiogram is negative for ischemia. A ventilation-perfusion scan shows a low probability of pulmonary embolism. Right heart catheterization reveals a mean pulmonary artery pressure of 48 mm Hg and a pulmonary capillary wedge pressure of 12 mm Hg.

Which of the following is the most likely diagnosis?

(A) Chronic thromboembolic pulmonary hypertension
(B) Hepatopulmonary syndrome
(C) Portopulmonary hypertension
(D) Pulmonary veno-occlusive disease

Item 14

A 72-year-old man is evaluated for fever in the hospital after being on mechanical ventilation for 1 week for hypoxic respiratory failure due to influenza. After an initial period of improvement, his level of purulent sputum production has increased over the past 24 hours, and over the previous 48 hours it has been necessary to increase his FIO_2 to maintain his oxygenation. His only medication is oseltamivir delivered by orogastric tube.

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 110/60 mm Hg, pulse rate is 115/min, and respiration rate is 18/min (ventilator set rate is 14/min). Pulmonary examination reveals diffuse crackles.

Laboratory studies reveal a leukocyte count of 18,000/μL (18×10^9/L), increased from 12,500/μL (12.5×10^9/L) 2 days ago.

Chest radiograph shows worsening pulmonary infiltrates.

Which of the following is the most appropriate next step in management?

(A) Begin empiric ceftriaxone and azithromycin
(B) Chest physiotherapy
(C) Deep sampling of the lower respiratory tract
(D) Substitute zanamivir for oseltamivir

Item 15

A 59-year-old man is evaluated in the emergency department for rapidly progressive dyspnea. His medical history is notable for coronary artery disease, chronic heart failure, and chronic atrial fibrillation. His medications are warfarin; aspirin; lisinopril; metoprolol; atorvastatin, and furosemide, 20 mg/d.

On physical examination, he is alert and in moderate respiratory distress. Temperature is 37.0 °C (98.6 °F), blood pressure is 150/94 mm Hg, pulse rate is 63/min and irregular, and respiration rate is 30/min; BMI is 30. Oxygen saturation is 88% breathing ambient air and increases to 93% breathing 4 L/min of oxygen by nasal cannula. Jugular venous distention is present. Cardiac examination reveals an irregular rhythm and a grade 2/6 holosystolic murmur best heard at the cardiac apex. Pulmonary examination reveals crackles bilaterally and basilar dullness.

A chest radiograph is shown (see top of next page).

An intravenous bolus of furosemide, 40 mg, is administered.

Which of the following is the most appropriate management?

(A) Begin intravenous furosemide infusion
(B) Initiate intubation and mechanical ventilation
(C) Initiate noninvasive positive pressure ventilation
(D) Initiate ultrafiltration

Item 16

A 67-year-old woman is evaluated in the emergency department for a 2 day history of fever, dyspnea, and increased cough with production of green sputum. She has severe

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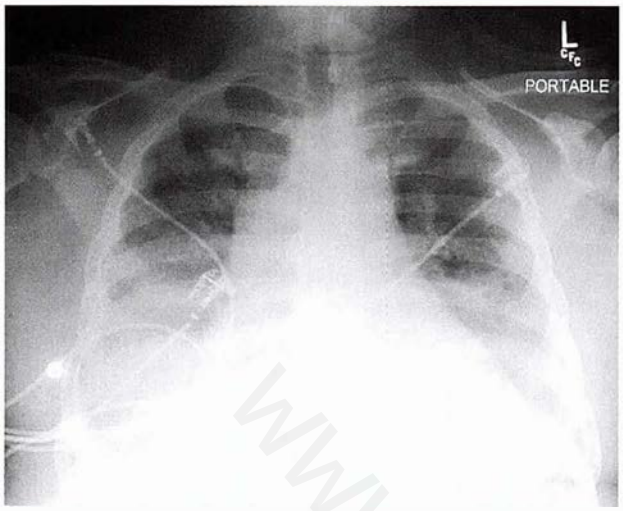

ITEM 15

H CONT.

COPD, which was diagnosed 2 years ago. She used albuterol several times yesterday with no relief of dyspnea, and she was unable to sleep last night. Her last spirometry, performed 6 months ago, showed an FEV_1 of 48% of predicted. She is a current smoker with a 24-pack-year history. Medications are tiotropium and as-needed albuterol.

On physical examination, temperature is 38.9 °C (102.0 °F), blood pressure is 124/80 mm Hg, pulse rate is 118/min, and respiration rate is 30/min. Oxygen saturation is 82% breathing ambient air. Pulmonary examination reveals bilateral diffuse expiratory wheezing. After an albuterol nebulizer treatment and breathing 2 L of oxygen by nasal cannula, oxygen saturation is 91%. She remains tachypneic with bilateral expiratory wheezing.

Chest radiograph shows no infiltrate.

In addition to continuing this patient's supplemental oxygen and short-acting bronchodilator, which of the following is the most appropriate treatment?

(A) Azithromycin and prednisone
(B) Clarithromycin and fluticasone
(C) Doxycycline and salmeterol/fluticasone
(D) Erythromycin and roflumilast

Item 17

A 67-year-old man is evaluated for a 6-month history of worsening exertional dyspnea. He has a history of severe COPD diagnosed 4 years ago and previously had minimal exertional symptoms. However, he now notes shortness of breath when walking short distances that is limiting his activity level. He does not have chest pain, gastrointestinal symptoms, or sleep-related symptoms. Medical history is otherwise unremarkable. Medications are a twice-daily fluticasone/salmeterol inhaler and an as-needed albuterol/ipratropium metered-dose inhaler. He has a 55-pack-year smoking history but stopped smoking at the time of his COPD diagnosis.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 130/84 mm Hg, pulse rate is 82/min, and respiration rate is 16/min; BMI is 24. Oxygen saturation breathing ambient air is 93%. Jugular venous distention is noted. Pulmonary examination reveals distant breath sounds and no wheezes. Cardiac examination discloses an accentuated S_2 and regular rhythm. Abdominal examination is unremarkable, and there is bilateral lower extremity edema to the level of the ankles.

A chest radiograph shows hyperinflation, prominent central pulmonary arteries, and no infiltrates. A transthoracic echocardiogram shows normal left ventricular size and function with an ejection fraction of 60% and a right ventricular systolic pressure of 52 mm Hg.

Which of the following is the most appropriate diagnostic test to perform next?

(A) High-resolution CT
(B) Oxygen measurement during sleep and exertion
(C) Polysomnography
(D) Right heart catheterization for pressure measurement

Item 18

H

A 62-year-old man was admitted to the ICU 3 days ago with community-acquired pneumonia complicated by septic shock and acute respiratory distress syndrome. In the past 24 hours, his fever and lactic acidosis have resolved, and the patient no longer requires vasopressors to maintain adequate blood pressure. However, he has become oliguric and is requiring higher Fio_2 and positive end-expiratory pressure (PEEP) to maintain oxygenation. He is receiving normal saline maintenance fluid at 100 mL/h. The net fluid balance since admission is positive 8.2 L. His current medications are ceftriaxone, azithromycin, and propofol.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 92/52 mm Hg, pulse rate is 88/min, and respiration rate is 28/min; BMI is 26. Oxygen saturation is 91% on an Fio_2 of 0.8 and a PEEP of 16 cm H_2O. Mentation seems clear, and the skin is warm. Central venous pressure is 17 cm H_2O. Cardiac examination reveals a regular rhythm without gallop or rub. Chest examination reveals diffuse inspiratory crackles with decreased breath sounds at the bases. There is pitting edema present in all extremities.

Laboratory studies:

Creatinine	2.2 mg/dL (194.5 µmol/L) (baseline 1.2 mg/dL [106.1 µmol/L])
Potassium	4 mEq/L (4 mmol/L)
Arterial blood gases:	
pH	7.30
Pco_2	50 mm Hg (6.7 kPa)
Po_2	86 mm Hg (11.4 kPa)

A chest radiograph shows bilateral infiltrates and interval development of small bilateral pleural effusions.

Which of the following is the most appropriate next step in treatment?

(A) Administer 250 mL of 5% albumin every 6 hours
(B) Discontinue intravenous maintenance fluids
(C) Initiate continuous venovenous hemodialysis
(D) Start hydrocortisone

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Item 19

A 58-year-old woman is evaluated because of daily wheezing and breathlessness during allergy season. She has a long history of seasonal allergies, and her usual symptoms include itchy eyes and runny nose. However, over the past several years, these symptoms have been periodically accompanied by episodes of wheezing and shortness of breath. These episodes have increased to the point that they limit her activities several times a week. Medical history is otherwise unremarkable. Her medications are as-needed fexofenadine and antihistamine eye drops. She is a never-smoker.

On physical examination, the patient is afebrile, blood pressure is 130/76 mm Hg, pulse rate is 79/min, and respiration rate is 14/min; BMI is 28. Watery eyes and conjunctival irritation are noted. Pulmonary examination reveals expiratory wheezing. Cardiac examination is normal.

A chest radiograph is unremarkable. Spirometry shows an FEV_1 of 74% of predicted, which improves by 18% with a bronchodilator.

In addition to a short-acting β_2-agonist, which of the following is the most appropriate treatment?

(A) Add a leukotriene antagonist
(B) Add a low-dose inhaled glucocorticoid
(C) Add a low-dose inhaled glucocorticoid and long-acting β_2-agonist
(D) Recommend daily oral antihistamine use

Item 20

An 18-year-old woman is evaluated in follow-up after a recent visit to the emergency department for a 12-day history of shortness of breath, wheezing, and cough productive of yellow sputum. She was started on levofloxacin for a diagnosis of community-acquired pneumonia, and her cough and shortness of breath have now resolved. She was diagnosed with asthma 2 years ago and has been treated for pneumonia twice since that time. Her symptoms typically improve with antibiotics; however, symptoms recur shortly after completing the course of antibiotics. She has tried several inhalers, including a combination inhaled glucocorticoid and long-acting bronchodilator, without relief.

On physical examination, she appears comfortable. Temperature is 37.7 °C (99.9 °F), blood pressure is 114/68 mm Hg, pulse rate is 94/min, respiration rate is 12/min, and oxygen saturation by pulse oximetry is 96% breathing ambient air; BMI is 25. There is no cervical or supraclavicular lymphadenopathy. Decreased breath sounds are noted posteriorly one quarter of the way up on the right, with dullness to percussion and increased tactile fremitus. A localized wheeze is noted over the right lower lung field. There is no clubbing.

Laboratory studies, including a complete blood count with differential, are normal.

Posteroanterior and lateral chest radiographs show a right lower lobe infiltrate that has persisted over the last 8 months.

Which of the following is the most likely diagnosis?

(A) Allergic bronchopulmonary aspergillosis
(B) Bronchial carcinoid tumor
(C) Chronic eosinophilic pneumonia
(D) Cystic fibrosis

Item 21

An 81-year-old man is evaluated in follow-up after a recent hospitalization. He was admitted 2 weeks ago for pneumonia and was discharged 12 days ago with a 10-day course of appropriate antibiotics. For the last week, he has had low-grade fever, fatigue, and increased shortness of breath. He currently is taking no medications.

On physical examination, temperature is 38.4 °C (101.1 °F), blood pressure is 120/65 mm Hg, pulse rate is 80/min, and respiration rate is 28/min. BMI is 21. Oxygen saturation is 90% breathing ambient air. Pulmonary examination reveals decreased fremitus, dullness to percussion, and decreased breath sounds over the lower third of the right hemithorax.

Chest radiograph reveals a moderate right-sided pleural effusion and no effusion on the left side. Thoracic ultrasound shows a moderate echogenic pleural effusion with loculations. Thoracentesis is performed.

Pleural fluid analysis:

Leukocyte count	22,000/μL (22×10^9/L)
Glucose	40 mg/dL (2.2 mmol/L)
Lactate dehydrogenase	1256 U/L
pH	7.1
Gram stain	Negative

Which of the following is the most appropriate management?

(A) Begin ceftriaxone and azithromycin
(B) Insert a large-bore pleural drain (>28 Fr [9.3 mm]) and begin levofloxacin
(C) Insert a small-bore pleural drain (<14 Fr [4.7 mm]) and begin piperacillin-tazobactam
(D) Repeat the chest radiograph in 2 weeks

Item 22

An 18-year-old man is evaluated for a 6-month history of significant chest and throat tightness and acute episodes of a barking cough and a prolonged wheeze that occur during his college basketball practice and games. He also notices episodes of these symptoms occasionally when he is not exerting himself. He has a history of moderate persistent asthma, which had been well controlled. He takes an as-needed short-acting β_2-agonist inhaler at the time his symptoms occur, but this does not relieve his symptoms. He otherwise feels well. Medical history is otherwise unremarkable. In addition to his short-acting β_2-agonist, medications are a low-dose inhaled glucocorticoid and a long-acting inhaled β_2-agonist.

On physical examination, vital signs are normal. There is no jugular venous distention. The lungs are clear without wheezing. Cardiac examination shows no murmur. The remainder of the examination is unremarkable.

Chest radiograph is normal. Spirometry shows no evidence of obstruction.

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Which of the following is the most appropriate next step in management?

(A) Allergen immunotherapy
(B) Echocardiography
(C) Otolaryngology evaluation
(D) Switch to a medium-dose inhaled glucocorticoid

Item 23

A 24-year-old man is evaluated in the emergency department for sudden onset of shortness of breath and left-sided chest discomfort. There was no preceding trauma. Medical history is negative and he takes no medications. He does not smoke or use alcohol or illicit drugs.

On physical examination, he appears uncomfortable but is not in acute respiratory distress. Temperature is 37.2 °C (99.0 °F), blood pressure is 117/62 mm Hg, pulse rate is 90/min, and respiration rate is 24/min; BMI is 21. Oxygen saturation is 98% breathing ambient air. There is no jugular venous distention. There is no tracheal deviation. There is hyperresonance to percussion and decreased air entry over the left hemithorax. Asymmetric chest expansion is noted. The cardiac examination is normal, and the remainder of the examination is unremarkable.

A chest radiograph demonstrates a left-sided pneumothorax (4 cm from chest wall to hilum) but no evidence of significant parenchymal disease or lymphadenopathy.

In addition to starting high-flow supplemental oxygen, which of the following is the most appropriate management?

(A) Insert a small-bore thoracostomy tube
(B) Perform needle aspiration of the pneumothorax
(C) Start noninvasive positive pressure ventilation
(D) Observe for 3 to 6 hours, then repeat the chest radiograph

Item 24

A 57-year-old woman is evaluated for a 6-month history of exertional dyspnea. Her medical history is notable for long-standing type 2 diabetes mellitus controlled by diet.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 144/88 mm Hg, pulse rate is 60/min, and respiration rate is 18/min; BMI is 24. Oxygen saturation is 92% breathing ambient air. Pulmonary examination is normal. Cardiac examination shows a prominent S_2.

Laboratory studies reveal normal hemoglobin, serum electrolyte, and serum creatinine levels.

An electrocardiogram shows left ventricular hypertrophy. Chest radiograph reveals increased pulmonary venous markings. Echocardiogram shows a left ventricular ejection fraction of 54%, normal valves, left ventricular hypertrophy, left atrial dilatation, Doppler evidence of diastolic dysfunction, and a right ventricular systolic pressure of 52 mm Hg.

Which of the following is the most appropriate initial management?

(A) Epoprostenol
(B) Lisinopril
(C) Right heart catheterization
(D) Sildenafil

Item 25

A 44-year-old woman is evaluated in follow-up after multiple recent emergency department visits for worsening asthma. She has had asthma since childhood, but her asthma symptoms have progressively worsened recently. Over the past 2 years, she has had twice-yearly visits to the emergency department requiring treatment with prolonged glucocorticoid tapers. She has required hospitalization twice within the last 4 months. She has no symptoms of gastroesophageal reflux, sinus disease, or other symptoms, and she diligently avoids environmental exposures and likely triggers. Medical history is significant for multiple allergies; skin testing has been positive for allergy to dust mites, cats, and ragweed. She is a never-smoker. Medications are a high-dose inhaled glucocorticoid, a long-acting β_2-agonist, a leukotriene antagonist, a long-acting anticholinergic agent, and an as-needed short-acting β_2-agonist.

On physical examination, vital signs are normal. BMI is 26. Slightly puffy facies are noted. The lungs reveal decreased air movement and mild, diffuse wheezes. Skin fragility is observed on the arms. The remainder of the examination is unremarkable.

Laboratory studies show a serum IgE level of 362 U/mL (362 kU/L) and 6% eosinophils on peripheral blood smear.

Which of the following is the most appropriate treatment?

(A) Allergen immunotherapy
(B) Daily prednisone
(C) Infliximab
(D) Omalizumab

Item 26

A 56-year-old woman is evaluated in the ICU for management of acute respiratory distress syndrome (ARDS) after elective revision of a prosthetic knee. The operation was successful with moderate blood loss, some of which was replaced using an autologous transfusion system. She received no other blood products. Her medical history is notable for osteoarthritis. Her only medication is acetaminophen.

Ventilator settings are unchanged from the operating room: volume-controlled continuous mandatory ventilation (assist control) mode with a respiration rate of 16/min, a tidal volume of 500 mL, an FIO_2 of 0.5, and a positive end-expiratory pressure of 10 cm H_2O.

On physical examination, she is afebrile. Blood pressure is 140/88 mm Hg, pulse rate is 90/min, and respiration rate is 16/min. Her height is 152 cm and weight is 75 kg (165 lb); BMI is 32, and her ideal body weight is 48 kg (106 lb). There is no jugular venous distention. Cardiac examination reveals a grade 2/6 early systolic murmur over the aortic area. There is no S_3 or S_4 and no evidence of peripheral edema. Pulmonary examination reveals diffuse inspiratory crackles. Other than postoperative changes, the remainder of the physical examination is normal.

A chest radiograph shows patchy opacification of airspaces involving all lung fields.

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CONT.

Her plateau pressure is 30 cm H_2O at the time of ICU admission and rises to 38 cm H_2O over the next 24 hours. Her oxygen requirement also increases despite diuresis with a negative fluid balance.

Which of the following is the most likely cause of this patient's acute respiratory distress syndrome?

(A) Obesity hypoventilation syndrome
(B) Pulmonary embolism
(C) Transfusion-associated lung injury
(D) Ventilator-induced lung injury

Item 27

A 57-year-old man is evaluated in follow-up for a right-sided pleural effusion. He initially presented with increasing dyspnea and a constant dull ache on his right side. He also has lost 9.1 kg (20.0 lb) over the last 6 months. Medical history is otherwise unremarkable, and he takes no medications. He has never smoked and is employed as an auto mechanic.

Initial chest radiograph showed a moderate-sized, free-flowing pleural effusion on the right; the left lung field was unremarkable. Thoracentesis showed 3500/μL (3.5×10^9/L) nucleated cells with 45% lymphocytes and an exudative profile with negative Gram stain, culture, and cytology. Chest CT following thoracentesis showed no parenchymal lesions but several areas of pleural thickening. A repeat thoracentesis performed 2 weeks later showed similar results, also with negative cultures and cytology.

On physical examination, temperature is 36.7 °C (98.1 °F), blood pressure is 128/72 mm Hg, pulse rate is 81/min, and respiration rate is 18/min; BMI is 23. There is no jugular venous distention. Heart sounds are normal with no murmurs. Dullness to percussion and decreased breath sounds are noted over the lower third of the right hemithorax. The left lung is clear to auscultation. No lower extremity edema is noted.

Repeat chest radiograph shows reaccumulation of the right pleural effusion.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bronchoscopy
(B) Large-volume pleural fluid cytology
(C) PET/CT scanning
(D) Thoracoscopy

Item 28

A 67-year-old man is evaluated in the emergency department for sepsis secondary to pyelonephritis. He takes no medications.

On physical examination, he is diaphoretic. Temperature is 40.0 °C (104.0 °F), blood pressure is 90/55 mm Hg, pulse rate is 119/min, and respiration rate is 33/min. Oxygen saturation is 93% breathing 50% oxygen by face mask. Respiratory efforts are short and shallow, and the lungs are clear to auscultation. There is tenderness to palpation over the right costovertebral angle. The remainder of the examination is unremarkable.

Urinalysis is positive for too numerous to count leukocytes and many gram-negative rods.

Intravenous fluids and empiric antibiotics are begun, but his mental status declines acutely and he is urgently intubated.

Which of the following is the most appropriate mode of ventilation for this patient?

(A) Continuous mandatory ventilation with pressure control
(B) Continuous mandatory ventilation with volume control
(C) Intermittent mandatory ventilation with pressure control
(D) Intermittent mandatory ventilation with volume control

Item 29

A 28-year-old man is evaluated for shortness of breath, fatigue, and nighttime cough. He has been employed in an auto body shop for the past 4 years and notes that his symptoms began about 6 months ago. He believes his symptoms may be associated with his work. He is being evaluated after several days off from work and currently has no symptoms or medical concerns. Medical history is unremarkable and he takes no medications. He is a never-smoker.

On physical examination, vital signs are normal. BMI is 25; his weight has remained the same for 2 years. Oxygen saturation breathing ambient air is 99%. The sinus examination is normal and the lungs are clear, with no wheezing or crackles noted. The remainder of the examination is unremarkable.

A chest radiograph is normal, and spirometry results are normal.

Which of the following is the most appropriate next step in management?

(A) Advise him to switch employment
(B) High-resolution chest CT
(C) Inhaled glucocorticoid daily
(D) Repeat spirometry after workplace exposure

Item 30

A 42-year-old man is evaluated in follow-up after being diagnosed with obstructive sleep apnea (OSA) 6 weeks ago. Polysomnography showed moderate-severity OSA that was adequately controlled with continuous positive airway pressure (CPAP) at 8 cm H_2O. He has noticed improved daytime alertness since starting CPAP, but he finds that the apparatus is very cumbersome to transport on his frequent business trips. Medical history is otherwise unremarkable, and he takes no medications. He works as a national sales representative.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 132/82 mm Hg, pulse rate is 82/min, and respiration rate is 14/min; BMI is 27. The neck circumference is 43 cm (17 in). Oropharyngeal examination reveals patent nasal airways, a low-lying soft palate, and a slight dental overjet. Cardiopulmonary examination is normal.

Weight loss is recommended.

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Which of the following is the most appropriate alternative treatment to continuous positive airway pressure?

(A) Oral mandibular advancement appliance
(B) Supplemental oxygen
(C) Surgical maxillomandibular advancement
(D) Uvulopalatopharyngoplasty

Item 31

A 61-year-old woman is admitted to the hospital for fever, shortness of breath, and weakness. Symptoms began following initiation of her latest round of chemotherapy for treatment of non-Hodgkin lymphoma 1 week ago. Other than lymphoma, her medical history is unremarkable. Subcutaneous low-molecular weight heparin is begun for venous thromboembolism prophylaxis. She is allergic to penicillin, which caused a rash.

Empiric treatment with meropenem and vancomycin is begun. She experiences steady clinical improvement over the next 2 days. All cultures show no growth, and antibiotics are discontinued. On the morning of the third hospital day, she is found unresponsive in her hospital room.

On physical examination, blood pressure is 68/38 mm Hg, pulse rate is 120/min, and respiration rate is 26/min. Oxygen saturation is 88% on a 100% oxygen nonrebreather mask. Jugular venous distention is noted. The lungs are clear bilaterally with normal breath sounds. Heart rate is regular and a prominent P_2 is noted. There is no rash.

Electrocardiogram shows tachycardia and nonspecific ST-T wave changes.

Which of the following is the most likely diagnosis?

(A) Anaphylaxis
(B) Myocardial infarction
(C) Pulmonary embolism
(D) Septic shock

Item 32

A 55-year-old man is evaluated in follow-up for severe COPD, which was diagnosed 2 years ago. He has had two exacerbations in the past year requiring hospitalization, and his baseline exercise tolerance is low. He completed pulmonary rehabilitation 3 months ago without much improvement in exercise capacity. He quit smoking 1 year ago. His medications are tiotropium, fluticasone/salmeterol, daily roflumilast, and albuterol as needed.

On physical examination, vital signs are normal; BMI is 22. Oxygen saturation is 92% breathing ambient air. Scattered wheezing is noted bilaterally.

Chest radiograph and CT scan both show emphysematous changes in the upper lobes. Spirometry shows an FEV_1 of 40% of predicted and a DLCO of 25% of predicted. His 6-minute walking distance is 240 meters (787 feet), consistent with decreased exercise tolerance.

Which of the following is most likely to benefit this patient?

(A) Change fluticasone/salmeterol to fluticasone/vilanterol
(B) Daily prednisone
(C) Lung transplantation
(D) Lung volume reduction surgery

Item 33

A 47-year-old man is evaluated for a 6-month history of dry cough. His symptoms began 6 months ago when he noted the paroxysmal onset of persistent coughing spells that make it difficult to carry on a conversation. He was initially diagnosed with allergic rhinitis and was started on a glucocorticoid nasal inhaler with some improvement of his rhinitis symptoms but not his cough. He reports no symptoms of gastroesophageal reflux disease. Medical history is otherwise unremarkable except for a history of dust allergies. Medications are a fluticasone nasal inhaler and an over-the-counter antihistamine as needed. Family history is significant for seasonal allergies and asthma in his children. He is a never-smoker. He works as an upholsterer.

On physical examination, vital signs are normal. Oxygen saturation breathing ambient air is 98%. Slight nasal congestion and dry cough are noted during examination, but both are improved from his previous evaluation. No sinus tenderness is noted. Cardiovascular, pulmonary, and abdominal examination findings are unremarkable.

A chest radiograph is normal. Spirometry shows an FEV_1 of 82% of predicted, an FVC in the normal range, and a slightly reduced FEV_1/FVC ratio of 70%. After bronchodilator challenge, the FEV_1 is increased by 3%.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Allergy skin testing
(B) High-resolution chest CT
(C) Measurement of serum IgE levels
(D) Methacholine challenge testing

Item 34

A 63-year-old woman is evaluated in the emergency department following multiple wasp stings that occurred when she was working in her garden. She is in respiratory distress with wheezing and is confused.

On physical examination after receiving a normal saline fluid bolus, temperature is 37.1 °C (98.8 °F), blood pressure is 76/44 mm Hg, pulse rate is 114/min, and respiration rate is 28/min. Oxygen saturation is 93% breathing 3 L of oxygen per minute by nasal cannula. She appears confused and can follow only simple commands. The skin is flushed, and urticaria is noted. Chest examination reveals diffuse bilateral expiratory wheezes. Cardiac examination reveals regular tachycardic rhythm. The extremities are cool to the touch.

Which of the following is the most appropriate next step in treatment?

(A) Diphenhydramine
(B) Epinephrine
(C) Glucagon
(D) Methylprednisolone

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Item 35

A 69-year-old man is evaluated to determine the appropriateness of air travel. He has moderate-severity COPD (FEV_1 is 47% of predicted) with stable exertional dyspnea in the setting of previous cigarette smoking. He and his wife are planning a 4-hour flight. He has not flown in 5 years.

His medical history is also notable for coronary artery disease. His medications are a tiotropium inhaler, an albuterol/ipratropium inhaler, aspirin, rosuvastatin, and metoprolol.

On physical examination, temperature is 36.6 °C (97.9 °F), blood pressure is 124/74 mm Hg, pulse rate is 80/min, and respiration rate is 16/min; BMI is 23. Oxygen saturation is 93% at rest breathing ambient air. Pulmonary examination reveals distant breath sounds, resonance to percussion, and no wheeze.

A chest radiograph performed 6 months ago showed a flattened diaphragm.

Which of the following is the most appropriate management?

(A) Arterial blood gas studies
(B) Echocardiographic assessment of pulmonary artery pressures
(C) Hypoxia altitude simulation test
(D) Recommend not flying

Item 36

A 30-year-old woman is evaluated in follow-up for wheezing and cough that started 6 weeks ago after a viral respiratory illness. At that time she had daily wheezing and cough with nocturnal symptoms that would disturb her sleep. An as-needed β_2-agonist was prescribed for symptomatic relief. She reports feeling much better. Her daytime symptoms of wheezing and cough have resolved, but she notes that she awakens from sleep with shortness of breath approximately twice a week. Medical history is notable for mild asthma as a child that was treated for several years; however, she has not required treatment since age 15 years. Her only medication is as-needed inhaled albuterol. She is a never-smoker.

On physical examination, vital signs are normal. No wheezing is noted on pulmonary examination. The remainder of the examination is normal.

Spirometry demonstrates an FEV_1/FVC ratio of 76%, with an improvement of 15% in the FEV_1 following treatment with a bronchodilator.

Which of the following is the most appropriate management?

(A) Add a glucocorticoid inhaler
(B) Continue current therapy and reevaluate in 4 weeks
(C) Discontinue inhaler medication
(D) Switch to a long-acting β_2-agonist inhaler

Item 37

A 73-year-old man is evaluated for sleep difficulties. He notes unrefreshing sleep that is sometimes interrupted by nocturia, and he occasionally experiences episodes of shortness of breath that awaken him. He thinks he might snore but has no regular bed partner to provide confirmation. His normal sleep schedule is 10:30 PM to 6:30 AM. Most days of the week he feels sleepy during the daytime and naps for 45 minutes. He has a history of chronic atrial fibrillation and heart failure with stable exertional dyspnea. His medications are lisinopril, atorvastatin, warfarin, and metoprolol.

On physical examination, temperature is 36.6 °C (97.9 °F), blood pressure is 118/70 mm Hg, pulse rate is 76/min, and respiration rate is 14/min; BMI is 27. Respiratory examination shows a low-lying soft palate and clear lung fields. Cardiac examination discloses an irregularly irregular rhythm but no murmurs.

Which of the following is the most appropriate next step in management?

(A) Auto-titrating positive airway pressure (APAP)
(B) In-laboratory polysomnography
(C) Out-of-center sleep testing
(D) Overnight pulse oximetry

Item 38

A 74-year-old man is evaluated in follow-up for a diagnosis of silicosis related to his former occupation as a mine worker. Over the past 4 months he has noted a 4.5-kg (10.0-lb) weight loss. He has not had fever, chills, sweats, or change in his baseline cough or dyspnea with exertion. His medical history is otherwise unremarkable. He has a 15-pack-year smoking history but quit 30 years ago. He takes no medications.

On physical examination, temperature and blood pressure are normal, pulse rate is 85/min, and respiration rate is 18/min. Oxygen saturation breathing ambient air is 97%. No jugular venous distention is noted. Pulmonary examination reveals decreased breath sounds but no wheezes. Cardiac examination is normal. There is no peripheral edema.

His last chest CT 1 year ago showed profuse upper lobe scarring and nodularity. A current chest radiograph is consistent with these findings and is unchanged from a study 6 months ago. His tuberculin skin testing has always been negative, with the last test performed 6 months ago.

Which of the following is the most appropriate next step in management?

(A) Chest MRI
(B) Isoniazid, rifampin, pyrazinamide, and ethambutol
(C) Prednisone
(D) Repeat chest CT

Item 39

A 58-year-old man is evaluated for chronic cough, occasional wheezing, and shortness of breath associated with frequent stops to catch his breath when walking one to two blocks on level ground. His medical history is notable for an episode of bronchitis, for which he underwent outpatient treatment 6 months ago. He is a current smoker with a 30-pack-year smoking history.

On physical examination, vital signs are normal. Examination of the lungs shows mildly decreased breath sounds

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throughout both lung fields and occasional scattered expiratory wheezes. The remainder of the physical examination is normal. Spirometry shows an FEV_1 of 70% of predicted and a postbronchodilator FEV_1/FVC ratio of 62%. His modified Medical Research Council (mMRC) symptom score is 2.

In addition to smoking cessation, which of the following is the most appropriate treatment?

(A) Combination inhaled glucocorticoid and a long-acting bronchodilator
(B) Phosphodiesterase-4 inhibitor and combination inhaled glucocorticoid and long-acting bronchodilator
(C) Short-acting bronchodilator as needed, a long-acting bronchodilator, and pulmonary rehabilitation
(D) Short-acting bronchodilator as needed and an inhaled glucocorticoid

Item 40

A 55-year-old woman is evaluated in follow-up for a 1-year history of chronic, nonproductive cough. She was recently diagnosed with cough-variant asthma after a methacholine challenge test. She was started on inhaled fluticasone and as-needed albuterol 3 months ago. Her cough initially improved; however, her symptoms have not fully resolved and are worsened at times, most notably when she lies down. She also notes that mild hoarseness occasionally accompanies her cough. She uses alcohol socially, and she works long hours as an attorney.

On physical examination, the patient is afebrile, blood pressure is 132/75 mm Hg, and pulse rate is 82/min; BMI is 28. Dry cough with frequent throat clearing is noted. The chest is clear with no wheezing. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Add a long-acting β_2-agonist
(B) Add a proton pump inhibitor
(C) Repeat methacholine challenge testing
(D) Start nocturnal antitussive therapy

Item 41

A 44-year-old woman is evaluated for a 1-year history of fatigue. She has been on disability owing to chronic low back pain following a motor vehicle accident 18 months ago. She typically goes to bed between midnight and 1 AM. She awakens intermittently overnight because of musculoskeletal aches but usually returns to sleep without much difficulty. She spontaneously awakens between 8 AM and 9 AM and feels unrefreshed. She sometimes naps during the day if she is bored or tired. She does not experience drowsiness when driving. She has no regular bed partner to provide a collateral history. Medications are sustained-release oxycodone twice daily and immediate-release oxycodone/acetaminophen every 6 hours as needed.

On physical examination, temperature is 36.6 °C (97.9 °F), blood pressure is 122/68 mm Hg, pulse rate is 90/min, and respiration rate is 12/min; BMI is 24. The oropharyngeal airway is patent, and the nasal examination is normal. Cardiopulmonary examination is unremarkable. Trunk flexion is limited owing to pain. There is no peripheral edema.

In-laboratory polysomnography shows central sleep apnea.

Which of the following is the most appropriate next step in management for this patient's sleep apnea?

(A) Adaptive servoventilation
(B) Continuous positive airway pressure
(C) Modafinil
(D) Reduce opioid use

Item 42

A 35-year-old woman is evaluated in follow-up for worsening asthma. Medical history is significant for environmental and food allergies, allergic rhinitis, and asthma diagnosed at age 10 years. Although her asthma had been previously well controlled, her symptoms have worsened over the past year with increased wheezing and a cough productive of dark-colored mucus. She was admitted to the hospital 2 weeks ago for her asthma symptoms and was diagnosed with pneumonia. She was treated with antibiotics and a tapering course of glucocorticoids. Her respiratory symptoms have recurred following completion of therapy. Medical history is otherwise unremarkable. Medications are fluticasone/salmeterol and as-needed albuterol metered-dose inhalers. She works as a school teacher.

On physical examination, temperature is 37.1 °C (98.7 °F), blood pressure is 110/70 mm Hg, pulse rate is 92/min, and respiration rate is 16/min; BMI is 23. Diffuse wheezing is noted on expiration with diminished airflow across the upper right lung field. The remainder of the examination is unremarkable.

Laboratory studies show a leukocyte count of 10,500/μL (10.5×10^9/L) with 15% eosinophils. Chest radiograph shows a right upper lobe infiltrate and diffusely increased lung markings.

Which of the following is the most likely diagnosis?

(A) Allergic bronchopulmonary aspergillosis
(B) Cystic fibrosis
(C) Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
(D) Hypersensitivity pneumonitis

Item 43

A 58-year-old woman was hospitalized 1 week ago for acute-on-chronic kidney injury. Since her hospitalization, she has been receiving hemodialysis through a temporary femoral vein catheter. Last night, she developed a fever of 38.7 °C (101.7 °F).

On physical examination today, she is confused. Blood pressure is 76/40 mm Hg and pulse rate is 108/min. Weight is 60 kg (132 lb). She has adequate peripheral venous access and is given a 1000-mL bolus of intravenous normal saline over 30 minutes. After receiving the fluid bolus, blood

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CONT.

pressure is 78/44 mm Hg. Oxygen saturation is 96% breathing ambient air. Cardiac examination reveals an S_1 and S_2 with regular tachycardic rhythm. There is no jugular venous distention, murmur, or gallop. The chest is clear to auscultation. Erythema without purulent discharge is noted at the femoral catheter site. The extremities are warm with bounding pulses and without edema.

Laboratory studies:

Hemoglobin	9.8 g/dL (98 g/L) (baseline 10 g/dL [100 g/L])
Leukocyte count	16,000/μL (16×10^9/L)
Creatinine	2.6 mg/dL (229.8 μmol/L)
Potassium	5.6 mEq/L (5.6 mmol/L)

A blood culture obtained yesterday is growing gram-positive cocci.

A chest radiograph is normal. Electrocardiogram shows sinus tachycardia and no acute ischemic changes.

In addition to replacing the hemodialysis catheter, which of the following is the most appropriate next step in treatment?

(A) Administer another 1000-mL normal saline fluid bolus
(B) Initiate dobutamine infusion
(C) Insert a central venous catheter
(D) Transfuse one unit of packed red blood cells

Item 44

A 75-year-old man is evaluated in the hospital after being admitted 1 week ago for a 2-week history of increased shortness of breath. He was diagnosed with idiopathic pulmonary fibrosis 5 years ago and has had progressive decline in pulmonary function and functional status since then. Two months ago he began requiring 5 L/min of supplemental oxygen at rest. During his hospitalization he has received a 7-day course of meropenem, levofloxacin, and linezolid. He also received a 5-day course of high-dose intravenous methylprednisolone. Diagnostic evaluation in the hospital ruled out pulmonary embolism and infection. He also has hypertension and type 2 diabetes mellitus, for which he takes lisinopril, chlorthalidone, and metformin.

On physical examination, the patient is afebrile, blood pressure is normal, pulse rate is 118/min, and respiration rate is 42/min. Jugular venous distention is present. Pulmonary examination reveals diffuse crackles. The pulmonic component of S_2 is increased. He has peripheral edema and clubbing.

Arterial blood gas studies on 15 L of oxygen via nonrebreathing mask show a pH of 7.32, a Pco_2 of 55 mm Hg (7.3 kPa), and a Po_2 of 50 mm Hg (6.7 kPa). High-resolution CT scan shows progression of fibrosis without evidence of superimposed ground-glass opacity.

Which of the following is the most appropriate treatment?

(A) Additional intravenous methylprednisolone
(B) Hospice care
(C) Intubation and mechanical ventilation
(D) Lung transplantation

Item 45

An 18-year-old man is evaluated in the emergency department after being found somnolent in a wooded area close to his home. His shirt is covered with emesis. He was last seen in his normal state of health 3 hours ago. His medical history is notable for anxiety, and his only medication is sertraline.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 98/58 mm Hg, pulse rate is 108/min, and respiration rate is 12/min; BMI is 26. Oxygen saturation is 85% breathing ambient air. The skin is warm. Neurologic examination reveals obtundation and semipurposeful movement of all extremities with painful stimulation. Normal muscle tone is noted, but reflexes are difficult to elicit. Pulmonary examination reveals shallow inspiration with rhonchi in the right lower lung field. Cardiac examination reveals a regular rhythm. The abdomen is soft and nondistended with no overt tenderness.

Laboratory studies:

Blood urea nitrogen	14 mg/dL (5.0 mmol/L)
Electrolytes:	
Sodium	140 mEq/L (140 mmol/L)
Potassium	3.2 mEq/L (3.2 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	6 mEq/L (6 mmol/L)
Glucose	180 mg/dL (10 mmol/L)
Lactate	2.8 mEq/L (2.8 mmol/L)
Plasma osmolality	325 mOsm/kg H_2O
Blood ethanol	Absent
Arterial blood gases (breathing 50% oxygen by mask):	
pH	7.17
Pco_2	17 mm Hg (2.3 kPa)
Po_2	120 mm Hg (16.0 kPa)

Which of the following is the most likely diagnosis?

(A) Isopropyl alcohol poisoning
(B) Methanol poisoning
(C) Salicylate poisoning
(D) Serotonin syndrome

Item 46

A 38-year-old woman is evaluated for a 2-week history of fever, right-sided chest pain, cough, and occasional night sweats. Her chest discomfort is sharp and stabbing, and the cough is not productive. Medical history is significant for tuberculosis treated with 6 months of antimicrobial therapy 10 years ago when she lived in Africa; she immigrated to the United States 6 years ago. Medical history is otherwise unremarkable and she takes no medications.

On physical examination, temperature is 36.5 °C (97.7 °F), blood pressure is 132/83 mm Hg, pulse rate is 80/min, and respiration rate is 20/min; BMI is 30. Dullness to percussion and decreased breath sounds are noted over the lower third of the right hemithorax. A pleural rub is noted over the midlateral right lung field.

Chest radiograph shows a moderate right-sided pleural effusion with no infiltrate.

Thoracentesis is performed, and 500 mL of straw-colored fluid is removed.

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Laboratory studies:

Serum lactate dehydrogenase	90 U/L
Serum total protein	7.2 g/dL (72 g/L)
Pleural fluid lactate dehydrogenase	600 U/L
Pleural fluid pH	7.30
Pleural fluid total protein	5.6 g/dL (56 g/L)
Pleural fluid total nucleated cell count	5700/μL (5.7×10^9/L), with 15% neutrophils, 71% lymphocytes, 12% monocytes, and 2% eosinophils

Which of the following tests is most likely to lead to a diagnosis?

(A) Induced sputum culture and stain for acid-fast bacilli
(B) Pleural fluid adenosine deaminase measurement
(C) Pleural fluid culture for acid-fast bacilli
(D) Pleural fluid stain for acid-fast bacilli

Item 47

A 23-year-old man is evaluated in the emergency department for a worsening asthma exacerbation that began 2 days ago following an upper respiratory infection. He has been using an albuterol inhaler at home without improvement. He has a history of poorly controlled asthma and has been hospitalized once a year for the past 4 years; he required intubation 2 years ago. Medical history is otherwise unremarkable. Medications are a long-acting glucocorticoid and an as-needed albuterol inhaler. He is a never-smoker.

On physical examination, he is in moderate discomfort. Temperature is 37.3 °C (99.1 °F), blood pressure is 138/85 mm Hg, pulse rate is 124/min, and respiration rate is 20/min. Audible wheezing is heard, and pulmonary examination reveals diffuse expiratory wheezes. Except for tachycardia, the remainder of the examination is normal.

Chest radiograph shows hyperinflated lungs but is otherwise normal. Arterial blood gas studies breathing ambient air show a pH of 7.48, a Pco_2 of 30 mm Hg (4.0 kPa), and Po_2 of 85 mm Hg (11.3 kPa).

Systemic glucocorticoids and frequent β_2-agonist nebulizer treatments are administered. After 1 hour, he notes that he feels better. He appears tired, is not speaking in full sentences, and is using accessory muscles of breathing. Pulse rate is now 119/min, respiration rate is 19/min, and repeat arterial blood gas studies breathing ambient air show a pH of 7.38, a Pco_2 of 43 mm Hg (5.7 kPa), and a Po_2 of 80 mm Hg (10.6 kPa).

Which of the following is the most appropriate management?

(A) Admit to the general medical floor
(B) Admit to the ICU
(C) Continue current treatment and reassess in 2 hours
(D) Discharge home with next-day follow-up

Item 48

A 72-year-old man is evaluated for a 2-year history of cough and a 1-year history of increasing dyspnea. He describes the cough as nonproductive, and his shortness of breath is worse with exertion. He does not have chest pain, orthopnea, paroxysmal nocturnal dyspnea, or any other symptoms. Medical history is otherwise unremarkable. He has a 15-pack-year smoking history but quit 40 years ago. He worked as a construction worker for 40 years. He takes no medications.

On physical examination, temperature, blood pressure, and pulse rate are normal; respiration rate is 18/min. Oxygen saturation breathing ambient air is 96%. BMI is 24. Pulmonary examination reveals inspiratory crackles at the bases bilaterally. Cardiac examination is normal. The remainder of the physical examination is unremarkable.

Chest radiograph shows increased interstitial markings at the bases; calcified parietal pleural plaques are noted bilaterally. High-resolution CT shows bilateral peripheral- and basal-predominant septal line thickening with evidence of honeycomb change at the bases. Pulmonary function tests reveal an FEV_1 of 70% of predicted, an FVC of 75% of predicted, an FEV_1/FVC ratio of 85%, and a D_{LCO} of 65% of predicted.

Which of the following is the most likely diagnosis?

(A) Asbestosis
(B) COPD
(C) Hypersensitivity pneumonitis
(D) Idiopathic pulmonary fibrosis

Item 49

A 52-year-old man is evaluated in follow-up after being diagnosed with severe obstructive sleep apnea 8 weeks ago. Continuous positive airway pressure (CPAP) was prescribed based on a titration during in-laboratory polysomnography. He notes some improvement in his sleep with CPAP, but he still feels drowsy during the day. He does not have problems with nasal congestion. Medical history is otherwise negative and he takes no medications.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 138/86 mm Hg, pulse rate is 72/min, and respiration rate is 12/min; BMI is 32. A low-lying soft palate and patent nasal airways are noted. The cardiopulmonary examination is unremarkable, and the neurologic examination is normal.

Which of the following is the most appropriate next step in management to address this patient's continued drowsiness?

(A) Prescribe eszopiclone
(B) Prescribe modafinil
(C) Review data from the patient's continuous positive airway pressure device
(D) Switch to a bilevel positive airway pressure device

Item 50

A 30-year-old woman is admitted to the ICU for management of respiratory failure due to influenza A infection.

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She is intubated and mechanically ventilated. Ventilator settings are in the volume-controlled continuous mandatory ventilation (assist control) mode with a respiration rate of 18/min, a tidal volume of 360 mL (6 mL/kg of ideal body weight), an Fio_2 of 0.9, and a positive end-expiratory pressure (PEEP) of 14 cm H_2O. Her plateau pressure is 28 cm H_2O. Because of difficulty with oxygenation, she was paralyzed and is being appropriately monitored for depth of sedation and depth of paralysis. Her medical history is otherwise unremarkable. In addition to her sedative and paralyzing agents, her only medication is oseltamivir.

On physical examination, temperature is 38.8 °C (101.8 °F), blood pressure is 112/64 mm Hg, pulse rate is 85/min, and respiration rate is 18/min; BMI is 29. There is no jugular venous distention. Coarse breath sounds are auscultated throughout both lung fields. Cardiac examination is normal, and there are no other significant findings on her general medical examination.

A chest radiograph shows an appropriately placed endotracheal tube. Diffuse, patchy infiltrates are seen throughout both lung fields, consistent with acute respiratory distress syndrome. Arterial blood gas studies show a pH of 7.41, a Pco_2 of 38 mm Hg (5.0 kPa), and a Po_2 of 57 mm Hg (7.6 kPa).

Which of the following is the most appropriate next step in management?

(A) Aerosolized surfactant
(B) Inhaled nitric oxide
(C) Prone positioning
(D) Systemic glucocorticoids

Item 51

A 66-year-old woman is evaluated for a 6-week history of increasing dyspnea. She has also has right-sided pleuritic chest pain when lying down and an occasional cough. She has lost 9.1 kg (20.0 lb) in the last 3 months. She has no other medical problems and takes no medications.

On physical examination, temperature is 36.4 °C (97.5 °F), blood pressure is 119/63 mm Hg, pulse rate is 77/min, and respiration rate is 20/min; oxygen saturation is 92% breathing ambient air. BMI is 21. There is no jugular venous distention. Heart sounds are normal with no murmurs. Pulmonary examination reveals dullness to percussion and decreased breath sounds over both lower lung zones. A 4-cm right breast mass is palpated.

Chest radiograph demonstrates bilateral pleural effusions but no evidence of infiltrate or pulmonary vascular congestion.

Thoracentesis is performed, and 500 mL of serosanguineous fluid is removed.

Laboratory studies:

Serum lactate dehydrogenase	124 U/L
Serum total protein	6.2 g/dL (62 g/L)
Pleural fluid lactate dehydrogenase	320 U/L
Pleural fluid total protein	4 g/dL (40 g/L)
Pleural fluid glucose	55 mg/dL (3.1 mmol/L)
Pleural fluid total nucleated cells	3500/μL (3.5×10^9/L) (15% lymphocytes)

Pleural fluid Gram stain is negative. Cytology is negative for malignancy.

In addition to evaluation of the breast mass, which of the following is the most appropriate management?

(A) Closed pleural biopsy
(B) Pleural fluid flow cytometry
(C) Repeat thoracentesis and pleural fluid cytology
(D) Thoracoscopic pleural biopsy

Item 52

A 53-year-old woman is evaluated for a 3-month history of progressively worsening exertional dyspnea and chest pressure. She has not had fever, cough, sputum production, or weight loss. Four months ago she underwent left shoulder arthroplasty. Eighteen months ago she had a right lower extremity deep venous thrombosis attributed to hormone replacement therapy. Hormones were discontinued, and she completed a 6-month course of warfarin. She takes no medications at this time.

On physical examination, temperature is 36.0 °C (96.8 °F), blood pressure is 130/74 mm Hg, pulse rate is 90/min, and respiration rate is 18/min; BMI is 26. Oxygen saturation is 89% breathing ambient air. Pulmonary examination reveals clear lung fields. Cardiac examination reveals a single loud S_2. There is no peripheral edema.

Laboratory studies, including a complete blood count and electrolyte measurement, are normal.

Chest radiograph shows no cardiopulmonary abnormalities. Transthoracic echocardiogram shows normal left ventricular and right ventricular function, normal valves, and a right ventricular systolic pressure of 52 mm Hg. Pulmonary function testing reveals an isolated reduction in diffusing capacity. Bilateral lower extremity venous ultrasound shows no evidence of recurrent deep venous thrombosis.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT angiography of the chest
(B) Polysomnography
(C) Pulmonary angiography
(D) Ventilation-perfusion scan

Item 53

H

A 66-year-old man is evaluated in the emergency department following a fall 3 days ago, when he struck the right side of his chest against a table. Since that time he has experienced right-sided pleuritic chest pain and difficulty taking a deep breath. His only other medical problem is chronic atrial fibrillation, for which he takes warfarin.

On physical examination, temperature is 37.3 °C (99.1 °F), blood pressure is 132/80 mm Hg, pulse rate is 75/min and irregular, and respiration rate is 15/min with significant left-side splinting; BMI is 26. Oxygen saturation is 85% breathing ambient air. The right side of his chest shows extensive bruising. There is no jugular venous distention and, other than an irregularly irregular rhythm, the cardiac examination is unremarkable. There are diminished breath sounds over the right lower chest with occasional crackles.

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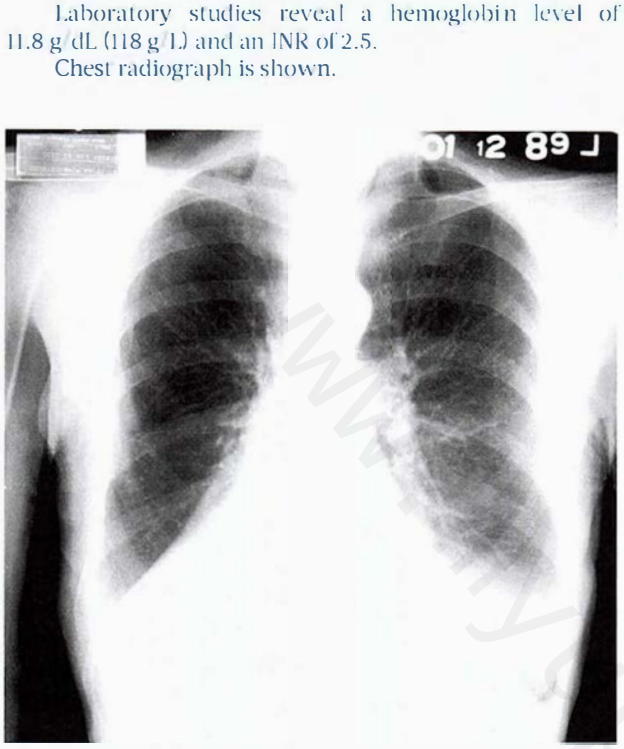
Oxygen saturation does not improve with increasing flow rates of supplemental oxygen delivered by nasal cannula. Oxygen saturation of 90% is achieved with 80% supplemental oxygen delivered by mask.

Laboratory studies reveal a hemoglobin level of 11.8 g/dL (118 g/L) and an INR of 2.5.

Chest radiograph is shown.



Which of the following is the most likely diagnosis?

(A) Hepatopulmonary syndrome
(B) Intracardiac shunt
(C) Intrapulmonary shunt
(D) Pulmonary arteriovenous malformation

Item 54

A 35-year-old woman is evaluated for a 6-month history of exertional dyspnea. She becomes dyspneic after climbing a flight of stairs or walking two blocks. Her medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 37.4 °C (99.3 °F), blood pressure is 134/86 mm Hg, pulse rate is 84/min, and respiration rate is 18/min; BMI is 26. The lungs are clear. Cardiac examination reveals a prominent S_2. Skin examination is normal. Trace bilateral ankle edema is noted.

Laboratory studies, including serum electrolytes, liver chemistry studies, and serum creatinine, are normal. Antinuclear antibody testing is negative.

Echocardiogram reveals normal left ventricular size and function; the valves are normal. Chest radiograph shows enlarged pulmonary arteries. Pulmonary function tests show an isolated reduction in diffusing capacity (40% of predicted). Ventilation-perfusion scan shows no evidence of venous thromboembolism, and a CT scan of the chest reveals normal lung parenchyma. Right heart catheterization reveals a mean pulmonary artery pressure of 35 mm Hg and a pulmonary capillary wedge pressure of 10 mm Hg.

During vasoreactivity testing using inhaled nitric oxide, the mean pulmonary artery pressure remained unchanged.

Which of the following is the most appropriate management?

(A) Epoprostenol
(B) Nifedipine
(C) Restriction of physical activity
(D) Sildenafil

Item 55

A 60-year-old man is admitted to the ICU for respiratory failure due to community-acquired pneumonia. He is intubated, started on mechanical ventilation, and receives appropriate antibiotic therapy. Over the next 4 days, he has improved significantly. Medical history is otherwise unremarkable and he was on no medications prior to admission.

Current physical examination findings include temperature of 37.0 °C (98.6 °F), blood pressure of 120/80 mm Hg, pulse rate of 85/min, and respiration rate of 12/min. Scattered coarse breath sounds are noted throughout both lung fields. The remainder of the examination is normal.

After 30 minutes of a spontaneous breathing trial (SBT), blood pressure is 135/90 mm Hg, pulse rate is 100/min, respiration rate is 28/min, and oxygen saturation is 92% on an FIO_2 of 0.35. He tolerated the SBT without evident onset of arrhythmia, respiratory distress, diaphoresis, or anxiety.

Chest radiograph shows clearing of diffuse infiltrates.

Which of the following is the most appropriate management?

(A) Arterial blood gas studies
(B) Continue mechanical ventilation for 24 hours and reassess
(C) Extubate and discontinue mechanical ventilation
(D) Extubate and initiate noninvasive positive pressure mechanical ventilation

Item 56

A 38-year-old woman is evaluated for exertional dyspnea and fatigue. Her symptoms began 4 months ago and have been steadily worsening. On two recent occasions, she experienced near-syncope walking up two flights of stairs. She notes no shortness of breath at rest or other respiratory symptoms. Medical history is significant for limited cutaneous systemic sclerosis. Her only medication is lansoprazole.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 122/72 mm Hg, pulse rate is 88/min, and respiration rate is 16/min; BMI is 26. Oxygen saturation breathing ambient air is 94%. Pulmonary examination reveals clear lung fields. Cardiac examination discloses a prominent S_2. Sclerotic changes are noted in the bilateral hands and forearms.

Chest radiograph is normal. Pulmonary function testing shows normal spirometry findings and a DLCO of 48% of predicted. CT angiography shows no evidence of pulmonary embolism. Transthoracic echocardiography shows normal left ventricular function, an enlarged right ventricle, and an estimated pulmonary artery pressure of 52 mm Hg.

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Which of the following is the most appropriate diagnostic test to perform next?

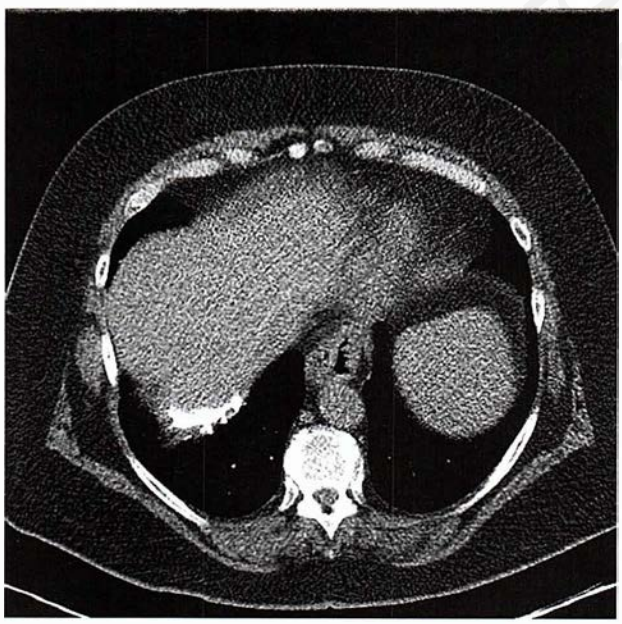
(A) 6-Minute walk test
(B) Overnight pulse oximetry
(C) Polysomnography
(D) Right heart catheterization

Item 57

A 66-year-old man is evaluated for a 4-month history of dyspnea on exertion. His symptoms are progressive, and he currently becomes short of breath when getting dressed in the morning. He has not had fever or chills but has lost 9 kg (20 lb) over the past 3 months. His medical history is otherwise unremarkable. He is an active smoker with a 46-pack-year smoking history. He is a retired plumber. He takes no medications.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 146/82 mm Hg, pulse rate is 90/min, and respiration rate is 16/min; BMI is 27. Oxygen saturation is 92% breathing ambient air. There is no jugular venous distention. There are no palpable cervical or supraclavicular lymph nodes. Decreased breath sounds are noted on the right, halfway up the hemithorax. There is dullness to percussion and decreased tactile fremitus but no egophony. No pedal edema is noted.

A low-dose chest CT, performed 5 months ago for lung cancer screening, is shown.



Current laboratory and imaging studies are pending.

Which of the following is the most likely diagnosis?

(A) Heart failure
(B) Lymphoma
(C) Mesothelioma
(D) Pneumonia

Item 58

A 32-year-old woman is evaluated for a 3-month history of dyspnea on exertion and intermittent dry cough. She continues to jog 3 miles per day but notes that it takes her longer than it used to because of increased dyspnea on exertion. She has no other symptoms and takes no medications.

On physical examination, vital signs are normal. The lungs are clear to auscultation. Skin thickening is noted on the backs of the hands, forearms, face, and thighs.

A chest radiograph is normal.

In addition to pulmonary function testing, which of the following will be most helpful in establishing a diagnosis?

(A) Anti–PM-Scl antibody testing and bronchoalveolar lavage
(B) Anti–Scl-70 antibody testing and high-resolution CT
(C) Anticentromere antibody testing and lung biopsy
(D) Antineutrophil cytoplasmic antibody testing and gallium-67 lung scanning

Item 59

A 30-year-old woman is evaluated in follow-up after recently discovering she is 6 weeks pregnant with her first child. Her medical history is notable for mild persistent asthma related to seasonal ragweed allergy. Her symptoms are well controlled on a low-dose inhaled glucocorticoid and an as-needed β_2-agonist. However, symptoms usually flare in fall and winter and with moderate exertion, and she treats these symptoms with an add-on oral leukotriene inhibitor. She currently has no asthma symptoms. Medications are budesonide and albuterol inhalers and montelukast when needed.

On physical examination, vital signs are normal. The lungs show good air movement and no wheezes. The remainder of the physical examination is unremarkable.

The patient's spirometry at the time of diagnosis showed an FEV_1 of 85% of predicted without a significant bronchodilator response. Her last routine spirometry 6 months ago demonstrated normal values with an FEV_1 of 93% of predicted.

Which of the following is the most appropriate treatment?

(A) Continue montelukast and albuterol but stop budesonide
(B) Continue the current drug regimen
(C) Increase budesonide to high dose
(D) Switch to as-needed albuterol therapy only

Item 60

A 70-year-old man is evaluated in follow-up for COPD, which was diagnosed 1 year ago. He has had two exacerbations in the last year, with the second exacerbation 1 month ago. He has also had baseline chronic cough with mucoid sputum consistently for the last 3 years. Sputum culture 6 months ago grew *Haemophilus influenzae* and *Mycobacterium avium-intracellulare*. He has to stop to catch his breath after walking 100 meters (328 feet). His inhaler

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technique is good. He quit smoking 2 years ago and completed a pulmonary rehabilitation program 4 months ago. His medications are tiotropium, fluticasone/salmeterol, and as-needed albuterol. Spirometry performed 3 months ago showed an FEV_1 of 32% of predicted and an FEV_1/FVC ratio of 50%. Chest radiograph performed last month showed no infiltrate, mass, or increased vascular congestion.

On physical examination, vital signs are normal. Oxygen saturation is 92% breathing ambient air. Pulmonary examination reveals diminished breath sounds.

Which of the following is the most appropriate long-term COPD treatment?

(A) Daily azithromycin
(B) Daily prednisone
(C) Roflumilast
(D) Simvastatin

Item 61

A 76-year-old man is evaluated in the emergency department after being found by his daughter lethargic and confused lying in bed in his apartment. He felt warm to the touch. Emergency medical services personnel noted that the apartment felt warm, with closed windows despite warm weather. He was given 1.5 L of normal saline on the way to the hospital. His medical history is notable for heart failure and depression. His medications are metoprolol, furosemide, lisinopril, and sertraline.

On physical examination, he is arousable only with physical stimulation. Temperature is 41.4 °C (106.5 °F), blood pressure is 98/74 mm Hg, pulse rate is 118/min, and respiration rate is 20/min. Oxygen saturation is 96% breathing ambient air. The mucous membranes and axillae are dry. Normal muscle tone and reflexes are noted.

Which of the following is the most appropriate next step in treatment?

(A) Administer dantrolene
(B) Perform external evaporative cooling
(C) Start cyproheptadine
(D) Start *N*-acetylcysteine

Item 62

A 50-year-old man is evaluated for a 2-year history of intermittent, nonproductive, chronic cough, as well as mild dyspnea with exertion. He has not had fever, chest pain, heartburn, loss of appetite, or weight loss. He has a 20-pack-year history of smoking and is a current smoker. His medical history is otherwise unremarkable and he takes no medications.

On physical examination, blood pressure is 125/76 mm Hg, pulse rate is 78/min, and respiration rate is 15/min; oxygen saturation is 98% breathing ambient air. BMI is 25. He appears comfortable. There is no jugular venous distention. Heart sounds are normal, and there is no murmur. The lungs are clear. No edema is noted. The remainder of the examination is normal.

A chest radiograph and electrocardiogram are normal.

Which of the following is the most appropriate next step in management?

(A) CT of the chest
(B) Polysomnography
(C) Spirometry
(D) Trial of a proton pump inhibitor

Item 63

A 29-year-old man is being discharged from the hospital following treatment of pneumonia. His medical history is notable for myotonic dystrophy with progressive muscle wasting and increasing dyspnea over the last 12 months. He sleeps in a seated to semirecumbent position and has difficulty breathing on his own when lying flat. He is being treated with cough assistance maneuvers and has not had difficulty in handling his secretions. He has no known underlying lung disease and responded well to antibiotic therapy.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 128/78 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. Chest examination is significant for mild crackles heard over the right lower lung field. The remainder of the examination is normal except for diffuse wasting of all major muscle groups.

Chest radiograph shows hypoinflation and an improving infiltrate in the upper portion of the right lower lobe. Forced vital capacity is 40% of predicted. Daytime arterial blood gas studies breathing ambient air show a pH of 7.35, a Pco_2 of 55 mm Hg (7.3 kPa), and a Po_2 of 86 mm Hg (11.4 kPa).

Which of the following is the most appropriate respiratory management for this patient?

(A) Continuous positive airway pressure
(B) Nocturnal noninvasive positive pressure ventilation
(C) Nocturnal supplemental oxygen by nasal cannula
(D) Tracheostomy and continuous mechanical ventilation

Item 64

A 53-year-old woman is evaluated in the emergency department for progressive somnolence. Her neighbors called emergency medical services because she sounded confused on the phone and would not come to her door. On arrival to the hospital, she experienced a generalized tonic-clonic seizure and was subsequently intubated for airway protection; she was admitted to the medical ICU. Her medical history is notable for hypertension, depression, and chronic pain. Her medications are amlodipine, ibuprofen, and amitriptyline.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 78/46 mm Hg, pulse rate is 108/min, and respiration rate is 16/min; BMI is 26. Oxygen saturation is 96% on an Fio_2 of 0.4. Neurologic examination reveals pupils that are dilated and minimally reactive to light. Muscle tone and reflexes are normal. Cardiovascular examination reveals a regular tachycardic rhythm. Bowel sounds are scarce, and the abdomen is slightly distended.

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Laboratory studies:

Creatinine	1.2 mg/dL (106.1 μmol/L)
Electrolytes:	
Sodium	140 mEq/L (140 mmol/L)
Potassium	4.1 mEq/L (4.1 mmol/L)
Chloride	102 mEq/L (102 mmol/L)
Bicarbonate	26 mEq/L (26 mmol/L)
Glucose	90 mg/dL (5.0 mmol/L)
Ethanol	Negative
Plasma osmolality	295 mOsm/kg H_2O
Arterial blood gases (performed 2 hours after intubation, on Fio_2 of 0.4):	
pH	7.43
Pco_2	30 mm Hg (4.0 kPa)
Po_2	130 mm Hg (17.3 kPa)

Urine toxicology studies are pending.

Electrocardiogram shows sinus tachycardia with a PR interval of 180 ms, a QRS interval of 125 ms, and a QTc interval of 420 ms. No ischemic changes are noted.

Which of the following is the most appropriate treatment for this patient?

(A) Calcium gluconate
(B) Fomepizole
(C) Physostigmine
(D) Sodium bicarbonate

Item 65

A 68-year-old man is evaluated in follow-up for a 6-mm solitary pulmonary nodule, which was incidentally discovered on imaging for abdominal pain 3 years ago. The nodule was located at the right lung base and had no associated ground-glass opacification. Follow-up chest CT was obtained at 1- and 2-year intervals, and the pulmonary nodule appears unchanged. He feels well and does not have any respiratory or constitutional symptoms. He has a 23-pack-year smoking history, but he quit smoking 20 years ago.

On physical examination, vital signs and cardiopulmonary examination findings are normal.

Which of the following is the most appropriate management?

(A) Obtain PET/CT now
(B) Perform chest radiograph in 1 year
(C) Repeat chest CT in 1 year
(D) Repeat chest CT in 2 years
(E) No further imaging is necessary

Item 66

A 62-year-old woman is evaluated in the hospital after being admitted 4 days ago for an acute exacerbation of COPD. She has responded well to treatment and is ready to be discharged today. Her medical history is notable for moderate-severity COPD, heart failure, depression, osteoporosis, hypertension, and hyperlipidemia. Her discharge medications are lisinopril, carvedilol, simvastatin, sertraline, alendronate, vitamin D, calcium, tiotropium, levofloxacin, prednisone, and albuterol.

On physical examination, temperature is normal, blood pressure is 120/84 mm Hg, pulse rate is normal, and respiration rate is 18/min. Oxygen saturation is 93% breathing ambient air. No jugular venous distention is noted. Pulmonary examination reveals a few scattered wheezes and a few basal crackles. She is not using accessory muscles of breathing. Trace pedal edema is noted. She ambulates well without oxygen.

Which of the following factors increases this patient's risk for early hospital readmission for COPD?

(A) Adequacy of discharge medications for COPD
(B) Female gender
(C) Length of hospitalization
(D) Multiple comorbid conditions

Item 67

A 45-year-old woman is evaluated for a history of recurrent bouts of bronchitis that have required treatment with antibiotics. She has had a mild, chronic cough productive of mucopurulent sputum over the past 20 years that has been present between her episodes of acute bronchitis. She does not have shortness of breath with routine activities. She has not had fever, loss of appetite, or weight loss. Medical history is significant for pertussis as a child but is otherwise unremarkable. She takes no medications, and she is a never-smoker.

On physical examination, vital signs are normal. Chest auscultation reveals wheezing over the right lower lung base but is otherwise normal. The remainder of the physical examination is unremarkable.

Chest radiograph shows increased bronchovascular markings in the right lower lobe. Pulmonary function tests show an FEV_1/FVC ratio of 72% and no change after administration of a bronchodilator.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bronchoscopy
(B) Chest MRI
(C) High-resolution chest CT
(D) Repeat chest radiograph in 8 weeks

Item 68

A 55-year-old woman is evaluated in the emergency department for respiratory failure due to an acute exacerbation of COPD. She is confused and her mental status is rapidly worsening. She is intubated and placed on mechanical ventilation with propofol for sedation. The initial peak inspiratory pressure is 30 cm H_2O and plateau pressure is 15 cm H_2O. Oxygen saturation is 98% on an Fio_2 of 0.6. Thirty minutes later, the peak inspiratory pressure is 42 cm H_2O and the plateau pressure is 30 cm H_2O. Oxygen saturation is 92% on an Fio_2 of 0.6.

On physical examination, she is afebrile, blood pressure is now 100/60 mm Hg (150/80 mm Hg on admission), pulse rate is 110/min (90/min on admission), and respiration

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rate is 30/min. There is jugular venous distention. Heart sounds are faint. Trachea is midline, and breath sounds are distant but equal bilaterally.

Which of the following is most likely responsible for this patient's change in airway pressures?

(A) Auto-positive end-expiratory pressure
(B) Endotracheal mucus plug
(C) Excessive sedation
(D) Kinked endotracheal tube

Item 69

A 75-year-old man is seen for routine follow-up for very severe COPD. He has constant dyspnea and air hunger and spends most of the day in a chair. He has had no change in baseline cough and sputum production. He has had multiple COPD exacerbations that required ICU admission and intubation. He has not benefited from pulmonary rehabilitation in the past. He quit smoking 3 years ago. His medical history is also notable for hypertension, type 2 diabetes mellitus, and a myocardial infarction 3 years ago. His medications are lisinopril, insulin glargine, budesonide/formoterol, tiotropium, roflumilast, as-needed albuterol, and 2 L of oxygen by nasal cannula. Spirometry performed 1 year ago showed an FEV_1 of 21% of predicted and a DLCO of 35% of predicted. Residual volume/total lung capacity is 105% of predicted.

On physical examination, the patient is very thin and demonstrates a significantly increased work of breathing. He is afebrile, blood pressure is 125/80 mm Hg, pulse rate is normal, and respiration rate is 32/min; BMI is 17. Oxygen saturation is 90% breathing 2 L of oxygen. Pulmonary examination reveals significantly decreased breath sounds, with no crackles or wheezing, and the remainder of the examination is unremarkable.

Laboratory studies reveal a serum albumin level of 2.3 g/dL (23 g/L).

Arterial blood gas studies reveal a Pco_2 of 55 mm Hg (7.3 kPa). Chest radiograph shows no acute changes. Echocardiogram shows normal left ventricular function; the estimated pulmonary artery pressure is elevated, suggesting cor pulmonale. CT scan shows diffuse emphysema.

Which of the following is the most appropriate management?

(A) Hospice referral
(B) Lung transplantation
(C) Lung volume reduction surgery
(D) Repeat pulmonary rehabilitation

Item 70

A 75-year-old woman is hospitalized, intubated, and mechanically ventilated for hypoxic respiratory failure due to community-acquired pneumonia. She is empirically started on ceftriaxone and azithromycin.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 110/65 mm Hg, pulse rate is 110/min, respiration rate is 14/min (ventilator is set at 14/min); BMI is 28. She appears anxious and uncomfortable with pleuritic chest pain, and she has become increasingly anxious with each painful breath. Pulmonary examination reveals diffuse crackles but no wheezing. The remainder of the physical examination is normal.

Chest radiograph shows multifocal infiltrates.

Which of the following is the most appropriate sedation and analgesia protocol for this patient?

(A) Continuous benzodiazepine infusion
(B) Interrupted benzodiazepine infusion
(C) Interrupted opioid infusion
(D) Neuromuscular blockade

Item 71

A 72-year-old woman is evaluated in the emergency department for severe, sharp, substernal chest pain that radiates to her back. Her medical history is notable for hypertension and a 50-pack-year smoking history. Her only medication is hydrochlorothiazide.

On physical examination, temperature is 36.6 °C (97.9 °F), blood pressure is 165/76 mm Hg, pulse rate is 90/min, and respiration rate is 14/min; BMI is 26. Oxygen saturation is 96% breathing ambient air.

Laboratory studies reveal normal serum electrolyte and plasma glucose levels and a serum creatinine level of 1.9 mg/dL (168.0 µmol/L). Arterial blood gas studies on 10 L/min of oxygen by face mask show a pH of 7.52, a Pco_2 of 25 mm Hg (3.3 kPa), and a Po_2 of 186 mm Hg (24.7 kPa).

A chest radiograph shows a right lower lobe infiltrate. A chest CT with intravenous contrast shows an aortic dissection extending from the descending aorta immediately distal to the left subclavian artery and extending distally into the left renal artery.

She is admitted to the ICU.

Which of the following is the most appropriate next step in treatment?

(A) Intravenous esmolol
(B) Intravenous fenoldopam
(C) Intravenous hydralazine
(D) Intravenous nitroglycerin

Item 72

A 25-year-old man is evaluated to establish care. His medical history is significant for asthma diagnosed as a child. He has a chronic productive cough but no dyspnea. He has also had recurrent sinus infections treated periodically with antibiotics. Medical history is otherwise unremarkable. He is a never smoker. Medications are a beclomethasone metered-dose inhaler and as-needed albuterol.

On physical examination, vital signs are normal; BMI is 20. Oxygen saturation breathing ambient air is 97%. Examination of the nasal passages shows multiple small polyps. Lung examination shows coarse breath sounds throughout both lung fields with occasional diffuse expiratory wheezes. The cardiac and abdominal examinations are unremarkable.

Chest radiograph is shown (see top of next page).

Spirometry shows an FEV_1/FVC ratio of 68%, with 8% improvement after administration of a bronchodilator. Laboratory studies show a normal complete blood count

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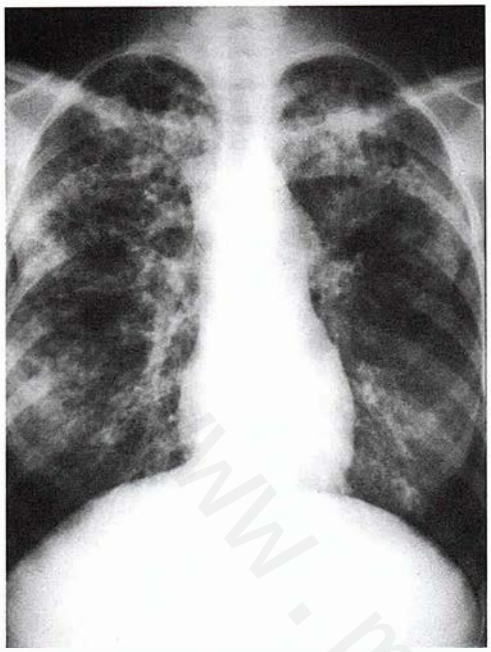


and leukocyte differential, and a normal metabolic profile including kidney function and liver chemistry tests. Urinalysis is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) α_1-Antitrypsin measurement
(B) Antineutrophil cytoplasmic antibody assay
(C) Sinus radiographs
(D) Sweat chloride testing

Item 73

A 56-year-old man is evaluated in the emergency department for an episode of coughing up blood. He has had an intermittent nonproductive cough for the past several weeks but has otherwise felt well. Three hours ago he coughed up approximately a half-cup of bright-red blood. Since that episode, he has had several episodes of cough productive of blood-tinged sputum, but he has not had further episodes of frank hemoptysis. Medical history is significant for COPD. His only medications are tiotropium and as-needed albuterol metered-dose inhalers. He has a 55-pack-year smoking history and continues to smoke.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 130/68 mm Hg, pulse rate is 88/min, and respiration rate is 12/min; BMI is 24. Oxygen saturation is 96% breathing ambient air. There are diffuse, mild expiratory wheezes noted on lung auscultation, but no focal findings. The remainder of the examination is unremarkable.

Laboratory studies reveal a leukocyte count of 9800/μL (9.8×10^9/L), a hemoglobin level of 14.5 g/dL (145 g/L), a normal platelet count, and normal kidney function.

Chest radiograph shows mild hyperinflation and a hazy infiltrate in the right lower lobe. A pulmonary embolism–protocol chest CT shows no evidence of pulmonary embolism; patchy ground-glass opacification is noted in the right lower lobe.

Which of the following is the most appropriate next step in management?

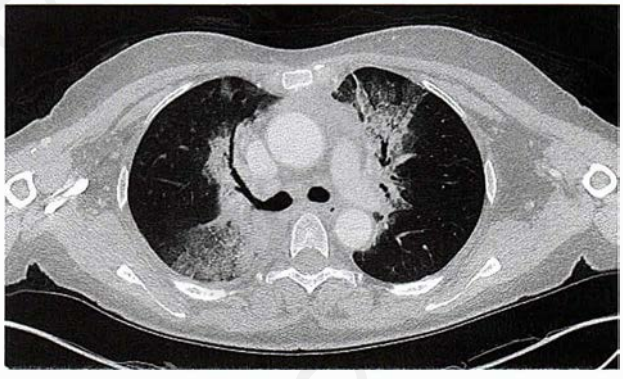
(A) Bronchoscopy
(B) Ceftriaxone and azithromycin
(C) High-resolution chest CT
(D) Upper endoscopy

Item 74

A 63-year-old woman is evaluated for a 2-week history of progressive dry cough and shortness of breath on exertion. She finished combined gemcitabine and radiation therapy 3 months ago for non–small cell lung cancer. Her medical history is otherwise notable for moderate COPD. Medications are a salmeterol inhaler and an ipratropium inhaler.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 100/60 mm Hg, pulse rate is 94/min, and respiration rate is 24/min. Oxygen saturation is 91% breathing ambient air. Pulmonary examination reveals inspiratory crackles over the left lung anteriorly; the lungs are otherwise clear to auscultation.

Chest radiograph shows increased interstitial markings in both the right and left mid- and upper lung lobes. A representative CT image is shown.



Which of the following is the most likely diagnosis?

(A) Progression of lung cancer
(B) Radiation fibrosis
(C) Radiation pneumonitis
(D) Viral pneumonia

Item 75

A 47-year-old man is evaluated in the emergency department after being found rain-soaked, unresponsive, and pulseless in a local city park by his wife. She had last seen him the previous night when he appeared in his

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normal state of health. Medical history is notable for alcohol dependence. When emergency medical services personnel arrived, his initial cardiac rhythm was pulseless electrical activity. He was endotracheally intubated and received cardiopulmonary resuscitation (CPR) during transport to the emergency department. Despite ongoing standard advanced cardiac life support, pulseless electrical activity persists. Rectal temperature is 26.0 °C (78.8 °F). His wet clothing is removed and warm blankets are placed over him. After 70 minutes of CPR, his cardiac rhythm converts to sinus bradycardia, but he requires high-dose norepinephrine to maintain a mean arterial blood pressure greater than 60 mm Hg.

On physical examination, temperature is 28.1 °C (82.6 °F), blood pressure is 88/52 mm Hg, pulse rate is 46/min with frequent premature ventricular complexes, and respiration rate is 16/min. Oxygen saturation is 96% on an Fio_2 of 0.5 and a positive end-expiratory pressure of 8 cm H_2O. Neurologic examination reveals mid-sized pupils without light reflex. Corneal reflex is negative. There is no response to verbal or painful stimulation. Muscle tone is normal. No other reflexes can be elicited. He has received no sedation.

Electrocardiogram shows sinus bradycardia, frequent premature ventricular complexes and couplets, and a J-wave in the precordial leads.

Which of the following is the most appropriate next step in management?

(A) Administer 1 L of normal saline warmed to 42.0 °C (107.6 °F)
(B) Administer a lidocaine loading dose followed by infusion
(C) Place on cardiopulmonary bypass for rewarming
(D) Recommend no further cardiopulmonary resuscitation if perfusing rhythm is lost

Item 76

A 58-year-old man is evaluated in follow-up for idiopathic pulmonary fibrosis (IPF), which was diagnosed 2 years ago. He has cough and shortness of breath and now requires supplemental oxygen at rest. Previous evaluations have not identified any cause for his symptoms other than progressive IPF. He has participated in pulmonary rehabilitation and continues in a maintenance program. He is a lifelong nonsmoker. His medical history is otherwise unremarkable, and he takes no medications.

On physical examination, the patient is afebrile, blood pressure is normal, pulse rate is 96/min, and respiration rate is 26/min; BMI is 27. Oxygen saturation is 92% breathing 4 L of oxygen by nasal cannula. Pulmonary examination reveals inspiratory crackles at the bases bilaterally. Results of a 6-minute walk test are 335 meters (1100 feet) (declined from 457 meters [1500 feet] 6 months ago).

Which of the following is the most appropriate management?

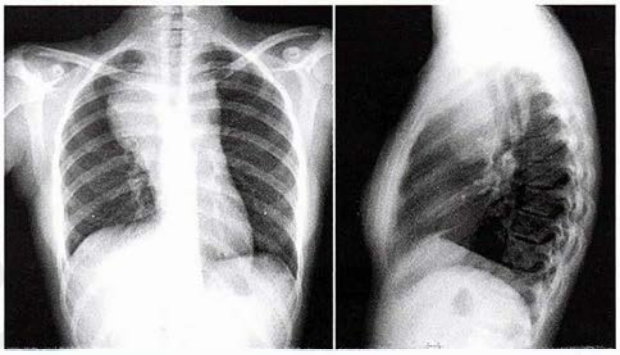
(A) Azathioprine
(B) Daily prednisone
(C) Etanercept
(D) Lung transplantation

Item 77

A 22-year-old woman is evaluated for a 3-day history of orthopnea and a 1-month history of progressively worsening dyspnea on exertion. She can no longer participate in lacrosse practice owing to dyspnea. She has generally felt well and has not had fever, chills, weight loss, or night sweats. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 118/64 mm Hg, pulse rate is 110/min, and respiration rate is 12/min; BMI is 22. Cardiac examination reveals a regular rhythm. The lungs are clear bilaterally.

A chest radiograph is shown.



Which of the following is the most likely diagnosis?

(A) Bronchogenic cyst
(B) Hodgkin lymphoma
(C) Neuroblastoma
(D) Schwannoma

Item 78

H

A 60-year-old woman is evaluated in the emergency department after an aspiration event. Her medical history is notable for multiple sclerosis with a history of infrequent aspiration episodes that occur when she is tired, but is otherwise negative. She is intubated for respiratory distress in the emergency department. She is initially hypotensive. A 3 L intravenous fluid bolus is given, a central venous catheter is placed, and vasopressor medication is started. She is transferred to the ICU 2 hours after intubation. Over the next 12 hours, her blood pressure improves and the day after admission her vasopressor is stopped.

On physical examination, the skin is warm and dry without any signs of underperfusion. Temperature is 37.0 °C (98.6 °F), blood pressure is 128/70 mm Hg, pulse rate is 88/min, and respiration rate is 24/min (set rate on the ventilator is 18/min); BMI is 27. On chest auscultation, diffuse crackles are heard bilaterally. The cardiac examination is normal.

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Chest radiograph and oxygenation findings are consistent with acute respiratory distress syndrome.

Which of the following is the most appropriate fluid management strategy?

(A) Insert a pulmonary artery catheter and titrate fluid volume to a pulmonary artery occlusion pressure of 4 to 9 mm Hg
(B) Insert a pulmonary artery catheter and titrate fluid volume to a pulmonary artery occlusion pressure of 10 to 14 mm Hg
(C) Titrate fluid volume to a central venous pressure of 4 mm Hg
(D) Titrate fluid volume to a central venous pressure of 10 to 12 mm Hg

Item 79

A 24-year-old man is evaluated for shortness of breath with occasional wheeze that occurs several times per week. He develops significant shortness of breath when playing tennis or soccer outdoors, particularly during cool weather. He notes that it takes several minutes to recover his breath when this occurs. He also notes coughing during exercise as well as episodes of cough in the evenings and nighttime, even when not exerting himself. Medical history is significant only for seasonal allergies as a child, although he now rarely experiences allergy symptoms. He takes no medications.

On physical examination, vital signs are normal. Mild nasal congestion is noted. Lung examination reveals normal air movement and no wheezes. Heart examination is unremarkable, and the remainder of the examination is normal.

A chest radiograph is normal. Spirometry findings are within normal parameters.

Which of the following is the most appropriate next step in management?

(A) Methacholine challenge test
(B) Nasal glucocorticoid
(C) Short-acting β_2-agonist inhaler as needed
(D) Clinical observation

Item 80

A 61-year-old man is admitted to the hospital for a COPD exacerbation requiring intubation and mechanical ventilation. He receives intravenous glucocorticoids, antibiotics, and supportive care. He is a former smoker and is moderately deconditioned.

After 5 days of mechanical ventilation, his condition has improved, but a spontaneous ventilation trial fails, with increased respiration rate and work of breathing after 20 minutes.

On physical examination, he is afebrile, blood pressure is 132/85 mm Hg, and pulse rate is 75/min. Breath sounds are decreased throughout both lung fields. At the end of his spontaneous breathing trial he appears fatigued but is awake and alert. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Extubate now and initiate bilevel noninvasive positive pressure ventilation immediately
(B) Extubate now and provide supplemental oxygen via nasal cannula
(C) Recommend tracheostomy placement
(D) Repeat spontaneous breathing trial in 1 hour

Item 81

A 25-year-old woman is evaluated in the ICU for difficulty in weaning from mechanical ventilation. Medical history is significant for type 1 diabetes mellitus, and she was admitted to the ICU 8 days ago with diabetic ketoacidosis secondary to sepsis from a rectal abscess. Her hospital stay has been prolonged and complicated. Her medications are piperacillin/tazobactam and basal and bolus insulin.

On physical examination, vital signs are normal. Neurologic examination reveals a weak hand grip and difficulty raising her arms. Reflexes are present but reduced.

Which of the following is the most likely diagnosis?

(A) Diabetic neuropathy
(B) Guillain-Barré syndrome
(C) ICU-acquired weakness
(D) Vasculitic neuropathy

Item 82

A 32-year-old woman is evaluated for a 2-year history of progressive dyspnea. She notes a mild, nonproductive cough but has no other symptoms. Medical history is significant only for a spontaneous pneumothorax 3 years ago. She is a never-smoker and takes no medications.

On physical examination, vital signs are normal except for a respiration rate of 20/min. BMI is 24. Oxygen saturation is 94% breathing ambient air. There are mildly decreased breath sounds and scattered crackles heard throughout all lung zones. Cardiac examination is normal. There is no digital clubbing or lower extremity edema. The remainder of the examination is unremarkable.

Laboratory studies reveal a normal complete blood count, comprehensive metabolic panel, and thyroid function studies. Chest radiograph reveals mild hyperinflation and nonspecific interstitial changes. High-resolution CT of the chest is shown (see top of next page).

Which of the following is the most likely diagnosis?

(A) Lymphangioleiomyomatosis
(B) Organizing pneumonia
(C) Pulmonary Langerhans cell histiocytosis
(D) Respiratory bronchiolitis–associated interstitial lung disease

Item 83

A 38-year-old man is evaluated in the emergency department after being found unresponsive in his closed garage

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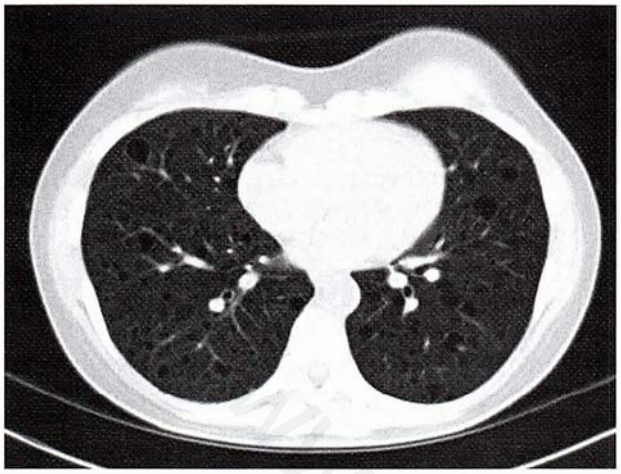

ITEM 82

H CONT. with a motor vehicle idling. He was last seen in his usual state of health 2 hours ago. His medical history is notable for epilepsy. His only medication is carbamazepine.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 106/52 mm Hg, pulse rate is 110/min, and respiration rate is 20/min; BMI is 26. Oxygen saturation is 96% breathing ambient air. He is unresponsive to voice and withdraws all extremities to painful stimulation. No tongue lacerations are noted. The pupils are mid-sized and reactive to light. The chest is clear. Cardiovascular examination reveals a normal S_1 and S_2 with regular tachycardic rhythm and no murmur or gallop.

Laboratory studies reveal a serum troponin I level of 2.4 ng/mL (2.4 µg/L) and a plasma lactate level of 4.2 mEq/L (4.2 mmol/L). Electrocardiogram reveals T-wave inversions involving leads V_2 through V_4. Chest radiograph is normal.

Which of the following tests is most likely to provide the diagnosis?

(A) Carboxyhemoglobin measurement
(B) Cardiac catheterization
(C) Electroencephalography
(D) Urine drug screen

H Item 84

A 52-year-old woman is brought to the emergency department after being found walking in the middle of a freeway on-ramp. She was given intramuscular haloperidol by emergency medical personnel for agitation on the way to the hospital. Her medical history is notable for polysubstance use.

On physical examination in the emergency department, she is alert and restless but calms down with verbal reassurance. Blood pressure is 155/90 mm Hg, and pulse rate is 110/min. She is admitted to the observation unit.

One hour later, she becomes severely agitated and tries to leave. Temperature is 38.2 °C (100.8 °F), blood pressure is 210/104 mm Hg, pulse rate is 124/min, and respiration rate is 14/min. Oxygen saturation is 97% breathing ambient air. The pupils are symmetric, dilated, and reactive to light. Slight tremor of the hands is noted. No tongue fasciculations are observed. The skin is warm and diaphoretic. The chest is clear to auscultation.

Laboratory studies reveal a serum creatine kinase level of 6600 U/L, creatinine level of 1.1 mg/dL (97.2 µmol/L), and a normal troponin level.

An electrocardiogram reveals sinus tachycardia without ischemic changes.

Which of the following is the most appropriate next step in treatment?

(A) Activated charcoal
(B) Lorazepam
(C) Physostigmine
(D) Propranolol

Item 85

A 62-year-old man is evaluated in follow-up after the recent discovery of a 2-cm right apical spiculated pulmonary nodule that in 3 months of follow-up grew 0.5 cm. His medical history is notable for emphysema, but he is otherwise healthy. He uses a tiotropium inhaler daily and an albuterol inhaler as needed.

On physical examination, temperature is 36.6 °C (97.9 °F), blood pressure is 138/74 mm Hg, pulse rate is 82/min, and respiration rate is 12/min; BMI is 30. Pulmonary examination reveals a prolonged expiratory phase, but the lungs are clear to auscultation bilaterally. Clubbing is noted.

Pulmonary function testing shows mild obstruction with a mild diffusion defect. Transthoracic needle aspiration is positive for non–small cell lung cancer (adenocarcinoma of the lung). Hormone receptor testing is negative. PET/CT shows positive uptake in the right apical lung nodule but no other abnormal uptake. MRI of the brain is normal.

Which of the following is the most appropriate treatment?

(A) Airway stent placement
(B) Radiation therapy
(C) Resection
(D) Systemic chemotherapy

Item 86

A 28-year-old man is evaluated for a 6-month history of fatigue, increase in exertional dyspnea, and cough. He has not had weight loss, fever, night sweats, or recent respiratory illness. He lives in the Northeast and has no travel history, occupational exposures, or illness contacts. His medical history is noncontributory and he takes no medications.

On physical examination, vital signs and cardiopulmonary examination are normal. There is no cervical or axillary lymphadenopathy and no skin findings.

Complete blood count and comprehensive metabolic profile are normal. Spirometry testing reveals an FVC of 72% of predicted, an FEV_1 of 75% of predicted, and an FEV_1/FVC ratio of 78%.

Chest radiograph shows bilateral hilar lymphadenopathy and normal lung parenchyma. Chest CT scan with contrast shows bilateral hilar and mediastinal and subcarinal lymphadenopathy, along with bilateral small lung nodules with a perihilar distribution.

Tuberculin skin testing is negative.

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Which of the following is the most appropriate next step in management?

(A) Bronchoscopic biopsy
(B) Empiric therapy with prednisone
(C) Interferon-γ release assay
(D) Measurement of angiotensin-converting enzyme level

Item 87

A 63-year-old man is admitted to the ICU for an exacerbation of COPD. He has a 10-year history of COPD with chronic hypercapnia. He recently developed a viral upper respiratory tract infection that worsened his baseline dyspnea, and his family reports increased use of his rescue inhaler. He was brought to the hospital because he became confused. His medical history is otherwise unremarkable. His medications on admission are tiotropium and fluticasone/salmeterol metered-dose inhalers and an as-needed albuterol metered-dose inhaler.

On physical examination, he is responsive but confused and disoriented. Temperature is 36.9 °C (98.4 °F), blood pressure is 117/83 mm Hg, pulse rate is 99/min, and respiration rate is 32/min; BMI is 20. Oxygen saturation is 86% breathing 60% oxygen by Venturi mask. Use of accessory muscles of breathing is present. On oral examination, pooling of secretions in the posterior pharynx and diminished gag reflex are noted. There is no jugular venous distention. Pulmonary examination reveals transmitted upper airway noise and decreased breath sounds with polyphonic end-expiratory wheezing heard throughout both lung fields. There is no clubbing or peripheral edema.

A chest radiograph demonstrates hyperinflation but no infiltrates.

Laboratory studies:

Leukocyte count	11,000/μL (11×10^9/L)
Hematocrit	32.8%
Arterial blood gases (breathing 60% oxygen):	
pH	7.25
Pco_2	72 mm Hg (9.6 kPa)
Po_2	48 mm Hg (6.4 kPa)

Glucocorticoids, antibiotics, and inhaled albuterol by nebulizer are started.

Which of the following is the most appropriate next step in management?

(A) Increase oxygen to 100% by nonrebreather mask
(B) Intubate and start mechanical ventilation
(C) Start noninvasive ventilation with continuous positive airway pressure
(D) Start noninvasive ventilation with inspiratory pressure support and positive end-expiratory pressure

Item 88

A 62-year-old woman is evaluated in follow-up after a 3-mm pulmonary nodule was discovered on chest imaging obtained 1 year ago. She feels well and has not had shortness of breath, cough, hemoptysis, weight loss, or chest pain. She has a 60-pack-year smoking history and is a current smoker.

On physical examination, vital signs are normal. No cervical or supraclavicular lymphadenopathy is noted. The lungs are clear to auscultation bilaterally. There is no evidence of clubbing.

Her repeat chest CT shows that the nodule has increased in size and now measures 8 mm in diameter. There is no evidence of mediastinal or hilar lymphadenopathy.

Which of the following is the most appropriate management?

(A) Perform bronchoscopy
(B) Perform transthoracic needle aspiration
(C) Refer for thoracic surgery
(D) Repeat chest CT imaging in 3 months

Item 89

A 33-year-old man is evaluated acutely on the inpatient general medicine service for increased heart rate. He was admitted earlier in the day for treatment of neutropenic fever following induction chemotherapy for a recent diagnosis of acute myeloid leukemia after presenting with shaking chills and fever. He was started on broad-spectrum antibiotics and intravenous fluids 8 hours ago.

On physical examination, temperature is 38.6 °C (101.5 °F), blood pressure is 112/60 mm Hg, and respiration rate is 33/min; BMI is 25. Pulse rate was 95/min on admission but has been 150/min for the past hour. Oxygen saturation is 94% breathing ambient air. The skin is very warm and dry. The chest is clear, and the cardiac examination is unremarkable except for tachycardia. The abdomen is soft and nontender. The remainder of the examination is unremarkable.

Laboratory studies on admission were significant for a hemoglobin level of 10 g/dL (100 g/L), a leukocyte count of 10/μL (0.01×10^9/L), and platelet count of 15,000/μL (15×10^9/L). A complete metabolic profile is normal.

Chest radiograph showed no evidence of infiltrates.

Activation of a rapid response team would be expected to decrease which of the following outcomes in a patient such as this?

(A) Chance of cardiopulmonary arrest
(B) ICU utilization
(C) Intubation rate
(D) Length of hospital stay

Item 90

A 28-year-old woman is evaluated for difficulty staying awake during work. She works as a respiratory therapist at a hospital. For the last 9 months, she has been alternating daytime (7 AM to 7 PM) and night shifts (7 PM to 7 AM). When working the night shift, she often feels sleepy by 3 AM and struggles to stay awake. She feels more awake by the time she drives home and then has difficulty falling asleep during the day. Her medical history is unremarkable, and she takes no medications.

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On physical examination, vital signs are normal; BMI is 25. The remainder of the examination is normal.

Which of the following is the most appropriate next step in management?

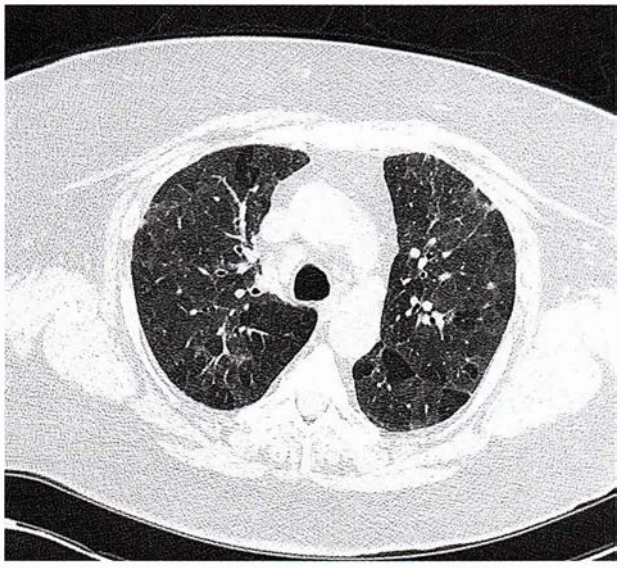
(A) Modafinil
(B) Multiple sleep latency testing
(C) Polysomnography
(D) Sleep hygiene counseling
(E) Zolpidem

Item 91

A 27-year-old man is evaluated for the acute onset of fever, chills, body aches, and dry cough that began last evening after returning home from trimming timber at a saw mill. He has similarsymptoms that have been occurring two to three times a month for the past 3 months. These episodes always occur at home and not at the saw mill but never occur on the weekends or when he is away from home on an extended vacation. Two other colleagues who trim timber at work have also reported similar symptoms over the same time period. His medical history is otherwise unremarkable. He takes no medications.

On physical examination, the patient is currently afebrile, blood pressure is normal, pulse rate is 103/min, and respiration rate is 26/min. Pulmonary examination reveals diffuse crackles throughout all lung zones. Cardiac examination is normal except for tachycardia.

Chest radiograph shows ill-defined haziness in the upper lung zones, but no clear infiltrates. CT of the chest shows mid-lobe–predominant changes; representative findings are shown.



Which of the following is the most likely diagnosis?

(A) Acute hypersensitivity pneumonitis
(B) Acute interstitial pneumonia
(C) Idiopathic pulmonary fibrosis
(D) Nonspecific interstitial pneumonia

Item 92

A 62-year-old woman is evaluated in follow-up after her first hospitalization for an acute exacerbation of COPD. She is currently completing a 5-day course of oral glucocorticoids. She has not had fever, and her cough and sputum production have improved. Although she feels much better, she notes that her exercise capacity has not returned to its preadmission baseline. Medical history is otherwise unremarkable. She has a 30-pack-year history of smoking but stopped smoking 3 years ago. Her medications are tiotropium, mometasone/formoterol, and as-needed albuterol.

On physical examination, vital signs are normal. Oxygen saturation breathing ambient air is 92%. Lung examination shows mildly diminished airflow but is otherwise clear. The remainder of the examination is unremarkable.

Pulmonary function testing performed 5 months ago showed an FEV_1 of 55% of predicted.

Which of the following is the most appropriate treatment?

(A) Add roflumilast
(B) Extend glucocorticoid taper for an additional 5 days
(C) Start 2 L of oxygen by nasal cannula
(D) Start pulmonary rehabilitation

Item 93

A 52-year-old man is hospitalized for a 1- to 2-week history of general malaise and lack of appetite. He has acute-on-chronic kidney injury and has recently been started on dialysis. He has no history of bleeding.

On physical examination, temperature is 36.5 °C (97.7 °F), blood pressure is 80/52 mm Hg, pulse rate is 120/min, and respiration rate is 18/min; BMI is 24. A tunneled dialysis catheter is noted over the left chest wall, and no drainage or redness is noted. The remainder of the physical examination is normal.

After administration of 1 L of fluid, blood pressure is 118/56, pulse rate is 92/min, and respiration rate is 21/min.

Laboratory studies:

Hemoglobin	7.7 g/dL (77 g/L)
Leukocyte count	6750/μL (6.75×10^9/L)
Platelet count	101,000/μL (101×10^9/L), with giant platelets

Blood cultures are positive for methicillin-resistant *Staphylococcus aureus*. Appropriate antibiotics are initiated.

Which of the following is the most appropriate next step in management for this patient's anemia?

(A) Administer epoetin
(B) Transfuse one unit of packed erythrocytes
(C) Transfuse two units of packed erythrocytes
(D) Do not transfuse

Item 94

A 52-year-old man is evaluated in follow-up after undergoing total knee arthroplasty 3 weeks ago. Although the surgical procedure was uncomplicated, he required reintubation

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in the recovery room owing to persistent hypoxia. He was extubated 24 hours later without difficulty. A postextubation chest radiograph and arterial blood gas study were normal, and the remainder of his hospitalization was unremarkable. Since discharge, he reports normal recovery from surgery and no respiratory problems. Medical history is notable for hypertension, for which he takes lisinopril.

On physical examination, temperature is 36.2 °C (97.2 °F), blood pressure is 128/84 mm Hg, pulse rate is 76/min, and respiration rate is 14/min; BMI is 36. Oxygen saturation breathing ambient air is 97%. Head and neck examination is notable for a low-lying soft palate and thick neck. The lungs are clear, and cardiac examination is normal. His surgical incision is healing well, and the remainder of the examination is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Overnight pulse oximetry
(B) Polysomnography
(C) STOP-Bang questionnaire
(D) No additional testing

Item 95

A 49-year-old woman is evaluated after discharge from the hospital following treatment in the ICU for 6 days for severe sepsis with septic shock requiring aggressive fluid resuscitation and vasopressor support in addition to antibiotic therapy. She feels significantly better since returning home but has had difficulty sleeping. She works as a university professor and has been experiencing anxiety and difficulty with multitasking and other simple cognitive tasks, such as setting up and coordinating meetings with her faculty. She has been able to resume some of her hobbies, including taking short hikes and gardening, but she continues to be limited by fatigue and weakness.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 115/65 mm Hg, pulse rate is 80/min, and respiration rate is 10/min. BMI is 23, which is an improvement since discharge when BMI was 20. Motor strength is mildly decreased in the major muscle groups and reflexes are normal. Cardiac and pulmonary examinations are unremarkable.

Laboratory studies, including a complete blood count, basic chemistry tests, thyroid-stimulating hormone, and urinalysis, are normal.

Which of the following is the most likely cause of this patient's symptoms?

(A) Critical illness neuromyopathy
(B) Debilitation after prolonged bed rest
(C) Generalized anxiety disorder
(D) Postintensive care syndrome

Item 96

A 67-year-old man is evaluated in the emergency department for the sudden onset of severe periumbilical pain followed by an episode of emesis. His medical history is notable for hypertension, type 2 diabetes mellitus, and chronic atrial fibrillation. His medications are metformin, metoprolol, glyburide, aspirin, and losartan.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 92/44 mm Hg, pulse rate is 112/min, and respiration rate is 22/min. Oxygen saturation is 95% breathing ambient air. The chest is clear to auscultation bilaterally. Cardiac examination reveals an irregularly irregular rhythm. The abdomen is nondistended and mildly tender to palpation but without guarding or rebound tenderness. During the examination the patient has a forceful bowel evacuation.

Laboratory studies:

Hemoglobin	14.2 g/dL (142 g/L)
Leukocyte count	18,600/μL (18.6×10^9/L)
Amylase	320 U/L
Lactate	2.2 mEq/L (2.2 mmol/L)

Findings on abdominal radiograph are normal.

Which of the following is the most likely diagnosis?

(A) Acute mesenteric ischemia
(B) Acute pancreatitis
(C) *Campylobacter* enteritis
(D) Colonic ischemia

Item 97

A 63-year-old woman is admitted to the hospital for septic shock secondary to community-acquired pneumonia. After receiving antibiotics, fluids, and vasopressors, her condition stabilizes. However, she subsequently develops respiratory distress and is intubated. Her oxygen requirement increases until she is receiving 100% oxygen. Ventilator settings are in the volume-controlled continuous mandatory ventilation (assist/control) mode with a respiration rate of 15/min, a tidal volume of 330 mL (6 mL/kg of ideal body weight), an F_{IO_2} of 1.0, a positive end-expiratory pressure (PEEP) of 5 cm H_2O, a peak inspiratory pressure of 25 cm H_2O, and a plateau pressure of 22 cm H_2O.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 115/60 mm Hg, pulse rate is 105/min, and respiration rate is 15/min. The skin is cool. There is no jugular venous distention. Heart sounds are rapid and regular but otherwise unremarkable. Diffuse crackles are heard on pulmonary examination. There is no edema. The remainder of the physical examination is noncontributory.

Arterial blood gas studies show a pH of 7.32, a P_{CO_2} of 50 mm Hg (6.7 kPa), and a P_{O_2} of 54 (7.2 kPa). Chest radiograph shows extensive patchy areas of opacification of the lung fields.

Which of the following is the most appropriate management?

(A) Decrease tidal volume
(B) Implement a prone positioning maneuver
(C) Increase positive end-expiratory pressure
(D) Increase set respiration rate on the ventilator

Item 98

A 59-year-old woman is evaluated in follow-up in November after being diagnosed with moderate COPD 3 months ago.

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She has never received the influenza or pneumococcal vaccine. She has no allergies. Her medications are a long-acting inhaled anticholinergic agent and an as-needed short-acting β_2-agonist inhaler.

On physical examination, vital signs and the remainder of the physical examination are normal.

Which of the following vaccinations are recommended for this patient?

(A) Inactivated influenza vaccine and 13-valent pneumococcal conjugate vaccine (PCV13)
(B) Inactivated influenza vaccine and 23-valent polysaccharide pneumococcal vaccine (PPSV23)
(C) Inactivated influenza vaccine, PPSV23, and PCV13
(D) Live attenuated influenza vaccine and PPSV23
(E) Live attenuated influenza vaccine, PPSV23, and PCV13

Item 99

A 20-year-old woman is evaluated in the emergency department for an acute exacerbation of asthma. She has not used her inhalers for several days because she ran out of medications.

On physical examination, she appears to be in respiratory distress. Temperature is 37.1 °C (98.8 °F), blood pressure is 130/75 mm Hg, and pulse rate is 90/min. Oxygen saturation is 96% breathing 4 L/min oxygen by nasal cannula. There is minimal air movement with inspiration and minimal musical wheezing.

Blood gas analysis shows acute respiratory acidosis.

She is intubated. Ventilator settings are in the volume-controlled continuous mandatory ventilation (assist/control) mode with a set respiration rate of 16/min (actual respiration rate is 24/min), a tidal volume of 400 mL, an F_{IO_2} of 0.4, and a positive end-expiratory pressure of 5 cm H_2O. She is admitted to the ICU. Shortly after arriving in the ICU, peak inspiratory pressure rises to 45 cm H_2O. Blood pressure is now 80/40 mm Hg, pulse rate is 115/min, and oxygen saturation is 80%.

Which of the following is the most appropriate immediate next step in management?

(A) Decrease the set respiration rate to 12/min
(B) Decrease the tidal volume to 300 mL
(C) Increase the inspiratory flow rate
(D) Increase the sedative infusion rate and prepare for therapeutic paralysis
(E) Temporarily disconnect the endotracheal tube from the ventilator

Item 100

An 18-year-old man is evaluated in the emergency department after a near-drowning episode. He was intubated by emergency medical services before arrival at the hospital. He is admitted to the ICU and is mechanically ventilated. The ventilator is set in the volume-controlled continuous mandatory ventilation (assist/control) mode with a respiration rate of 18/min, a tidal volume of 360 mL, an F_{IO_2} of 0.65, and a positive end-expiratory pressure (PEEP) of 12 cm H_2O. The ventilator shows a peak inspiratory pressure of 28 cm H_2O and a plateau pressure of 25 cm H_2O.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 122/68 mm Hg, pulse rate is 75/min, and respiration rate is 18/min. Ideal body weight is 60 kg (132 lb). Crackles are auscultated bilaterally. The remainder of the physical examination is normal.

Arterial blood gas studies show a pH of 7.25, a P_{CO_2} of 60 mm Hg (8.0 kPa), and a P_{O_2} of 66 mm Hg (8.8 kPa). Serum bicarbonate level is 26 mEq/L (26 mmol/L). Oxygen saturation is 92%. Chest radiograph shows extensive bilateral opacification.

Which of the following is the most appropriate management?

(A) Decrease tidal volume to 260 mL
(B) Maintain tidal volume at 360 mL
(C) Increase tidal volume to 420 mL
(D) Increase tidal volume to 550 mL

Item 101

A 65-year-old man is evaluated for a 14-month history of progressively worsening cough and shortness of breath, most notable with exertion. His cough is nonproductive and is not associated with fever, chills, or sweats. He has no other symptoms. He is a retired carpenter. He has a 20-pack-year history of smoking but quit 15 years ago. He takes no medications.

On physical examination, respiration rate is 22/min; other vital signs are normal. Oxygen saturation is 95% breathing ambient air. BMI is 27. Pulmonary examination reveals inspiratory dry crackles at the bases bilaterally. Cardiac examination is normal. Mild clubbing is present. There is no lower extremity edema.

Pulmonary function tests reveal an FVC of 60% of predicted, an FEV_1 of 63% of predicted, an FEV_1/FVC ratio of 85%, and a D_{LCO} of 50% of predicted. High-resolution CT shows bilateral peripheral- and basal-predominant septal line thickening with evidence of honeycomb change at the bases. No ground-glass opacities are noted, and there is no mediastinal or hilar lymphadenopathy.

Which of the following is the most likely diagnosis?

(A) COPD
(B) Hypersensitivity pneumonitis
(C) Idiopathic pulmonary fibrosis
(D) Respiratory bronchiolitis–associated interstitial lung disease

Item 102

A 64-year-old man is evaluated for left-sided pleuritic chest pain. The discomfort is localized to the upper left chest and supraclavicular region. He is otherwise asymptomatic. Medical history is unremarkable except for 35-pack-year cigarette use; he continues to smoke. He takes no medications.

On physical examination, blood pressure is 132/72 mm Hg, pulse rate is 68/min, and respiration rate is 12/min.

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Multiple firm, nonmobile lymph nodes are present in the left supraclavicular space. The lungs are clear to auscultation bilaterally. The remainder of the examination is normal.

A plain chest radiograph shows a left upper lobe opacity, bilateral hilar lymphadenopathy, and no pleural effusion.

CT of the chest is shown.



Which of the following is the most appropriate diagnostic test to perform next?

(A) Bronchoscopy with needle aspiration of mediastinal lymph nodes
(B) Bronchoscopy with transbronchial biopsy of the left apical mass
(C) CT-guided biopsy of the left apical mass
(D) Needle aspiration of the left supraclavicular lymph nodes

Item 103

A 29-year-old woman is evaluated for shortness of breath while mountain climbing. She is currently at an elevation of 3200 meters (10,500 feet) and has developed cough and dyspnea, which are present both with exertion and at rest; these symptoms prevent her from continuing the climb. Her medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 36.0 °C (96.8 °F), blood pressure is 154/90 mm Hg, pulse rate is 120/min, and respiration rate is 22/min; BMI is 23. Oxygen saturation is 86% breathing ambient air. She is in moderate respiratory distress. Pulmonary examination reveals a few bibasilar crackles.

Supplemental oxygen is given and arrangements are made for descent from altitude.

Which of the following is the most appropriate adjunctive treatment for this patient?

(A) Acetazolamide
(B) Dexamethasone
(C) Ibuprofen
(D) Nifedipine

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Answers and Critiques

Item 1 Answer: C

Educational Objective: Treat thermal upper airway injury with endotracheal intubation.

The most appropriate next step in treating this patient's respiratory findings is to perform endotracheal intubation. This patient sustained significant thermal injury to his upper airway as evidenced by an edematous oropharynx and monophonic wheeze consistent with inspiratory stridor. Intense heat can cause edema and blistering from the mouth to the larynx, and patients with a visibly damaged airway or stridor are at high risk of complete upper airway obstruction due to swelling. It is difficult to predict which patients with acute inhalational injury will develop complete upper airway obstruction, and even patients with minimally apparent inhalational airway injury may develop worsening obstruction associated with intravenous hydration or analgesia needed for burn treatment. Therefore, ensuring upper airway patency is the first priority in patients with significant smoke exposure, and endotracheal intubation is indicated in this patient at high risk of obstruction.

Because helium is less dense than nitrogen, a mixture of helium and oxygen (heliox) may be used in situations in which there is increased airway resistance. The combination of helium and oxygen improves laminar airflow and may decrease the work of breathing in patients with increased airway resistance. However, it would not treat the underlying inhalation-associated airway obstruction.

Methylprednisolone is useful for COPD exacerbations, but systemic glucocorticoids do not have a role in treating upper airway edema or smoke-induced injury of the lower airways.

Nebulized epinephrine can transiently reduce upper airway edema from allergic or anaphylactic reactions, but it does not have a role in the treatment of inhalational injury.

This patient's expiratory wheezes and acute respiratory acidosis suggest the presence of a COPD exacerbation triggered by smoke inhalation, in which case noninvasive ventilation would be appropriate. However, noninvasive ventilation will not prevent this patient from developing complete airway obstruction, and securing the airway with an endotracheal tube while it is still possible takes precedence.

KEY POINT

- In patients with significant smoke inhalation, a visibly damaged airway and stridor are indicators of a high risk for complete upper airway obstruction due to swelling; such patients require immediate endotracheal intubation.

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Item 2 Answer: B

Educational Objective: Perform early mobilization in a critically ill patient.

The most appropriate management is early mobilization with progressive physical activity as tolerated starting now. Disabling weakness and motor function impairments are common in ICU survivors and can last up to 5 years following critical illness. Traditionally, patients in the ICU were believed to be too ill to participate in significant physical activity, and any attempt at full mobilization and exercise was reserved until more aggressive therapies were withdrawn or the acute illness had resolved. This was especially true of patients on mechanical ventilation and vasopressors. In many cases, only passive range of motion exercises were provided in the ICU until the patient was believed to be appropriate for mobilization and increased amounts of active physical activity. However, studies have shown that exercise and physical therapy are the only interventions that have a significant effect on decreasing weakness and motor function deficits associated with critical illness. Additionally, it has been demonstrated that patients on ventilators and low-level vasopressors may safely participate in a progressive mobility program once stability is established.

Early mobilization is defined as patient mobilization (such as sitting up in bed and dangling feet over the edge of the bed) within 48 hours of admission to the ICU. Once the patient is awake and interactive, more aggressive bed exercises can be done. If these activities are tolerated without instability, the patient should be assessed for the next level of activity. Early mobilization, along with careful attention to management of pain, agitation, and delirium, has been shown to reduce ICU and hospital length of stay, shorten return to independent functional status, and improve survival. Waiting for discontinuation of vasopressors or extubation is not appropriate because these may not occur for a significant period of time, in which substantial deconditioning may develop.

KEY POINT

- Early mobilization with progressive physical activity, along with careful attention to management of pain, agitation, and delirium, has been shown to reduce ICU and hospital length of stay, shorten return to independent functional status, and improve survival.

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Item 3 Answer: C

Educational Objective: Evaluate a subcentimeter pulmonary nodule.

The most appropriate next step in management is to review any previous chest imaging the patient may have had. This patient's chest CT shows an incidental finding of a subcentimeter pulmonary nodule. Appropriate evaluation of a subcentimeter pulmonary nodule depends on the patient's risk for lung cancer, which relates to the patient's past or present smoking status and history of other malignancy. Regardless of risk stratification, however, any previous imaging of the chest should be obtained as a comparison. If previous chest imaging confirms stability of the nodule for more than 24 months, further imaging may not be necessary. Previous imaging can also help in determining the best next step in management as well as when to repeat future imaging. For example, if the nodule has been increasing in size, short term follow-up may be indicated whereas documented stability would allow the clinician to extend the time until next imaging. If no previous imaging is available, the clinician should refer to the Fleischner criteria to establish the timing of the next imaging.

Bronchoalveolar lavage provides samples from small bronchi and alveoli and is typically used to diagnose infection or to obtain cell counts in the diagnosis of parenchymal lung disease. It is rarely helpful in determining the cause of a solitary subcentimeter pulmonary nodule. Given the absence of other symptoms to suggest an infection or parenchymal lung disease, bronchoalveolar lavage is not indicated at this time.

Even if previous imaging is not available, a PET/CT would not be indicated at this time. The CT shows a 5-mm nodule, and PET imaging is usually normal in a subcentimeter pulmonary nodule even if the nodule is malignant.

Biopsy of a solitary pulmonary nodule can be obtained by bronchoscopy, CT-guided needle aspiration, or surgical excision. An enlarging pulmonary nodule or a suspicious-appearing nodule warrants more aggressive evaluation with tissue diagnosis or excision depending on the pretest probability of malignancy. This patient, however, has a low pretest probability of cancer because she is a lifetime nonsmoker and has no history of active malignancy. Even if previous imaging is not available, this nodule should be monitored with repeat imaging based on the Fleischner criteria.

KEY POINT

- In patients with a subcentimeter pulmonary nodule, any previous imaging of the chest should be obtained to establish whether the nodule has remained stable or has grown over time.

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Item 4 Answer: D

Educational Objective: Evaluate worsening COPD symptoms with repeat spirometry.

The most appropriate management is to repeat spirometry. Lung function can worsen over time in patients with COPD. During each visit, new or worsening symptoms (cough, sputum, dyspnea, fatigue), smoking status, adherence to and effectiveness of the medication regimen, adverse effects of treatment, and inhaler technique should be assessed. The frequency, severity, and causes of exacerbations should be evaluated. Comorbidities should be identified and managed. Spirometry is indicated when patients with COPD experience a change in symptoms. Annual spirometry can help determine which patients have rapid decline in lung function. Because this patient had pulmonary function testing done 3 years ago and has since had a decrease in his exercise capacity, spirometry is indicated. If spirometry shows worsening airflow obstruction in this patient, addition of a long-acting β_2-agonist and an inhaled glucocorticoid may help with symptom control. If spirometry does not show significant worsening of airflow, other comorbidities such as cardiovascular disease should be considered.

Roflumilast is a phosphodiesterase-4 inhibitor that is indicated in patients with severe and very severe COPD with recurrent exacerbations. This patient does not meet these criteria for use of this medication.

Monitoring patients with COPD using complete pulmonary function testing (with lung volumes and diffusing capacity) rather than spirometry is not cost effective and does not change management. Complete pulmonary function testing is not required unless lung volume reduction surgery (LVRS) or lung transplantation is being considered.

CT of the chest is not routinely recommended in the monitoring of COPD. This patient had a recent chest radiograph, which was normal, and there are no symptoms or signs to suggest a tumor that would warrant a CT scan at this time. Chest CT would be useful if this patient was being evaluated for LVRS or lung transplantation.

Oxygen therapy is not indicated because an oxygen saturation greater than 88% is adequate. If oxygen saturation is less than 92%, arterial blood gas studies should be performed.

KEY POINT

- Spirometry is indicated when patients with COPD experience a change in symptoms; annual spirometry can help determine which patients have rapid decline in lung function.

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Item 5 Answer: D

Educational Objective: Diagnose pulmonary lymphangitic spread of metastatic cancer.

The most likely diagnosis is lymphangitic carcinomatosis. Pulmonary metastases most commonly present as multiple, peripheral, or subpleural pulmonary nodules but can also present as solitary pulmonary nodules or lymphangitic spread. Lymphangitic spread of tumor is most commonly associated with adenocarcinoma (lung, breast, and gastrointestinal tract), melanoma, lymphoma, and leukemia; it should be considered if an interstitial abnormality is identified on CT in a patient with one of these malignancies, and is best defined with high-resolution CT if suspected. This patient presents with likely metastatic breast cancer to the mediastinal and hilar lymph nodes with new interstitial changes on chest CT, which raises concern for lymphangitic spread.

Atypical pneumonia can present with interstitial changes. However, this patient has no symptoms to suggest an infection, did not improve with appropriate antibiotic therapy, has had symptoms for 1 month, and has unexplained mediastinal and hilar lymphadenopathy.

Bronchiolitis obliterans organizing pneumonia may be associated with solid-organ malignancies. However, the most common radiographic presentation shows areas of lung consolidation.

The usual CT scan findings associated with idiopathic pulmonary fibrosis are bilateral peripheral and lower lobe–predominant interstitial thickening with honeycombing. Clubbing is present in approximately half of patients. It is not associated with mediastinal and hilar lymphadenopathy.

Patients with radiation pneumonitis present with cough and/or dyspnea approximately 6 weeks after the exposure. CT imaging typically shows hazy opacities with ground-glass attenuation. Affected areas are most commonly found in the field of radiation but can occasionally occur outside the field. The abnormalities in classic radiation pneumonitis typically resolve within 6 months but can progress to a well-demarcated area of fibrosis with volume loss and bronchiectasis. Radiation fibrosis is not consistent with this patient's time course or imaging findings.

KEY POINT

- Lymphangitic spread of tumor to the lungs is most commonly associated with adenocarcinoma (lung, breast, and gastrointestinal tract), melanoma, lymphoma, and leukemia and should be considered if a peripheral interstitial abnormality is identified on CT in a patient with one of these malignancies.

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Item 6 Answer: B

Educational Objective: Treat COPD with long-term oxygen therapy.

The most appropriate treatment is to start long-term oxygen therapy (LTOT) for greater than 15 hours per day. The need for oxygen therapy should be evaluated in all stable patients with an FEV_1 less than 35% of predicted or in patients with clinical symptoms or signs suggestive of respiratory failure or right-sided heart failure. LTOT is indicated if patients meet the following criteria: (1) chronic respiratory failure and/or severe resting hypoxemia, defined as an arterial Po_2 less than or equal to 55 mm Hg (7.3 kPa) or oxygen saturation less than or equal to 88% breathing ambient air, with or without hypercapnia; and/or (2) if there is evidence of pulmonary hypertension, peripheral edema suggesting right-sided heart failure, or polycythemia, in combination with an arterial Po_2 less than 60 mm Hg (8.0 kPa) or oxygen saturation less than 88% breathing ambient air. This patient's examination findings (loud pulmonic component of S_2, peripheral edema) and estimated mean pulmonary artery pressure of 52 mm Hg on echocardiography indicate the presence of pulmonary hypertension. Therefore, this patient is an appropriate candidate for LTOT. The resting arterial Po_2 or oxygen saturation values should be repeated and confirmed twice over a 3-week period before a decision about LTOT is made in a stable patient.

A short course of systemic glucocorticoids is recommended in the treatment of acute exacerbations of COPD. However, long-term therapy with systemic glucocorticoids is associated with significant side effects and is not recommended in the management of COPD.

Nocturnal oximetry may be useful in diagnosing hypoxia occurring overnight in patients with COPD that might benefit from oxygen therapy while sleeping. However, this patient's indication for continuous LTOT may be established with available data; therefore, an overnight pulse oximetry study would not be needed to guide therapy.

Although pulmonary rehabilitation is helpful in improving quality of life in patients with advanced COPD, this patient has completed therapy on two occasions, and repeating pulmonary rehabilitation would not address her hypoxemia-associated pulmonary hypertension. However, after LTOT is started, entering a pulmonary rehabilitation program might be appropriate.

KEY POINT

- Long-term oxygen therapy is indicated if patients with COPD meet the following criteria: (1) chronic respiratory failure and/or severe resting hypoxemia, defined as an arterial Po_2 less than or equal to 55 mm Hg (7.3 kPa) or oxygen saturation less than or equal to 88% breathing ambient air, with or without hypercapnia; and/or (2) if there is evidence of pulmonary hypertension, peripheral edema suggesting right-sided heart failure, or polycythemia, in combination with an arterial Po_2 less than 60 mm Hg (8.0 kPa) or oxygen saturation less than 88% breathing ambient air.

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Item 7 Answer: B

Educational Objective: Diagnose COPD using clinical history and pulmonary function testing.

The most likely diagnosis is COPD. The spirometric findings, in conjunction with this patient's clinical history, are most consistent with this diagnosis. His FEV_1/FVC ratio is low, consistent with an obstructive lung defect. The FEV_1/FVC ratio is used to assess for airway obstruction; a value less than 70% (the lower limit of normal) is consistent with airflow obstruction. With evidence of obstruction, the degree of reduction in FEV_1 is then used to characterize the degree of obstruction. An FEV_1 of 50% to 80% of predicted is classified as moderately reduced, 34% to 50% of predicted is severely reduced, and less than 34% of predicted is very severely reduced. This patient's reduction in FEV_1 qualifies as moderately severe. Increased lung volumes with higher than predicted total lung capacity suggests hyperinflation, and high residual volume suggests air trapping from increased lung compliance. The lower than predicted DLCO suggests an effect on the lung parenchyma, which in this patient is most consistent with emphysema. This patient's clinical history demonstrates a progressive course of dyspnea, in contrast to an episodic course with resolution, which would be more compatible with asthma.

Bronchiectasis is a condition that shares features with COPD, including mild to moderate airflow obstruction on pulmonary function testing and an abnormal lung examination with wheezing and crackles. However, patients with bronchiectasis usually have significant coughing with daily sputum (often thick sputum) and airways that are easily inflamed and collapsible. Chest radiographs and CT imaging often show distorted airway architecture. This patient, in contrast, has features of indolent dyspnea, a significant smoking history, and relatively unremarkable chest radiograph, which is more compatible with COPD.

Idiopathic pulmonary fibrosis is a form of diffuse parenchymal lung disease. This condition more typically causes a restrictive pattern on spirometry with parallel decreases in both the FEV_1 and FVC, unlike in this patient who has a decreased FEV_1 but preserved FVC. Additionally, pulmonary fibrosis is more likely to result in decreased lung volumes in contrast to the increased lung volumes seen in this patient.

Obesity hypoventilation syndrome is characterized by fatigue and daytime somnolence in patients who are obese (BMI >30), and the diagnosis is confirmed by arterial blood gas testing showing daytime hypercapnia with an arterial P_{CO_2} greater than 45 mm Hg (6.0 kPa). However, pulmonary function testing typically shows a restrictive pattern without obstruction, with a decreased FEV_1 and FVC but preserved FEV_1/FVC ratio. Although this patient is obese, his clinical symptoms and pulmonary function studies are not consistent with a diagnosis of obesity hypoventilation syndrome.

KEY POINT

- The FEV_1/FVC ratio is used to assess for airway obstruction; a value less than 70% (the lower limit of normal) is consistent with airflow obstruction.

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Item 8 Answer: B

Educational Objective: Establish intravenous access in an actively bleeding patient.

Large-caliber peripheral intravenous (IV) access is the preferred route of access in this patient with a hemodynamically significant gastrointestinal bleed. She requires emergent fluid resuscitation because of her bleeding and intravascular volume depletion. When large volumes of crystalloid fluid and blood are needed quickly, large-caliber, shorter catheters allow the highest flow rates to be achieved. Flow of fluid through a catheter is inversely proportional to catheter length and proportional to the fourth radius of the diameter of the catheter. Therefore, the highest flow rates may be achieved through shorter, large-bore catheters. Peripheral IV catheters are typically significantly shorter than either catheters used for central access or peripherally inserted central catheters. Peripheral IV catheters may also be significantly larger than most central catheters, allowing for increased fluid flow. For example, potential flow rates for a 14-gauge (1.73-mm inner diameter) catheter are approximately 3 times greater than an 18-gauge (0.95-mm inner diameter) catheter of equal length. For this reason, use of larger, shorter peripheral catheters is preferred for fluid resuscitation in patients requiring emergent treatment.

Although central access remains a way to administer fluids, it is not recommended for rapid volume infusion. Therefore, a single-lumen peripherally inserted central venous catheter or triple-lumen internal jugular venous catheter would not be appropriate for this patient who requires large fluid volumes quickly. Central access may ultimately be necessary to administer vasopressor therapy, which cannot be given through peripheral access, if this patient does not respond to fluid resuscitation.

Intraosseous infusion is an immediate alternative in medical or trauma resuscitation when other forms of access cannot be rapidly obtained. Sites for intraosseous access in adults include 1 to 2 cm below the tibial tuberosity and the humeral head. Alternative access should replace the intraosseous access catheter within approximately 24 hours of placement to minimize complications.

KEY POINT

- Large-caliber peripheral intravenous access is the preferred route of infusion when large volumes of crystalloid fluid and blood are needed quickly.

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Item 9 Answer: C

Educational Objective: Recognize clinical features of small cell lung cancer.

The most likely diagnosis is small cell lung cancer (SCLC). SCLC comprises approximately 15% of all new lung cancer cases diagnosed in the United States and occurs almost exclusively in patients with a history of cigarette smoking. SCLC is the most common pulmonary neuroendocrine tumor in adults. Signs and symptoms of cough, hemoptysis, chest pain, hoarseness, and dyspnea occur frequently. Patients may also present with symptoms related to metastatic disease or to various paraneoplastic syndromes. This patient presents with symptoms of lower extremity weakness with confirmation of upper and lower extremity weakness on neurologic examination. This presentation is consistent with Lambert-Eaton myasthenic syndrome, which has a strong association with SCLC. Because of their rapid growth rate, these tumors are rarely found incidentally. The most common radiographic presentation is a hilar mass with bulky mediastinal lymphadenopathy. It is important to recognize patients with possible SCLC because the cancer is highly aggressive, and most patients start initial chemotherapy during the same hospitalization. SCLC tends to be more aggressive than non–small cell lung cancer (NSCLC); it is usually already disseminated at presentation but is usually more sensitive to chemotherapy and radiation therapy initially.

Most (80%) lung cancers are NSCLC. The most common type is adenocarcinoma of the lung (38% of all lung cancers), followed by squamous cell carcinoma of the lung (20% of all lung cancers). Although NSCLC is still in the differential diagnosis for this patient, the radiographic appearance is classic for SCLC.

Bronchial carcinoid tumors represent only a small percentage of lung cancers and are more common in children and adolescents. Typically, they present with an endobronchial lesion causing proximal airway obstruction.

KEY POINT

- Small cell lung cancer typically presents on imaging as a large hilar mass with bulky mediastinal lymphadenopathy.

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Item 10 Answer: C

Educational Objective: Treat advanced COPD with lung transplantation.

The most appropriate management is to evaluate for lung transplantation. Criteria for referral for lung transplantation include a history of COPD exacerbations associated with acute hypercapnia (arterial P_{CO_2} >50 mm Hg [6.7 kPa]); pulmonary hypertension, cor pulmonale, or both despite oxygen therapy; or FEV_1 less than 20% of predicted with DLCO less than 20% of predicted or homogeneous distribution of emphysema. This 60-year-old patient has a history of hospitalization for exacerbations, hypercapnia, an FEV_1 of less than 20% of predicted, and bilateral homogeneous distribution of emphysema. Therefore, he is a candidate for lung transplantation. Absolute contraindications to lung transplantation include malignancy within the last 2 years, infection with hepatitis B or C virus with histologic evidence of significant liver damage, active or recent cigarette smoking, drug or alcohol abuse, severe psychiatric illness, documented nonadherence with medical care, and absence of social support. Age greater than 65 years is a relative contraindication, as well as the presence of multiple comorbid conditions, which are not present in this patient.

Short-term use of systemic glucocorticoids is recommended for acute exacerbations of COPD. However, long-term use of oral glucocorticoids has not been shown to improve quality of life or reduce the rate of exacerbations. Because this patient has no evidence of an acute exacerbation, there is no indication for oral glucocorticoid therapy.

Lung volume reduction surgery (LVRS) is indicated in patients with predominantly upper lobe emphysema. Because this patient has homogeneous emphysema, LVRS is not an option. Additionally, LVRS results in higher mortality in patients with an FEV_1 less than 20% of predicted.

Hospice is an approach to care in patients with life-limiting illness and focuses on quality of life rather than an attempt at cure of the underlying disease based on the patient's and family's goals and values. Although this patient is significantly limited in his daily activities, it is not clear that he has entered the last months to weeks of life, which is the usual time frame for hospice care (compared with palliative care, which is appropriate for all patients with severe or advanced disease). Additionally, because this patient meets criteria for possible lung transplantation, it is reasonable to offer this as a potential treatment option. Hospice care may be a consideration if he is not a transplant candidate or if he declines further aggressive treatment and his condition progresses.

KEY POINT

- In patients with advanced COPD, criteria for referral for lung transplantation include a history of exacerbations associated with acute hypercapnia (arterial P_{CO_2} >50 mm Hg [6.7 kPa]); pulmonary hypertension, cor pulmonale, or both despite oxygen therapy; or FEV_1 less than 20% of predicted with DLCO less than 20% of predicted or homogeneous distribution of emphysema.

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Item 11 Answer: D

Educational Objective: Diagnose diffuse parenchymal lung disease.

The most appropriate diagnostic test to perform next is high-resolution chest CT (HRCT). This patient has symptoms (progressive dyspnea on exertion and nonproductive cough), physical examination findings (impaired oxygenation, dry crackles on lung examination, and clubbing), and plain chest radiographic imaging findings (interstitial thickening at the lung bases) consistent with diffuse parenchymal lung disease. HRCT is the most effective CT study for evaluating parenchymal lung disease and is the preferred modality for evaluating patients with possible diffuse parenchymal lung disease. Because of its high resolution, it can help narrow the differential diagnosis based on the distribution of the parenchymal disease and the presence or absence of associated findings such as fibrosis. The HRCT protocol employs very thin image sections that are reconstructed at high resolution to obtain very detailed information about the lung parenchyma. However, these image sections are obtained at relatively wide intervals (typically 1 cm between images); they represent a sampling of the lung parenchyma and do not provide a complete picture of the lungs. Because of this, HRCT should not be performed for suspected localized lung disease (such as pulmonary nodules) as it may miss smaller lesions.

Unenhanced chest CT scanning obtains images at closer intervals and is indicated for evaluation of focal lung lesions, including pulmonary nodules. Contrast may be added to the study when better definition of the mediastinal structures is needed (for example, to assess for lymphadenopathy).

CT pulmonary angiography opacifies the pulmonary arteries and is not designed for detailed definition of the pulmonary parenchyma. It is mainly used in the diagnosis of pulmonary embolism or aortic dissection and would not be an appropriate next diagnostic study in this patient.

KEY POINT

- High-resolution CT is the most effective CT study for evaluating parenchymal lung disease and is the preferred modality for evaluating patients with possible diffuse parenchymal lung disease.

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Item 12 Answer: C

Educational Objective: Diagnose diffuse parenchymal lung disease.

High-resolution CT (HRCT) is the gold standard for evaluating parenchymal opacities seen on a plain radiograph. In addition, approximately 20% of patients with diffuse parenchymal lung disease have subtle interstitial abnormalities not detectable on a chest radiograph. For this reason, HRCT should even be considered in symptomatic patients with restrictive physiology on spirometry and a normal chest radiograph, such as this patient. The patterns seen on CT correlate with pathologic findings on an open lung biopsy and are a key diagnostic tool for evaluation of diffuse parenchymal lung disease, as may be present in this patient.

Bronchoscopic lung biopsy can provide enough tissue to demonstrate specific histopathologic features diagnostic of several specific disease processes, including carcinoma, sarcoidosis, and eosinophilic pneumonia. Bronchoalveolar lavage can provide additional diagnostic information, including culture, cytology, and cell differential. However, a lung biopsy and bronchoalveolar lavage would not be indicated until imaging studies confirmed the presence of diffuse parenchymal lung disease.

Cardiopulmonary exercise testing includes assessment of respiratory gas exchange during treadmill or bicycle exercise for a more detailed assessment of functional capacity and differentiation between potential causes of exercise limitation (cardiac, pulmonary, or deconditioning, versus volitional). It would not be the most appropriate next choice in a patient with increasing exercise limitation, pulmonary crackles, and restrictive findings on pulmonary function testing.

A ventilation-perfusion (V/Q) lung scan is the recommended initial test for evaluating chronic thromboembolic pulmonary hypertension (CTEPH). Patients with CTEPH have nonspecific symptoms and the diagnosis is often missed. However, patients with CTEPH typically have a mild restrictive or obstructive defect, although spirometry is often normal. Most patients will have a reduction in the DLCO out of proportion to any abnormalities in spirometry. A V/Q lung scan may be a consideration if this patient's HRCT scan is normal.

KEY POINT

- High-resolution CT (HRCT) is the preferred initial diagnostic study for evaluating diffuse parenchymal lung disease because the pattern and distribution of findings may suggest the underlying disease process, and there is strong correlation of patterns seen on HRCT with findings on an open lung biopsy.

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Item 13 Answer: C

Educational Objective: Diagnose portopulmonary hypertension.

The most likely diagnosis is portopulmonary hypertension. This diagnosis is suggested by evidence of pulmonary hypertension in the setting of portal hypertension, typically associated with liver cirrhosis. Pulmonary hypertension suggested by echocardiography was confirmed by right

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heart catheterization. In the classification of pulmonary hypertension, portopulmonary hypertension is part of group 1 (pulmonary arterial hypertension [PAH]). Although the coupling with portal hypertension makes the diagnosis of portopulmonary hypertension most likely, other causes of PAH (such as HIV infection, drug toxicity, connective tissue disease) should be ruled out. However, none of these other causes of PAH are likely in this patient.

This patient has no history of venous thromboembolism; however, some patients with chronic thromboembolic pulmonary hypertension (CTEPH) do not report a history of deep venous thrombosis. This patient's low-probability ventilation-perfusion scan makes CTEPH very unlikely.

Hepatopulmonary syndrome is a disorder caused by dilated small vessels in the pulmonary vasculature resulting in shunting of blood, and it should be considered in a patient with liver disease who is hypoxic. Pulmonary hypertension is not a defining feature. Intrapulmonary shunting is confirmed by the appearance of contrast (bubbles from agitated saline) in the left heart following injection into a peripheral vein. In this patient, the contrast echocardiographic study was normal.

Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary hypertension caused by fibrous occlusion of distal pulmonary veins. Detection in this patient's age group is unusual; most cases are diagnosed in children and young adults. PVOD is confirmed by pathology but can be suggested by radiographic abnormalities such as pleural effusions or a prominent interstitium on chest radiograph and septal thickening on chest CT. This patient had clear lung fields on chest radiograph. PVOD is much less likely than pulmonary hypertension in this patient.

KEY POINT

- The diagnosis of portopulmonary hypertension is suggested by evidence of pulmonary hypertension in the setting of portal hypertension.

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Item 14 Answer: C

Educational Objective: Manage ventilator-associated pneumonia.

The most appropriate next step in management is to perform deep sampling of the lower respiratory tract. Ventilator-associated pneumonia (VAP) is a serious, preventable complication of mechanical ventilation. It is defined as pneumonia with onset at least 48 hours after endotracheal intubation. VAP is difficult to diagnose, but potential clues to its presence include temperature greater than 38.0 °C (100.4 °F), leukocytosis or leukopenia, increased purulent secretion, new or progressive pulmonary infiltrates, and worsening ventilation parameters, particularly after a period of improvement. Patients suspected of having VAP should undergo lower respiratory tract sampling, followed by microscopic analysis and culture of the specimen. Nonbronchoscopic sampling methods are simple suctioning of the endotracheal tube and mini-bronchoalveolar lavage (BAL), which involves use of a telescoping catheter (instead of a bronchoscope) to instill and aspirate physiologic saline for microbiologic analysis. Bronchoscopic methods are standard BAL and protected specimen brush. Deep sampling methods may allow for narrower antibiotic choices and more rapid de-escalation of antibiotics.

While waiting for the microscopic and culture results from the lower respiratory tract sampling, initiating empiric antibiotics is a reasonable option. However, this patient has been in the hospital for 7 days and is at risk for multidrug-resistant organisms, including *Pseudomonas* species. In this situation, an antipseudomonal cephalosporin or carbapenem would be appropriate. Ceftriaxone and azithromycin would be good coverage for community-acquired pneumonia but are inadequate for this patient.

Chest physiotherapy is useful for assisting with the removal of secretions in patients with COPD, cystic fibrosis, and ciliary dyskinesia. In addition to standard chest percussion and drainage, a large number of mechanical devices are now available that help encourage mobilization of secretions with variable results. Although chest physiotherapy will assist with removal of secretions, it will not provide additional information to clarify the diagnosis in this patient. The most appropriate next step in management is a microbiologic diagnosis to guide further therapy.

Switching from oseltamivir to zanamivir is unlikely to help this patient, who demonstrated an initial clinical response to influenza therapy and then declined. VAP is the most likely diagnosis, not influenza resistance to oseltamivir.

KEY POINT

- Patients suspected of having ventilator-associated pneumonia should undergo lower respiratory tract sampling, followed by microscopic analysis and culture of the specimen.

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Item 15 Answer: C

Educational Objective: Treat respiratory failure due to heart failure with noninvasive positive pressure ventilation.

The most appropriate management is noninvasive positive pressure ventilation (NPPV) and supplemental oxygen. This patient has developed respiratory insufficiency due to heart failure with pulmonary edema and pleural effusions. His dyspnea and hypoxia are due to fluid in the alveolar space and interstitium of the lungs, as well as to some degree of

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pulmonary restriction caused by the effusions. NPPV consists of delivery of positive airway pressure breaths without the use of an endotracheal tube; the interface between the patient and NPPV device is a tight-fitting mask. NPPV settings include an inspiratory positive airway pressure (IPAP) and an end-expiratory positive airway pressure (EPAP). The EPAP component of NPPV helps maintain airway patency and recruits atelectatic or flooded alveoli; it also counters the increased workload imposed by high airway resistance. NPPV decreases the need for mechanical ventilation, improves respiratory parameters, and is associated with improved survival, especially in patients with hypercapnia.

The initial dose of loop diuretic should be at least equivalent to, but preferably greater than, the dose of the patient's chronic outpatient diuretic. If response is not adequate, the diuretic dose should be increased, and an additional synergistic diuretic should be added (usually a thiazide). There is no difference in efficacy or safety of furosemide administration for bolus versus continuous infusion, and there is no indication to change this patient's furosemide dosing.

Intubation and mechanical ventilation could be used to deliver positive pressure support, but this process is invasive, requiring intubation and often sedation, and is associated with an increased risk of hospital-acquired pneumonia. Intubation and mechanical ventilation are options if this patient does not respond to NPPV.

Ultrafiltration is an option for fluid removal and can be performed in the setting of diuretic failure before overt need for kidney replacement therapy. Trials of early ultrafiltration for patients hospitalized with acute decompensated heart failure with volume overload did not demonstrate any definitive effects on mortality. This patient has just received a dose of furosemide, and the diagnosis of diuretic failure has not been established.

KEY POINT

- In patients with hypoxemic respiratory failure due to heart failure, noninvasive positive pressure ventilation decreases the need for mechanical ventilation, improves respiratory parameters, and may decrease mortality.

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Item 16 Answer: A

Educational Objective: Treat an acute exacerbation of COPD with antibiotics and systemic glucocorticoid therapy.

The most appropriate treatment is to start short courses of antibiotics and prednisone. This patient has an acute exacerbation of COPD. In addition to short-acting bronchodilators and supplemental oxygen as needed, antibiotics and systemic glucocorticoids (such as prednisone) are indicated for treatment of acute COPD exacerbations. Acute exacerbations of COPD are mostly caused by bacterial or viral infections. The combination of cough, dyspnea, and sputum purulence that is increased from baseline generally indicates the need for antibiotics in the treatment of acute COPD exacerbations, especially in patients with severe and very severe COPD. The most common bacterial pathogens that cause exacerbations are *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. Empiric antibiotic therapy should be chosen on the basis of local bacterial resistance patterns. Commonly used regimens include an advanced macrolide, a cephalosporin, or doxycycline. Systemic glucocorticoids decrease recovery time, improve lung function, improve arterial hypoxemia, and reduce the risk of early relapse. A prednisone dose of 40 mg/d for 5 days is recommended. Earlier studies suggested a 2-week course of prednisone, but a recent study showed that a 5-day course is sufficient. A prompt follow-up visit is necessary after discharge, and pulmonary rehabilitation should be recommended.

The benefits of glucocorticoids in acute COPD exacerbation have been documented with systemic treatment and not with inhaled agents such as fluticasone. Although adding a combination of a long-acting β_2-agonist (LABA) and inhaled glucocorticoid at the time of discharge may be appropriate, treating an acute exacerbation with antibiotics and an inhaled glucocorticoid would not be appropriate.

Short-acting β_2-agonists (albuterol) with or without short-acting anticholinergic agents are preferred for treatment of acute COPD exacerbations. Guidelines suggest adding a LABA or a combination of a LABA and an inhaled glucocorticoid at the time of discharge, in addition to the long-acting anticholinergic agent (tiotropium) that this patient was already taking. However, a combination of a LABA and an inhaled glucocorticoid (such as fluticasone/salmeterol) is not appropriate therapy during an acute COPD exacerbation.

Roflumilast is an oral phosphodiesterase-4 inhibitor that reduces airway inflammation. Roflumilast is indicated for patients with severe or very severe COPD with recurrent exacerbations; it is not indicated for use during acute exacerbations.

KEY POINT

- Antibiotics and systemic glucocorticoids are primary treatments for acute COPD exacerbations in addition to short-acting bronchodilators and as needed oxygen supplementation.

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Item 17 Answer: B

Educational Objective: Diagnose pulmonary hypertension related to lung disease.

The most appropriate diagnostic test to perform next is an oxygen measurement during sleep and exertion. This patient

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with underlying lung disease has a 6-month history of exertional dyspnea with evidence of pulmonary hypertension (PH) on physical examination and echocardiography. In this setting, PH is most commonly the result of chronic hypoxia causing diffuse pulmonic vasoconstriction; if untreated, this may result in vascular remodeling and sustained PH. Treatment of this form of PH due to underlying lung disease (group 3 classification) focuses on treatment of the underlying lung disease and specifically addressing hypoxia, if present. Although this patient's resting oxygen saturation is within the low-normal range, he may be experiencing sustained hypoxia while asleep or with periods of increased oxygen demand, such as exercise. Therefore, measurement of oxygen saturation with sleep (overnight pulse oximetry) and with exertion (such as with a 6-minute walk test) may determine the need for oxygen therapy in this patient.

High-resolution CT (HRCT) scanning provides detailed information about the lung parenchyma and is particularly valuable for evaluating suspected diffuse parenchymal lung diseases. However, this patient has documented COPD without evidence of another underlying lung process. Therefore, HRCT would not be expected to provide additional useful clinical information in this patient.

There is little evidence in this patient's clinical history to suggest sleep-disordered breathing, and he is not overweight. Therefore, polysomnography is not immediately indicated as a next step in evaluation.

Right heart catheterization is typically used to evaluate PH of unclear cause, and it is generally not necessary when PH is believed to be related to underlying lung disease. In addition, right heart catheterization would not effectively assess the status of the underlying lung disease or the need for supplemental oxygen.

KEY POINT

- Oxygen measurement during sleep (overnight pulse oximetry) and exertion (such as with a 6-minute walk test) may determine the need for oxygen therapy in patients with pulmonary hypertension due to underlying lung disease (group 3 classification).

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Item 18 Answer: B

Educational Objective: Treat septic shock in a patient developing acute kidney injury.

The most appropriate next step in treatment is to discontinue intravenous maintenance fluids and perhaps start a trial of diuretics. This patient is well past the window (within the first several hours after diagnosis) in which early aggressive fluid resuscitation is known to be beneficial in septic shock. Although individual markers of volume status are imperfect, the combination of a normalized lactic acid level, substantial positive fluid balance, improved blood pressure, and elevated central venous pressure suggest that the patient is euvolemic if not hypervolemic. Additional fluid resuscitation is unlikely to improve kidney function, may make it worse, and could exacerbate this patient's hypoxemia given his acute respiratory distress syndrome and pleural effusions.

Albumin is unlikely to be beneficial and may cause harm in a patient who is in the recovery phase of septic shock and has evidence of intravascular volume overload. Administration of colloids offers no advantage over crystalloids in resuscitating critically ill patients in general; however, sepsis guidelines note that albumin may be advantageous in patients with refractory shock not responding to crystalloids.

Hemodialysis is not clearly indicated at this time. Some concern exists that this patient is developing intravascular volume overload, but reducing intravenous fluids, avoiding nephrotoxins, and perhaps starting a trial of diuretics would be appropriate first steps. This patient does not have other indications for dialysis such as hyperkalemia, uremia, or severe acidosis. His declining kidney function is likely from the residual effect of acute tubular necrosis and may improve in the next few days now that his septic shock is resolving.

Studies of stress-dose glucocorticoids have not consistently shown benefit in patients with septic shock. Their use is generally reserved for patients with persistent shock despite fluid resuscitation and vasopressor support.

KEY POINT

- In patients with septic shock, aggressive fluid resuscitation after the early resuscitation phase (within the first several hours after diagnosis) can be detrimental.

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Item 19 Answer: C

Educational Objective: Treat moderate persistent asthma with combination inhaled glucocorticoid and long-acting β_2-agonist therapy.

The most appropriate treatment is the combination of a low-dose inhaled glucocorticoid and long-acting β_2-agonist (LABA) in addition to an as-needed short-acting β_2-agonist. Appropriate initial classification of asthma is important in guiding the strength and type of therapy that is likely to be most effective. Underestimating asthma severity may delay resolution of symptoms and may inadequately manage airway inflammation. This patient has newly diagnosed moderate persistent asthma based on her daily symptoms and spirometry showing an FEV_1 of greater than or equal to 60% but less than 80% of predicted that responds to bronchodilator

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therapy. The preferred regimen for treating moderate persistent asthma is the combination of a low-dose inhaled glucocorticoid and LABA. Adding a LABA to inhaled glucocorticoid therapy has increased synergistic anti-inflammatory properties compared with either agent alone. Additionally, recent data have demonstrated that long-acting anticholinergic therapy may be appropriate as step-up therapy if moderate persistent asthma does not resolve with combination inhaled glucocorticoid and LABA therapy.

A leukotriene agonist or low-dose inhaled glucocorticoid are recommended treatment options for patients with mild persistent asthma, defined as asthma symptoms occurring more than 2 days per week but not daily with an FEV_1 of greater than or equal to 80% of predicted. The addition of either therapy alone may not adequately treat the degree of asthma seen in this patient.

This patient requires anti-inflammatory controller therapy. Recommending daily use of her oral antihistamine would not address her lower airway inflammation and would not be an appropriate intervention to control her asthma symptoms.

KEY POINT

- The most appropriate therapy for moderate persistent asthma is combination low-dose inhaled glucocorticoid and long-acting β_2-agonist therapy.

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Item 20 Answer: B

Educational Objective: Diagnose a bronchial carcinoid tumor.

The most likely diagnosis is a bronchial carcinoid tumor. This patient presents with evidence of airway obstruction with a likely postobstructive pneumonia. This should be suspected in patients who have a persistent pulmonary infiltrate and a localized wheeze on examination. Although bronchial carcinoid tumors represent only a small percentage of all lung cancers, they are the most common lung cancer in children and adolescents. Most bronchial carcinoid tumors involve the proximal airways, so patients may present with symptoms related to endobronchial narrowing or obstruction, including postobstructive pneumonia. Only approximately 1% to 5% of patients present with symptoms of carcinoid syndrome. Other endobronchial cancers should be considered in older patients. Foreign body aspiration or airway strictures may also lead to airway obstruction.

Patients with allergic bronchopulmonary aspergillosis can present with recurrent asthma exacerbations in the setting of peripheral eosinophilia, elevated serum IgE levels, and bronchiectasis. Thick sputum can result in airway obstruction with associated atelectasis. However, patients typically respond to systemic glucocorticoids rather than antibiotic treatment, as in this patient. In addition, she has no evidence of peripheral eosinophilia.

Chronic eosinophilic pneumonia is associated with peripheral and upper lobe-predominant areas of consolidation that improve with glucocorticoid therapy. Antibiotics would have no effect on the course of the disease.

Patients with cystic fibrosis can present with recurrent respiratory infections in the setting of bronchiectasis. However, this patient's chest radiograph showed no evidence of bronchiectasis.

KEY POINT

- Most bronchial carcinoid tumors involve the proximal airways, so patients may present with symptoms related to endobronchial narrowing or obstruction, including postobstructive pneumonia.

Bibliography

Travis WD. Advances in neuroendocrine lung tumors. Ann Oncol. 2010 Oct;21 Suppl 7:vii65-71. [PMID: 20943645]

Item 21 Answer: C

Educational Objective: Treat parapneumonic effusion and empyema with thoracostomy drainage and antibiotics.

The most appropriate management is to insert a small-bore pleural drain and begin piperacillin-tazobactam. Complicated parapneumonic effusion and empyema should be suspected in all patients who do not respond to appropriate antibiotic therapy for pneumonia. This patient presented with subacute onset of fever, fatigue, and worsening shortness of breath after antibiotics for pneumonia. Pleural fluid analysis is consistent with a neutrophil-predominant exudate with low pH (<7.2) and negative Gram stain. This defines a complicated parapneumonic effusion that should be drained. If pleural loculations prevent adequate drainage by a single tube, multiple tubes may be needed. Small-bore (10-14 Fr [3.3-4.7 mm]) thoracostomy tubes have been demonstrated to be adequate for most patients with pleural infection and are associated with increased patient comfort.

Large-bore thoracostomy tubes have not demonstrated any advantage over small-bore thoracostomy tubes in the drainage of pleural effusion and are associated with increased patient discomfort.

Some patients with a complicated parapneumonic effusion may respond to appropriate antibiotic therapy alone; however, in most cases simultaneous drainage of the effusion speeds clinical recovery. Empirically selected antibiotics must provide adequate coverage for anaerobic organisms that are common in patients with empyema. Reasonable options include clindamycin, β-lactam plus β-lactamase inhibitors, and carbapenems. Piperacillin-tazobactam is an appropriate antibiotic for this patient, whereas ceftriaxone plus azithromycin and monotherapy

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with levofloxacin are not appropriate owing to their lack of anaerobic coverage.

Repeating the chest radiograph is not appropriate because this patient requires intervention for his complicated parapneumonic effusion.

KEY POINT

- Complicated parapneumonic effusions should be managed with drainage and antibiotics that will treat anaerobic infection.

Bibliography

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Item 22 Answer: C

Educational Objective: Diagnose vocal cord dysfunction.

The most appropriate management is otolaryngology evaluation for possible vocal cord dysfunction. Also known as paradoxical vocal fold motion disorder, this condition is characterized by adduction of the vocal cords (instead of abduction) during inspiration. This is an involuntary maneuver that can occur without other chronic conditions, but it can also happen in patients with asthma. Some patients have episodes related to performance (athletes) or exposure to certain irritants such as smoke or perfume. Symptoms include mid-chest tightness, dyspnea, and lack of symptom relief with asthma treatment. Patients may also note cough and dysphonia, and stridor may be present that may be perceived on examination as an inspiratory monophonic wheeze. The gold standard for diagnosis is observation of vocal cord adduction during inspiration with laryngoscopy after provocation with exercise or irritant exposure. Treatment consists of laryngeal control techniques, biofeedback, and relaxation techniques, usually under the direction of a speech pathologist. Management of other potential conditions that might contribute to vocal cord irritation, such as reflux, sinus disease/allergies, and obstructive sleep apnea, can also be very helpful.

Allergen immunotherapy is not indicated in this patient who has no clinical history of allergy symptoms and has normal findings on his upper airway and nasopharyngeal examinations.

Although the patient is experiencing episodes of shortness of breath, mostly with exertion, there is no additional history or findings on physical examination suggestive of heart disease as the cause of his symptoms. Echocardiography is therefore not indicated.

Stepping up asthma therapy by increasing the intensity of inhaled glucocorticoid therapy is not appropriate because this patient's clinical presentation and spirometry results are not consistent with asthma as the cause of his symptoms.

KEY POINT

- Vocal cord dysfunction (also known as paradoxical vocal fold motion disorder) is characterized by adduction of the vocal cords during inspiration; symptoms include mid-chest tightness, dyspnea, and lack of symptom relief with asthma treatment.

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Matrka L. Paradoxic vocal fold movement disorder. Otolaryngol Clin North Am. 2014 Feb;47(1):135-46. [PMID: 24286687]

Item 23 Answer: B

Educational Objective: Manage a large spontaneous pneumothorax.

The most appropriate management is to perform needle aspiration of the pneumothorax. This patient has a primary spontaneous pneumothorax, because it occurred in the absence of trauma with no clinically apparent lung disease. He is clinically stable but has breathlessness associated with a large pneumothorax (>2 cm from the lung margin to the chest wall at the level of the hilum). High-flow supplemental oxygen is usually given to most patients with pneumothorax to facilitate absorption of the pleural air. Emergent needle thoracostomy followed by thoracostomy tube placement is indicated in patients with a large, hemodynamically significant (tension) pneumothorax. However, in patients such as this one with a large pneumothorax that is symptomatic but stable, it is reasonable to perform needle aspiration of the pneumothorax. If the lung expands after aspiration, the patient may be appropriately observed for several hours with reimaging and discharge if stable. Placement of a one-way (Heimlich) valve is another option with outpatient follow-up.

Insertion of a small-bore thoracostomy tube (<14 Fr [4.7 mm]) is indicated as initial treatment for larger (>2 cm) secondary pneumothoraces in patients who are symptomatic, but it would not be a recommended initial treatment for this patient with a primary pneumothorax.

Noninvasive positive pressure ventilation would not be appropriate, because it does not have an established role in the management of pneumothorax.

Observation alone is not appropriate because this patient is symptomatic, with increased breathlessness, and has a large pneumothorax.

KEY POINT

- A large (>2 cm), symptomatic, primary spontaneous pneumothorax may be initially managed with high-flow supplemental oxygen and needle aspiration.

Bibliography

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Item 24 Answer: B

Educational Objective: Treat pulmonary hypertension due to heart disease.

The most appropriate initial management is treatment of systemic arterial hypertension with lisinopril. This patient has pulmonary hypertension (PH) in the setting of diastolic heart failure (also known as heart failure with preserved ejection fraction [HFpEF]). HFpEF, an increasingly common cause of PH, is often seen in association with systemic hypertension and left ventricular hypertrophy. PH related to left-sided heart disease is classified as group 2, and treatment is directed at the underlying cardiac disease. Therefore, therapy for HFpEF is based on treating the causes and symptoms of the heart failure. Because hypertension is a common cause of HFpEF, aggressive control of the systemic arterial blood pressure is necessary. Because no specific agent has definitively proved to be more effective than another, therapy should follow hypertension treatment guidelines.

Epoprostenol is an advanced therapy; it is an intravenous pulmonary vasodilator reserved for management of group 1 PH (pulmonary arterial hypertension) associated with advanced symptoms and functional limitation.

Right heart catheterization is not an appropriate initial test in the diagnosis or management of patients with PH related to heart failure, although it may be useful later if initial treatments aimed at the underlying condition are not effective in improving symptoms or pulmonary artery pressures.

The pulmonary vasodilator sildenafil is considered advanced therapy, which is directed at PH itself rather than the underlying cause, and is indicated for the treatment of group 1 pulmonary arterial hypertension. Not only is the role of such drugs in the treatment of groups 2 to 5 PH unclear, advanced therapy can alter ventilation-perfusion relationships and be deleterious in these patients.

KEY POINT

- Pulmonary hypertension related to left-sided heart disease is classified as group 2; treatment is directed at the underlying cardiac disease.

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Item 25 Answer: D

Educational Objective: Treat severe asthma with omalizumab.

The most appropriate treatment is omalizumab. Severe asthma occurs in 10% of patients with asthma and is associated with long-term treatment with high-dose glucocorticoids, frequent exacerbations, and high health care utilization, as in this patient. This patient's asthma has not been controlled despite aggressive nonpharmacologic interventions and treatment with multiple drugs. Omalizumab, a humanized monoclonal antibody directed at IgE, is the first biologic agent approved by the FDA for use in asthma. Administered subcutaneously every 2 to 4 weeks, omalizumab is indicated in patients with moderate to severe persistent asthma with the following characteristics: (1) symptoms inadequately controlled with inhaled glucocorticoids, (2) evidence of allergies to perennial aeroallergens, and (3) serum IgE levels between 30 and 700 U/mL (30-700 kU/L) (normal range, 0-90 U/mL [0-90 kU/L]). Although it is very expensive, omalizumab has been shown to reduce emergency department visits and appears to be cost effective in appropriately selected patients; it is not indicated for use in patients other than those meeting these treatment parameters.

Allergen immunotherapy (allergy shots) can be useful when a single trigger is identified or when a trigger is consistently the source of asthma instability. It is a reasonable longer-term plan in this patient; however, immunotherapy may take 3 to 5 years to achieve a noticeable therapeutic effect. Omalizumab would be expected to provide more immediate control of her asthma than is possible with allergen immunotherapy.

This patient has required frequent and high doses of systemic glucocorticoids and is exhibiting side effects (skin thinning and cushingoid facies). Because of the long-term detrimental effects of prolonged systemic glucocorticoid therapy, particularly in this younger patient, daily glucocorticoid therapy would not be appropriate.

Other forms of immune modulation, such as with tumor necrosis factor-α inhibitors (such as infliximab) or other immunosuppressive agents (such as cyclophosphamide and azathioprine), have not been shown to be effective in controlling severe asthma and are associated with a high level of adverse effects in these patients.

KEY POINT

- Omalizumab is indicated in patients with moderate to severe persistent asthma with the following characteristics: (1) symptoms inadequately controlled with inhaled glucocorticoids, (2) evidence of allergies to perennial aeroallergens, and (3) serum IgE levels between 30 and 700 U/mL (30-700 kU/L) (normal range, 0-90 U/mL [0-90 kU/L]).

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Item 26 Answer: D

Educational Objective: Diagnose ventilator-induced lung injury.

The most likely diagnosis is ventilator-induced lung injury (VILI), which represents iatrogenic acute respiratory distress syndrome (ARDS) caused by mechanical ventilation. VILI

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is most likely to occur when tidal volume and/or plateau pressure are too high. It can occur even in patients with no evidence of lung injury at the time of intubation. This patient was ventilated throughout her surgery. Her ideal body weight is 48 kg (106 lb); based on this, the protective tidal volume would be 288 mL (6 mL/kg of ideal body weight). In addition to low tidal volume, protective ventilation also entails keeping the plateau pressure below 30 cm H_2O if possible. An early clue to nonprotective ventilator settings could have been an elevated plateau pressure, as in this patient when she arrived in the ICU.

Obesity hypoventilation syndrome could be seen in a patient with this body habitus and could include low respiratory system compliance, but this condition would not explain the airspace opacification on imaging, poor oxygenation, or worsening compliance over time.

Pulmonary embolism is always a risk postoperatively, especially in those who undergo orthopedic procedures, such as this patient. Pulmonary embolism would certainly worsen ventilation-perfusion matching and oxygenation, but it would not typically worsen lung compliance over the first 24 hours postoperatively.

ARDS can develop in response to transfusion of blood products when antibodies in transfused plasma activate recipient neutrophils; this is known as transfusion-associated lung injury (TRALI). This can occur after transfusion of any blood product, and it appears to be most likely when the volume of transfused plasma is high and comes from a multiparous female donor. TRALI is generally the least severe form of ARDS; however, it can be fatal if not managed appropriately. This patient received an autologous transfusion only and is not at risk for TRALI.

KEY POINT

- Ventilator-induced lung injury is most likely to occur when the tidal volume and/or plateau pressure are too high; tidal volume should be limited to 6 mL/kg of ideal body weight and plateau pressure less than 30 cm H_2O.

Bibliography

Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013 Nov 28;369(22):2126-36. Erratum in: N Engl J Med. 2014 Apr 24;370(17):1668-9. [PMID: 24283226]

Item 27 Answer: D

Educational Objective: Diagnose malignant pleural disease.

The most appropriate diagnostic test to perform next is thoracoscopy. This patient has an unexplained unilateral exudative effusion. Owing to his occupation as an auto mechanic, he has a history of potential asbestos exposure (car brakes previously contained asbestos). This potential exposure increases his risk for mesothelioma, which is suggested by his clinical presentation (exudative pleural effusion, chronic chest pain, weight loss) and imaging findings (pleural thickening). Thoracoscopy allows for the direct visualization of the pleural surface and enables biopsy of pleural sites likely to have a high diagnostic yield. It has a diagnostic sensitivity for malignant disease of greater than 90%. Thoracoscopy is indicated in this patient in whom imaging and thoracentesis have not achieved a diagnosis, which occurs relatively frequently with mesothelioma.

Because endobronchial lesions are rarely seen in mesothelioma, bronchoscopy would not be an appropriate next diagnostic study.

Repeat pleural fluid cytology is not appropriate because this patient has already had two negative studies. The overall mean sensitivity of pleural fluid cytology for identifying malignant disease is approximately 60%. Approximately 65% of positive results are obtained on the initial thoracentesis. The diagnostic yield from sending more than two samples is very low. One study demonstrated an additional yield of 27% on the second sample and only 5% on the third.

PET/CT scanning is a useful tool for staging disease, particularly for identifying extrathoracic disease. However, it is not a preferred initial diagnostic study because both malignant and nonmalignant pleural thickening can be avid for fluorodeoxyglucose and yield a positive finding on this study.

KEY POINT

- If repeat pleural fluid cytology is negative and the suspicion for malignancy is high in an exudative effusion, thoracoscopy is the next step in the evaluation; it has a diagnostic sensitivity for malignant disease of greater than 90%.

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Item 28 Answer: B

Educational Objective: Manage initial ventilator settings.

The most appropriate ventilator mode in this patient is volume controlled continuous mandatory ventilation (VC-CMV). The ventilator mode defines the means by which the ventilator interacts with the patient. Unfortunately, there are numerous mode names (nearly 300 according to a recent review), and the same mode may have different labels depending on the ventilator manufacturer. In an effort to standardize ventilator modes, a taxonomy has been described in an attempt to simplify ordering and understanding the function of the ventilator, although this classification system has not been universally adopted.

Two main variables must be considered when ordering mechanical ventilation. The breath sequence must be determined, with spontaneous and mandatory breaths being the two primary options. Because this patient has respiratory failure and is unable to effectively breathe on his own, a spontaneous breath sequence (in which the patient breathes

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on his own with no back-up rate) would not be appropriate, and mandatory ventilation is indicated. Mandatory ventilation may be either intermittent or continuous. Intermittent mandatory ventilation allows for spontaneous breaths between or during mandatory breaths; however, this may lead to dyssynchrony, in which the phases of mechanical breaths do not match the phases of patient breaths and is believed to contribute to lung injury. With CMV, all breaths are supported by the ventilator, and the patient may trigger additional supported breaths above the preset frequency; this consistent breath pattern reduces the risk for dyssynchrony. In general, for acutely ill patients who are hemodynamically unstable, supporting all respiratory efforts with CMV is recommended.

The second variable, the breath control method, determines whether breaths are provided based on pressure or volume. Pressure-controlled ventilation, in which a breath is delivered according to a preset inspiratory pressure, has been associated with ventilator-induced lung injury; therefore, volume control, in which tidal volume and inspiratory flow are designated, is the preferred breath control method as the initial strategy for ventilation of critically ill patients.

KEY POINT

- For acutely ill patients who are hemodynamically unstable, supporting all respiratory effort with the volume-controlled continuous mandatory ventilation setting to minimize risk for ventilator-induced lung injury is recommended as the best strategy for initial mechanical ventilation.

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Item 29 Answer: D

Educational Objective: Diagnose suspected occupational asthma.

The most appropriate next step in management is to repeat spirometry after workplace exposure. Occupational asthma, related to workplace exposures to agents associated with airway hyperreactivity, should be suspected in all adults with a diagnosis of asthma because it may be a primary target for treatment. It should also be suspected in patients with asthma-like symptoms that vary with exposure to the workplace, as in this patient. This patient has likely been exposed to diisocyanates from spray painting in the auto body shop where he works, which are associated with triggering bronchospasm. Early recognition of an association of asthma symptoms with potential workplace exposure, and testing if indicated, is important for diagnosis and to guide therapy. Serial monitoring of peak flows throughout the workday, with comparison to a baseline time period away from exposures, can be helpful to support the diagnosis. Similarly, spirometry before and after rechallenge with workplace exposures is helpful to confirm the diagnosis. Because of the possibility that this patient's occupational exposure may be responsible for his asthma symptoms, it is appropriate to perform spirometry before and after exposure to the potential causative agent. If documented, treatment of occupational asthma should follow guidelines for typical asthma, and allergen exposure should be controlled or eliminated if possible. If significant changes in spirometry are not seen post workplace exposure and a suspicion for any underlying asthma remains, a methacholine challenge test may be appropriate.

Advising a change in workplace venue to avoid allergen exposure for occupational asthma would be premature because the diagnosis has not been confirmed.

High-resolution chest CT is indicated for evaluation of suspected parenchymal lung disease. However, this patient's symptoms are most consistent with airways disease, and he has no clinical evidence of a parenchymal process. Therefore, this testing would not be expected to be of benefit.

Empiric therapy for asthma without documentation of the diagnosis or an association of his asthma symptoms with workplace exposure would not be appropriate.

KEY POINT

- Spirometry before and after rechallenge with workplace exposures is helpful to confirm the diagnosis of occupational asthma.

Bibliography

Tarlo SM, Lemiere C. Occupational asthma. N Engl J Med. 2014 Feb 13;370(7):640-9. [PMID: 24521110]

Item 30 Answer: A

Educational Objective: Treat obstructive sleep apnea with an oral mandibular advancement appliance.

The most appropriate treatment alternative to continuous positive airway pressure (CPAP) in this patient is an oral mandibular advancement appliance. This patient has symptomatic obstructive sleep apnea (OSA) of moderate severity. Although CPAP provided symptomatic improvement and is generally the preferred treatment for OSA, patient preference or intolerance of CPAP should prompt consideration of other treatments. Oral appliances are an alternative to CPAP therapy for mild to moderate OSA. Randomized controlled trials on the use of oral appliances have demonstrated reasonable control of OSA and improvement in symptoms such as daytime sleepiness. In addition, their use as an alternative therapy is consistent with the American College of Physicians Clinical Practice Guideline for Management of Obstructive Sleep Apnea in Adults. These devices act by one of two mechanisms to increase upper airway caliber: (1) advancement of the mandible by traction or (2) preventing posterior displacement of the tongue by suction.

Treatment of OSA should be directed at maintaining upper airway patency. Supplemental oxygen has no effect on the upper airway and is not indicated as primary therapy for OSA.

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Evidence supporting surgical procedures as a treatment for OSA is limited. Patient selection is not standardized, and outcomes related to the long-term adverse consequences of OSA are either unknown or inconsistent. Case series have demonstrated significant improvements in the apnea-hypopnea index (AHI) following maxillomandibular advancement; however, in most patients it would not be considered a primary treatment owing to its level of invasiveness. Literature examining uvulopalatopharyngoplasty, a soft-palate procedure, shows limited improvements in the AHI, so it should generally not be recommended for treatment of OSA.

KEY POINT

- Although continuous positive airway pressure (CPAP) is the preferred treatment for obstructive sleep apnea, patient preference or intolerance of CPAP should prompt consideration of other treatments such as oral mandibular advancement appliances.

Bibliography

Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med. 2013 Apr 15;187(8):879-87. [PMID: 23413266]

Item 31 Answer: C

Educational Objective: Diagnose acute pulmonary embolism.

This patient most likely has obstructive shock from a hemodynamically significant acute pulmonary embolism (PE). Patients with malignancy are at increased risk of thrombosis and embolic events. Obstructive shock is a subset of cardiogenic shock in which there is mechanical blockage in the central circulation, as can occur with massive PE (as in this patient) or tension pneumothorax. The findings that support obstructive shock due to PE include hypotension, an accentuated P_2, and profound hypoxemia. With hemodynamically significant PE, the electrocardiogram (ECG) may show the classic S1Q3T3 pattern caused by right ventricular strain due to acute obstruction of the pulmonary artery, but this is not a sensitive finding for PE and its absence does not exclude the diagnosis. Thrombolytic therapy or surgical thrombectomy are therapeutic considerations in patients with massive PE causing shock.

Anaphylactic shock is a type of distributive shock, as might occur if a patient with an allergy to penicillin were given either penicillin or a related agent to which she reacted. Anaphylaxis is an IgE-mediated reaction and manifests within minutes to 1 hour after exposure to the implicated antigen. Ninety percent of patients have a cutaneous reaction such as urticaria, angioedema, or flushing. Bronchospasm and wheezing are common. This patient received meropenem 2 days before developing shock and has no evidence of skin changes or wheezing, making anaphylaxis an unlikely diagnosis.

Acute myocardial infarction could lead to sudden deterioration in clinical status based on a rapid decrease in left ventricular output. However, more specific changes associated with significant myocardial ischemia would be expected on the ECG. Additionally, the severe hypoxia in the setting of acute myocardial infarction is usually due to acute PE caused by inadequate cardiac output, and this patient's clear lungs on auscultation are not consistent with this diagnosis. Septic shock is a type of distributive shock and could account for the hypotension seen in this patient, but the sudden appearance of hypotension and hypoxemia in a patient whose clinical condition was improving is not typical of septic shock.

KEY POINT

- Obstructive shock is a subset of cardiogenic shock in which there is mechanical blockage in the central circulation, as can occur with massive pulmonary embolism or tension pneumothorax.

Bibliography

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Item 32 Answer: D

Educational Objective: Treat severe COPD with lung volume reduction surgery.

The most appropriate next step in management is to evaluate for lung volume reduction surgery (LVRS). To be eligible for LVRS, patients must meet the following criteria: (1) severe COPD; (2) symptomatic despite maximal pharmacologic therapy; (3) completed pulmonary rehabilitation; (4) evidence of bilateral predominant upper-lobe emphysema on CT; (5) postbronchodilator total lung capacity greater than 100% and residual lung volume greater than 150% of predicted; (6) maximum FEV_1 greater than 20% and less than or equal to 45% of predicted and DLCO greater than or equal to 20% of predicted; and (7) ambient air arterial PCO_2 less than or equal to 60 mm Hg (8.0 kPa) and arterial PO_2 greater than or equal to 45 mm Hg (6.0 kPa). In patients with severe COPD and predominantly upper-lobe emphysema and low post-rehabilitation exercise capacity, LVRS results in improved survival compared with medical treatment. However, higher mortality is seen in patients with severe emphysema with an FEV_1 of less than or equal to 20% of predicted and a DLCO less than or equal to 20% of predicted or homogeneous emphysema on high-resolution CT scan. Because of this patient's severe disability associated with his COPD and available parameters suggesting he may be a candidate for LVRS, further evaluation of this option would be appropriate.

This patient is on appropriate medical treatment, and switching from one combination medication to another medication in the same class is not likely to be helpful. Vilanterol is a newer ultra-long-acting β_2-agonist that may

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be used once daily. Although a once-daily inhaler regimen may be more convenient for some patients than a twice-daily regimen, these formulations tend to be of significantly higher cost, and there are no evidence-based clinical benefits for these newer ultra-long-acting agents. Therefore, making this change in medication would not be expected to have a significant effect in this patient.

Systemic glucocorticoids are recommended for the short-term treatment of acute exacerbations of COPD. However, continuous therapy with systemic glucocorticoids is associated with significant side effects and is not recommended for the chronic management of COPD.

Criteria for referral for lung transplant evaluation include one of the following: pulmonary hypertension, cor pulmonale, or both despite oxygen therapy; history of exacerbation associated with acute hypercapnia; and FEV_1 less than 20% of predicted with DLCO less than 20% of predicted or homogeneous distribution of emphysema. This patient has an FEV_1 greater than 20% of predicted, a DLCO greater than 20% of predicted, and emphysema in the upper lobes; therefore, he is not a candidate for lung transplantation.

KEY POINT

- In patients with severe COPD and predominantly upper-lobe emphysema and low post-rehabilitation exercise capacity, lung volume reduction surgery results in improved survival compared with medical treatment.

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Item 33 Answer: D

Educational Objective: Evaluate chronic cough with methacholine challenge testing.

The most appropriate diagnostic test to perform next is methacholine challenge testing. This patient has a history of allergies and a family history of asthma, and he is presenting with paroxysms of cough. This presentation is suggestive of possible cough-variant asthma, in which reversible airway obstruction occurs but the primary presenting symptom is a nonproductive cough. Although a classic presentation of asthma on spirometry includes an obstructive pattern and a significant bronchodilator response (200 mL and 12% increase in FEV_1), this finding is not present in all patients with asthma. Asthma is a dynamic airway condition, and obstruction may not be seen at rest or in the absence of an exposure to the asthma trigger. In patients with clinical symptoms suggestive of bronchospastic disease (such as unexplained dyspnea or cough, as in this patient) but with normal spirometry, bronchial challenge testing may be diagnostically helpful. Bronchial challenge testing uses a controlled inhaled stimulus to induce bronchospasm in association with spirometry; a positive test is indicated by a drop in the measured FEV_1. Methacholine is a commonly used agent that induces cholinergic bronchospasm at low concentrations in patients with asthma.

Although this patient has a history of allergies and allergic rhinitis, it is not clear that the cause of his cough symptoms is associated with an allergic trigger. Allergy testing may be helpful in patients with allergies and asthma in whom treatment for specific triggers would be beneficial and in those whose symptoms are not adequately controlled with usual allergy or asthma therapies.

High-resolution chest CT (HRCT) is used to define the lung parenchyma in great detail and is useful in patients with suspected parenchymal lung disease. However, this patient has no suggestion of an underlying parenchymal disease, and HRCT is therefore not indicated.

Measurement of serum IgE levels may be helpful in diagnosing allergic bronchopulmonary aspergillosis (ABPA), a hypersensitivity reaction of the airways that occurs when bronchi become colonized by *Aspergillus* species. ABPA is characterized by recurrent episodes of fever, bronchial obstruction, and cough productive of brownish mucus plugs. This patient's presentation is not consistent with ABPA; therefore, serum IgE testing is not indicated.

KEY POINT

- In patients with clinical symptoms suggestive of bronchospastic disease (such as cough or unexplained dyspnea) but with normal spirometry, bronchial challenge testing (such as with methacholine) may be helpful to evaluate for asthma.

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Item 34 Answer: B

Educational Objective: Treat anaphylaxis with epinephrine.

The most appropriate next step in treatment is to administer epinephrine. This patient's hypotension, bronchospasm, and urticaria are characteristic of a severe anaphylactic reaction. Epinephrine is the drug of choice for anaphylaxis, preferably given as an intramuscular injection because of more rapid and consistent absorption compared with subcutaneous injection. Intravenous delivery may be advantageous in patients with compromised muscle perfusion from shock. Food allergies and insect stings are important anaphylaxis triggers, while a medication is the most likely trigger in a hospitalized patient.

Although antihistamines are the most commonly prescribed drug for anaphylaxis, they do not treat the life-threatening manifestations of anaphylaxis such as bronchospasm and hypotension. It is also likely that epinephrine, rather than antihistamines, is the agent responsible for the resolution of urticaria in these patients.

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In patients taking β-blocker therapy, glucagon may be an effective treatment for hypotension and bradycardia that is resistant to epinephrine. The inotropic and chronotropic effects of glucagon are not mediated through β-receptors. However, glucagon is a second-line treatment for anaphylaxis, even in patients taking β-blockers.

Methylprednisolone is an adjunctive therapy to prevent delayed or protracted reactions in patients with anaphylaxis. However, the drug takes several hours to take effect and therefore is not useful for rapidly reversing the life-threatening manifestations of anaphylaxis. A recent systematic review did not discover any randomized controlled trials that confirmed the effectiveness of glucocorticoids in the treatment of anaphylaxis.

KEY POINT

- Intramuscular epinephrine is the drug of choice for anaphylaxis; however, intravenous delivery may be advantageous in patients with compromised muscle perfusion from shock.

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Item 35 Answer: C

Educational Objective: Manage air travel in a patient with lung disease.

The most appropriate next step is a hypoxia altitude simulation test (HAST). Initial evaluation of patients with lung disease who are not on long-term oxygen therapy and are planning air travel is usually with pulse oximetry at sea level. If the oxygen saturation is greater than 95%, it is unlikely that the patient will have significant desaturation at higher altitudes, and further testing or supplemental oxygen is not usually indicated. For patients with an oxygen saturation of less than 92%, in-flight supplemental oxygen is usually recommended. In patients with sea-level oxygen saturation between 92% and 95%, simulators that mimic altitude hypoxia, available at some centers, can be used to determine the need for oxygen supplementation during flight. Patients at high risk for in-flight hypoxia and its complications are those with COPD with hypercapnia, a recent exacerbation of chronic lung disease, pulmonary hypertension, and restrictive lung disease, in addition to those who have had previous in-flight symptoms. This patient, who has a resting oxyhemoglobin saturation of 93% breathing ambient air, has risk factors for altitude-related hypoxia, which include an FEV_1 less than 50% of predicted and cardiac disease. The HAST predicts the in-flight arterial partial pressure of oxygen and whether supplemental oxygen is needed, accounting for the pressurization of airline cabins that simulate an altitude of less than 2440 meters (8000 feet).

In patients with COPD and a sea-level oxygen saturation between 92% and 95%, an alternative approach in locations where HAST testing is not available is to perform a 6-minute walk test. An oxygen saturation less than 84% suggests likely significant desaturation with altitude, and supplemental oxygen is usually prescribed without additional testing. Those with a walk test saturation greater than or equal to 84% should be referred for HAST testing.

Arterial blood gas studies alone are unlikely to provide important information beyond what is already known about this patient's oxygenation status. It is possible that this patient has chronic hypercapnia due to underlying lung disease, a finding that would support further testing in the form of HAST.

Similarly, echocardiographic evidence of pulmonary hypertension would represent a risk factor for in-flight hypoxia and would require further evaluation, but it does not have adequate predictive value alone in determining the need for in-flight oxygen.

With a proper pre-travel evaluation, it is unlikely that this patient with stable chronic lung disease would have an in-flight problem. Unless the patient declines further testing, recommending against travel is premature.

KEY POINT

- In patients with lung disease and sea-level oxygen saturation between 92% and 95%, hypoxia altitude simulation testing can be used to determine the need for oxygen supplementation during air travel.

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Item 36 Answer: A

Educational Objective: Treat inadequately controlled asthma by stepping up therapy.

The most appropriate management is to step up therapy for this patient's asthma by adding a low-dose glucocorticoid inhaler. This patient has a history of asthma as a child, which has been quiescent for many years and has not required treatment as an adult. She recently experienced a viral respiratory tract infection with associated wheezing and cough. Viral respiratory infections, most commonly with rhinoviruses, may induce bronchospasm in patients without preexisting reactive airways disease and may require acute treatment for symptom relief. However, viral respiratory infections may also exacerbate underlying asthma and require a step-up in treatment. Although this patient has not required therapy for asthma for many years, she remains persistently symptomatic with evidence of ongoing obstruction beyond the time frame when virally induced bronchospasm in patients without asthma typically resolves, which is usually by 6 to 8 weeks after a respiratory infection. Her symptoms and spirometry results are consistent with mild persistent asthma; therefore, the addition of an inhaled glucocorticoid, consistent with guideline-based treatment recommendations, is indicated to control her asthma.

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Because this patient remains symptomatic beyond the time frame in which patients without asthma would be expected to have symptom resolution, continuing either an as-needed or long-acting β_2-agonist would not address the underlying mechanism of obstruction and would not provide optimal control of her asthma. Therefore, neither of these interventions is indicated.

Similarly, discontinuing the inhaler medication would not be appropriate in this patient with asthma who remains symptomatic.

KEY POINT

- Viral respiratory infections, frequently due to rhinovirus, may cause airway hyperresponsiveness and obstruction through nonallergic mechanisms in patients without a history of asthma; they may also exacerbate underlying asthma and require step-up therapy.

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Item 37 Answer: B

Educational Objective: Diagnose suspected obstructive sleep apnea or central sleep apnea.

The most appropriate next step is in-laboratory polysomnography. This patient has risk factors for both obstructive sleep apnea (OSA) (male gender, snoring, overweight) and central sleep apnea (CSA) (heart failure and atrial fibrillation). The lack of history from a bed partner hampers determination of pretest probability. Although out-of-center (performed outside of a sleep laboratory or at home) sleep testing is appropriate for patients with a high pretest probability of uncomplicated moderate to severe OSA, those with heart failure or advanced pulmonary disease or those at risk for CSA should undergo in-laboratory polysomnographic diagnostic testing. In-laboratory polysomnography allows more detailed analysis of the possible underlying disorder than out-of-center methods. Once the type of apnea is clarified during the diagnostic portion of the in-laboratory study, the technician may then utilize the most appropriate mode of positive airway pressure (PAP) therapy and assess the response to treatment. Treatment options include continuous positive airway pressure (CPAP) for OSA, adaptive servoventilation (ASV) for CSA, and the addition of supplemental oxygen, if needed, for gas exchange abnormalities due to chronic heart failure or lung disease.

In this patient, auto-titrating positive airway pressure (APAP) would not be appropriate before diagnostic testing is performed to clarify the predominant type of apnea. APAP is indicated for treatment of OSA but is unlikely to be an effective treatment for CSA or complex sleep apnea, if present.

Out-of-center sleep testing should be used in patients without comorbid cardiopulmonary disease who are likely to have OSA of at least moderate severity, such as in an obese middle-aged man who snores loudly, pauses breathing, and gasps during sleep.

This patient has symptoms of interrupted sleep and daytime sleepiness, which are strong indications for treatment of sleep-disordered breathing. Further screening with overnight pulse oximetry is unlikely to add reliably important diagnostic information, and it will not alter the decision to treat.

KEY POINT

- Although out-of-center sleep testing is appropriate for patients with a high pretest probability of uncomplicated moderate to severe obstructive sleep apnea, those with heart failure or advanced pulmonary disease or those at risk for central sleep apnea should undergo in-laboratory polysomnographic diagnostic testing.

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Item 38 Answer: D

Educational Objective: Evaluate lung cancer risk in a patient with silicosis.

The most appropriate next step in management is to perform repeat CT imaging of the chest. This patient has a history of previously diagnosed silicosis, and silicosis is an independent risk factor for the development of lung cancer. Additionally, this patient also has a smoking history that increases the risk for malignancy. This increased risk, in combination with his history of weight loss, warrant further evaluation for malignancy. Evaluation may be more difficult in patients with silicosis, in whom lung findings tend to be upper lobe predominant, which tends to be the same distribution where lung cancers are more likely to occur. Because of this, plain chest radiography may not define small lesions in the background of nodularity and scarring. Therefore, a more sensitive imaging modality, such as CT, is indicated despite this patient's unchanged plain chest radiograph.

Chest MRI may be useful in evaluating chest wall, pleural, and mediastinal pathology, but it has limited utility in assessing bronchial or parenchymal lesions, primarily due to poorer spatial resolution and longer imaging times required than CT. Therefore, even in the presence of significant lung disease such as in this patient, CT is the preferred imaging modality.

Patients with silicosis are also at increased risk for tuberculosis (TB), which may also cause blood in the sputum and systemic features such as weight loss. This patient's

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persistently negative tuberculin skin tests and unchanged chest radiograph make this a less likely diagnosis; therefore, empiric treatment for TB would be an inappropriate next step in management. However, further diagnostic evaluation for TB would be reasonable if his evaluation for malignancy is negative.

Although patients with silicosis often have a concomitant smoking exposure and smoking-related lung disease, there is little role for the use of glucocorticoids in treating patients with silicosis who do not have another indication for their use.

KEY POINT

- Silicosis is an independent risk factor for the development of lung cancer.

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Liu Y, Steenland K, Rong Y, et al. Exposure-response analysis and risk assessment for lung cancer in relationship to silica exposure: a 44-year cohort study of 34,018 workers. Am J Epidemiol. 2013 Nov 1;178(9):1424-33. [PMID: 24043436]

Item 39 Answer: C

Educational Objective: Treat COPD in a patient with risk category B disease.

The most appropriate treatment for this patient with COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] risk category B) is a short-acting bronchodilator as needed, regular use of a long-acting bronchodilator, and pulmonary rehabilitation. The new GOLD risk stratification can be used to classify risk and help make management decisions.

Risk category A COPD is characterized by an FEV_1/FVC ratio less than 70%, an FEV_1 greater than or equal to 50% of predicted, and zero to one exacerbation(s) in the past year. These patients have mild or infrequent symptoms. Symptoms can be objectively quantified using either the Modified Medical Research Council (mMRC) Questionnaire or the COPD Assessment Test (CAT) score. Patients in risk category A have a mMRC score of 0 to 1 or CAT score less than 10. Therapy for category A COPD is an inhaled bronchodilator as needed; a short-acting bronchodilator is preferred.

Patients in risk category B have all the same spirometry measurements and exacerbation frequency as in category A but are more symptomatic, often having to walk slowly or stop owing to breathlessness (mMRC score of ≥2 or CAT score ≥10). These patients are also treated with bronchodilators, typically a short-acting bronchodilator as needed and regular use of a long-acting bronchodilator, as well as with pulmonary rehabilitation. Combinations of a long-acting β_2-agonist (LABA) and long-acting anticholinergic (also known as long-acting muscarinic agent [LAMA]) bronchodilators can be used as alternative therapy.

Risk category C COPD is characterized by an FEV_1/FVC ratio less than 70%, an FEV_1 less than 50% of predicted, or two or more exacerbations per year or one or more hospitalizations for an exacerbation. Otherwise, patients have mild or infrequent symptoms (mMRC score of 0-1 or CAT score <10). Regular treatment with a combination inhaled glucocorticoid plus a LABA or monotherapy with a LAMA is preferred. Alternatives may include dual combination therapy with a LAMA plus an inhaled glucocorticoid or a LABA, or a phosphodiesterase-4 (PDE-4) inhibitor and a long-acting bronchodilator.

Patients in risk category D have all the same spirometry measurements and exacerbation frequency as category C, but they are more symptomatic (mMRC score of ≥2 or CAT score ≥10). Preferred therapy includes a short-acting bronchodilator as needed and regular use of combination therapy with an inhaled glucocorticoid and a LABA and/or a LAMA, and pulmonary rehabilitation. Alternative therapy includes triple combinations of two long-acting bronchodilators and an inhaled glucocorticoid; an inhaled glucocorticoid plus a LABA and PDE-4 inhibitor; or double combinations of two long-acting bronchodilators, or a LAMA and PDE-4 inhibitor.

KEY POINT

- The recommended therapy for stable patients with symptomatic (Global Initiative for Chronic Obstructive Lung Disease risk category B) COPD consists of a short-acting bronchodilator as needed and regular use of a long-acting bronchodilator, as well as with pulmonary rehabilitation.

Bibliography

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Item 40 Answer: B

Educational Objective: Treat gastroesophageal reflux disease complicating cough-variant asthma.

The most appropriate treatment is to add a proton pump inhibitor to this patient's current asthma treatment regimen. Although she has a clear diagnosis of asthma (based on her methacholine challenge testing results) and her cough has partially responded to asthma therapy, she continues to have symptoms and has additional clinical findings consistent with gastroesophageal reflux disease (GERD) as a potential cause of her persistent cough symptoms. Respiratory symptoms associated with GERD are common, and reflux is frequently a cause of chronic cough. GERD is also extremely common in patients with asthma, with some estimates suggesting some degree of reflux in as many as 90% of patients. GERD can make underlying asthma worse through direct reflux of acidic gastric contents into the respiratory system, resulting in upper airway inflammation or direct airway injury. The reflux of gastric contents into the lower part of the esophagus can also cause reflex bronchoconstriction. There is evidence that treating GERD in patients with asthma improves asthma control. In most patients with asthma and

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suboptimal control of symptoms, a history consistent with GERD is adequate to justify a trial of empiric antacid therapy without further testing for evidence of reflux. There is no evidence, however, that treating all patients with asthma but without symptoms consistent with GERD is of benefit.

In the setting of asthma treatment, it is necessary to control for confounders such as GERD before escalating the intensity of asthma therapy, such as adding a long-acting β_2-agonist. Stepping up asthma treatment in this patient would be appropriate in the absence of a possible diagnosis of GERD or if her symptoms do not respond to antacid therapy.

Repeating a methacholine challenge test is not indicated if the initial study was adequate for diagnosing asthma and the patient has had a response to treatment. In addition, bronchoprovocation studies carry some risk, making it inappropriate to repeat the study without a clear indication.

Antitussives are frequently used in treating acute cough and may be helpful in patients with chronic cough refractory to other therapies, based on the underlying cause. Treatment with antitussive therapy in this patient with cough-variant asthma and possible comorbid GERD would not be appropriate without further assessing control of these underlying issues.

KEY POINT

- In most patients with asthma and suboptimal control of symptoms, a history consistent with gastroesophageal reflux disease is adequate to justify a trial of empiric antacid therapy without further testing for evidence of reflux.

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Hom C, Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease. Gastroenterol Clin North Am. 2013 Mar;42(1):71-91. [PMID: 23452632]

Item 41 Answer: D

Educational Objective: Treat opioid-related central sleep apnea.

The most appropriate management is an attempt to reduce this patient's opioid use. A sleep study showed this patient to have central sleep apnea (CSA). Comorbid illnesses that predispose to instability of the ventilatory control system are the most common risk factors for CSA. The most important and prevalent association is between CSA and heart failure, which classically manifests as the Cheyne-Stokes breathing pattern. However, the association between opioid analgesics and CSA is increasingly recognized. Reduction or withdrawal of opioids improves CSA. This patient does not have a history or findings suggestive of heart failure; therefore, opioid analgesics are the most likely cause. The most appropriate next step in management is to seek ways to reduce this patient's opioid intake, possibly through a pain rehabilitation program or in consultation with a pain management specialist.

Adaptive servoventilation (ASV) is a form of positive airway pressure (PAP) therapy sometimes used in patients with CSA. ASV provides a variable amount of pressure during inspiration superimposed on a low level of expiratory PAP, combined with a baseline respiration rate. There is some evidence that ASV may have a positive effect in patients with opioid-induced CSA, but controlled trials showing improvements in important outcomes are lacking. Although a trial of ASV may be warranted in some patients, it should be preceded by an attempt at reduction of opioids.

Continuous positive airway pressure (CPAP) is effective at maintaining upper airway patency in obstructive sleep apnea but is generally ineffective in treating CSA, a disorder of ventilatory control. In fact, CPAP can exacerbate CSA.

Modafinil is used to combat excessive sleepiness associated with the hypersomnia syndromes (such as narcolepsy) and residual sleepiness associated with obstructive sleep apnea despite adequate PAP therapy. There is no role for stimulant medication in the setting of CSA due to opioids.

KEY POINT

- The association between opioid analgesics and central sleep apnea (CSA) is increasingly recognized; reduction or withdrawal of opioids improves CSA.

Bibliography

Rose AR, Catcheside PG, McEvoy RD, et al. Sleep disordered breathing and chronic respiratory failure in patients with chronic pain on long term opioid therapy. J Clin Sleep Med. 2014 Aug 15;10(8):847-52. [PMID: 25126029]

Item 42 Answer: A

Educational Objective: Diagnose allergic bronchopulmonary aspergillosis.

The most likely diagnosis is allergic bronchopulmonary aspergillosis (ABPA). ABPA is a chronic hypersensitivity reaction that occurs in response to colonization of the lower airways with *Aspergillus* species. It occurs most commonly in patients with atopic asthma or cystic fibrosis (CF). The resulting inflammation causes difficult-to-control asthma, impaired mucociliary clearance, destruction of pulmonary parenchyma, and bronchiectasis. Symptoms typically include severe and uncontrolled asthma, cough with expectoration of mucus plugs, and systemic symptoms such as low-grade fever and fatigue. Radiologic findings may be normal or may show recurrent infiltrates or evidence of centrilobular bronchiectasis. Patients will have immediate skin test reactivity to *Aspergillus* antigens; this is often used as an initial diagnostic test. Laboratory studies show peripheral eosinophilia (usually greater than 1000/μL [1×10^9/L]), serum IgE levels greater than 1000 U/mL (1000 kU/L), and precipitating serum antibodies to *Aspergillus*. Treatment consists of standard asthma therapies and the lowest dose of systemic glucocorticoids that effectively controls symptoms. Antifungal agents may be warranted to reduce fungal colonization, and omalizumab may also have a role in therapy.

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Cystic fibrosis (CF) is an autosomal recessive disorder causing abnormal chloride transport resulting in thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract with associated multiorgan dysfunction, with the most prominent disease occurring in the lungs. Although an increasing number of cases of CF are diagnosed in adulthood, this patient has a long history of allergies and asthma, but not chronic respiratory infections or other evidence of multisystem disease suggestive of CF. This lack of consistent symptoms and her older age make CF an unlikely diagnosis in this patient.

Eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome) is an autoimmune small-vessel vasculitis that presents with peripheral eosinophilia and characteristically involves the lungs as asthma. However, it typically has additional manifestations such as purpura on the hands and legs and sensory or motor neuropathy. This patient does not demonstrate these findings.

Hypersensitivity pneumonitis is an immunologic reaction within the pulmonary parenchyma to a wide variety of inhaled agents. It may be acute, intermittent, or chronic and typically presents with cough, shortness of breath, and fatigue. However, this patient has no clear exposure history, and hypersensitivity pneumonitis is not usually associated with peripheral eosinophilia or wheezing.

KEY POINT

- Allergic bronchopulmonary aspergillosis is a chronic hypersensitivity reaction that occurs in response to colonization of the lower airways with *Aspergillus* species; it occurs most commonly in patients with atopic asthma or cystic fibrosis.

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Item 43 Answer: A

Educational Objective: Treat septic shock with appropriate fluid resuscitation.

The most appropriate next step in treatment is to administer another 1000-mL normal saline fluid bolus. This patient's findings are highly compatible with septic shock from a catheter-related bloodstream infection based on her fever, hypotension, organ failure (encephalopathy), and bacteremia. Aggressive fluid resuscitation and early administration of antibiotics are the highest priorities in managing septic shock. After receiving 1000 mL of fluid, this patient has no evidence of volume overload despite her known kidney injury, and a second bolus of fluid is indicated. Patients with sepsis typically need multiple fluid boluses to achieve adequate intravascular volume repletion.

Dobutamine is not appropriate because this patient's clinical picture is indicative of septic, rather than cardiogenic, shock. There are no changes on electrocardiogram, she has warm extremities consistent with a low systemic vascular resistance state, and she has signs of infection. Dobutamine is included in early goal-directed therapy protocols, but it is appropriate only after confirming adequate intravascular volume repletion. Also, the recent ProCESS trial calls into question dobutamine use in the absence of confirmed cardiac dysfunction.

The ProCESS trial included 31 emergency departments in the United States that were randomly assigned patients with septic shock to one of three groups for 6 hours of resuscitation: protocol-based early goal-directed therapy (EGDT); protocol-based standard therapy that did not require the placement of a central venous catheter, administration of inotropes, or blood transfusions; or usual care. Protocol-based resuscitation of patients in septic shock did not improve outcomes. In April 2014, the National Quality Forum downgraded use of central venous lines in the resuscitation of patients with septic shock to be at the discretion of clinicians. Because this patient has adequate peripheral venous access, the placement of a central venous catheter is not a priority management step.

Blood transfusion is not appropriate because this patient's stable hemoglobin level and manifestations of sepsis reliably exclude hypovolemic shock from acute blood loss. Crystalloids are the preferred choice for initial resuscitation of patients with sepsis because of their ready access, ease of rapid infusion, safety profile, and low cost. The efficacy of protocol-based blood transfusion as part of early goal-directed therapy is unclear given the results of the ProCESS trial.

KEY POINT

- Aggressive fluid resuscitation and early administration of antibiotics are the highest priorities in managing septic shock; the routine use of central venous catheters, inotropic drugs, and blood transfusion does not improve outcomes in patients with septic shock.

Bibliography

ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014 May 1;370(18):1683-93. [PMID: 24635773]

Item 44 Answer: B

Educational Objective: Treat advanced idiopathic pulmonary fibrosis with hospice care.

The most appropriate treatment is to recommend hospice care. This patient presents with worsening of his idiopathic pulmonary fibrosis (IPF). The median survival in patients with IPF is 3 to 5 years. IPF has no apparent reversible cause, and patients with IPF have an extremely poor long-term prognosis. This patient has demonstrated significant declines prior to admission with a high supplemental oxygen requirement, and he has now progressed to frank respiratory failure with hypercapnia and hypoxemia refractory to high-flow oxygen. The most common cause of death in IPF is respiratory failure.

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CONT.

Although high-dose glucocorticoids are often used for acute exacerbation, their efficacy remains unknown. This patient has already been treated with glucocorticoids without apparent improvement; this indicates that administration of additional glucocorticoids is not likely to be of benefit.

For individuals who develop severe respiratory distress for which there is no underlying reversible cause, intubation and supportive mechanical ventilation is of little long-term benefit. Therefore, the American Thoracic Society recommends palliation of symptoms and consideration of hospice rather than mechanical ventilation for respiratory failure due to progressive IPF.

The only intervention shown to improve survival in selected patients with IPF is lung transplantation. Given the average age of onset of disease and the increased comorbidities associated with increasing age, this intervention is only available to a small portion of patients with IPF. This patient's advanced age, comorbidities, and advanced state of his lung disease (he is likely to die prior to transplantation) make him a poor candidate for lung transplantation.

KEY POINT

- The American Thoracic Society recommends palliation of symptoms rather than intubation and mechanical ventilation for patients with respiratory failure due to progressive idiopathic pulmonary fibrosis.

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Item 45 Answer: B

Educational Objective: Diagnose methanol poisoning.

This patient's encephalopathy, high anion gap, and elevated osmolal gap are most consistent with methanol (wood alcohol) or ethylene glycol (antifreeze) ingestion. This patient's anion gap is 30 mEq/L (30 mmol/L), and the upper limit of normal is typically 10 mEq/L (10 mmol/L). The osmolal gap is the difference between calculated and measured plasma osmolality. Plasma osmolality (mOsm/kg H_2O) is calculated as follows:

$$2 \times \text{serum sodium (mEq/L)} + \text{plasma glucose (mg/dL)}/18 + \text{blood urea nitrogen (mg/dL)}/2.8$$

The measured osmolality is 325 mOsm/kg H_2O. The calculated osmolality is 295 mOsm/kg H_2O. The osmolal gap is 30 mOsm/kg, and the normal range is less than 10 mOsm/kg. Methanol is converted to formic acid, which is toxic to the retina of the eye. Ethylene glycol is converted by alcohol dehydrogenase to oxalic acid, which crystalizes in renal tubules and causes kidney injury. Conversion to toxic metabolites and clearance of these alcohols is greatly diminished by ethanol or intravenous fomepizole. All alcohols can be removed rapidly with dialysis.

Patients with isopropyl alcohol poisoning present with intoxication and an elevated osmolal gap, but they do not have an increased anion gap acidosis as is seen in this patient.

Salicylate toxicity is another cause of increased anion gap acidosis, encephalopathy, and vomiting. However, it does not cause elevation of the osmolal gap, as is seen in this patient.

Serotonin syndrome is a cause of fever and encephalopathy, but it typically manifests with agitation, muscle rigidity, and hyperreflexia, none of which are present in this patient. Serotonin syndrome also would not explain this patient's increased anion gap acidosis and osmolal gap. This patient's fever is most likely related to an aspiration event.

KEY POINT

- Methanol and ethylene glycol ingestion are characterized by encephalopathy, an increased anion gap acidosis, and an elevated osmolal gap.

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Kruse JA. Methanol and ethylene glycol intoxication. Crit Care Clin. 2012 Oct;28(4):661-711 [PMID: 22998995]

Item 46 Answer: B

Educational Objective: Diagnose a tuberculous pleural effusion.

The most appropriate next test in this patient is pleural fluid adenosine deaminase (ADA) measurement. This patient likely has a tuberculous pleural effusion from reactivation tuberculosis. She presented with subacute onset of fever, pleuritic chest pain, and nonproductive cough with a history of tuberculosis, and pleural fluid analysis is consistent with a lymphocyte-predominant exudate. All of these features are consistent with a tuberculous pleural effusion. When clinical suspicion is moderate to high, the most appropriate test is pleural fluid ADA measurement. Pleural fluid ADA has been demonstrated to be highly sensitive and specific when levels are greater than 60 U/L (sensitivity 95%, specificity 96%). A level of less than 40 U/L virtually excludes the diagnosis of tuberculosis effusion. In patients with lymphocytic-predominant effusions and elevated ADA levels, empiric therapy for tuberculosis should be initiated and pleural biopsy should be pursued to confirm the diagnosis. In the absence of treatment, patients have a 65% risk of developing pulmonary or extrapulmonary tuberculosis within 5 years.

Sputum culture is more likely to be positive in a patient with concomitant pulmonary parenchymal disease. In the absence of identifiable parenchymal disease, the sensitivity of sputum culture, if present or induced, ranges from 20% to 50%.

Both pleural fluid stain and culture for acid-fast bacilli lack sensitivity to exclude the diagnosis of tuberculosis. In

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patients without HIV infection, staining is positive in less than 5% of cases, and pleural fluid cultures are positive in only 20% to 30% of cases.

KEY POINT

- When clinical suspicion is moderate to high, the most appropriate test to diagnose a possible tuberculous effusion is pleural fluid adenosine deaminase measurement.

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Light RW. Pleural effusions. Med Clin North Am. 2011 Nov;95(6):1055-70. [PMID: 22032427]

Item 47 Answer: B

Educational Objective: Identify the appropriate venue of care for a high-risk asthma exacerbation.

The most appropriate management is to admit the patient to the ICU because of his high-risk asthma and arterial blood gas studies suggesting the possibility of impending respiratory failure. Patients with asthma who are at risk of poorer outcomes include those with limited access to health care or difficulty with medication adherence, poor perception of low lung function (and inability to gauge worsening of airways obstruction), an acute increase in use of short-acting β_2-agonist therapy, and lack of improvement with outpatient treatment. This patient has several of these factors, and he also had severe symptoms before seeking care. His initial blood gas studies showed an acute respiratory alkalosis, which is a typical finding in patients with an acute asthma exacerbation. However, his second blood gas determination after 1 hour of treatment showed a developing respiratory acidosis despite a continued high work of breathing, as reflected by his respiration rate. These changes suggest progressively ineffective ventilation and the possibility of impending respiratory collapse. Therefore, the most appropriate venue for treatment is an ICU setting, in which ventilatory failure could be managed if it occurs.

Admission to a general medical floor would not be appropriate because this patient's clinical indicators suggest the need for more intense monitoring that could not be provided in that setting.

Although ventilatory failure could be managed in an emergency department setting, continued therapy with reassessment in 2 hours would not be appropriate given this patient's changing clinical course.

Discharge with close follow-up would not be appropriate given this patient's current respiratory status and previous issues with poor asthma control.

KEY POINT

- Patients with high-risk asthma exacerbations who are not responding to initial treatment and have persistently high work of breathing are best managed in an ICU.

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Item 48 Answer: A

Educational Objective: Diagnose asbestosis.

The most likely diagnosis is asbestosis. The extent of asbestos exposure correlates with risk for disease, with the most common occupational exposures occurring in the construction, automotive servicing, and shipbuilding industries. This patient has a significant exposure history from his construction work for 40 years. History regarding exposure can often be difficult to obtain; however, asking questions regarding limited visibility in the work place due to particulate matter as well as failure to wear protective equipment can suggest an extensive exposure. The latency period between exposure and development of asbestosis is prolonged (15-35 years) and is consistent with this patient's clinical picture. This patient has evidence of fibrosis on lung examination and no evidence to suggest an alternative diagnosis. Pulmonary function testing is consistent with restriction, and chest imaging demonstrates fibrosis and bilateral pleural plaques, which provide evidence of past asbestos exposure. The history, physical examination, and imaging findings are all consistent with diffuse parenchymal lung disease due to asbestosis.

This patient's presentation and laboratory studies are less consistent with COPD. He does not have an extensive tobacco use history, and his physical examination findings are not suggestive of airflow obstruction, which is confirmed by pulmonary function studies. Therefore, COPD is an unlikely cause of this patient's symptoms.

Hypersensitivity pneumonitis in its chronic form may present with indolent symptoms of cough and dyspnea, and it would occur secondary to exposure to an antigen that leads to an immune response. This patient has no exposures other than asbestos. In addition, imaging findings in individuals with hypersensitivity pneumonitis are mid- and upper-lung predominant. Therefore, hypersensitivity pneumonitis is not the most likely diagnosis in this patient.

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonia and commonly affects individuals later in life. It is associated with a history of increased dust exposure, and it is also a diagnosis of exclusion. However, this patient has a clear history of asbestos exposure, which is associated with the development of pulmonary fibrosis and precludes a diagnosis of IPF. This is particularly important because the prognosis for patients with asbestosis is better than for those with well-documented IPF.

KEY POINT

- Asbestosis is characterized by slowly progressive pulmonary fibrosis; the presence of pleural plaques confirms asbestos exposure.

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Item 49 Answer: C

Educational Objective: Diagnose nonadherence to continuous positive airway pressure therapy.

The most appropriate next step in management is to review data from the patient's continuous positive airway pressure (CPAP) device to assess adherence to therapy. This patient has severe, symptomatic obstructive sleep apnea (OSA), for which positive airway pressure (PAP) is the preferred therapy. The response to treatment is dependent on adherence, and a substantial proportion of patients, particularly early in the course of therapy, do not wear the PAP device as intended (all night, every night). Downloading and reviewing data from the PAP device yields important information about usage that can be discussed with the patient to explore barriers and formulate a plan to promote compliance.

Despite some limited evidence that the use of hypnotic agents such as eszopiclone may be helpful in promoting CPAP adherence early in therapy, the role of hypnotic agents in promoting CPAP compliance remains controversial. Their use later in the course of PAP, as in this patient, is not established, and the risk of side effects may outweigh the benefit.

Modafinil is a stimulant medication that is approved for use in patients with OSA who are using CPAP optimally and continue to have residual excessive sleepiness. Compliance with CPAP therapy should be established in this patient before prescribing modafinil.

There are few data to support the superiority of a bilevel positive airway pressure (BPAP) device in promoting treatment compliance for OSA. BPAP, which promotes ventilation by delivery of pressure support derived from the gradient between inspiratory and expiratory pressure, is the preferred therapy for hypoventilation syndromes, such as those associated with neuromuscular disease or obesity.

KEY POINT

- The response to obstructive sleep apnea treatment is dependent on adherence to continuous positive airway pressure (CPAP) therapy; the level of adherence to therapy can be established by downloading and reviewing data from the CPAP device.

Bibliography

Epstein LJ, Kristo D, Strollo PJ Jr, et al; Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009 Jun 15;5(3):263-76. [PMID: 19960649]

Item 50 Answer: C

Educational Objective: Manage acute respiratory distress syndrome using prone positioning.

Prone positioning is most likely to improve this patient's chance of survival. This patient has severe acute respiratory distress syndrome (ARDS) due to viral pneumonia, which has significantly impaired oxygenation. A randomized controlled trial has shown that survival was dramatically improved for patients who were placed in the prone position for at least 16 hours per day until their oxygenation improved, compared with patients who were managed identically except for being kept in the supine position. In the study, the 90-day mortality in the group with prone positioning was 23.6%, whereas it was 41% in the supine group. This technique was not associated with increased adverse consequences. The mechanisms by which prone positioning improves oxygenation are likely multifactorial, with optimization of ventilation-perfusion matching likely playing a major role. Therefore, for this patient with severe ARDS, the best option is daily prone positioning based on its demonstrated benefit in improving oxygenation and reducing mortality.

Aerosolized surfactant has been used in infant respiratory distress syndrome, but trials of this therapy in adults have not shown benefit.

Nitric oxide dilates the pulmonary vasculature when administered by inhalation and may have a role in treating patients with pulmonary arterial hypertension. In studies of patients with ARDS, inhaled nitric oxide has been shown to improve oxygenation by temporarily improving ventilation-perfusion mismatch; however, a mortality benefit has not been demonstrated in patients with ARDS. It would therefore not be the most appropriate next step in the management of this patient.

Studies of glucocorticoids in ARDS have shown inconsistent results and have not generally demonstrated improved outcomes. Therefore, systemic glucocorticoids would not be an optimal therapy for treating this patient.

KEY POINT

- Prone positioning is associated with dramatically improved survival for patients with acute respiratory distress syndrome.

Bibliography

Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013 Jun 6;368(23):2159-68. [PMID: 23688302]

Item 51 Answer: C

Educational Objective: Diagnose a malignant pleural effusion.

The most appropriate management is repeat thoracentesis and pleural fluid cytology, owing to the increased sensitivity with subsequent samples. If malignancy is suspected, a cytologic analysis is a quick and easy way to obtain a diagnosis. When the suspicion for malignancy is high (breast mass and pleural effusion in this patient), it is appropriate to repeat cytology if the first specimen is negative. The overall mean sensitivity of pleural fluid cytology is 60%. Approximately 65% of positive results are obtained on the initial thoracentesis. The second

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sample provides an additional 27%, and the third sample provides only 5%.

Closed pleural biopsy is less sensitive than cytology for pleural malignancy and should not be performed.

Flow cytometry is useful with lymphocyte-predominant effusions when lymphoma is a diagnostic consideration. However, this patient's breast mass, weight loss, and bloody effusion suggest otherwise.

Thoracoscopic pleural biopsy is indicated for all undiagnosed exudative pleural effusions following three pleural fluid samplings. Thoracoscopic biopsy is more than 90% sensitive for pleural malignancy. However, this patient has only had one pleural fluid sampling.

KEY POINT

- When suspicion for pleural malignancy is high, it is appropriate to repeat pleural fluid cytology if the first specimen is negative owing to the increased sensitivity with subsequent samples.

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Light RW. Clinical practice. Pleural effusion. N Engl J Med. 2002 Jun 20;346(25):1971-7. [PMID: 12075059]

Item 52 Answer: D

Educational Objective: Diagnose chronic thromboembolic pulmonary hypertension.

The most appropriate diagnostic test to perform next is a ventilation-perfusion (V/Q) scan. This patient's presentation strongly suggests chronic thromboembolic pulmonary hypertension (CTEPH), for which V/Q scanning is the preferred and most sensitive diagnostic imaging study. CTEPH usually presents with progressive exertional dyspnea that correlates with the extent of hemodynamic derangement and right ventricular involvement. Patients with CTEPH may have findings of pulmonary hypertension and cor pulmonale and invariably have defects on V/Q scan. This patient's cardiac examination, with an accentuated pulmonic component of S_2, is compatible with pulmonary hypertension, as are the findings on echocardiography. Additionally, her clear lung fields, hypoxia, and findings on pulmonary function testing are consistent with a diffusion defect. If she has an abnormal V/Q scan, right heart catheterization with pulmonary angiography is required to confirm the diagnosis and characterize the degree of thrombosis, which may help guide therapy. The absence of deep venous thrombosis on venous studies of the legs is insufficient to rule out recurrent pulmonary emboli. V/Q scanning can also differentiate CTEPH (group 4 pulmonary hypertension) from pulmonary arterial hypertension (group 1 pulmonary hypertension), which is the other major diagnostic consideration in this patient.

Although CT angiography can identify proximal pulmonary arterial webs and luminal narrowing when present, it is less sensitive than V/Q scanning in detecting CTEPH. Furthermore, in this patient with clear lung fields on chest radiograph, CT scanning is unlikely to provide additional diagnostically useful information about the pulmonary parenchyma.

Pulmonary hypertension of this severity is typically associated with severe obstructive sleep apnea and marked sleep-related hypoxemia. There is little evidence suggesting sleep-disordered breathing in this nonobese woman; therefore, polysomnography is not indicated at this time.

In operative candidates, CTEPH is best managed surgically with pulmonary thromboendarterectomy. Pulmonary angiography is performed preoperatively to assess the extent and distribution of thrombus. It is not, however, an appropriate test during the initial evaluation.

KEY POINT

- Ventilation-perfusion scanning is the preferred and most sensitive diagnostic imaging study for chronic thromboembolic pulmonary hypertension.

Bibliography

Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D92-9. [PMID: 24355646]

Item 53 Answer: C

Educational Objective: Diagnose right-to-left intrapulmonary shunt as a cause of hypoxemia.

The most likely diagnosis is intrapulmonary shunt. This patient's profound hypoxia is most likely due to intrapulmonary shunting of blood through his collapsed right lower lobe. Evidence of a collapsed right lower lobe is indicated by the triangular opacity above the diaphragm on the right side on his chest radiograph. Right-to-left intrapulmonary shunts may be anatomical or physiological, but all result in hypoxemia that does not readily correct with supplemental oxygen, as seen in this patient. This patient's physiological shunt results in perfusion of nonventilated alveoli of the collapsed right lower lobe. In most situations, a lobar collapse will not cause such severe shunting because of hypoxic vasoconstriction of arterioles in parts of the lung that are not ventilated; however, in some cases, such as this patient, this compensatory mechanism directing blood flow to other aerated areas of the lung is ineffective.

Hepatopulmonary syndrome, intracardiac shunt, and pulmonary arteriovenous malformation are all examples of anatomic shunts. Although these conditions can be responsible for hypoxemia that is difficult to correct with supplemental oxygen, this patient's trauma, splinting, and abnormal radiographic findings suggest a lower lobe collapse as the most likely diagnosis. In conditions of diagnostic uncertainty, a bubble contrast echocardiogram could be performed. These anatomic shunts are associated with the appearance of left atrial or ventricular bubbles after several cardiac cycles.

Hepatopulmonary syndrome should be suspected in patients with cirrhosis who develop hypoxemia in the

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CONT.

absence of other causes. Their shunt worsens with upright posture (orthodeoxia). However, this is not a likely diagnosis in a patient without evidence of cirrhosis.

KEY POINT

- Right-to-left intrapulmonary shunts may be anatomic or physiologic, but all result in hypoxemia that is difficult to correct with supplemental oxygen.

Bibliography

Rodríguez-Roisin R, Roca J. Mechanisms of hypoxemia. Intensive Care Med. 2005 Aug;31(8):1017-9. [PMID: 16052273]

Item 54 Answer: D

Educational Objective: Treat pulmonary arterial hypertension.

The most appropriate management is sildenafil. In patients with pulmonary arterial hypertension (PAH) and respiratory symptoms occurring during exertion but not at rest, oral medications are the preferred initial therapy. Examples of oral agents include phosphodiesterase-5 inhibitors (sildenafil, tadalafil) and endothelin receptor antagonists (bosentan, ambrisentan). Prostanoids are available only as parenteral (epoprostenol) or inhaled (iloprost) forms and are typically reserved for patients with more advanced disease and symptoms and for those in whom disease progresses despite oral therapy. Additional treatments that are provided for most patients with PAH include supplemental oxygen for documented hypoxemia and chronic warfarin therapy. Pregnancy can worsen pulmonary hemodynamics and increase the risk of mortality in patients with PAH, so women of childbearing age should be counseled to avoid pregnancy.

In patients who have a positive response to vasoreactivity testing (a decrease in mean pulmonary artery pressure of at least 10 mm Hg without significant reductions in cardiac output or systemic blood pressure), oral calcium channel blockers such as nifedipine are a reasonable initial therapy. In those with a negative vasoreactivity test, as in this patient, calcium channel blockers are not beneficial.

Recent clinical trials have shown supervised exercise programs to be safe and to improve walking distances and quality of life in patients with PAH. Excessive exertion resulting in respiratory distress should be avoided.

KEY POINT

- In patients with pulmonary arterial hypertension and a negative vasoreactivity test, calcium channel blockers are not beneficial and phosphodiesterase-5 inhibitors (sildenafil, tadalafil) or endothelin receptor antagonists (bosentan, ambrisentan) are preferred.

Bibliography

Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D60-72. [PMID: 24355643]

Item 55 Answer: C

Educational Objective: Recognize characteristics of a patient ready for extubation.

This patient has had a successful spontaneous breathing trial (SBT) and is ready for discontinuation of mechanical ventilation and extubation. The purpose of a SBT is to assess the likelihood that mechanical ventilation can be discontinued successfully. A SBT is performed by placing the patient on a T-piece through which no positive pressure is delivered (only supplemental oxygen) or by adjusting the ventilator so that it applies only enough pressure to overcome the resistance of the endotracheal tube. Criteria that have been suggested for a successful SBT include the ability to tolerate a weaning trial for 30 minutes; maintain a respiration rate of less than 35/min; and maintain an oxygen saturation of at least 90% without arrhythmias, sudden increases in heart rate and blood pressure, or development of respiratory distress, diaphoresis, or anxiety. Because this patient successfully completed a SBT, an attempt at discontinuation of mechanical ventilation and extubation is appropriate.

Arterial blood gas studies are performed when there are concerns about acute or worsening chronic carbon dioxide retention or when exact arterial oxygenation measurement is needed. Even if the carbon dioxide level is elevated, it would not necessarily indicate that the patient is not an appropriate candidate for extubation, especially if the patient is able to perform a SBT and has an otherwise unremarkable examination, as in this patient.

It is unnecessary to continue mechanical ventilation and observe for an additional 24 hours with an endotracheal tube in place. Patients who meet the parameters of success during a SBT can be disconnected from mechanical ventilation and extubated. Continuing mechanical ventilation beyond the time when successful weaning parameters are met adds additional risks to the patient, including ventilator-associated infections or other potential complications of mechanical ventilation.

Direct extubation to noninvasive positive pressure ventilation is effective at weaning patients with obstructive lung disease with ventilatory respiratory failure from mechanical ventilation. However, it is not necessary for patients with primarily hypoxemic respiratory failure such as this patient with pneumonia.

KEY POINT

- Criteria that have been suggested for a successful spontaneous breathing trial in patients requiring intubation and mechanical ventilation include the ability to tolerate a weaning trial for 30 minutes; maintain a respiration rate of less than 35/min; and maintain an oxygen saturation of at least 90% without arrhythmias, sudden increases in heart rate and blood pressure, or development of respiratory distress, diaphoresis, or anxiety.

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Item 56 Answer: D

Educational Objective: Diagnose pulmonary arterial hypertension.

The most appropriate diagnostic test to perform next is right heart catheterization. This patient has a diagnosis of limited cutaneous systemic sclerosis. Systemic sclerosis, particularly limited cutaneous systemic sclerosis, is associated with pulmonary vascular disease caused by direct proliferative effects on the vascular wall that obliterate pulmonary arterioles and capillaries and lead to fibrosis of the surrounding lung interstitium. These changes result in pulmonary arterial hypertension (PAH, group 1 classification). This patient's symptoms (exertional dyspnea, fatigue), physical examination findings (prominent S_2), and echocardiographic findings (right ventricular enlargement, elevated pulmonary artery pressure) are consistent with PAH. Because echocardiography may underestimate true pulmonary artery pressures, right heart catheterization is required to confirm pulmonary hemodynamics as well as to determine whether there is a specific response to vasodilator infusion, which may help guide therapy. Right heart catheterization should be used to confirm mean pulmonary artery pressures of at least 25 mm Hg, a normal pulmonary capillary wedge pressure, and to determine whether the pulmonary vasculature is vasodilator-responsive to assist defining treatment options.

The 6-minute walk test provides a useful baseline prior to initiation of specific PAH therapy; however, it does not provide the specific diagnostic information obtained by right heart catheterization.

This patient may have gas exchange impairment that causes nocturnal hypoxia, which would be detectable on overnight pulse oximetry. However, this test will not provide specific information about the underlying pulmonary vascular problem and therefore will not be a useful diagnostic study at present.

Polysomnography is useful in diagnosing possible sleep-disordered breathing, such as sleep apnea, as a cause of pulmonary hypertension. However, this patient has no clinical suggestion of sleep apnea, and her clinical presentation is most consistent with PAH associated with her known connective tissue disease. Therefore, polysomnography would not be an appropriate next diagnostic test.

KEY POINT

- In patients with suspected pulmonary arterial hypertension, right heart catheterization is required to confirm pulmonary hemodynamics as well as to determine whether there is a specific response to vasodilator infusion, which may help guide therapy.

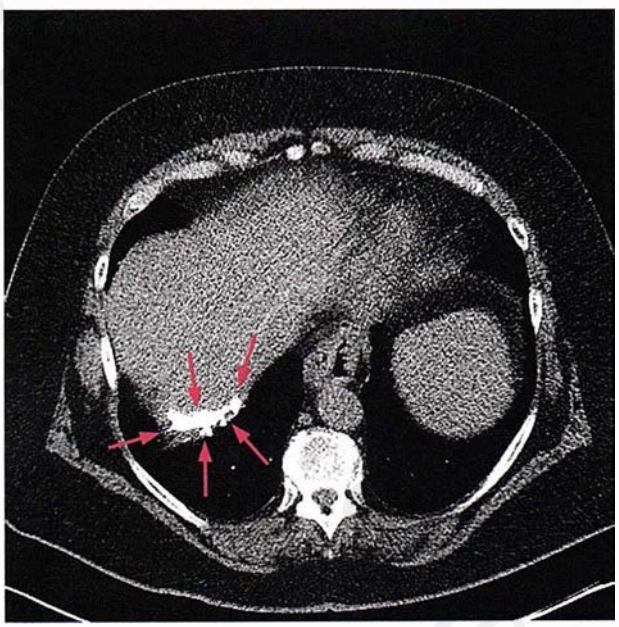
Bibliography

Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D60-72. [PMID: 24355643]

Item 57 Answer: C

Educational Objective: Diagnose mesothelioma.

The most likely diagnosis is mesothelioma. Malignant pleural mesothelioma is a very aggressive tumor that arises from the mesothelial cells of the pleura. Patients most commonly present with symptoms of a slowly enlarging pleural effusion. This patient's physical examination findings (decreased breath sounds, dullness to percussion, decreased tactile fremitus, and no egophony) are consistent with a pleural effusion. The absence of an effusion on this patient's previous screening CT 5 months ago suggests that the effusion developed since then and correlates with development of his symptoms. His previous chest imaging also showed a calcified pleural plaque (*arrows*) that confirms his exposure to asbestos, which likely occurred when he worked as a plumber and is a strong risk factor for mesothelioma. His risk for mesothelioma is further increased by his tobacco use. This combination of history, physical examination, and previous radiographic findings makes mesothelioma the most likely cause of this patient's newly diagnosed pleural effusion.



There are many other causes of a pleural effusion, including heart failure. However, this is unlikely in this patient because he has no evidence of volume overload on examination.

Although lymphoma can result in pleural effusions, the patient has no constitutional symptoms or other signs suggestive of lymphoma. Isolated pleural lymphoma is incredibly rare and is much less likely than mesothelioma in this patient.

Both pneumonia (areas of consolidation) and pleural effusion can result in decreased breath sounds and dullness

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to percussion on physical examination. However, consolidation would cause increased, rather than decreased, tactile fremitus, and egophony would be present.

KEY POINT

- Patients with malignant pleural mesothelioma most commonly present with symptoms of a slowly enlarging pleural effusion.

Bibliography

Wong CL, Holroyd-Leduc J, Straus SE. Does this patient have a pleural effusion? JAMA. 2009 Jan 21;301(3):309-17. [PMID: 19155458]

Item 58 Answer: B

Educational Objective: Diagnose diffuse systemic sclerosis-associated parenchymal lung disease.

In addition to pulmonary function testing, anti-Scl-70 antibody testing and high-resolution CT (HRCT) would be most helpful in establishing a diagnosis. In this particular patient, there are findings of skin thickening in the distal extremities, which suggests diffuse cutaneous systemic sclerosis (dcSSc). Patients with dcSSc are more likely to develop diffuse parenchymal lung disease (DPLD), serositis, and kidney disease (including scleroderma renal crisis). DPLD most commonly occurs in patients with dcSSc and elevated antibody titers to anti-Scl-70. Alveolitis may precede the development of DPLD; presenting manifestations include dyspnea, nonproductive cough, and exercise intolerance. Fine bibasilar Velcro-like inspiratory crackles are frequently present on physical examination. A restrictive impairment with decreased lung volumes and decreased DLCO is typically present on pulmonary function tests. Chest imaging is best performed with HRCT, which is more sensitive than plain radiography in detecting alveolitis and reticular linear opacities present in patients with early stages of lung disease. As a result, anti-Scl-70 antibody testing and HRCT scan are most likely to establish the diagnosis.

Complete pulmonary function testing (spirometry, lung volumes, and diffusing capacity) is an important component of evaluating parenchymal lung disease. It can assess the severity of disease, and the discovery of different patterns can confirm the presence of restrictive lung diseases, such as DPLD, or the presence of obstructive or mixed patterns that can help further focus the differential diagnosis. The finding of a low diffusing capacity that is out of proportion to the decrease in lung volumes suggests the presence of other conditions such as pulmonary hypertension.

Anti-PM-Scl antibody is associated with myositis. Anticentromere antibody is associated with limited cutaneous systemic sclerosis and the risk of developing pulmonary hypertension. Antineutrophil cytoplasmic antibody is associated with granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome); it is not associated with systemic sclerosis.

Bronchoalveolar lavage, lung biopsy, and gallium-67 scanning are generally not helpful in the diagnosis of systemic sclerosis-associated DPLD and would not be performed prior to HRCT scanning.

KEY POINT

- Diffuse parenchymal lung disease most commonly occurs in patients with diffuse cutaneous systemic sclerosis and elevated antibody titers to anti-Scl-70.

Bibliography

Fan MH, Feghali-Bostwick CA, Silver RM. Update on scleroderma-associated interstitial lung disease. Curr Opin Rheumatol. 2014 Nov;26(6):630-6. [PMID: 25191993]

Item 59 Answer: B

Educational Objective: Treat asthma during pregnancy.

The most appropriate management is to continue the current drug regimen. As in all patients with asthma, treatment of asthma during pregnancy should aim for optimal control, and a regimen that adequately controls asthma should be continued. Controlled asthma ensures safety for the fetus as well as the mother and reduces the risk for preeclampsia and preterm birth. Inhaled glucocorticoids are considered safe in pregnancy, and abundant long-term safety evidence exists for budesonide. Short-acting β_2-agonists are considered safe in pregnancy, and existing data for long-acting β_2-agonists are reassuring that these agents are safe as well. The leukotriene antagonist montelukast is also considered safe in pregnancy. In this patient, who has a history of reduced lung function, it is appropriate to maintain the current regimen that is controlling her asthma because the medications she is taking have evidence of safety in pregnancy. This patient also should have frequent monitoring with regular visits, should be offered a peak flow monitor, and should be counseled regarding the safety of and need for continued asthma medications. The most appropriate management is to continue the current regimen and follow up frequently.

Empirically stepping up asthma therapy in anticipation of worsening asthma symptoms during pregnancy is not warranted. During pregnancy, one third of women have no significant change in their asthma, one third experience worsening of symptoms, and one third experience improvement of symptoms.

Stopping inhaled glucocorticoids and/or montelukast would not be appropriate owing to this patient's likely impairment without controller medications, particularly because these agents are considered safe in pregnancy.

KEY POINT

- Inhaled glucocorticoids, most β_2-agonists, and the leukotriene antagonist montelukast are considered safe in pregnancy.

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National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007 Nov;120 (5 Suppl):S94-138. Erratum in: J Allergy Clin Immunol. 2008 Jun;121(6):1330. [PMID: 17983880]

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Item 60 Answer: C

Educational Objective: Treat severe COPD with recurrent exacerbations.

The most appropriate treatment is roflumilast. Roflumilast is a phosphodiesterase-4 (PDE-4) inhibitor that is used as add-on therapy to reduce exacerbations in patients with severe COPD associated with chronic bronchitis and a history of recurrent exacerbations despite other therapies. Inhibition of PDE-4 decreases inflammation, which may be helpful in a limited number of patients with COPD in whom inflammation is a significant factor. Roflumilast has minimal bronchodilator activity; however, small improvements in FEV_1 are seen in patients also treated with a long-acting anticholinergic agent or a long-acting β_2-agonist. Roflumilast should always be used with at least one long-acting bronchodilator. This patent has severe symptomatic COPD (Global Initiative for Chronic Obstructive Lung Disease category D) with recurrent exacerbations, so roflumilast is indicated, along with other agents.

Some studies of macrolide antibiotics suggest that their use reduces exacerbations in a select group of patients with COPD. Macrolides have been shown to reduce exacerbations and improve lung function in patients with cystic fibrosis. However, there is currently insufficient evidence to routinely recommend daily macrolide therapy for the long-term treatment of COPD. There are concerns that long-term azithromycin therapy may be associated with increasing bacterial resistance, especially in patients who previously had *Mycobacterium avium-intracellulare* infection, and an increased risk of QT prolongation.

Oral glucocorticoids should be reserved for limited periodic use to treat acute exacerbations in patients with COPD. Long-term oral glucocorticoid therapy has been shown to have limited, if any, benefits in COPD. In addition, long-term glucocorticoid therapy has a high risk for significant side effects, including diabetes mellitus, muscle weakness, osteoporosis, and decrease in functional status.

The anti-inflammatory effects of simvastatin were previously believed to reduce exacerbations in COPD. However, a large randomized prospective study showed that, in patients at risk for exacerbations, simvastatin along with usual treatment did not reduce exacerbations or the time to first exacerbation. In addition, simvastatin was found to have no effect on lung function, quality of life, rate of severe adverse events, or mortality.

KEY POINT

- Roflumilast is a phosphodiesterase-4 inhibitor that is used as add-on therapy to reduce exacerbations in patients with severe COPD associated with chronic bronchitis and a history of recurrent exacerbations despite other therapies.

Bibliography

Wedzicha JA, Rabe KF, Martinez FJ, et al. Efficacy of roflumilast in the COPD frequent exacerbator phenotype. Chest. 2013 May;143(5):1302-11. [PMID: 23117188]

Item 61 Answer: B

Educational Objective: Treat nonexertional heat stroke with external evaporative cooling.

The most appropriate next step in treatment is external evaporative cooling. Hyperthermia occurs most commonly owing to heat stroke, malignant hyperthermia, and neuroleptic malignant syndrome. A temperature greater than 40.0 °C (104.0 °F) and encephalopathy in the setting of environmental heat exposure are characteristic of heat stroke. The majority of patients with nonexertional heat stroke are older than 70 years or have chronic medical conditions. Medications and recreational drugs with anticholinergic, sympathomimetic, and diuretic effects, including alcohol, pose added risk. This patient's advanced age and diuretic use place him at increased risk for nonexertional heat stroke. External evaporative cooling involves removing all clothing and spraying the patient with a mist of lukewarm water while continuously blowing fans on the patient. Ice water immersion is commonly used for patients with exertional heat stroke, who typically are younger and need less monitoring.

Heat stroke is a cause of rhabdomyolysis, but the combination of fever, encephalopathy, and rhabdomyolysis should also raise the possibility of neuroleptic malignant syndrome (NMS) and serotonin syndrome. NMS can be treated with dantrolene or bromocriptine. However, this patient has no muscle rigidity or medication exposure (antipsychotics in particular), which are characteristic of NMS. Therefore, treatment with dantrolene would not be appropriate.

Cyproheptadine is used to treat serotonin syndrome. Although this patient takes sertraline, serotonin syndrome would not be expected to cause severe hyperthermia. Furthermore, characteristic muscle rigidity and neurologic signs, including tremor, hyperreflexia, and clonus, are absent.

N-acetylcysteine is used to treat acetaminophen toxicity, which is a diagnostic consideration in a patient with encephalopathy and a history of depression and possible suicidality. However, acetaminophen overdose is not associated with severe hyperthermia.

KEY POINT

- Factors that increase risk for nonexertional heat stroke include alcohol use, advanced age, chronic medical conditions, and use of medications or recreational drugs with anticholinergic, sympathomimetic, or diuretic effects.

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Atha WF. Heat-related illness. Emerg Med Clin North Am. 2013 Nov;31(4):1097-108. [PMID: 24176481]

Item 62 Answer: C

Educational Objective: Diagnose COPD with spirometry.

The most appropriate next step in management is spirometry. This patient, who is a smoker with intermittent cough and

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dyspnea, likely has COPD. Although dyspnea, cough, and sputum production are characteristic symptoms of COPD, these symptoms can be variable and the cough can be nonproductive. This patient requires spirometry, which measures the FEV_1 and FVC, and the FEV_1/FVC ratio to assess for and quantify any degree of airflow obstruction present. Patients with COPD have a FEV_1/FVC ratio of less than or equal to 70%. Spirometry is reproducible and provides an objective measurement of airflow obstruction. Screening for COPD with spirometry in individuals without respiratory symptoms is not recommended, but it is indicated in this patient with symptoms and a suggestive clinical history for COPD.

CT scanning is used to evaluate parenchymal lung lesions (such as nodules) and other potential chest pathology (such as pleural or mediastinal disease). However, it is not effective in diagnosing COPD, particularly in this patient with a normal plain chest radiograph. In addition, guidelines recommend low-dose CT scanning for current or former smokers aged 55 to 80 years with a smoking history of at least 30-pack-years with no history of lung cancer; this patient does not fit these criteria.

Polysomnography is used for evaluation of suspected sleep-disordered breathing (such as sleep apnea). However, this patient does not have symptoms suggestive of sleep apnea or other sleep or nocturnal breathing disorders. Therefore, polysomnography is not indicated.

Although gastroesophageal reflux disease (GERD) is a common cause of chronic cough, and a trial of an empiric proton pump inhibitor is reasonable in patients with unexplained cough and otherwise negative evaluation, GERD would not account for this patient's dyspnea symptoms. Because his clinical presentation is more consistent with mild COPD, empiric treatment for GERD would not be the preferred next management step.

KEY POINT

- Spirometry should be performed to evaluate for COPD in patients with suggestive symptoms (dyspnea, cough, sputum production) and risk factors such as a history of smoking.

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Item 63 Answer: B

Educational Objective: Treat chronic respiratory failure due to muscular weakness.

The most appropriate respiratory management for this patient is nocturnal noninvasive positive pressure ventilation (NPPV). He has chronic respiratory failure due to progressive muscular weakness. Although there are no clear guidelines regarding when to institute respiratory support in patients with progressive muscle weakness, this patient's inability to breathe while lying flat is highly suggestive of diaphragm weakness, and his low vital capacity is below the threshold at which most patients require mechanical support. Frequently used clinical indicators for the need of ventilatory assistance include an FVC less than 50% of predicted, a vital capacity below 60% of predicted (or 1 L), or a maximal inspiratory pressure of less than -30 cm H_2O. In patients requiring ventilator support, NPPV is the usual initial method used, typically on an intermittent, nocturnal basis. NPPV has been shown to improve quality of life and delay the progression of respiratory failure in patients with progressive neuromuscular disease.

Nocturnal continuous positive airway pressure is typically used in patients with upper airway obstruction such as obstructive sleep apnea, but it would not improve this patient's respiratory mechanics and ventilatory impairment.

Nocturnal oxygen therapy is not indicated and would not be expected to be helpful in this patient with adequate arterial oxygenation despite his chronic hypoventilation.

Continuous mechanical ventilation, usually through a tracheostomy, is generally indicated for patients with a contraindication to NPPV or for those requiring continuous mechanical ventilation for an extended period of time. This patient does not have a contraindication to noninvasive ventilation, and his response to a trial of NPPV therapy is not yet known. Therefore, pursuing tracheostomy and continuous mechanical ventilation would be premature in this patient. It should be noted that he will probably eventually require a tracheostomy, and this would be a good time to introduce that idea for ongoing discussion.

KEY POINT

- No clear guidelines exist for when to start mechanical ventilation in patients with chronic respiratory failure due to progressive muscular weakness; however, signs that ventilatory support is required include the inability to breathe while lying flat, low FVC, low vital capacity, and decreased negative inspiratory pressure.

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Item 64 Answer: D

Educational Objective: Treat tricyclic antidepressant overdose with sodium bicarbonate therapy.

The most appropriate next step in treatment is to begin intravenous sodium bicarbonate therapy. The combination of progressive somnolence, hypotension, widening of the QRS interval, seizure, and anticholinergic signs (fever, tachycardia, mydriasis, reduced bowel sounds) is concerning for severe tricyclic antidepressant overdose. Tricyclic antidepressants inhibit fast sodium channels in the myocardium

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CONT.

and conduction system, resulting in decreased ventricular function and increased duration of repolarization that predisposes to ventricular arrhythmias. Electrocardiographic findings in tricyclic overdose include nonspecific changes in QRS morphology and QRS prolongation that predisposes to ventricular arrhythmia; a QRS duration of greater than 100 ms is often used as an indicator of significant tricyclic cardiotoxicity. Sodium bicarbonate increases the serum pH, which inhibits the ionized form of the drug that binds sodium channels, making it less available. Sodium bicarbonate also increases extracellular sodium, which increases the electrochemical gradient across myocardial cell membranes and minimizes the effect of blockade of rapid sodium channels. Clinically, this improves myocardial contractility and results in a reduction in the risk of arrhythmias.

Intravenous calcium gluconate is used in the management of calcium channel blocker overdose, which is a possibility given this patient's baseline use of amlodipine, her hypotension, and the possibility of hypotension-associated encephalopathy. Verapamil and diltiazem poisoning is associated with bradycardia, but this is not typically seen in the case of poisoning with dihydropyridines like amlodipine. Amlodipine poisoning would not explain this patient's anticholinergic signs, widened QRS interval, and seizure.

Fomepizole is an alcohol dehydrogenase inhibitor that prevents the breakdown of methanol and ethylene glycol into toxic metabolites. This patient's somnolence and history of depression raise the possibility of methanol and ethylene glycol poisoning, but the normal osmolal gap, QRS interval widening, and anticholinergic signs would not be expected.

Physostigmine is a potential antidote for anticholinergic toxicity and may be particularly helpful in the management of associated agitated delirium. Although this patient has anticholinergic symptoms, her somnolence, widened QRS interval, and baseline use of amitriptyline are more compatible with tricyclic antidepressant overdose. Physostigmine has reportedly precipitated asystole when used in the setting of tricyclic overdose and should not be given to this patient.

KEY POINT

- The combination of progressive somnolence, hypotension, widening of the QRS interval, seizure, and anticholinergic signs (fever, tachycardia, mydriasis, reduced bowel sounds) is characteristic of severe tricyclic antidepressant overdose.

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Item 65 Answer: E

Educational Objective: Manage surveillance of a solitary pulmonary nodule.

The most appropriate management is to discontinue further imaging. This patient was found to have a subcentimeter pulmonary nodule. The Fleischner criteria recommend surveillance with repeat chest imaging in a high-risk patient (history of smoking or other risk factors for lung cancer) at intervals based on the size of the nodule. For subcentimeter nodules at 6 mm, the recommendation is initial follow-up CT at 6 to 12 months and then at 18 to 24 months if no change. If imaging demonstrates stability of the nodule (and no other new findings) for 24 months, no further imaging is required.

Given the higher probability of malignancy with ground-glass opacification and partly solid nodules, patients with these types of tumors may warrant longer, if not lifelong, surveillance. Patients with such nodules would benefit from a pulmonary consultation. This patient, however, has no evidence of associated ground-glass opacification and does not currently meet any other criteria for further imaging with a repeat CT, PET/CT, or chest radiograph.

Recent guidelines recommend screening with annual low-dose CT for 3 consecutive years in patients with at least a 30-pack-year history of smoking who are currently smoking or quit within the last 15 years if the patient is between the ages of 55 and 80 years. This patient, however, quit smoking 20 years ago, so he does not meet criteria for screening.

KEY POINT

- If imaging demonstrates stability of a solitary pulmonary nodule (and no other new findings) for 24 months, no further imaging is required.

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Item 66 Answer: D

Educational Objective: Identify risk factors for early readmission in a patient hospitalized for COPD exacerbation.

Comorbidities such as heart failure, lung cancer, anxiety, depression, and osteoporosis are important causes of increased early hospital readmission in patients with COPD exacerbation. The rates of early readmission for COPD exacerbation increase as the number of comorbidities increases. Higher rates of readmissions were noted in patients with COPD and combinations of comorbidities like heart failure and osteoporosis (21%), heart failure and anxiety (18.2%), heart failure and depression (15.9%), and heart failure and alcohol abuse (14.4%).

Inadequate discharge medications for COPD exacerbation were also associated with early readmission rates, specifically the failure to prescribe a short-acting bronchodilator, oral glucocorticoid, and an antibiotic. This patient was discharged on all of these medications; therefore, inadequate discharge medications should not be a cause of early readmission.

Another patient factor associated with early readmission is male gender. Female gender does not increase the risk for early readmission.

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Patients who were discharged less than 2 days or more than 5 days after admission are at risk for early readmission. This patient's hospital stay was 4 days, so this is unlikely to contribute to her risk of early readmission.

KEY POINT

- The rates of early hospital readmission for COPD exacerbation increase as the number of comorbidities increases.

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Item 67 Answer: C

Educational Objective: Diagnose bronchiectasis with high-resolution CT.

The most appropriate diagnostic test to perform next is high-resolution CT (HRCT). This patient most likely has bronchiectasis. Symptoms of bronchiectasis include chronic cough with purulent sputum and recurrent pneumonia (in both smokers and nonsmokers). Pulmonary function tests commonly detect mild to moderate airflow obstruction, which may overlap with other disease findings (such as COPD). Physical examination findings may include crackles and/or wheezing on lung auscultation. This patient has a history of pertussis as a child, has a chronic cough with mucopurulent sputum, and has increased bronchovascular markings on chest radiograph. The cause of bronchiectasis in this patient may be lung damage associated with her history of pertussis. In most patients with bronchiectasis, the chest radiograph shows nondiagnostic radiologic findings, including linear atelectasis or dilated and thickened airways ("tram" or "parallel" lines). HRCT is the gold standard diagnostic test for parenchymal lung disease, such as bronchiectasis, and should be performed in this patient. Contrast enhancement is not necessary. Airway dilatation with lack of tapering, bronchial wall thickening, and cysts may be seen on HRCT. After the diagnosis is confirmed, evaluation for underlying causes, such as cystic fibrosis, immunoglobulin deficiencies, and mycobacterial disease, should be performed based on the clinical circumstances of the patient.

Bronchoscopy may be helpful for evaluating a mass or foreign body if identified on CT. However, bronchoscopy is less useful in evaluating bronchiectasis and would not be the next study of choice in this patient.

MRI of the chest has a limited role in evaluating bronchiectasis owing to multiple technical factors. It is an established diagnostic modality for evaluating pleural, hilar, and mediastinal abnormalities. However, it would not be an indicated study in this patient.

Although repeat chest imaging might be helpful to document resolution or progression of a pulmonary finding, delaying further evaluation in this patient with chronic symptoms would likely not be beneficial.

KEY POINT

- High-resolution CT is the gold standard diagnostic test for bronchiectasis.

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Item 68 Answer: A

Educational Objective: Diagnose auto-positive end-expiratory pressure.

This patient with severe COPD has developed auto-positive end-expiratory pressure (auto-PEEP) on mechanical ventilation. Her obstructive lung disease slows her expiratory flow rate so that she cannot completely exhale before the next breath is initiated by the ventilator (breath stacking). The volume of air that remains in the lungs after each breath builds up, resulting in increased intrathoracic pressure; this can progress to severe consequences such as hypoxemia, cardiovascular collapse (due to decreased venous return and reduced cardiac preload), and barotrauma. When auto-PEEP is diagnosed, the ventilator circuit should be disconnected from the patient's endotracheal tube to allow for a prolonged exhalation which enables trapped intrathoracic air to escape, intrathoracic pressure to drop, and venous return to improve. The ventilator settings should then be adjusted to allow for more effective exhalation to avoid further air trapping. Slowing the respiration rate, decreasing the tidal volume, and increasing the inspiratory flow rate while tolerating respiratory acidosis are ways to increase the exhaled volume with each cycle.

Partial tube obstruction (as with a kink or partially obstructing mucus plug) usually causes a rise in only the peak inspiratory pressure because it affects resistance to flow of air through the tube. Plateau pressure is measured in the absence of flow, so it is unaffected by changes in resistance. Because this patient's plateau pressure increased along with the peak inspiratory pressure, partial tube obstruction is not the most likely cause of her findings.

If a patient has anxiety and triggers breaths more frequently than the set rate, sedation may be required to slow the respiration rate and avoid potential auto-PEEP. This is especially true with hypercapnia, as it is a potent stimulus to increase respiration rate. However, sedation itself is not associated with increased airway and plateau pressures.

KEY POINT

- Patients with obstructive lung disease on mechanical ventilation are susceptible to air trapping due to resistance to expiratory flow, which leads to auto-positive end-expiratory pressure (auto-PEEP) and subsequently to increased intrathoracic pressure.

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Item 69 Answer: A

Educational Objective: Manage advanced COPD with referral to hospice care.

The most appropriate management is to refer this patient for hospice care. Hospice is considered appropriate for patients in whom attempted curative therapy is not likely to be beneficial, and specifically in those who are predicted to have less than 6 months to live. In hospice care, treatment goals are refocused from cure and life-prolonging therapy toward maintaining the highest possible quality of life. In patients with COPD, parameters that portend a poor prognosis and trigger more extensive discussions regarding end-of-life care include an FEV_1 of less than 30% of predicted, oxygen dependence, multiple hospital admissions for COPD exacerbations, significant comorbidities, weight loss and cachexia, decreased functional status, and increasing dependence on others. This patient has very severe COPD, cor pulmonale, decreased functional capacity, constant dyspnea and air hunger, poor nutritional status, and a history of multiple COPD exacerbations on maximal medical therapy and home oxygen. Given these factors and an overall poor prognosis, discussion of a hospice approach to care would be an appropriate next step in management.

In any patient with advancing COPD, it is important to have ongoing discussions regarding the goals of care as the disease progresses so that appropriate management decisions may be made based on anticipated outcomes and patient values and preferences. Involvement of clinicians trained in palliative care may be helpful in these discussions. Palliative care focuses on the many implications of any significant illness with an emphasis on establishing patient-centered goals of care and symptom management. Palliative care does not preclude active treatment of disease and is appropriate regardless of estimated survival time.

Although this patient might meet several of the criteria for possible lung transplantation, most transplant centers use 65 years of age as an arbitrary cutoff, and the presence of other comorbidities such as diabetes mellitus, coronary artery disease, and osteoporosis should also be considered. This patient's age and comorbid conditions likely would preclude lung transplantation.

Lung volume reduction surgery (LVRS) is indicated for patients with severe COPD with predominant upper lobe emphysema who are symptomatic despite optimal medications. Because this patient has diffuse emphysema, he is not a candidate for LVRS.

This patient has completed pulmonary rehabilitation in the past without improvement, and chair-bound patients may not benefit from it; therefore, pulmonary rehabilitation is not an appropriate option for this patient.

KEY POINT

- In patients with COPD, parameters that portend a poor prognosis and trigger more extensive discussions regarding end-of-life care include an FEV_1 of less than 30% of predicted, oxygen dependence, multiple hospital admissions for COPD exacerbations, significant comorbidities, weight loss and cachexia, decreased functional status, and increasing dependence on others.

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Item 70 Answer: C

Educational Objective: Manage pain and sedation in a patient with critical illness.

The most appropriate management of this patient's pain and related anxiety is to use an opioid such as fentanyl as an interrupted infusion. Untreated pain increases the risk of posttraumatic stress disorder in patients in the ICU. Although pain assessment is difficult in critically ill patients, it should be monitored with a validated pain scale and not just with vital signs alone; physiologic indicators such as hypertension and tachycardia correlate poorly with valid measures of pain. The 2013 Society of Critical Care Medicine clinical practice guidelines for pain, agitation, and delirium recommend preemptive analgesia and or nonpharmacologic interventions to alleviate pain. Opioids are considered the drug class of choice for treatment of non-neuropathic pain in critically ill patients, including mechanically ventilated adult patients in the ICU. Therefore, for this patient, an opioid analgesic such as fentanyl should be given as an interrupted infusion. Daily interruption of analgesia and sedation and spontaneous breathing trials should be used as a standard of care for appropriate patients in ICUs. Their use will shorten the need for mechanical ventilation by an average of 1.5 days, dramatically decrease the number of patients who require mechanical ventilation for more than 3 weeks, decrease ICU length of stay, and lower 1-year mortality.

Benzodiazepines, such as lorazepam, given either intermittently or continuously, should generally be avoided or used sparingly because benzodiazepines are a risk factor for delirium in patients in the ICU.

Neuromuscular blocking agents are sometimes used in patients with acute respiratory distress syndrome or in other critical care scenarios where control of carbon dioxide or patients' movements to allow mechanical ventilation are needed. This patient does not have an indication for neuromuscular blockade. Additionally, if needed, neuromuscular blockade should never be used as a single agent. It should only be used when adequate pain control and sedation of the patient are assured prior to its administration.

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KEY POINT

- Opioids are the drug class of choice for treatment of non–neuropathic pain in critically ill patients, including mechanically ventilated adult patients in the ICU, and should be given in an interrupted fashion when needed.

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Item 71 Answer: A

Educational Objective: Treat a dissecting aortic aneurysm.

The most appropriate next step in treatment is to start an esmolol infusion. Acute medical therapy is indicated in aortic dissection to lower blood pressure and heart rate, both of which are elevated in this patient. β-Blockers are the drug of choice owing to their antihypertensive and negative chronotropic effects, which lead to reduced shear stress on the aortic wall. Options include propranolol, labetalol, and esmolol. Esmolol is a very short-acting intravenous agent that allows careful titration of blood pressure and heart rate and may be useful in patients with aortic dissection. Nondihydropyridine calcium channel blockers are preferred second-line agents in patients who are unable to tolerate β-blockade. In patients with aortic dissection, the target systolic blood pressure should be 100 to 120 mm Hg, and the target heart rate should be below 65/min.

Fenoldopam is a dopamine agonist that acts as an antihypertensive agent. Because it effectively lowers blood pressure without impairing kidney perfusion, it may be advantageous in patients with hypertensive emergencies accompanied by acute kidney injury. However, unlike β-blockers, it does not reliably lower the heart rate and would not be a preferred treatment for this patient with acute aortic dissection.

Direct vasodilators such as hydralazine increase aortic wall shear stress and are more difficult to use in predictably controlling blood pressure. They are therefore not used in treating acute aortic dissection.

Nitroglycerin produces relatively greater venodilation than arteriolar dilation and would not reliably reduce blood pressure into target range in this patient. A second agent would also be required to lower heart rate, as nitroglycerin does not have chronotropic effects.

KEY POINT

- In patients with aortic dissection, initial medical therapy (preferably with β-blockers) is indicated to lower the blood pressure and heart rate and reduce shear stress on the aortic wall.

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Item 72 Answer: D

Educational Objective: Diagnose cystic fibrosis.

The most appropriate diagnostic test to perform next is sweat chloride testing. Although traditionally considered a pediatric disease, an increasing number of cases of cystic fibrosis (CF) are diagnosed in adult patients. Conditions suggesting the diagnosis of CF in adults include chronic asthma-like symptoms, chronic sinusitis, nasal polyposis, recurrent pancreatitis, male infertility, nontuberculous mycobacterial infection, allergic bronchopulmonary aspergillosis, bronchiectasis, and positive sputum culture for *Burkholderia cepacia* and/or *Pseudomonas aeruginosa*. This young patient has a history of pulmonary disease since childhood with a chronic productive cough, chronic sinus disease, nasal polyps on physical examination, findings suggestive of CF (such as hyperinflation) on chest radiograph, and pulmonary function tests showing obstruction; therefore, based on this history, he should be evaluated for CF. Diagnosis of CF is based on a combination of CF-compatible clinical findings in conjunction with either biochemical (sweat chloride testing, nasal potential difference) or genetic (*CFTR* mutations) techniques. Sweat chloride testing and *CFTR* analysis are the definitive diagnostic tests.

α_1-Antitrypsin (AAT) is an inhibitor of proteolytic enzymes, with deficiency leading to accelerated emphysema and liver disease. A characteristic radiographic finding of the emphysema associated with AAT is bullous changes most prominent at the bases, which are not present in this patient. Additionally, liver disease is more common in younger patients, which is also not present in this patient; lung disease usually occurs beyond the second and third decades of life. Therefore, AAT testing would not be the most appropriate next diagnostic test in this patient with a clinical history suggestive of possible CF.

Antineutrophil cytoplasmic antibody assays are useful in diagnosing granulomatosis with polyangiitis (GPA), which may present with both upper and lower airway disease as well as kidney involvement. Although this patient has evidence of both upper and lower airway disease, he has no apparent kidney involvement, and his lung imaging is more consistent with bronchiectasis, compared with the common findings in GPA of nodules, diffuse opacities, transient pulmonary infiltrates, and hilar lymphadenopathy. Additionally, GPA tends to affect an older patient population and also has a more acute onset than the symptoms present in this patient, making this a less likely diagnostic consideration. ANCA antibodies are also associated with eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome). There is no eosinophilia in this patient, and the chronicity since childhood makes this an unlikely diagnosis.

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Although imaging of the sinuses may be helpful in defining the extent of polyposis noted on examination, it would not be useful in determining the cause of the polyps or underlying lung disease. Additionally, CT is the preferred imaging modality for sinus disease because of inadequate sensitivity and specificity of plain radiography, making this an inappropriate next diagnostic intervention.

KEY POINT

- Cystic fibrosis should be a diagnostic consideration in young adults presenting with suggestive findings, including chronic asthma-like symptoms, chronic sinusitis, nasal polyposis, recurrent pancreatitis, male infertility, nontuberculous mycobacterial infection, allergic bronchopulmonary aspergillosis, bronchiectasis, and positive sputum culture for *Burkholderia cepacia* and/or *Pseudomonas aeruginosa*.

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Item 73 Answer: A

Educational Objective: Evaluate hemoptysis with bronchoscopy.

The most appropriate next step in management is bronchoscopy. Bronchoscopy is generally indicated for evaluation of new respiratory symptoms that may be associated with airway pathology (for example, hemoptysis or stridor). This patient presents with massive hemoptysis, which is generally defined as expectoration of at least 100 mL of blood (one-half U.S. cup equals approximately 120 mL). Chest imaging in this patient showed no evidence of pulmonary embolism but did show ground-glass opacification in the right lower lobe. Although this could represent a source of infection, it more likely represents aspirated blood in this patient without symptoms of an infection. Because of this patient's extensive smoking history, he is at increased risk of lung cancer, which may present as an endobronchial lesion causing hemoptysis. Therefore, he should undergo bronchoscopy with airway inspection to evaluate for an endobronchial lesion; a bronchial wash can also be sent for cytologic and microbiologic studies. Even if there is no endobronchial lesion, bronchoscopy could confirm the source of bleeding if blood is seen originating from the right lower lobe.

Although respiratory infections can lead to hemoptysis, this patient has no symptoms or laboratory studies suggesting an infection such as community-acquired pneumonia or an exacerbation of his COPD, for which antibiotic therapy might be indicated. It is also unusual for pulmonary parenchymal infections to cause massive hemoptysis. Therefore, antibiotic treatment would not be indicated in this patient.

High-resolution CT is used to evaluate the pulmonary parenchyma in greater detail than standard-protocol chest CT and is the study of choice for evaluating disorders such as interstitial lung disease. However, it would not adequately define endobronchial lesions as a possible cause of hemoptysis and would therefore not be an appropriate next study in this patient.

Some patients may have difficulty distinguishing between hemoptysis and hematemesis, making the history a key component of evaluation to identify the likely source of bleeding. In patients in whom a gastrointestinal cause is suspected, upper endoscopy would be appropriate for further evaluation. However, this patient's presentation is consistent with a pulmonary source of bleeding, and upper endoscopy would not be appropriate before excluding hemoptysis.

KEY POINT

- Bronchoscopy is generally indicated for evaluation of new respiratory symptoms that may be associated with airway pathology (for example, hemoptysis or stridor).

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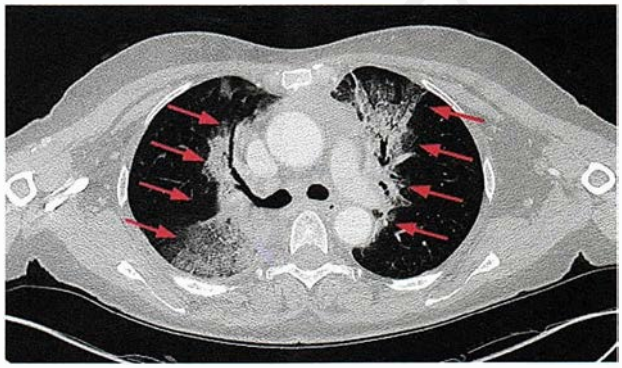
Item 74 Answer: C

Educational Objective: Diagnose radiation pneumonitis.

The most likely diagnosis is radiation pneumonitis. Patients with radiation pneumonitis present with cough and/or dyspnea approximately 6 to 12 weeks after the exposure. Patients with a high total dose of radiation, preexisting lung disease (especially COPD), and concomitant chemotherapy and radiation therapy are at increased risk. The disease can be severe, with progression over days to weeks leading to acute respiratory failure. Gemcitabine is associated with radiation pneumonitis and drug-induced pneumonitis. The factor that is most pathognomonic of radiation pneumonitis is the imaging finding of a nonanatomic straight line demarcating involved versus uninvolved lung parenchyma as can be seen in this patient's CT scan (*arrows*). However, this finding is no longer an absolute diagnostic criterion owing to differing types of radiation delivery, such as stereotactic



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and conformal regimens. The abnormalities in classic radiation pneumonitis typically resolve within 6 months but can progress to a well-demarcated area of fibrosis with volume loss and bronchiectasis.

Although this patient is at risk for progression of her malignancy, the ground-glass and nonanatomic straight line imaging findings are not typical for non–small cell lung cancer recurrence. Additionally, the clinical and radiographic worsening over days to weeks is a helpful clue to distinguish radiation pneumonitis from recurrent local or metastatic cancer.

Radiation fibrosis is clinically distinct from radiation pneumonitis, although the diseases may have overlapping clinical presentations. Radiation fibrosis can occur in patients with or without a history of radiation pneumonitis. Radiation fibrosis occurs 6 to 24 months after radiation therapy and represents a long-term fibrotic sequela of lung damage, most often within the radiation field. Symptoms are uncommon, but patients with previous marginal lung function may have worsening dyspnea. The fibrotic process is irreversible. This patient's symptoms and time course are not compatible with radiation fibrosis.

Viral pneumonia is also part of the differential diagnosis, but the radiographic finding of a straight line of demarcation makes this an unlikely diagnosis.

KEY POINT

- The imaging finding of a nonanatomic straight line demarcating involved versus uninvolved lung parenchyma is pathognomonic of radiation pneumonitis.

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Item 75 Answer: C

Educational Objective: Treat severe hypothermia in a patient with hemodynamic instability.

This patient is hemodynamically unstable as a result of severe accidental hypothermia and should undergo extracorporeal rewarming to maximize the rate of temperature correction. Passive external rewarming (blankets, insulation) and active external rewarming (heating pads, radiant heat) are used for mild or moderate hypothermia. However, this patient has severe hypothermia with hemodynamic instability, and more aggressive warming techniques are indicated. In this case, extracorporeal support, including cardiopulmonary bypass, is recommended because it maximizes the rewarming rate and can also provide hemodynamic support. Cardiopulmonary bypass, most frequently used in cardiac surgical procedures, can provide hemodynamic stabilization and can increase the body temperature by approximately 9.0 °C (16.2 °F) per hour.

Other forms of active internal warming, such as administering warmed intravenous fluids or intraperitoneal and pleural irrigation, are indicated for severe hypothermia, as in this patient. However, these methods do not provide hemodynamic support and do not raise body temperature as rapidly as cardiopulmonary bypass. For example, 1 L of fluid at 42.0 °C (107.6 °F) would raise this patient's core temperature by approximately 0.25 °C (0.45 °F).

This patient is at risk of developing hypothermia-related sustained ventricular tachycardia and fibrillation, but limited data indicate that core temperatures greater than 34.0 °C (93.2 °F) are needed for pharmacologic therapies such as lidocaine to be effective. Additionally, electrical cardioversion is often ineffective in patients with core temperatures less than 30.0 °C (86.0 °F). Rewarming is the surest method of stabilizing this patient, and attempts at treating or preventing arrhythmias should not detract from this.

Although this patient's clinical presentation is concerning for potential severe anoxic encephalopathy, there are numerous reports of survival with good neurologic outcomes in patients with hypothermia requiring prolonged periods of cardiopulmonary resuscitation. The neurologic examination is not reliable in assessing neurologic injury in severe hypothermia. Given the potential for recovery, recommending no CPR in the event of recurrent nonperfusing cardiac rhythm is not the best option for this patient.

KEY POINT

- In patients with severe hypothermia and hemodynamic instability, extracorporeal support, including cardiopulmonary bypass, is recommended because it maximizes the rewarming rate and can provide hemodynamic support.

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Item 76 Answer: D

Educational Objective: Manage idiopathic pulmonary fibrosis with evaluation for lung transplantation.

The most appropriate management is referral to a lung transplantation program. Individuals considered for lung transplantation are most often at high risk of death within 2 years due to respiratory failure and also have a high likelihood of long-term survival following the procedure. This patient with idiopathic pulmonary fibrosis (IPF) has a significant oxygen requirement at rest in addition to a documented decline in his 6-minute walk distance. Both of these factors substantially increase his risk for the development of respiratory failure. Furthermore, he has no history of comorbidities that would limit posttransplant survival, and he continues to actively participate in pulmonary rehabilitation. Lung transplantation remains the only intervention with a clear survival benefit for select patients with IPF.

Medical options for treatment of IPF are limited. The immunosuppressant azathioprine, given along with prednisone

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and *N*-acetylcysteine, has been studied in patients with IPF. However, this combination therapy was associated with increased mortality and adverse effects. Therefore, azathioprine is not recommended for use in patients with IPF. In related studies, *N*-acetylcysteine used as single-agent therapy in IPF showed no benefit over placebo; thus, *N*-acetylcysteine is also no longer considered of value for treatment of IPF.

Although there is some debate as to the benefit of glucocorticoids in the treatment of patients with an acute exacerbation of IPF, there is no benefit to either short- or long-course prednisone in patients with IPF without an exacerbation. IPF is a disease with ongoing fibrosis but with limited inflammation. Consequently, glucocorticoids do little to affect the progressive fibrosis, and their many associated side effects only place the patient at increased risk of complications.

Treatment with tumor necrosis factor-α (TNF-α) inhibitors has been proposed as a method for decreasing the progressive pulmonary fibrosis associated with IPF. However, a trial of the TNF-α inhibitor etanercept failed to show benefit, and its use is not recommended in IPF.

Two new medical therapies have recently been approved for treatment of IPF. These are nintedanib, a tyrosine kinase inhibitor that moderates production of fibrogenic growth factors, and pirfenidone, whose mechanism is unclear but also modulates production of fibrosis. Both agents slow the decline in pulmonary function tests but do not affect quality of life and are not curative. The effect of these agents on disease progression appears to be very similar. To date, these agents have not been studied extensively in patients with acute exacerbation of IPF or severely advanced IPF. Pulmonary subspecialty assessment to confirm IPF and assess risk/benefit for the use of these drugs in selected patients is recommended. Consideration of participation in clinical trials for patients with this progressive disorder remains important for the development of future, more effective, medical therapies.

KEY POINT

- Patients with idiopathic pulmonary fibrosis who have a high risk for the development of respiratory failure and a high likelihood of long-term posttransplant survival should be referred to a lung transplantation program.

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Item 77 Answer: B

Educational Objective: Diagnose Hodgkin lymphoma.

The most likely diagnosis in this patient is Hodgkin lymphoma. This patient's chest radiograph shows a mass that originates from the mediastinum, given the convex angles resulting from the mass impinging on the pleura. The lateral film localizes the mass to the anterior mediastinum. Thymomas are the most common mediastinal lesion in adults and are also located in the anterior mediastinum. However, they occur more commonly in patients between the ages of 40 and 50 years old and can present with paraneoplastic syndromes such as myasthenia gravis. The second most common cause of anterior mediastinal masses is lymphoma; affected patients, such as this one, are typically younger at the time of presentation. Hodgkin lymphoma is the most common lymphoma to involve the mediastinum, followed by lymphoblastic lymphoma and primary mediastinal diffuse large B-cell lymphoma. Other causes of anterior mediastinal masses include germ cell tumors, including teratomas. However, Hodgkin lymphoma is the most common cause of anterior mediastinal masses in patients aged 20 to 30 years, such as this patient.

Bronchogenic cysts are congenital anomalies that develop in the middle mediastinal compartment and most commonly present in the second decade of life. Although they may be found incidentally as rounded lesions on imaging, they may be symptomatic if large owing to compression of normal tissues. Other anomalies such as pericardial cysts and esophageal duplication cysts may also be seen in this compartment. The mass seen on this patient's chest radiograph does not arise from the middle mediastinum compartment.

A mass in the posterior mediastinum is usually a neurogenic tumor. In children, these typically arise from the sympathetic ganglia (for example, neuroblastomas), whereas in adults neurogenic tumors tend to arise from the nerve sheaths (for example, schwannomas). The mass on this patient's chest radiograph is located in the anterior mediastinal compartment.

KEY POINT

- The second most common cause of anterior mediastinal masses is lymphoma; affected patients are typically younger at the time of presentation than are patients with thymomas, which are the most common anterior mediastinal masses.

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Item 78 Answer: C

Educational Objective: Manage acute respiratory distress syndrome with a conservative fluid strategy.

The most appropriate fluid-management strategy is to titrate this patient's fluid volume to a central venous pressure (CVP) of 4 mm Hg or less. This patient has acute respiratory distress syndrome (ARDS). A large multicenter trial has shown that a conservative fluid strategy leads to discontinuing mechanical ventilation sooner than the traditional or "liberal" fluid

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strategy. Limiting intravenous fluids and using diuretics to keep CVPs at lower targets has been associated with a more rapid improvement in lung function, shorter duration of mechanical ventilation, and shorter ICU length of stay. However, the study did not show an effect on mortality. The target CVP for the conservative strategy was 4 mm Hg.

A CVP target of 12 mm Hg would be more consistent with the "liberal" fluid management arm of the study, which was associated with longer duration of ventilation and is therefore not recommended.

Traditionally, a pulmonary artery catheter had been used to guide hemodynamic resuscitation; however, at least four international studies have shown that neither pulmonary artery catheters nor specific protocols that incorporate data from such catheters yield superior outcomes in most patients. In addition, these catheters have more risk associated with their use compared with a simple central line.

KEY POINT

- In patients with acute respiratory distress syndrome, a conservative fluid-management strategy is associated with more rapid improvement in lung function, shorter duration of mechanical ventilation, and shorter ICU length of stay.

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National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006 Jun 15;354(24):2564-75. [PMID: 16714767]

Item 79 Answer: A

Educational Objective: Diagnose exercise-induced bronchospasm and possible asthma with bronchial challenge testing.

The most appropriate next step in management is a methacholine challenge test. Testing will confirm the degree to which this patient's symptoms are caused by hyperreactivity of the lungs. The frequency and degree of this patient's symptoms are concerning, and he has several risk factors and clinical factors (such as a history of allergies, cough without exercise, and symptoms occurring several times a week) that suggest the possibility of asthma as the underlying diagnosis. Though some patients with asthma wheeze with exercise, it is not a necessary symptom to consider the diagnosis; exercise intolerance, breathlessness, and cough can be the primary symptoms as well. Because of the significant morbidity and mortality associated with undiagnosed and untreated asthma, further evaluation of this possibility is indicated in this patient. Because spirometry results are normal, which can occur in patients with asthma, further confirmatory testing with a bronchial challenge test (such as with methacholine) is warranted to further evaluate for possible asthma.

Managing only this patient's allergic rhinitis with a nasal glucocorticoid would not treat possible underlying asthma adequately to protect him from nighttime cough and shortness of breath during exercise. However, counseling avoidance of exercise in locations with allergens would be appropriate.

Although a therapeutic trial of an as-needed β_2-agonist inhaler may seem reasonable, a more extensive assessment and proper diagnosis of this patient's symptoms concerning for asthma will ensure that adequate medications are prescribed for chronic management.

In patients with asthma, spirometry results between episodes are often normal. Additionally, this patient is experiencing frequent and disruptive symptoms. Therefore, clinical observation without further evaluation would not be appropriate.

KEY POINT

- In patients with symptoms of exercise-induced bronchospasm and/or asthma but normal spirometry findings, bronchial challenge testing is warranted for further evaluation.

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Item 80 Answer: A

Educational Objective: Manage extubation in a patient with hypercapnic COPD using noninvasive positive pressure ventilation.

The most appropriate management is to extubate the patient now and initiate bilevel noninvasive positive pressure ventilation (NPPV). This patient's condition is improving after intubation for a COPD exacerbation with hypercapnic respiratory failure. For most patients on invasive ventilatory support, the use of NPPV after extubation to facilitate weaning has not been shown to have improved outcomes. However, patients such as this one, with COPD and hypercapnia who can be extubated and started on NPPV, are an exception to this general rule. This strategy has been shown in some studies to decrease the ICU length of stay and improve survival, and would be a reasonable next step in this patient who has been steadily improving, is otherwise stable, and has a normal mental status. These patients require careful follow-up and observation for reintubation if they do not remain stable on NPPV.

Extubating this patient without immediate NPPV support could be considered, but there are indications that he may not be ready for unsupported breathing yet.

Tracheostomy is a good option for patients who have been intubated for an extended period of time and likely require continued mechanical ventilation to avoid damage to the vocal cords and subglottic airway. However, this patient's condition is improving and he is unlikely to need mechanical ventilation for an extended period of time; therefore, placing a tracheostomy tube is unnecessary.

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Continuing spontaneous breathing trials on invasive ventilation would probably lead to gradual improvement and eventual extubation, but the risk of complications from mechanical ventilation increases with longer use, and the opportunity to extubate sooner should be pursued if available.

KEY POINT

- In patients with COPD and hypercapnia, extubation followed by noninvasive positive pressure ventilation support may decrease the ICU length of stay and improve survival.

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Burns KE, Meade MO, Premji A, Adhikari NK. Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure. Cochrane Database Syst Rev. 2013 Dec 9;12:CD004127. [PMID: 24323843]

Item 81 Answer: C

Educational Objective: Diagnose ICU-acquired weakness.

The most likely diagnosis is ICU-acquired weakness. ICU-acquired weakness includes critical illness polyneuropathy (with axonal nerve degeneration) and critical illness myopathy (with muscle myosin loss), resulting in profound weakness. These two conditions are difficult to differentiate and may overlap. Some experts recommend that biopsies and more formal electrophysiologic studies be reserved for patients in whom the diagnosis is more ambiguous and where other diagnoses are more likely to exist. ICU-acquired weakness is associated with long-term functional disability, prolonged ventilation, and in-hospital mortality. Risk factors include female sex, hyperglycemia, sepsis, multiple organ dysfunction and systemic inflammatory response, immobility, and long duration of mechanical ventilation. Strategies to limit or prevent ICU-acquired weakness include sedation limitation, early mobilization, and moderate glucose control. The strategies that have the most impact are not yet known.

Diabetes predisposes to multifactorial nerve injury due to nerve compression, ischemia, inflammation, and metabolic changes. Distal sensorimotor peripheral neuropathy is the most common disorder and presents with numbness, tingling, and burning pain in a stocking-glove distribution. Weakness may occur late in the course of the disease. However, this pattern is not present in this patient and would be unlikely to account for this patient's symmetric muscle weakness.

Guillain-Barré syndrome is the most common cause of acute diffuse neuromuscular paralysis. Affected patients initially experience rapid onset of symmetric weakness of the upper and lower limbs over days to weeks, generally in the setting of a recent infection, trauma, or surgery. The disorder generally progresses over 2 weeks, with 90% patients at their worst by 4 weeks. Although many patients describe paresthesias or neuropathic pain in the hands and feet, objective sensory loss is usually mild or absent. Neurologic examination reveals weakness and decreased or absent deep tendon reflexes. The time course and absence of paresthesias in this patient make Guillain-Barré syndrome an unlikely diagnosis.

Vasculitic neuropathy is usually found in association with a systemic vasculitis that involves other organs (skin, lungs, kidneys), but it can be found in isolation. Patients most commonly present with both sensory and motor nerve dysfunction that is asymmetric and distal, typically involving the longest nerves of the body first. This patient's painless and symmetric loss of muscle function is not compatible with vasculitis neuropathy.

KEY POINT

- ICU-acquired weakness includes critical illness polyneuropathy (with axonal nerve degeneration) and critical illness myopathy (with muscle myosin loss), resulting in profound weakness; it may impair weaning from the ventilator.

Bibliography

Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014 Jul 17;371(3):287-8. [PMID: 25014703]

Item 82 Answer: A

Educational Objective: Diagnose lymphangioleiomyomatosis.

The most likely diagnosis is lymphangioleiomyomatosis (LAM). LAM is a very uncommon disorder that occurs in association with the genetic changes found in tuberous sclerosis complex, and a sporadic form that is seen almost exclusively in women during childbearing years. Histopathology shows infiltration of atypical smooth muscle cells into the pulmonary interstitium caused by activation of the mammalian target of rapamycin (mTOR) signaling pathway. This results in the development of thin-walled cysts scattered throughout the pulmonary parenchyma and increases the risk of spontaneous pneumothorax. Diagnosis is based on imaging studies showing the characteristic diffuse cystic changes and elevated levels of vascular endothelial growth factor-D (VEGF-D). Hormonal therapy, which was used in the past, is not effective in altering the disease course. Sirolimus, an mTOR inhibitor, has shown promise in stabilizing pulmonary function in patients with LAM and is increasingly used to treat patients with progressive lung disease.

Organizing pneumonia is a noninfectious diffuse parenchymal lung disease that may occur in association with other underlying conditions (such as collagen vascular diseases or use of certain drugs), but may also occur in the absence of another condition or exposure (cryptogenic organizing pneumonia). Onset is typically over 4 to 6 weeks and symptoms rarely persist for longer than 6 months; its presentation may mimic community-acquired pneumonia. Chest imaging typically shows patchy airspace disease with consolidation and ground-glass opacities but no cystic changes.

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This patient's presentation and imaging findings are not consistent with a diagnosis of organizing pneumonia.

Pulmonary Langerhans cell histiocytosis (PLCH), which involves an increased number of Langerhans and inflammatory cells in the lung interstitium, may present with nonspecific respiratory symptoms and a history of spontaneous pneumothorax. Most cases occur in young adults between 20 and 40 years of age. There is also a very strong association with smoking. The duration of symptoms is usually less than 1 year before the diagnosis is made. Although pulmonary cysts are found in PLCH, they tend to be thicker-walled and are accompanied by interstitial thickening and nodularity seen in radiographic findings. This patient's clinical course and imaging studies make a diagnosis of PLCH unlikely.

Respiratory bronchiolitis–associated interstitial lung disease results from inflammation of bronchioles and occurs primarily in smokers. It results in characteristic radiographic findings of centrilobular nodules with air-trapping and scattered ground-glass attenuation. This patient's absence of a smoking history and CT findings do not support this diagnosis.

KEY POINT

- Lymphangioleiomyomatosis is a rare cystic lung disease that occurs sporadically in women of childbearing age or in association with tuberous sclerosis; characteristic findings include diffuse, thin-walled, small cysts on CT.

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Item 83 Answer: A

Educational Objective: Diagnose carbon monoxide poisoning with carboxyhemoglobin measurement.

The most appropriate diagnostic test is measurement of the carboxyhemoglobin level. The history of exposure to an idling car in an enclosed space is a risk factor for carbon monoxide poisoning. Symptoms of carbon monoxide poisoning vary and include headache, confusion, nausea, vomiting, and, in severe cases, loss of consciousness. Routine pulse oximetry measures and compares the light absorption of oxygenated and deoxygenated hemoglobin to calculate the percentage of hemoglobin saturated with oxygen. However, it is not able to detect the presence of other abnormal hemoglobin moieties, such as methemoglobin or carboxyhemoglobin. Because of this, standard pulse oximetry may not indicate the presence of either of these abnormal hemoglobins, and a normal hemoglobin saturation by pulse oximetry is inadequate to exclude their presence. Therefore, co-oximetry of an arterial blood gas sample, which measures both types of hemoglobin, is indicated if either of these conditions is suspected, as in this patient.

This patient's troponin level and electrocardiogram findings suggest the presence of myocardial ischemia. Myocardial ischemia occurs in roughly one third of patients with carbon monoxide poisoning, often independent of any known history of, or risk factors for, coronary artery disease. Vascular occlusive coronary artery disease is also less likely in this patient without clear cardiovascular risk factors. Therefore, cardiac catheterization would not be an appropriate next diagnostic step in this patient with possible myocardial ischemia due to carbon monoxide poisoning.

Electroencephalography is also not appropriate for this patient. Although he may have developed a seizure or acute coronary syndrome after pulling his car into the garage, neither possibility fully accounts for the multiple signs of end-organ damage seen with carbon monoxide poisoning. This patient has a history of seizures and could have postictal encephalopathy with an accompanying lactic acidosis, but this would not explain his myocardial ischemia. There are no corroborating signs of seizure such as a tongue laceration. Given the absence of hemodynamic instability, acute coronary syndrome is unlikely to present with encephalopathy.

This patient's clinical scenario is highly consistent with carbon monoxide poisoning, and the combination of obtundation, preserved respiratory drive, low blood pressure, and normal pupil findings are not typical of sedating or sympathomimetic drug ingestions.

KEY POINT

- Patients with carbon monoxide poisoning may have normal oxygen saturation measured by pulse oximetry; therefore, co-oximetry of an arterial blood gas sample should be used to measure the carboxyhemoglobin level and confirm the diagnosis.

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Item 84 Answer: B

Educational Objective: Treat sympathomimetic overdose with lorazepam.

The most appropriate next step in treatment is to start lorazepam on an as-needed basis. The combination of hypertension, tachycardia, fever, diaphoresis, mydriasis, and rhabdomyolysis is most consistent with sympathomimetic intoxication. Common causes of sympathomimetic intoxication include cocaine, amphetamines, ephedrine, and caffeine. Benzodiazepines are first-line therapy for sympathomimetic intoxication.

Activated charcoal can be used to reduce drug levels in patients with therapeutic drug overdose but generally should not be administered if the patient is at risk of aspirating or more than 1 to 2 hours have elapsed since the time

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of ingestion. The potential harms of activated charcoal outweigh the benefits for this patient.

Physostigmine is an antidote for anticholinergic toxicity, which also presents with agitation, mydriasis, fever, and tachycardia. However, this degree of hypertension and the presence of diaphoresis rather than anhidrosis make anticholinergic toxicity less likely in this patient.

Experience in patients with cocaine-induced hypertension suggests use of β-blockers can paradoxically worsen hypertension due to loss of β-mediated vascular smooth muscle relaxation. Given these concerns with cocaine, it is reasonable to avoid β-blockers, such as propranolol, in sympathomimetic intoxication in general. Furthermore, this patient has no clear evidence of end-organ damage (for example, stroke, acute coronary syndrome, aortic dissection) that would mandate rapid, tightly controlled blood pressure reduction.

KEY POINT

- The combination of hypertension, tachycardia, fever, diaphoresis, mydriasis, and rhabdomyolysis is most consistent with sympathomimetic intoxication; benzodiazepines are first-line therapy for sympathomimetic toxicity.

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Item 85 Answer: C

Educational Objective: Treat localized non-small cell lung cancer.

The most appropriate treatment is resection. The transthoracic needle biopsy obtained in this patient was consistent with a diagnosis of adenocarcinoma of the lung. After non–small cell lung cancer (NSCLC) is diagnosed based on biopsy findings of a suspicious lung mass, staging studies are obtained to develop an appropriate treatment plan. Because the cancer may spread systemically, studies are also done to detect common sites of involvement, typically liver, bone, adrenal glands, or brain. Imaging studies include CT of the chest and abdomen plus a bone scan or PET/CT plus contrast-enhanced MRI of the brain. In this patient, the PET/CT showed only localized disease and his MRI of the brain did not show evidence of metastatic disease. If the mediastinum and distant sites are disease-free, surgical resection is considered feasible. The next steps are determining the extent of the surgical procedure to remove all known disease and deciding whether postoperative residual lung function will be adequate. Because most patients with lung cancer have damage to the lungs from tobacco use, pulmonary function studies should be obtained to evaluate total lung capacity, forced expiratory volumes, and DLCO. Values below a certain level may preclude surgery. In this patient with localized NSCLC who can tolerate surgery, complete resection should be attempted. The 5-year survival rate in patients diagnosed with resectable disease ranges from 30% to 75%. If surgery is not possible, radiation therapy is recommended as an alternative.

Airway stent placement can be performed in instances of airway obstruction, including those caused by endobronchial involvement of a primary lung cancer. However, this patient has no evidence of airway obstruction on chest imaging and is currently asymptomatic.

In more advanced NSCLC that includes mediastinal, hilar, or contralateral lymph node involvement, outcomes have not been shown to be improved with surgical resection; therefore, chemotherapy in combination with radiation therapy is considered first-line therapy. This patient has no evidence of advanced disease. Patients with distant metastasis are generally treated with chemotherapy alone, but this patient has no evidence of metastatic disease. Adjuvant chemotherapy could be considered in some patients with resectable disease.

KEY POINT

- In patients with localized non–small cell lung cancer who can tolerate surgery, complete resection should be attempted.

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Item 86 Answer: A

Educational Objective: Diagnose pulmonary sarcoidosis with bronchoscopic biopsy.

The most appropriate next step in management is to perform a bronchoscopic biopsy of the mediastinal lymph nodes and lung. The diagnosis is most likely sarcoidosis. Sarcoidosis is a multiorgan inflammatory disease characterized by tissue infiltration by mononuclear phagocytes, lymphocytes, and noncaseating granulomas. The cause remains unknown, but there is increasing evidence to suggest it is the end result of interactions among a persistent antigen, HLA class II molecules, and T-cell receptors. Ninety percent of patients with sarcoidosis have pulmonary involvement; however, diagnosis is often difficult because symptoms can be nonspecific. Pulmonary function tests often show restriction, but obstruction can be seen as well; these findings are not specific to sarcoidosis. Sarcoidosis is a diagnosis of exclusion based on multisystem involvement and histologic evidence of noncaseating granulomas when all other causes are ruled out. Bronchoscopy with transbronchial biopsies combined with endobronchial biopsies has been shown to have sensitivities as high as 90% for diagnosing sarcoidosis. Most patients require a tissue diagnosis, but there are some exceptions that do not warrant histologic confirmation. These include classic clinical presentations of known sarcoid syndromes such as Löfgren syndrome (hilar lymphadenopathy, acute oligoarthritis, and erythema nodosum) and Heerfordt syndrome (uveitis, parotid gland enlargement, and fever).

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Sarcoidosis often spontaneously resolves and the decision to treat is based on symptoms. Glucocorticoids are the treatment of choice, but in this patient the decision to treat should be made only after confirming a diagnosis and then assessing the risks and benefits of treatment.

The Centers for Disease Control and Prevention endorses the use of interferon-γ release assays (IGRAs) in all clinical settings in which the tuberculin skin test (TST) is recommended. IGRAs are as sensitive as but more specific than the TST in diagnosing tuberculosis. Testing for tuberculosis with both an IGRA and TST is generally not recommended, and this patient's recent negative TST makes a diagnosis of tuberculosis an unlikely cause of his clinical findings.

Although serum angiotensin-converting enzyme levels are elevated in 75% of patients with chronic sarcoidosis, the test lacks specificity and is therefore of limited use diagnostically.

KEY POINT

- Sarcoidosis is a diagnosis of exclusion based on multisystem involvement and histologic evidence of noncaseating granulomas when all other causes are ruled out.

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Item 87 Answer: B

Educational Objective: Manage hypoxic and hypercapnic respiratory failure in a patient with a contraindication to noninvasive ventilation.

The most appropriate next step in management is intubation and mechanical ventilation. This patient is experiencing an exacerbation of his COPD with hypercapnic respiratory failure with hypoxia and mental status changes. Although the majority of patients with acute exacerbation of COPD should undergo a trial of noninvasive ventilation (NIV) and reevaluation prior to intubation and mechanical ventilation, encephalopathy that impairs the ability to cooperate with NIV or manage secretions is a contraindication to NIV. Other contraindications to NIV include conditions that make airway protection difficult (for example, bulbar dysfunction or ineffective gag or cough reflexes), medical instability (such as hemodynamic instability, severe acidosis, arrhythmias, or active upper gastrointestinal bleeding), and mechanical issues associated with NIV (including upper airway obstruction, recent facial trauma or surgery, or esophageal or transsphenoidal surgery). Because this patient would likely not be able to adhere with NIV because of confusion and may not be able to protect his airway, intubation and mechanical ventilation are indicated.

Although increasing the level of inspired oxygen to maintain an oxygen saturation of greater than 90% in acute COPD exacerbations has been shown to be beneficial, doing so would not address this patient's hypercapnia and associated mental status changes, which need to be treated with ventilatory support.

The use of NIV in eligible patients is effective and can avoid intubation in several disease states, particularly with COPD exacerbations or decompensated heart failure. In COPD, NIV has been shown to decrease the need for intubation, decrease mortality, and reduce length of hospital stay and complication rates. Compared with invasive mechanical ventilation, NIV uses pressure instead of volume to assist ventilation, and multiple different modes are available for use with limited data regarding the effectiveness of one mode of ventilation relative to another. However, none of the NIV modes would be appropriate in this patient with a contraindication to this therapy.

KEY POINT

- Contraindications to noninvasive ventilation (NIV) include conditions that make airway protection difficult (for example, encephalopathy or bulbar dysfunction), medical instability (such as hemodynamic instability, severe acidosis, arrhythmias, or active upper gastrointestinal bleeding), and mechanical issues associated with NIV (including upper airway obstruction, recent facial trauma or surgery, or esophageal or transsphenoidal surgery).

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Item 88 Answer: C

Educational Objective: Manage a pulmonary nodule with a high pretest probability of primary lung cancer.

The most appropriate management is to refer for thoracic surgery. One year ago this patient had a 3-mm pulmonary nodule. As a cigarette smoker, she is at high risk for lung cancer and was managed appropriately with repeat imaging in 12 months. On repeat imaging, the nodule has enlarged. The pretest probability that this nodule represents a primary lung cancer is high. Not only is this patient an active and long-time smoker, but her nodule has more than doubled in size over the previous year. Therefore, tissue diagnosis is warranted. An enlarging pulmonary nodule warrants more aggressive evaluation with tissue diagnosis or excision depending on the nodule's pretest probability of malignancy. Provided she is an appropriate candidate, surgical resection may be the best management. It would confirm the suspected diagnosis of primary lung cancer and would also be curative in this patient with likely stage I non–small cell lung cancer (based on the small size and absence of lymphadenopathy or other evidence of metastatic disease).

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Although bronchoscopy could potentially provide a diagnosis, resection is the treatment of choice in a patient with stage IA lung cancer. Since she has no evidence of lymphadenopathy or other nodules, surgical resection may provide both diagnosis and cure. If the bronchoscopy is negative, the pretest probability of a primary lung cancer is high enough that the patient would still require further tissue diagnosis as well.

Similarly, a negative transthoracic needle aspiration would not be reassuring since it only obtains a small number of cells; therefore, if the needle aspiration were negative for malignancy the patient would still require a second diagnostic procedure. If the transthoracic needle aspiration confirmed malignancy, surgical resection would be indicated in the absence of any evidence of additional foci of malignancy.

This patient's pulmonary nodule has already significantly increased in size. Therefore, further surveillance imaging, even if obtained sooner, is not indicated at this time. At this point, the clinician should focus on the diagnosis, staging, and treatment.

KEY POINT

- An enlarging pulmonary nodule warrants more aggressive evaluation with tissue diagnosis or excision depending on the nodule's pretest probability of malignancy.

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Item 89 Answer: A

Educational Objective: Understand the role of the rapid response team in managing deteriorating clinical status in hospitalized patients.

Activation of a rapid response team would be expected to decrease the chance of cardiopulmonary arrest in a patient such as this. Unrecognized deterioration of a patient's clinical status in general medical settings allows patients to progress to cardiopulmonary arrest, which carries a very poor prognosis for hospital outcome and survival. It has been found that the signs and symptoms of deterioration are usually present several hours before arrest (with a median time of 6 hours). A strategy to improve the recognition and response to deteriorating patients has been developed in the form of rapid response systems. These systems seek to alter management in deteriorating patients who are at risk of cardiopulmonary collapse by intervening before irreversible instability occurs.

Although there are no standard structures of rapid response teams, they are frequently composed of intensivists and others with experience in identifying and managing patients with worsening clinical parameters who may be helpful in guiding further treatment interventions and assist in determining the appropriate setting of care for a specific patient. Unfortunately, clear criteria do not exist for activating rapid response teams. However, a number of indicators have been identified that are associated with increased risk of decompensation; when these indicators are present, rapid response intervention may be effective. These indicators include changes in vital signs (heart rate of <30/min or ≥139/min; systolic blood pressure <70 mm Hg or ≥200 mm Hg; respiration rate <9/min or >35/min, temperature <34.0 °C [93.2 °F] or ≥39.0 °C [102.2 °F]), oxygen saturation less than 85%, and development of altered mental status or coma. This patient's persistent tachycardia indicates possible vital sign instability warranting further evaluation as a potential early indicator of deterioration. Studies of rapid response teams have shown reduced rates of cardiopulmonary arrest outside of the ICU and reduced mortality.

Implementation of rapid response teams has not been consistently shown to reduce rates of intubation, ICU utilization, or length of hospital stay.

KEY POINT

- Indicators for activating rapid response teams may include changes in vital signs (heart rate of <30/min or ≥139/min; systolic blood pressure <70 mm Hg or ≥200 mm Hg; respiration rate <9/min or >35/min, temperature <34.0 °C [93.2 °F] or ≥39.0 °C [102.2 °F]), oxygen saturation less than 85%, and development of altered mental status or coma

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Item 90 Answer: D

Educational Objective: Treat shift work sleep disorder.

The most appropriate management is sleep hygiene counseling. This patient has symptoms of shift work sleep disorder, in which sleepiness and fatigue occur during the nighttime work shift and insomnia occurs during the daytime sleep period. The first step in management is to address sleep-related behaviors and the sleep environment, referred to as sleep hygiene. Strategies that may be useful include caffeinated beverages and bright light exposure during the evening work shift; avoiding direct sunlight in the early morning (by using sunglasses and darkening the bedroom); avoiding exertion, eating, and alcohol prior to the morning sleep period; and, if feasible, considering a short (30-minute) nap overnight, perhaps during a meal break.

Modafinil, a novel stimulant, is approved for use in shift work sleep disorder. However, it should be considered only after conservative measures such as sleep hygiene counseling are tried. Modafinil is limited by cost and side effects, which include headache, anxiety, and (rarely) serious skin reactions.

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Multiple sleep latency testing (MSLT) is a laboratory-based sleep test that objectively measures sleepiness and is used primarily as a diagnostic aid in testing for narcolepsy or idiopathic hypersomnia. MSLT should not be performed in sleep-deprived patients. There is no indication for MSLT in this patient.

Polysomnography is indicated when there is strong pretest evidence of a primary sleep disorder, such as sleep-disordered breathing. Because of this patient's lack of previous symptoms and association of her symptoms with her work schedule, there is low suspicion for an underlying sleep problem requiring diagnosis by polysomnography. However, if her symptoms persist following conservative therapy, in-laboratory polysomnography could be considered for a more comprehensive evaluation.

Hypnotic medications such as zolpidem have been used empirically to aid sleep initiation following a night shift, but their efficacy is not well known. Furthermore, there is increasing concern about side effects and complex behaviors (sleep driving and sleep eating) associated with hypnotics in patients who may be sleep-deprived. A short course of hypnotics could be considered, but only after conservative measures, such as sleep hygiene counseling, are attempted.

KEY POINT

- The first step in management of shift work sleep disorder is to address sleep-related behaviors and the sleep environment, referred to as sleep hygiene.

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Item 91 Answer: A

Educational Objective: Diagnose hypersensitivity pneumonitis.

The most likely diagnosis is acute hypersensitivity pneumonitis (HP). HP is the result of an immunologic response to repetitive inhalation of antigens. Acute HP presents within 48 hours of a high-level exposure and is often associated with fever, flulike symptoms, cough, and shortness of breath. Radiographic imaging can demonstrate bilateral hazy opacities, and high-resolution CT imaging of the chest shows findings of ground-glass opacities and centrilobular micronodules that are upper- and mid-lobe predominant. Symptoms typically wane within 24 to 48 hours after removal from the exposure. Recurrence of symptoms with exposure to the respiratory antigen is the hallmark of this disorder, and careful attention to the history helps identify the cause. This patient presents with a known or likely exposure to a possible antigen related to his work as a timber trimmer (exposure to agricultural dusts that can readily become colonized with mold), symptoms occurring shortly after possible exposure, a history of similar symptoms, and inspiratory crackles on examination. This constellation of signs and symptoms in conjunction with the radiographic appearance makes HP the most likely diagnosis.

Acute interstitial pneumonia (AIP) is an uncommon form of diffuse lung injury that develops in response to an often unknown insult over a short period of time (days to weeks). Clinically, AIP presents with findings similar to the acute respiratory distress syndrome (ARDS), with severe and progressive hypoxia and imaging showing diffuse bilateral air space opacification. Although the time course of this patient's presentation might be consistent with this diagnosis, his other clinical findings do not support a diagnosis of AIP.

Idiopathic pulmonary fibrosis typically presents in older individuals, and its presentation is more chronic, usually with symptom duration greater than 6 months at the time of presentation. It is therefore not a likely diagnosis in this patient.

Although nonspecific interstitial pneumonia presents in younger patients such as this one, it typically presents as a chronic, rather than acute, process.

KEY POINT

- Acute hypersensitivity pneumonitis presents within 48 hours of a high-level exposure to respiratory antigens and often is associated with fever, flulike symptoms, cough, and shortness of breath; high-resolution CT imaging of the chest shows findings of ground-glass opacities and centrilobular micronodules that are upper- and mid-lobe predominant.

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Item 92 Answer: D

Educational Objective: Treat a patient with a recent COPD exacerbation with pulmonary rehabilitation.

The most appropriate treatment is to start pulmonary rehabilitation. Pulmonary rehabilitation is recommended for all symptomatic patients with COPD and an FEV_1 less than 50% of predicted and specifically for those hospitalized with an acute exacerbation of COPD. Pulmonary rehabilitation may also be considered in symptomatic or exercise-limited patients with an FEV_1 greater than or equal to 50% of predicted, such as this patient. This patient has had a recent acute exacerbation, has diminished exercise capacity, and is on maximal medical treatment; therefore, she would benefit from pulmonary rehabilitation.

Roflumilast is indicated only in patients with severe or very severe COPD with recurrent exacerbations. This is this patient's first exacerbation, and this treatment is therefore not indicated.

Long-term glucocorticoid therapy is not indicated in patients with COPD owing to serious side effects; however,

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short-term use is helpful during an acute exacerbation. A recent study showed that, in addition to optimizing COPD therapy, a 5-day course of an oral glucocorticoid is adequate for most patients with COPD exacerbation. Increasing the duration of therapy by an additional 5 days would not likely be of benefit because this patient is completing a 5-day course of glucocorticoids, her symptoms have already improved, and the anti-inflammatory effect of glucocorticoids extends beyond completion of the course of medication.

Long-term oxygen therapy is indicated in patients with an arterial Po_2 at or below 55 mm Hg (7.3 kPa) or oxygen saturation breathing ambient air at or below 88% (confirmed twice over a 3-week period), with or without hypercapnia. Other indications are evidence of pulmonary hypertension, peripheral edema suggesting right-sided heart failure, or polycythemia, in combination with an arterial Po_2 less than 60 mm Hg (8.0 kPa), or oxygen saturation less than 88% breathing ambient air. This patient's oxygen saturation is 92% breathing ambient air; therefore, oxygen supplementation is not currently indicated.

KEY POINT

- Pulmonary rehabilitation is recommended for all symptomatic patients with COPD who have an FEV_1 less than 50% of predicted and specifically for those hospitalized with an acute COPD exacerbation; it may also be considered for symptomatic or exercise-limited patients with an FEV_1 greater than or equal to 50% of predicted.

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Item 93 Answer: D

Educational Objective: Manage anemia in the ICU setting.

The most appropriate management of this patient's anemia is to not transfuse. This patient is hemodynamically stable with no evidence of active bleeding. The decision to transfuse erythrocytes should be based on hemodynamic parameters, the acuity of anemia, coexisting medical problems, and ongoing blood loss. In patients with critical illness, restricting blood transfusions for a hemoglobin of less than 7 g/dl. (70 g/L) significantly reduces cardiac events, rebleeding, bacterial infections, and total mortality as compared with a less restrictive strategy allowing transfusion at higher hemoglobin levels. Four critical care organizations (the American College of Chest Physicians, the American Thoracic Society, the Society of Critical Care Medicine, and the Association of Critical Care Nurses) recommend avoiding transfusion of erythrocytes in nonbleeding, hemodynamically stable patients with a hemoglobin concentration greater than 7 g/dl. (70 g/L). Because this patient's hemoglobin is above the recommended threshold and he is hemodynamically stable with no clinical findings suggesting the need for increased oxygen-carrying capacity, transfusion is not indicated.

The recommendation to avoid transfusion in nonbleeding, hemodynamically stable patients has been included in the Choosing Wisely Campaign, an initiative of the American Board of Internal Medicine Foundation to encourage physicians, patients, and other health care agencies to consider the risks and benefits of medical tests and procedures, noting that all tests may not be necessary and some, in fact, may cause harm. Part of the initiative is to help physicians be better stewards of finite health care resources.

The erythropoiesis-stimulating agents (ESAs) should be considered for patients with chronic kidney disease (CKD) and symptomatic anemia attributable to erythropoietin deficiency when the hemoglobin level is less than 10 g/dl. (100 g/L). Before attributing anemia to CKD, it is important to exclude other causes. Iron deficiency is common in patients with CKD. ESAs are associated with an increased risk of thrombotic and cardiovascular events as well as increased blood pressure and are generally not an appropriate intervention for a critically ill patient.

KEY POINT

- Do not routinely transfuse erythrocytes in nonbleeding, hemodynamically stable patients in the ICU with a hemoglobin concentration greater than 7 g/dL (70 g/L).

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Item 94 Answer: B

Educational Objective: Diagnose obstructive sleep apnea complicating anesthesia.

The most appropriate next step in management is polysomnography in this patient with likely undiagnosed obstructive sleep apnea (OSA). OSA may first come to clinical recognition immediately following a surgical procedure involving general anesthesia and/or narcotic analgesia that exacerbates the underlying pathophysiologic processes that contribute to OSA, and it may present with repeated episodes of postoperative hypoxia or as frank respiratory failure. The increased risk of postoperative complications associated with OSA highlights the importance of identifying the presence of the disorder preoperatively in high-risk patients. This patient has multiple risk factors for OSA, including age, male gender, obesity, hypertension, and a thick neck. His need for reintubation in the postanesthesia period suggests the possible presence of a sleep-related breathing disorder. Therefore, testing with polysomnography is indicated for further evaluation.

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Overnight pulse oximetry has not been validated as a method for evaluating for OSA, primarily because of a high rate of false-positive and false-negative results. It would therefore not be an appropriate next study in this patient with a high pretest probability of OSA.

Multiple screening instruments are available that use clinical parameters to assess for the possible presence of OSA; these include the STOP-Bang questionnaire, Sleep Apnea Clinical Score, and the Berlin questionnaire. They are most commonly used to assess risk in patients with symptoms possibly attributable to OSA or as part of preoperative pulmonary assessment. This patient, however, already has a high probability of disease given his known risk factors for OSA along with his postoperative respiratory complications. A low score on a screening instrument would not alter the need for further evaluation.

Not pursuing further diagnostic information in this patient with multiple risk factors accompanied by postoperative pulmonary complications would be inappropriate.

KEY POINT

- Polysomnography is indicated in patients at high risk for obstructive sleep apnea due to the increased risk of postoperative complications, which may manifest as repeated episodes of postoperative hypoxia or frank respiratory failure.

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Item 95 Answer: D

Educational Objective: Diagnose postintensive care syndrome.

The most likely diagnosis is postintensive care syndrome. The patient was severely ill and in an ICU for several days where she was treated for severe sepsis and shock. Postintensive care syndrome is a term used to describe new or worsening function in one or more physical, cognitive, or mental domains that persists after hospital discharge following a critical illness, as in this patient. Examples of clinical findings include cognitive deficits resembling traumatic brain injury or mild cognitive impairment; psychiatric symptoms such as depression, anxiety, and posttraumatic stress disorder (PTSD); and physical deficits such as weakness and fatigue. Although the cause of this syndrome is not understood, possible mechanisms include hypoxia, hypotension, inflammation, the catabolic state, hypoglycemia, other nutritional disorders, immobility, and agents used for sedation. This syndrome may also be applied to symptoms experienced by family members of post-ICU patients who may experience sleep disturbances, anxiety, depression, a complicated grief reaction, and PTSD. The efficacy of preventive measures and treatment interventions is not known, but efforts to maintain light sedation and avoid glycemic extremes and hypoxia may be of benefit. Treatment otherwise focuses on the specific symptoms experienced by the patient or family.

Critical illness neuromyopathy is a generalized axonal sensorineural polyneuropathy associated with severe illness and treatment in an ICU setting. Although it could explain this patient's physical limitations, it is not associated with psychiatric symptoms such as anxiety or cognitive deficits such as difficulty multitasking.

Similarly, prolonged bed rest in patients in the ICU may result in significant deconditioning and physical limitations following recovery from acute illness; however, it would not be expected to cause problems with psychiatric or cognitive function.

Patients treated in the ICU for severe illness are at increased risk for depression, anxiety, and PTSD, which may result in the psychiatric and cognitive symptoms seen in this patient. Generalized anxiety disorder develops over time and is characterized by excessive worrying about many things of little or no need for concern. Sleep disturbances along with anxiety are reasons patients seek help from their physicians. However, this diagnosis would not explain this patient's overall symptom complex, which includes cognitive limitations and physical symptoms such as weakness.

KEY POINT

- Postintensive care syndrome is a term used to describe new or worsening function in one or more physical, cognitive, or mental domains that persists after hospital discharge following a critical illness.

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Item 96 Answer: A

Educational Objective: Diagnose acute mesenteric ischemia.

The most likely diagnosis is acute mesenteric ischemia. Acute mesenteric ischemia is caused by inadequate blood flow to all or part of the small bowel. Causes include superior mesenteric artery (SMA) embolism, SMA thrombosis, nonocclusive mesenteric ischemia (usually due to splanchnic vasoconstriction), mesenteric venous thrombosis, and focal segmental ischemia. SMA embolism from the left atrium or ventricular mural thrombi is the most common cause. The classic presentation is acute onset of severe abdominal pain; the abdomen is typically soft and less tender than expected based on the patient's symptoms (pain out of proportion to the examination).This patient has many findings that should heighten the suspicion for acute mesenteric ischemia including chronic atrial fibrillation, onset of periumbilical abdominal pain, emesis, hypotension, abdominal pain that is out of proportion to the abdominal examination, and

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a forceful bowel evacuation. An elevated leukocyte count, metabolic acidosis, and elevated plasma lactate level are common, but their absence should not exclude the diagnosis. Plain abdominal films may be normal early in the course of disease. A high degree of clinical suspicion is necessary to diagnose mesenteric ischemia in time for potentially life-saving interventions to be effective. Immediate surgical consultation and angiography are appropriate for this patient.

Acute pancreatitis is almost always associated with the sudden onset of pain. The pain is generally located in the epigastrium and radiates to the back. Pain is often accompanied by fever, nausea, and repeated vomiting. Although an elevated serum amylase level is usually from a pancreatic source, hyperamylasemia can be seen in a variety of other conditions including intestinal ischemia. This patient's presentation is not typical for acute pancreatitis.

Campylobacter enteritis could account for this patient's abdominal pain, elevated leukocyte count, and hypotension; however, this patient's absence of bloody stools and diarrhea, along with the presence of persistent hypotension, make this diagnosis less likely.

Colonic ischemia comprises 75% of all cases of intestinal ischemia. Typical symptoms are the acute onset of mild, crampy abdominal pain with tenderness on examination over the affected region of colon. Bleeding often occurs within a few days of pain onset. The location of this patient's pain and early vomiting are not compatible with colonic ischemia.

KEY POINT

- The abrupt onset of central abdominal pain, emesis, forceful bowel evacuation, and severe hypotension along with an unremarkable abdominal examination in the setting of atrial fibrillation is highly suggestive of acute embolic mesenteric ischemia.

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Item 97 Answer: C

Educational Objective: Manage acute respiratory distress syndrome using positive end-expiratory pressure.

The most appropriate management is to increase the positive end-expiratory pressure (PEEP). This patient is hypoxic due to acute respiratory distress syndrome (ARDS). Her gas exchange has worsened to the point of an arterial Po_2/Fio_2 ratio of 54 mm Hg (7.2 kPa), which indicates very severe ARDS. PEEP improves lung compliance, ventilation-perfusion (V/Q) matching, and oxygenation. A 2013 systematic review found no difference in survival using higher PEEP (approximately 15 cm H_2O) versus lower PEEP (approximately 8 cm H_2O); however, the patients with the most severe ARDS did show improvement in oxygenation when treated with higher PEEP, but there was no improvement in the number of ventilator-free days. Current recommendations are to use a PEEP level that achieves adequate oxygenation with an Fio_2 of less than 0.6 and does not cause hypotension.

Decreasing the tidal volume could be considered a lung-protective measure, but this patient's tidal volume is already at the target of 6 mL/kg of ideal body weight. Reducing the tidal volume further will likely result in greater alveolar hypoventilation and increasing hypoxemia.

Prone positioning is a maneuver for improving oxygenation, and may be helpful in patients with ARDS in whom it is difficult to maintain adequate levels of oxygenation. However, its effect on oxygenation is slow, and it would not be the best next step toward improving this patient's gas exchange.

Increasing the set respiration rate on the ventilator probably would not improve this patient's oxygenation unless it induced auto-PEEP, which would raise the effective PEEP level indirectly. This would not be the best way to recruit alveoli, however, because the auto-PEEP in this situation is impossible to regulate as lung mechanics change over time. It is safer and more reliable to raise the set level of PEEP.

KEY POINT

- In patients with severe acute respiratory distress syndrome, current recommendations are to use a positive end-expiratory pressure level that achieves adequate oxygenation with an Fio_2 of less than 0.6 and does not cause hypotension.

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Item 98 Answer: B

Educational Objective: Recommend appropriate influenza and pneumococcal vaccinations in a patient with COPD.

This patient should receive inactivated influenza vaccine and 23-valent polysaccharide pneumococcal vaccine (PPSV23). Influenza vaccination has been shown to reduce serious illness (such as lower respiratory tract infections that require hospitalization) and death in patients with COPD. These vaccines should be administered annually in all patients with COPD. Pneumococcal vaccination with PPSV23 should be given to all patients aged 19 to 64 years with COPD, with revaccination at age 65 years if 5 years have elapsed since the previous pneumococcal immunization. All patients (with or without COPD) should also receive the 13-valent pneumococcal conjugate vaccine (PCV13) at age 65 years, although the polysaccharide and conjugate vaccines should be given sequentially rather than together for optimal effect. Ideally, PCV13 should be administered at least 1 year following PPSV23. PPSV23 and PCV13 are also indicated in patients

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with functional or anatomic asplenia, cochlear implants, persistent cerebrospinal fluid leak, and significant immunocompromising conditions. Preferably, these patients should receive PCV13 first followed by PPSV23 at least 8 weeks later. This patient will require another dose of PPSV23 at the age of 65 years. Patients with COPD who received their first PPSV23 dose at age 65 years or older do not require revaccination.

Because this patient is younger than 65 years, she does not require the PCV13 vaccination at this time.

The live attenuated influenza vaccination is recommended for healthy persons between the ages of 2 and 49 years. Because this patient has COPD and because she is older than 49 years, live attenuated influenza vaccination should not be administered.

KEY POINT

- Patients with COPD should receive inactivated influenza vaccination annually, and the 23-valent polysaccharide pneumococcal vaccine (PPSV23) should be given to all patients aged 19 to 64 years with COPD, with revaccination at age 65 years or older if 5 years have elapsed since the previous pneumococcal immunization; the 13-valent pneumococcal conjugate vaccine should also be administered at age 65 years or older if 1 year has elapsed since the last PPSV23 immunization.

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Item 99 Answer: E

Educational Objective: Manage auto-positive end-expiratory pressure.

The most appropriate immediate next step in management is to disconnect the endotracheal tube from the ventilator circuit and reconnect it after a few seconds. This patient has developed severe auto-positive end-expiratory pressure (auto-PEEP) as a result of breath stacking on the ventilator due to her obstructive lung disease. The intrathoracic pressure has risen to the point of impairing her central venous return, so her cardiac output is falling because of inadequate preload. Her oxygenation has worsened, owing to both her low cardiac output and to ventilation-perfusion mismatch in the lungs resulting from hyperinflation. The most immediate need is to release the pressure by disconnecting the ventilator circuit and allowing her to passively exhale for several seconds. The ventilator should then be reconnected and the settings changed to allow for more expiratory time.

Slowing the respiration rate, decreasing the tidal volume, and increasing the inspiratory flow rate while tolerating respiratory acidosis are strategies to increase the exhaled volume with each cycle. However, these interventions are not appropriate until after the increased intrathoracic pressure is released by temporarily disconnecting the ventilator circuit. This patient's unstable condition must be addressed before changes to the ventilator settings will be helpful.

Similarly, increased sedation and preparation for therapeutic paralysis may be useful for this patient, but her increased intrathoracic pressure must be released before other interventions are pursued.

KEY POINT

- If auto-positive end-expiratory pressure (auto-PEEP) is observed in a patient on mechanical ventilation, the most appropriate initial intervention is to disconnect the ventilator circuit from the patient's endotracheal tube for a few seconds to allow for a prolonged exhalation to release the increased intrathoracic pressure.

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Item 100 Answer: B

Educational Objective: Treat acute respiratory distress syndrome using a lung-protective ventilator strategy.

The intervention most likely to improve this patient's chance of survival is maintaining the tidal volume at 360 mL. This patient has acute respiratory distress syndrome (ARDS); he meets the criteria for ARDS with bilateral lung opacities and very poor oxygenation with an arterial Po_2/Fio_2 ratio of 101 mm Hg (13.4 kPa). Very few interventions have evidence supporting a survival benefit in ARDS, but the mainstay of management is a lung-protective ventilator strategy, with low tidal volume (6 mL/kg of ideal body weight [IBW]) and low plateau pressure (<30 cm H_2O). Other interventions with supporting evidence include a conservative fluid strategy to keep the lungs as dry as possible, prone positioning, and early therapeutic paralysis (for the first 48 hours) if severely hypoxemic.

The physiologic result of reducing the tidal volume would be a lower minute ventilation, and the Pco_2 would likely rise further above its current elevated level, resulting in an additional decrease in arterial pH. Allowing hypercapnia to achieve lung-protective ventilation goals in ARDS (termed permissive hypercapnia) is acceptable and even desirable if it means ventilating at lower tidal volumes and plateau pressures despite causing a reduction in arterial pH. In general, a pH as low as 7.25 is considered acceptable in this situation; however, decreasing the minute ventilation would likely lower the pH below this level. Some evidence exists that hypercapnia may also be protective in ARDS independent of the low tidal volume strategy that causes it, but this is controversial.

Raising the tidal volume would improve the abnormal Pco_2, but might cause greater injury to the lung tissue, leading to higher risk of mortality.

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KEY POINT

- The mainstay of management for acute respiratory distress syndrome is a lung-protective ventilator strategy, with low tidal volume (6 mL/kg of ideal body weight) and low plateau pressure (<30 cm H_2O), even if this results in hypercapnia.

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Item 101 Answer: C

Educational Objective: Diagnose idiopathic pulmonary fibrosis.

The most likely diagnosis is idiopathic pulmonary fibrosis (IPF). This patient's presentation of progressively worsening cough and dyspnea is typical for this rare disease. He has multiple risk factors, including smoking history, organic dust exposure from his previous work as a carpenter, and current age; the prevalence of IPF increases significantly with each decade of life, and the disease essentially only affects individuals who are older than 50 years. This is important because an individual younger than 40 years who presents with similar symptoms has a significantly higher likelihood of an alternative cause, such as connective tissue disease-related pulmonary disease. Therefore, in younger patients with a similar presentation, more intensive screening for autoimmune disorders may be appropriate. In addition, this patient's high-resolution CT (HRCT) findings are classic for usual interstitial pneumonia (UIP), which is the typical pathologic correlate of IPF. A definite UIP pattern on CT imaging in a patient whose clinical history does not suggest an underlying alternative disorder is consistent with a diagnosis of IPF.

Although this patient is at risk for COPD because of his smoking history, his pulmonary function tests show a normal FEV_1/FVC ratio. Clubbing is also noted on physical examination. Although the etiology of clubbing remains unclear, this is more commonly reported in patients with diffuse parenchymal lung disease rather than COPD. Most importantly, CT imaging is not consistent with the findings usually seen with COPD.

Hypersensitivity pneumonitis presents in acute and chronic forms. This patient's presentation is not consistent with acute disease given the lack of flulike symptoms. The chronic form of the disease can present similarly to IPF, but this patient lacks a history of a clear ongoing exposure to a likely offending agent associated with hypersensitivity pneumonitis (such as organic antigens from domestic birds), and his CT findings are basal predominant. Hypersensitivity pneumonitis typically affects the upper and mid-lung zones, and micronodules are often present.

Respiratory bronchiolitis-associated interstitial lung disease is strongly associated with smoking exposure. However, the CT imaging demonstrates mid to upper lung-predominant centrilobular micronodules. Although advanced cases can be associated with septal line thickening and scarring, the distribution on the CT scan is not consistent with this.

KEY POINT

- Idiopathic pulmonary fibrosis is characterized by progressive dyspnea and cough, with high-resolution CT findings of peripheral- and basal-predominant septal line thickening and honeycomb change; risk factors include smoking history, organic dust exposure, and older age.

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Item 102 Answer: D

Educational Objective: Diagnose and stage lung cancer.

The most appropriate diagnostic test to perform next is needle aspiration of the left supraclavicular lymph nodes. Given this patient's significant smoking history and his imaging findings consistent with a pulmonary mass and associated lymphadenopathy, he has a high pretest probability of primary lung cancer. The most appropriate diagnostic test is the one that not only confirms the diagnosis but also provides adequate staging to help plan treatment options. Needle aspiration of the left supraclavicular lymph nodes is the least invasive procedure, and it would also stage the likely malignancy by documenting metastatic disease to these lymph nodes.

Bronchoscopy with needle aspiration of the mediastinal lymph nodes would both diagnose and provide some information about staging. However, it is more invasive than aspiration of the palpable supraclavicular lymph nodes.

Bronchoscopy with transbronchial biopsy of the left apical mass may be technically difficult given the apical position of the mass. However, more importantly, it would not provide any information about possible metastases to the lymph nodes.

CT-guided needle biopsy could potentially diagnose the patient with lung cancer. However, the needle would need to pass through normal lung tissue, which carries a risk of inducing pneumothorax. In addition, similar to bronchoscopy with transbronchial biopsy of the left apical mass, it would not provide information on staging because it would not assess whether there is involvement of the mediastinal or supraclavicular lymph nodes.

KEY POINT

- The most appropriate diagnostic test for lung cancer is the one that not only confirms the diagnosis in the least invasive fashion but also provides adequate staging to help plan treatment options.

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Item 103 Answer: D

Educational Objective: Treat high-altitude pulmonary edema.

The most appropriate adjunctive treatment is nifedipine. This patient is exhibiting signs of high-altitude pulmonary edema (HAPE). The mechanism of HAPE is believed to be a noncardiogenic exaggerated hypoxic vasoconstriction of the pulmonary vasculature. HAPE usually occurs at altitudes in excess of 2500 meters (8200 feet). Typical symptoms consist of cough, dyspnea, and exertional intolerance; symptoms are usually insidious in onset but may occasionally occur abruptly and awaken a patient from sleep. Other features, such as headache, fatigue, nausea, vomiting, and disturbed sleep, may or may not be present. Dyspnea at rest is a key feature of HAPE. On physical examination, tachypnea and tachycardia are typical, and crackles or wheezing can be auscultated. Pink frothy sputum or frank hemoptysis may occur, followed by worsening gas exchange and possibly respiratory failure. Treatment is with supplemental oxygen and rest, both of which will acutely reduce pulmonary artery pressures. Descent from altitude should be considered, particularly if oxygen is not available. Adjunctive therapies include vasodilators such as nifedipine or phosphodiesterase-5 inhibitors (sildenafil or tadalafil). Nifedipine may act by relaxing vascular smooth muscle and can be used as a treatment as well as a preventive agent in patients who have previously experienced HAPE.

Acetazolamide is the preferred drug for preventing acute mountain sickness and high-altitude cerebral edema, but it is not useful in preventing HAPE.

Dexamethasone is the preferred drug (in addition to supplemental oxygen) for the treatment of severe acute mountain sickness and high-altitude cerebral edema. It is not effective in the treatment of HAPE.

Ibuprofen is a reasonable first choice for symptoms of mild acute mountain sickness such as headache and nausea; however, it is not useful in treating HAPE.

KEY POINT

- Treatment of high-altitude pulmonary edema is with supplemental oxygen, rest, and consideration of descent from altitude; vasodilators such as nifedipine can be used as adjunctive treatment.

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In these pages, you will find updated information on approaches to the patient with rheumatologic disease, principles of therapeutics, rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, infectious arthritis, idiopathic inflammatory myopathies, systemic vasculitis, systemic sclerosis, autoinflammatory diseases, true connective tissue diseases, and other clinical challenges. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of rheumatology.

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On behalf of the many internists who have offered their time and expertise to create the content for MKSAP 17 and the editorial staff who work to bring this material to you in the best possible way, we are honored that you have chosen to use MKSAP 17 and appreciate any feedback about the program you may have. Please feel free to send us any comments to mksap_editors@acponline.org.

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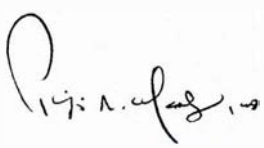

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Rheumatology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 17 in several important ways. MKSAP 17 now includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Rheumatology section of MKSAP 17.

- A physical examination is essential when diagnosing musculoskeletal pain and can help to avoid unnecessary laboratory and radiographic testing.
- The most appropriate and cost-effective means of assessing the cause of acute monoarthritis is by aspiration and analysis of the synovial fluid for leukocytes, Gram stain with culture, and crystals.
- Laboratory studies such as erythrocyte sedimentation rate, rheumatoid factor, and antinuclear antibodies have low specificity for diagnosing rheumatologic disease in patients with low pretest probability, thus limiting their utility in this population.
- The dose of glucocorticoid therapy should not be prolonged or increased in patients with polymyalgia rheumatica who have clinically improved based on an elevated erythrocyte sedimentation rate, as this is a nonspecific test (see Item 94).
- CT is useful in assessing bony abnormalities but is more expensive than plain radiography and exposes the patient to more radiation.
- MRI is useful in detecting soft-tissue abnormalities, inflammation, and fluid collections.
- Musculoskeletal ultrasonography is a low risk and relatively inexpensive way to detect soft-tissue abnormalities such as synovitis, tendinitis, bursitis, and joint fluid.
- Topical NSAIDs provide similar pain relief for inflammatory conditions as oral medications with fewer gastrointestinal effects and are preferred for patients 75 years or older; however, they are associated with more skin reactions and are significantly more expensive than oral NSAIDs.
- Rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and inflammatory markers assist in confirming a diagnosis of rheumatoid arthritis; however, serologies should never be used as the sole criterion for diagnosis and should be avoided in patients with low pretest probability for disease due to the high rate of false-positive results.
- Plain radiography of the hands, wrists, and/or feet are indicated to aid in the diagnosis and to follow progression of rheumatoid arthritis; in contrast, MRI of peripheral joints should not be routinely performed to monitor disease progression.
- Methotrexate is the initial treatment of choice for patients with new-onset, rapidly progressive, or erosive rheumatoid arthritis (see Item 54).
- Leflunomide-induced liver chemistry elevation is common (seen in up to 20% of patients taking the medication) and is usually reversible with dose reduction or drug discontinuation; thus, further evaluation, including liver biopsy, is not necessary (see Item 75).
- Laboratory studies are indicated only when needed to rule out other diagnoses in patients with primary osteoarthritis (OA); the diagnostic role for MRI and ultrasonography in OA has not been established.
- In patients with suspected osteoarthritis, confirmatory plain radiographs with standing views are appropriate to solidify the diagnosis and rule out less common findings such as avascular necrosis, fractures, and malignancies (see Item 37).
- Additional testing such as autoantibody measurements or radiography is unnecessary in patients with clinically diagnosed hand osteoarthritis (see Item 43).

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- In patients with osteoarthritis, initial treatment with acetaminophen for pain control is generally recommended (see Item 72).
- An NSAID should be initiated in patients with osteoarthritis if first-line therapy with acetaminophen does not provide adequate relief (see Item 89).
- Fibromyalgia is a clinical diagnosis characterized by chronic widespread pain, tenderness of the skin and muscles to pressure, fatigue, sleep disturbance, and exercise intolerance.
- Initial laboratory evaluation of fibromyalgia includes a complete blood count, chemistry panel, thyroid-stimulating hormone, and erythrocyte sedimentation rate or C-reactive protein; routine testing for antinuclear antibodies, rheumatoid factor, anti–cyclic citrullinated peptide antibodies, or muscle enzymes should be avoided.
- Nonpharmacologic therapy, including regular aerobic exercise, is the cornerstone of fibromyalgia treatment and should be initiated in all affected patients (see Item 67).
- Conventional radiography of the spine and sacroiliac joints is generally adequate to demonstrate synovitis, axial erosion, or new bone formation in patients with spondyloarthritis; CT should be reserved for identifying occult spine fractures and bony erosions in patients at high risk due to expense and higher level of radiation exposure.
- Patients with ankylosing spondylitis who are responding well to treatment should be monitored clinically and do not require periodic imaging studies less than every 2 years unless absolutely necessary (see Item 33).
- In patients with strongly suspected spondyloarthritis, MRI of the sacroiliac joints and/or spine should only be considered if conventional radiographs are negative.
- Age-appropriate cancer screening is recommended for patients with dermatomyositis or polymyositis, with consideration of additional testing for ovarian cancer; additional CT or PET scanning to look for underlying malignancy is not cost effective unless the patient has additional risk factors.
- Immediate treatment with prednisone, 60 mg/d (or 1 mg/kg/d), is indicated for patients with suspected giant cell arteritis to prevent visual complications (see Item 17).
- Sarcoidosis can manifest as Löfgren syndrome, which is characterized by acute arthritis, bilateral hilar lymphadenopathy, and erythema nodosum; when all three occur together, there is a 95% specificity for the diagnosis, and further diagnostic tests are unnecessary.
- Primary Raynaud phenomenon is common and carries a low risk for progression; thus, a serologic evaluation for underlying connective tissue disease is low yield and not cost effective unless severe and prolonged vasospastic episodes, asymmetric involvement of the digits, and abnormal nailfold capillary examination or digital pitting are present (see Item 73).

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Rheumatology

Approach to the Patient with Rheumatologic Disease

Introduction

In the United States, the estimated prevalence of chronic arthritis among adults is 33%; older persons (>65 years of age) have a higher prevalence than younger persons (<44 years of age).

Inflammatory Versus Noninflammatory Pain

In patients with musculoskeletal pain, it is critical to distinguish between inflammatory and noninflammatory pain, which typically have different causes. Inflammatory pain involves classic signs and symptoms of redness, swelling, warmth, and tenderness. Inflammation is often associated with prolonged morning stiffness and, potentially, constitutional symptoms. Although noninflammatory pain may also manifest with tenderness, other signs of inflammation are generally mild or absent. **Table 1** compares the features of inflammatory and noninflammatory pain.

KEY POINT

- Inflammatory pain involves redness, swelling, warmth, and tenderness; prolonged morning stiffness and constitutional symptoms may also occur.

The Musculoskeletal Examination

A physical examination is essential when diagnosing musculoskeletal pain and can help to avoid unnecessary laboratory and radiographic testing. Pain may be articular (from the joint), periarticular (from soft-tissue structures around the joint such as tendons, bursae, or muscles), or referred (from structures proximal or distal to the joint, or neurogenic in origin). Inspection, palpation, and range of motion are generally sufficient to establish whether there is an articular or a periarticular condition. Peripheral joints are usually straightforward to examine, although adiposity or edema can make inspection and palpation difficult. Axial joints such as the spine, shoulders, and hips are more difficult to assess for warmth and swelling; tenderness, range of motion, and special maneuvers are often required to adequately assess these areas.

Differentiating between active (patient moves the joint using his/her own power) and passive (examiner moves the joint for the patient) range of motion is important because

TABLE 1. Features of Inflammatory Versus Noninflammatory Pain

Feature	Inflammatory Pain	Noninflammatory Pain
Physical examination findings	Erythema; warmth; soft-tissue swelling	No soft-tissue swelling; minimal or no warmth; bony enlargement and joint effusions may occur in osteoarthritis
Morning stiffness	>60 min	<30 min
Constitutional symptoms	Fever; fatigue; malaise	Generally absent
Synovial fluid	Leukocyte count >2000/μL (2.0×10^9/L), predominantly neutrophils in acute inflammation and monocytes in chronic inflammation	Leukocyte count between 200/μL and 2000/μL (0.2×10^9/L and 2.0×10^9/L), predominantly monocytes
Other laboratory findings	Elevated inflammatory markers (ESR, CRP); anemia of chronic disease	Inflammatory markers usually normal or minimally elevated
Arthritis imaging studies	Symmetric/diffuse joint-space narrowing; periarticular osteopenia; erosions; bony proliferation in secondary osteoarthritis or spondyloarthritis; synovitis on MRI or ultrasound	Asymmetric/compartmental joint-space narrowing; osteophytes; subchondral sclerosis; limited or no synovitis on MRI or ultrasound

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

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pain with both passive and active range of motion implies an intrinsic joint condition, whereas pain with only active range of motion may be due to a periarticular condition.

See Musculoskeletal Pain in MKSAP 17 General Internal Medicine for more information.

KEY POINTS

HVC

- A physical examination is essential when diagnosing musculoskeletal pain and can help to avoid unnecessary laboratory and radiographic testing.
- Pain with both passive and active range of motion implies an intrinsic joint condition, whereas pain with only active range of motion may be due to a periarticular condition.

Arthritis

In addition to the presence or absence of inflammation, other features help to refine the differential diagnosis of musculoskeletal pain: pattern of joint involvement, number of joints involved, duration of symptoms, and presence or absence of symmetry.

Monoarticular Arthritis

Monoarticular arthritis (monoarthritis) involves a single joint. The differential diagnosis depends upon whether there is inflammation, the acuity of symptoms, and the patient's demographic and epidemiologic risk factors.

Inflammatory monoarthritis may be due to infection: bacterial in acute cases, and atypical organisms such as fungi, mycobacteria, or spirochetes (Lyme) in chronic cases. Noninfectious causes include crystal-related and autoimmune diseases. Crystal-related diseases typically present acutely but occasionally can be chronic, especially those caused by calcium pyrophosphate deposition. Noninflammatory monoarthritis is usually due to osteoarthritis or mechanical derangement (such as a torn meniscus or ligament). A history of trauma prior to onset of symptoms points toward noninflammatory arthritis.

The most appropriate and cost-effective means of assessing the cause of acute monoarthritis is by aspiration and analysis of the synovial fluid for leukocytes, Gram stain with culture, and crystals. If there is high suspicion for infection (especially atypical organisms) and synovial fluid cultures are unrevealing, synovial biopsy or other special tests may be needed. Blood in the synovial fluid (hemarthrosis) is typically associated with trauma except in patients with bleeding diatheses such as hemophilia.

Oligoarthritis

Oligoarthritis involves two to four joints, commonly in the lower extremities, and is often asymmetric. Although many diseases can manifest with oligoarthritis, the most common autoimmune inflammatory forms of oligoarthritis are the spondyloarthritis diseases (Table 2). Disseminated gonococcal infection, rheumatic fever, and Lyme disease may also present as inflammatory oligoarthritis. Osteoarthritis may cause a noninflammatory oligoarthritis, particularly if the involved joints share a history of trauma or overuse.

Polyarthritis

Polyarthritis involves five or more joints. The most common causes of chronic inflammatory polyarthritis include rheumatoid arthritis, systemic lupus erythematosus (SLE), and psoriatic arthritis (see Table 2). In contrast, acute onset of inflammatory polyarthritis is more commonly caused by viral infections such as hepatitis, parvovirus, rubella, herpes, HIV, adenovirus, mumps, or enterovirus. Polyarthritis may also be caused by a drug-induced serum sickness reaction, an immune complex reaction to bacterial infections such as endocarditis, or other forms of crystal or autoimmune diseases.

KEY POINT

HVC

- The most appropriate and cost-effective means of assessing the cause of acute monoarthritis is by aspiration and analysis of the synovial fluid for leukocytes, Gram stain with culture, and crystals.

Extra-Articular Manifestations of Rheumatologic Disease

Many rheumatologic diseases are systemic and therefore cause extra-articular manifestations in various sites and organs.

Constitutional Symptoms

Constitutional symptoms are common in systemic inflammatory diseases. Fever is especially typical of adult-onset Still disease and the autoinflammatory diseases (also known as the periodic fever syndromes) but may also occur in SLE, rheumatoid arthritis, and vasculitis, in which it is commonly low grade. Malaise and unintended weight loss also occur. In the absence of a clear cause, such symptoms may also suggest occult malignancy and/or infection.

Dermatologic Manifestations

Skin involvement is common in many rheumatologic diseases (Table 3, on page 4). Because of easy access by physical examination and/or biopsy, skin manifestations can be helpful in establishing a diagnosis, especially SLE, systemic sclerosis, and vasculitis. Some cutaneous findings may be subtle or unnoticed by the patient (for example, nail pitting); therefore, a high index of suspicion and a thorough physical examination may be required.

Inflammatory Eye Disease

Eye involvement is common in systemic rheumatologic diseases and provides direct visual access to both mucosal and central nervous system tissues. The location and type of ocular involvement may help narrow the differential diagnosis (Table 4, on page 4). Some diseases are particularly notable for ocular involvement, including rheumatoid arthritis (episcleritis and scleritis); spondyloarthritis and sarcoidosis (uveitis);

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TABLE 2. Autoimmune Inflammatory Arthritis

Condition	Pattern of Joint Involvement	Extra-articular Features	Diagnostic Studies
Rheumatoid arthritis	Symmetric polyarthritis; involves small joints (wrist, MCP, PIP, MTP) but also can involve hips, knees, elbows, shoulders, and cervical spine; spares thoracic and lumbar spine and DIP joints	Rheumatoid nodules; dry eyes and mouth; interstitial lung disease; Felty syndrome (splenomegaly, leukopenia, leg ulcers)	Rheumatoid factor; anti-CCP; acute phase reactants; erosive changes on radiograph
Systemic lupus erythematosus	Symmetric polyarthritis with large and small joint involvement; minimal to no swelling	Constitutional (fever, fatigue); multi-organ involvement (rash, oral ulcers, alopecia, serositis, kidney disease, neurologic disease, cytopenias)	ANA; anti-double-stranded DNA; anti-Smith; anti-U1-RNP; anti-Ro/SSA; anti-La/SSB; no erosions on radiograph
Spondyloarthritis			
Ankylosing spondylitis	Sacroiliac and spinal involvement; symmetric; large joints (shoulders, hips); spares small joints	Uveitis	Calcification of anterior longitudinal ligament of spine on radiograph; sacroiliitis; usually HLA-B27 positive
Psoriatic arthritis	Asymmetric oligoarthritis or symmetric polyarthritis; DIP joint preference; dactylitis (sausage digits); enthesitis (insertion of tendon to bone); axial disease with sacroiliitis	Psoriasis; uveitis	"Pencil-in-cup" deformities; erosions and osteophytes on radiograph; sometimes HLA-B27 positive
Reactive arthritis (formerly known as Reiter syndrome)	Asymmetric oligoarthritis; knee and ankle involvement; enthesitis; Achilles tendinitis; plantar fasciitis; sacroiliitis	Uveitis; keratoderma blennorrhagicum; preceding infection (*Chlamydia*; enteropathic)	Sacroiliitis; sometimes HLA-B27 positive
Inflammatory bowel disease–associated arthritis	Asymmetric; sacroiliitis; knee and feet involvement	Crohn disease; ulcerative colitis	Sacroiliitis; sometimes HLA-B27 positive

ANA = antinuclear antibodies; CCP = cyclic citrullinated peptide; DIP = distal interphalangeal; MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal; RNP = ribonucleoprotein.

CONT.

and vasculitis, especially granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), which can affect all parts of the eye. Dry eyes (keratoconjunctivitis sicca) are a major feature of Sjögren syndrome, whether primary or in association with other rheumatologic diseases.

Scleritis can result in permanent loss of vision, especially if scleral perforation occurs. Severe uveitis can also cause permanent visual loss. Recognition and treatment of these entities are therefore an urgent matter.

Internal Organ Involvement

Internal organs are potential targets for rheumatologic diseases (**Table 5**, on page 5). Vasculitis may affect one or more internal organs and should be considered in the differential diagnosis of a multisystem disease. Certain patterns of involvement may be helpful in developing a differential diagnosis, such as pulmonary-renal syndrome (pulmonary vasculitis/hemorrhage and glomerulonephritis) that may occur with ANCA-associated vasculitis, SLE, or Goodpasture syndrome.

Rheumatologic and Musculoskeletal Manifestations in Systemic Disease

Nonrheumatologic systemic diseases may have rheumatologic or musculoskeletal manifestations (**Table 6**, on page 6).

KEY POINT

- Systemic rheumatologic diseases can cause constitutional symptoms and extra-articular manifestations in various sites, including the skin, eyes, and internal organs.

Laboratory Studies

In rheumatologic diseases, laboratory studies are used to aid in diagnosis, follow disease activity, assess the extent of disease-related internal organ involvement, and monitor patients taking chronic immunomodulatory medications. However, some

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TABLE 3. Dermatologic Manifestations of Rheumatologic Disease

Disease	Manifestations
Systemic lupus erythematosus	Butterfly (malar) rash; photosensitive rash; discoid lupus erythematosus; subacute cutaneous lupus erythematosus; oral ulcerations (on the tongue or hard palate that are usually painless); alopecia; lupus panniculitis (painful, indurated subcutaneous swelling with overlying erythema of the skin)
Dermatomyositis	Gottron papules (erythematous plaques on extensor surfaces of MCP and PIP joints); photodistributed poikiloderma, including shawl sign (over the back and shoulders) and V sign (over the posterior neck/back or neck/upper chest); heliotrope rash (violaceous rash on the upper eyelid); mechanic's hands (hyperkeratotic, fissured skin on the palmar and lateral aspects of fingers); nailfold capillary abnormalities; holster sign (poikilodermic rash along lateral thigh)
Amyopathic dermatomyositis	Skin findings listed above under Dermatomyositis but without myositis findings
Systemic sclerosis	Skin thickening and hardening (limited disease involves face and skin distal to elbows/knees; diffuse disease involves skin proximal to distal forearms/knees); nailfold capillary changes
Vasculitis	Palpable purpura; cutaneous nodules; ulcers
Behçet syndrome	Painful oral and genital ulcers; erythema nodosum; acne/folliculitis; pathergy (skin inflammation/ulceration from minor trauma)
Sarcoidosis	Erythema nodosum
Psoriatic arthritis	Plaque psoriasis typically on extensor surfaces, umbilicus, gluteal fold, scalp, and behind ears; pustular psoriasis on palms and soles; arthritis may precede rash by up to 10 years; nail pitting; onycholysis
Reactive arthritis (formerly known as Reiter syndrome)	Keratoderma blennorrhagicum (psoriasiform rash on soles, toes, palms); circinate balanitis (psoriasiform rash on penis)
Adult-onset Still disease	Evanescent, salmon-colored rash on trunk and proximal extremities
Rheumatic fever (secondary to streptoccocal infection)	Erythema marginatum (annular pink to red nonpruritic rash with central clearing)
Lyme disease	Erythema chronicum migrans (slowly expanding, often annual lesion with central clearing)

MCP = metacarpophalangeal; PIP = proximal interphalangeal.

TABLE 4. Ocular Manifestations of Systemic Inflammatory Disease

Ocular Manifestation	Associated Systemic Inflammatory Disease
Uveitis	Spondyloarthritis (ankylosing spondylitis, reactive arthritis [formerly known as Reiter syndrome], inflammatory bowel disease) (anterior chamber); sarcoidosis (anterior and/or posterior chamber); Behçet syndrome (anterior and/or posterior chamber); granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) (posterior chamber)
Episcleritis	Rheumatoid arthritis; spondyloarthritis; systemic vasculitis
Scleritis	Rheumatoid arthritis; relapsing polychondritis; inflammatory bowel disease; systemic vasculitis
Retinal disease	Systemic vasculitis; antiphospholipid antibody syndrome

commonly used laboratory studies have low specificity for diagnosing rheumatologic disease when the pretest probability of disease is low, and rigor must be applied when interpreting such results.

Tests That Measure Inflammation

Several tests may be abnormal when rheumatologic or other inflammation is present. These include erythrocyte sedimentation rate and acute phase reactants, particularly C-reactive protein but also fibrinogen and ferritin. Platelet counts also tend to rise with inflammation. Complement levels usually increase with inflammation but fall with immune complex formation.

Erythrocyte Sedimentation Rate

Erythrocyte sedimentation rate (ESR) measures the rate at which erythrocytes settle with gravity in an upright tube of anticoagulated whole blood. ESR is dictated by characteristics of the erythrocytes themselves (size, shape, surface charge) and by the presence of specific plasma proteins that alter the normal repulsive forces (that is, neutralize surface charge) between erythrocytes and promote their ability to aggregate and form rouleaux and sediment more quickly. Such plasma proteins include several acute phase reactants (especially fibrinogen) produced by the liver in response to proinflammatory cytokines arising in rheumatologic, infectious, or malignant conditions. The normal ESR rises with age and tends to be higher in women. An estimate of the maximal expected normal ESR based on age and gender is age in years/2 for men and (age in years + 10)/2 for women. Thus, a mildly elevated ESR in an older patient must be interpreted with caution.

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TABLE 5. Internal Organ Involvement in Rheumatologic Disease

Organ	Disease	Type of Involvement
Heart		
	Kawasaki disease	Coronary artery vasculitis
	Systemic sclerosis	Arrhythmia; cardiomyopathy; pulmonary hypertension
	SLE	Pericarditis; valvular disease; cardiomyopathy
	RA	Pericarditis; cardiomyopathy
	Rheumatic fever; antiphospholipid antibody syndrome	Valvular disease
	GCA; Takayasu arteritis	Aortitis; heart failure; large-vessel vasculitis
Lung		
	RA	Serositis; ILD; rheumatoid nodules
	SLE; CTDs; HSP	Serositis; pneumonitis; pulmonary hemorrhage from vasculitis
	AAV; systemic vasculitis	Pulmonary hemorrhage; cavitary nodules
	Systemic sclerosis	ILD; pulmonary hypertension
	Antiphospholipid antibody syndrome	Pulmonary embolism
	Sarcoidosis	Hilar lymphadenopathy; ILD
	Goodpasture syndrome	Pulmonary hemorrhage
Kidney		
	SLE; CTDs; AAV; systemic vasculitis (except PAN)	Glomerulonephritis
	PAN	Renal artery vasculitis
	Antiphospholipid antibody syndrome	Renal infarct; renal vein thrombosis
	Sjögren syndrome	Acute interstitial nephritis/RTA
	Goodpasture syndrome	Glomerulonephritis
Gastrointestinal		
	PAN	Mesenteric vasculitis
	Spondyloarthritis	Inflammatory bowel disease
	HSP	Intestinal vasculitis; ulcerations
	Behçet syndrome	Ulcerations; inflammatory bowel disease
	FMF	Peritonitis
Neurologic		
	SLE; CTDs; AAV; systemic vasculitis	Mononeuritis multiplex; peripheral neuropathy
	PACNS	CNS vasculitis

AAV = ANCA-associated vasculitis; CNS = central nervous system; CTD = connective tissue disease; FMF = familial Mediterranean fever; GCA = giant cell arteritis; HSP = Henoch-Schönlein purpura; ILD = interstitial lung disease; PACNS = primary angiitis of the central nervous system; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; RTA = renal tubular acidosis; SLE = systemic lupus erythematosus.

ESR elevations are used to identify and monitor disease activity in rheumatologic diseases, especially in polymyalgia rheumatica and giant cell arteritis; however, because the population with these diseases is older, ESR may be less reliable. ESR is an important component of several measures used to assess disease activity in rheumatoid arthritis and is included in the American College of Rheumatology's recommendations for use in clinical practice. Interpretation of an elevated ESR can be difficult in the presence of conditions independently causing elevated fibrinogen and/or other plasma proteins.

Although elevations in ESR most commonly indicate inflammation, some noninflammatory conditions (kidney disease, diabetes mellitus, pregnancy, and obesity) are also associated with elevated fibrinogen levels and can produce an elevated ESR. Some patients make paraproteins (for example, patients with multiple myeloma) that can also cause ESR elevations. Conditions associated with low ESR (due to

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TABLE 6. Rheumatologic and Musculoskeletal Manifestations in Systemic Disease

Systemic Disease	Rheumatologic/Musculoskeletal Manifestations
Diabetes mellitus	Dupuytren contracture; adhesive capsulitis of the shoulder; diabetic amyotrophy (ischemic lumbosacral plexopathy); carpal tunnel syndrome; diffuse idiopathic skeletal hyperostosis; trigger finger; cheiroarthropathy (scleroderma-like thickening of hands); diabetic osteoarthropathy/Charcot foot
Hypothyroidism	Arthralgia/myalgia; myopathy (with elevated serum creatine kinase)
Hyperthyroidism	Osteoporosis; myopathy (serum creatine kinase not elevated)
Hyperparathyroidism	Calcium pyrophosphate deposition; osteoporosis
Acromegaly	Arthralgia/osteoarthritis; bone pain; calcium pyrophosphate deposition
Sickle cell disease	Sickle crisis; osteonecrosis; bone pain
Hemophilia	Hemarthroses
Carcinoma	Inflammatory polyarthritis or tendinitis; dermatomyositis; hypertrophic osteoarthropathy
Myeloma/lymphoma/ leukemia	Cryoglobulinemia; amyloidosis; arthritis (particularly in children)
Hemochromatosis	Osteoarthritis (especially atypical joints such as metacarpophalangeal joints); calcium pyrophosphate deposition

reduced fibrinogen or abnormal erythrocyte shape and attraction) include heart and liver failure, sickle cell disease, polycythemia, and spherocytosis.

C-Reactive Protein

C-reactive protein (CRP) is an acute phase reactant synthesized by the liver during inflammation in response to proinflammatory cytokines. CRP can adhere to bacteria and activate complement, promoting phagocytosis. Values greater than 0.8 mg/dL (8.0 mg/L) are considered inflammatory, whereas levels between 0.2 mg/dL and 0.8 mg/dL (2.0 mg/L and 8.0 mg/L) are indeterminate.

CRP responds rapidly to inflammation, both rising and falling more quickly than ESR. CRP is more stable and less affected by other serum components compared with ESR. Like ESR, CRP is elevated with disease activity in most rheumatologic diseases and during other forms of inflammation (for example, infection or malignancy). However, in some patients with SLE, CRP will increase during infection but not during disease flare.

Complement

The complement system assists in bacterial opsonization and lysis during humoral immune responses; it also promotes inflammatory reactions. There are three complement cascades (classical, alternative, and mannose-binding lectin pathways); each is triggered differently, but all generate pro-opsonic and proinflammatory components.

Complement levels are generally increased in inflammatory states (that is, complement components are acute phase reactants). However, when immune complexes are present (for example, SLE or certain types of vasculitis), complement is consumed, leading to lower than normal levels. Rare genetic deficiencies of complement, particularly of the early complement components C1q, C2, and C4, paradoxically increase the risk of autoimmune disease, perhaps by impairing clearance of immune complexes and apoptotic cells; genetic C4 deficiency may also be seen in lupus-like autoimmunity.

Reductions in C3 and C4 levels usually are measured to assess for immune complex–mediated consumption. CH50 tests measure the ability of serum complement to lyse immunoglobulin-coated erythrocytes. CH50 thus assesses overall activation of the classical complement pathway and is abnormal when any component of the classical system is depleted. However, CH50 is no longer routinely used because it is labor intensive, expensive, and usually no more useful in diagnosis and assessment than C3 and C4.

Autoantibody Tests

The presence of autoantibodies is characteristic of many rheumatologic diseases. Rheumatoid factor and antinuclear antibodies (ANA) are the most commonly ordered autoantibody tests. Rheumatoid factor is an immunoglobulin directed against the Fc portion of IgG, and ANA is directed against nuclear antigens. The specificity of these autoantibodies for a particular rheumatologic disease is relatively low because they may occur in other rheumatologic and nonrheumatologic diseases and even in healthy persons.

Rheumatoid factor presence is characteristic of rheumatoid arthritis, but a significant minority of patients with rheumatoid arthritis lack rheumatoid factor. Anti-cyclic citrullinated peptide antibodies are more specifically characteristic of RA and often appear earlier in the disease; using the two antibody tests together may be helpful. Rheumatoid factor is frequently present in healthy persons, especially at older ages, but usually in low titer.

The immunofluorescence assay is considered more reliable than the enzyme-linked immunosorbent assay (ELISA) for detecting ANA, but ELISA is less expensive and less labor intensive. About one third of the healthy population have a positive low-titer (1:40) ANA, and 3% to 5% have a titer of 1:160 or higher. Asymptomatic ANA positivity is more common in

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women and healthy first-degree relatives of patients with autoimmune disease. Higher ANA titers are more likely to be associated with rheumatologic disease. More than 95% of patients with SLE have a positive ANA; conversely, a negative ANA is rare in those with SLE. ANA occurs in other autoimmune diseases, including rheumatoid arthritis, other connective tissue diseases, infection, and malignancy. ANA can also be drug induced. ANA titer does not correlate with disease activity and should not be checked repeatedly during disease management.

A positive ANA in a patient with nonspecific symptoms is difficult to interpret. As with all tests, the positive predictive value of ANA rests upon the pretest probability of disease. The American College of Rheumatology's Choosing Wisely list currently recommends against testing ANA subserologies without the combination of a positive ANA and clinical suspicion of immune-mediated disease.

Table 7 provides details on these and other autoantibodies.

KEY POINTS

HVC
- Laboratory studies such as erythrocyte sedimentation rate, rheumatoid factor, and antinuclear antibodies have low specificity for diagnosing rheumatologic disease in patients with low pretest probability, thus limiting their utility in this population.
- Although elevations in erythrocyte sedimentation rate (ESR) most commonly reflect the presence of inflammation, increasing age and some noninflammatory conditions are also associated with elevated ESR.
- C-reactive protein responds rapidly to inflammation, both rising and falling more quickly than erythrocyte sedimentation rate (ESR) and is more stable and less affected by other serum components compared with ESR.

Imaging Studies

Imaging studies can be useful to diagnose and follow patients with rheumatologic diseases. For example, inflammatory arthritis can be evaluated with studies ranging from plain radiography to MRI, and medium- and large-vessel vasculitis can be detected using angiography. For all studies, it is important to consider whether the ordering of imaging tests will aid in the diagnosis or management of a suspected condition, and whether the benefits of such testing clearly outweigh the potential risks and costs.

Radiography

Plain radiography is used to assess inflammatory and degenerative arthritis (**Table 8**, on page 9). Autoimmune inflammatory arthritis may produce joint-space narrowing, erosions, and osteopenia, and in the case of spondyloarthritis, productive bony overgrowth. Crystal-related inflammatory diseases have characteristic radiographic findings, including punched-out bone lesions in gout or cartilage calcification (also known as chondrocalcinosis) in calcium pyrophosphate deposition. Osteoarthritis causes compartmental joint-space narrowing and bony hypertrophy.

Plain radiography does not visualize soft tissues nearly as well as bone, and due to the two-dimensional nature of the images, not all bone findings are visible on every view (for example, visible on oblique but not anteroposterior imaging). Plain radiography may not detect early (within the first 6-12 months) or mild erosive arthritic changes. Despite these limitations, serial plain radiography can be useful for monitoring arthritis disease progression.

Plain radiography is relatively inexpensive and readily available. Despite low levels of ionizing radiation, plain radiography is considered safe except for pregnant women.

CT

In contrast to plain radiography, CT scanning permits multiple views and orientations from a single study. CT is more useful for bony abnormalities than for soft-tissue inflammation or fluid collections. Calcium pyrophosphate deposition is readily detected on CT, even when calcium deposits are overlooked on other modalities. CT is more sensitive in detecting bone erosions than plain radiographs or MRI.

CT is more expensive than plain radiography and exposes the patient to more radiation.

MRI

MRI is useful in detecting soft-tissue abnormalities, inflammation, and fluid collections, but is less effective than CT in demonstrating bony abnormalities and erosive changes. MRI is more sensitive than plain radiography in detecting early spine and sacroiliac joint inflammation.

MRI is more expensive than plain radiography and CT and is generally ordered when assessment of soft-tissue imaging is required. Although MRI does not expose the patient to radiation, MRI contrast (gadolinium) must be avoided in patients with kidney disease due to the risk of nephrogenic systemic fibrosis. Patient intolerance due to claustrophobia or inability of the patient to fit in the scanner due to large body habitus may limit the ability to obtain MRI data. Because data are currently inadequate to justify its use, the American College of Rheumatology Choosing Wisely list questions the utility of routinely ordering MRI of peripheral joints to monitor rheumatoid arthritis.

Ultrasonography

Musculoskeletal ultrasonography is increasingly utilized in rheumatologic disease. Ultrasonography can detect soft-tissue abnormalities such as synovitis, tendinitis, bursitis, and joint fluid, and Doppler can assess for increased tissue blood flow consistent with synovitis. Ultrasonography can diagnose and monitor disease, and can be used to guide arthrocentesis. Dynamic pathologies such as impingement can be visualized.

Unlike other modalities, ultrasonography is portable and can be used in the outpatient setting at the bedside for point-of-care evaluation and procedures. However, it is operator dependent, and training and practice are required

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TABLE 7. Autoantibodies in Rheumatologic Disease

Autoantibody	Rheumatologic Condition	Sensitivity/Specificity	Comments
ANA	SLE; also SSc, Sjögren, and MCTD	SLE: 95% sensitivity; poor specificity	Does not correlate with disease activity
Anti-double-stranded DNA	SLE	SLE: 60% sensitivity, >95% specificity; *Crithidia* IFA or Farr assays more specific than ELISA	Found in more severe disease, especially kidney disease; antibody levels commonly follow disease activity and are useful to monitor
Anti-Smith	SLE	SLE: 30% sensitivity, 99% specificity	Most specific test for SLE; does not correlate with disease activity
Anti-U1-RNP	MCTD; SLE	100% sensitivity	High titer seen in MCTD (>1:10,000); does not correlate with disease activity
Anti-Ro/SSA; anti-La/SSB	Sjögren; SLE; RA; SSc	Sjögren: 70% sensitivity; SLE: 30% sensitivity	Sicca symptoms; in SLE, associated with photosensitive rash and neonatal lupus erythematosus (rash and conduction block)
Anti-Scl-70 (antitopoisomerase)	DcSSc	10%-30% sensitivity	Seen more often in patients with SSc who have pulmonary fibrosis
Anticentromere	LcSSc (CREST)	10%-30% sensitivity	Patients with SSc with this antibody are more likely to develop pulmonary hypertension
c-ANCA (antiproteinase-3)	GPA	90% sensitivity when disease is active; high specificity in classic presentations	Correlation with disease activity is unclear
p-ANCA (antimyeloperoxidase)	MPA; EGPA	MPA: 80% sensitivity; EGPA: 60% sensitivity; less specific than c-ANCA	Atypical p-ANCA (antimyeloperoxidase negative) can be seen in inflammatory bowel disease and with positive ANA
Anti-Jo-1	Myositis	20%-30% sensitivity	Associated with antisynthetase syndrome
Rheumatoid factor	RA; Sjögren; cryoglobulinemia	RA: 70% sensitivity; limited specificity, especially in patients without a classic disease presentation	RF is an antibody to Ig and hence many false positives (hepatitis C, SLE); 30% with RA are RF negative; may convert to positive later in RA course
Anti-cyclic citrullinated peptide	RA	RA: 70% sensitivity; more specific than RF for RA	Can be positive in RF-negative RA patients; often present before RF becomes positive; associated with erosions; predicts disease progression in undifferentiated arthritis
Antihistone	DILE	95% sensitivity; poor specificity	Also seen in patients with native lupus
Cryoglobulins	Vasculitis; hepatitis C; myeloma; SLE; RA	Type II or III cryoglobulins seen in patients with cryoglobulinemic vasculitis	May be present in connective tissue diseases in the absence of vasculitis

ANA = antinuclear antibodies; CREST = calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; DcSSc = diffuse cutaneous systemic sclerosis; DILE = drug-induced lupus erythematosus; EGPA = eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome); ELISA = enzyme-linked immunosorbent assay; GPA = granulomatosis with polyangiitis (formerly known as Wegener granulomatosis); IFA = immunofluorescent assay; LcSSc = limited cutaneous systemic sclerosis; MCTD = mixed connective tissue disease; MPA = microscopic polyangiitis; RA = rheumatoid arthritis; RF = rheumatoid factor; RNP = ribonucleoprotein; SLE = systemic lupus erythematosus; SSc = systemic sclerosis.

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TABLE 8. Radiographic Findings of Common Rheumatologic Diseases

Rheumatologic Disease	Radiographic Findings
Rheumatoid arthritis	Bony erosions; periarticular osteopenia; subluxations; soft-tissue swelling; MCP and PIP involvement on hand radiograph
Osteoarthritis	Asymmetric joint-space narrowing; osteophytes; subchondral sclerosis and cystic changes; degenerative disk disease with collapse of disks; degenerative joint disease with facet joint osteophytes; these findings lead to spondylolisthesis (anterior/posterior misalignment of the spine) and kyphosis
Diffuse idiopathic skeletal hyperostosis	Calcification of the anterior longitudinal ligament; bridging horizontal syndesmophytes; usually more prominent on right side of spine than left
Ankylosing spondylitis	Sacroiliitis; squaring of the vertebral bodies; bridging vertical enthesophytes; shiny corners
Psoriatic arthritis	Destructive arthritis with erosions and osteophytes; DIP involvement; "pencil-in-cup" deformities on hand radiograph; arthritis mutilans
Gout	Punched-out erosions with sclerotic border and overhanging edge; periarticular soft-tissue swelling with calcifications in tophaceous deposits
Calcium pyrophosphate deposition	Chondrocalcinosis, most commonly of the knees, shoulders, wrists, pubic symphysis; leads to osteoarthritis

DIP = distal interphalangeal; MCP = metacarpophalangeal; PIP = proximal interphalangeal.

CONT. to achieve competency at performing and interpreting ultrasonography.

Ultrasonography is relatively inexpensive, and there is no ionizing radiation.

KEY POINTS

HVC
- CT is useful in assessing bony abnormalities but is more expensive than plain radiography and exposes the patient to more radiation.

HVC
- MRI is useful in detecting soft-tissue abnormalities, inflammation, and fluid collections but should not be routinely used to monitor rheumatoid arthritis disease activity in peripheral joints.

HVC
- Musculoskeletal ultrasonography is a low risk and relatively inexpensive way to detect soft-tissue abnormalities such as synovitis, tendinitis, bursitis, and joint fluid.

Joint Aspiration

Synovial fluid aspiration is essential when evaluating for infection and crystal-related disease and can distinguish between inflammatory and noninflammatory conditions. The most useful tests of synovial fluid for infection are leukocyte count, stains, and cultures, as well as evaluation of synovial fluid for crystals under polarized light. Synovial fluid autoantibodies and protein and glucose levels are of limited utility and used primarily in research investigations. The gross appearance of synovial fluid can predict results in the laboratory. Normal fluid is clear and highly viscous. Inflammatory fluid is cloudy and watery. Infected fluid is cloudy to opaque and, while "thick" like pea soup, lacks the viscosity of normal fluid.

Synovial fluid leukocyte counts less than 200/μL (0.2×10^9/L) are considered normal, between 200/μL and 2000/μL (0.2×10^9/L and 2.0×10^9/L) are associated with noninflammatory conditions, and greater than 2000/μL (2.0×10^9/L) are associated with inflammatory states. The higher the count is, the more inflammatory the fluid and the greater the suspicion for crystal-related or infectious disease.

There is no absolute cutoff value that distinguishes infection from crystal-related disease, because some infections may have lower counts than expected and crystal-related disease may have counts greater than 100,000/μL (100×10^9/L). Thus, the proper application of synovial fluid leukocyte counts requires conservative interpretation. Generally, counts greater than 50,000/μL (50×10^9/L) should be managed as infectious until explicitly proven otherwise; if there is clinical suspicion for infection, fluid should be sent for stains and cultures even in the setting of counts less than 50,000/μL (50×10^9/L).

See Crystal Arthropathies for a discussion on synovial fluid crystal evaluation.

KEY POINT

- Synovial fluid leukocyte counts less than 200/μL (0.2×10^9/L) are considered normal, between 200/μL and 2000/μL (0.2×10^9/L and 2.0×10^9/L) are associated with noninflammatory conditions, and greater than 2000/μL (2.0×10^9/L) are associated with inflammatory states.

Principles of Therapeutics

Introduction

This section discusses the uses, mechanisms of action, targets, potential toxicities, and common monitoring parameters of medications used in rheumatologic disease. Specific applications of individual drugs are further discussed in the disease-specific sections.

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Anti-Inflammatory Agents

Anti-inflammatory agents reduce pain and improve swelling, warmth, and redness but generally do not prevent disease progression.

NSAIDs

NSAIDs inhibit cyclooxygenase (COX) enzymes to block the generation of the lipid prostaglandin E_2 (PGE_2). PGE_2 stimulates inflammation, vasodilation, smooth muscle contraction, pain, and fever; NSAIDs therefore convey anti-inflammatory, analgesic, and antipyretic effects. However, PGE_2 also maintains gastric mucosa and promotes kidney sodium excretion and glomerular filtration. Other COX products include thromboxane A_2, a prothrombotic regulator of platelets, and prostacyclin, an antithrombotic and vasodilatory lipid. Because NSAIDs inhibit all of these, the consequences of COX inhibition are complex and accompanied by multiple potential side effects (**Table 9**). Side-effect risk is increased in older patients and those with preexisting comorbidities. Regular monitoring of blood pressure, kidney function, and blood counts during chronic NSAID use is recommended.

The identification of two distinct COX isoforms permitted the development of selective COX-2 inhibitors. Because the COX-1 isoform is responsible for platelet function and gastroprotection, COX-2 inhibitors cause less gastrotoxicity and bleeding than nonselective NSAIDs. However, COX-2 inhibitors are not less nephrotoxic and cause similar amounts of hypertension. The most selective COX-2 inhibitors also cause increased cardiovascular risk and have been removed from the market. However, nearly all NSAIDs may convey some cardiovascular risk.

In contrast to other NSAIDs, aspirin (acetylsalicylate) permanently inactivates COX enzymes. Platelets cannot generate replacement COX and are particularly vulnerable to this effect. Therefore, low-dose aspirin administration for cardiovascular disease permits a platelet-selective effect that reduces, but does not entirely alleviate, potential gastrointestinal toxicity. Higher doses promote more general COX inhibition and convey the same risks as other NSAIDs.

TABLE 9. Potential Toxicities of NSAID Use

Category	Toxicity
Cardiovascular	Hypertension; myocardial infarction; exacerbation of heart failure
Hemostatic	Bleeding diathesis
Gastrointestinal	Dyspepsia; reflux; peptic ulcer disease; gastrointestinal bleeding
Obstetric/ Gynecologic	Bleeding; delayed labor; premature ductus arteriosus closure
Pulmonary	Asthma exacerbation
Renal	Hypertension; decreased glomerular filtration; increased salt and water retention; increased renin production; uncommonly, allergic interstitial nephritis or acute tubular necrosis

Oral NSAIDs vary in potency, kinetics, metabolism, cost, and selectivity for COX-1 versus COX-2. Selection of a particular NSAID depends mainly upon convenience of use and individual tolerance, including consideration of the patient's comorbidities. All NSAIDs should be used at the lowest effective dose for the shortest time; however, effective use of NSAIDs in rheumatologic disease often requires high and prolonged dosing. NSAIDs are not generally disease modifying; they improve arthritis symptoms but not long-term outcomes.

Topical NSAIDs such as diclofenac (available as a solution, spray, gel, or patch) provide similar pain relief for inflammatory conditions as oral medications with fewer gastrointestinal effects. The American College of Rheumatology currently recommends topical NSAIDs rather than oral NSAIDs for patients aged 75 years or older. However, they are associated with more skin reactions than placebo and are significantly more expensive than oral NSAIDs.

Glucocorticoids

Glucocorticoids are potent anti-inflammatories and are effective in many rheumatologic diseases; however, they are associated with multiple potential toxicities and should be used at the lowest effective dose for the shortest period possible. Intermediate to long-term use is associated with an increased risk of diabetes mellitus, osteoporosis, osteonecrosis, weight gain, fluid retention, hypertension, cardiovascular disease, striae and bruising, and glaucoma and cataracts; monitoring for adverse events can help limit morbidity. Virtually all patients receiving chronic glucocorticoids or frequent tapering doses should take calcium and vitamin D supplementation; patients receiving glucocorticoids for more than 4 weeks at doses greater than 5 mg of prednisone daily should be considered for bisphosphonate treatment.

Colchicine

Colchicine disrupts microtubules to interfere with leukocyte adhesion and migration. Other potential effects include inhibition of interleukin (IL)-1 generation. Colchicine is used to treat gout, familial Mediterranean fever, and hypersensitivity vasculitis. At low doses, colchicine is generally safe and well tolerated; higher doses routinely cause diarrhea. Acute colchicine overdose can be fatal; chronic low-level colchicine overdose can cause neuromyopathy. Colchicine is renally cleared; patients with kidney disease require dose adjustment. Colchicine is metabolized in the liver by the CYP3A4 cytochrome, and its absorption from the stomach is limited by the P-glycoprotein export pump; consequently, patients must reduce or avoid colchicine when also taking moderate/strong CYP3A4 inhibitors (for example, clarithromycin, most antiretroviral drugs) or P-glycoprotein inhibitors (for example, cyclosporine). When used in combination with statins (especially those metabolized by CYP3A4), colchicine may increase the risk of drug-induced myopathy.

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KEY POINTS

HVC

- Topical NSAIDs provide similar pain relief for inflammatory conditions as oral medications with fewer gastrointestinal effects and are preferred for patients 75 years or older; however, they are associated with more skin reactions and are significantly more expensive than oral NSAIDs.
- Virtually all patients receiving chronic glucocorticoids or frequent tapering doses should take calcium and vitamin D supplementation; patients receiving glucocorticoids for more than 4 weeks at doses greater than 5 mg of prednisone daily should be considered for bisphosphonate treatment.

Analgesics

Simple analgesics are neither anti-inflammatory nor disease modifying but can help relieve pain in patients with arthritis.

Acetaminophen is generally well tolerated and has both analgesic and antipyretic effects; its mechanism of action is not well established. The maximum recommended daily dose by the FDA is 4 g/d, and doses greater than 4 g/d carry an increased risk for liver failure and even death. Because acetaminophen content in over-the-counter products (for example, for allergies, headaches, and colds) may not be taken into account by some patients when calculating the total daily dose, some guidelines limit maximum daily intake to 3 g/d in most patients and 2 g/d in patients with liver disease. In chronic acetaminophen use, periodic assessment of liver and kidney function may be prudent.

Opiates act on neurons to block pain signaling. Opiates are less effective for inflammatory than for malignancy pain, but milder opiates (for example, codeine or oxycodone) have an occasional role in treating patients with arthritis who cannot otherwise obtain relief. Opiates are potentially habit-forming, can cause constipation, and may cause respiratory depression at excessive doses. Tramadol is a centrally acting synthetic opioid analgesic that also weakly inhibits the reuptake of norepinephrine and serotonin; potential for addiction is lower than for traditional opioids.

Agents that modulate pain signals in the spinal cord (for example, pregabalin, gabapentin, tricyclic antidepressants such as amitriptyline, and dual serotonin-norepinephrine reuptake inhibitors such as duloxetine and milnacipran) are useful in patients with central chronic pain syndromes (for example, fibromyalgia) as well as musculoskeletal pain. Side effects include sedation and dry mouth. Concomitant use of serotonin reuptake inhibitors, tricyclic antidepressants, or monoamine oxidase inhibitors may lower seizure threshold and/or raise the risk of serotonin syndrome (mental status changes, autonomic instability, neuromuscular aberrations, and gastrointestinal symptoms).

Topical analgesics (such as capsaicin and lidocaine) may be useful and can limit systemic drug exposure when only a single area is painful.

KEY POINTS

- Simple analgesics are neither anti-inflammatory nor disease modifying but may help alleviate arthritis pain.
- Acetaminophen is generally well tolerated and beneficial, but excessive doses carry risk for liver failure and even death.

Disease-Modifying Antirheumatic Drugs

Disease-modifying antirheumatic drugs (DMARDs) are immunosuppressive agents used to achieve control and/or remission in rheumatologic disease. Most DMARDs increase the risk of infection, and each agent has its own specific potential toxicities.

Nonbiologic Disease-Modifying Antirheumatic Drugs

Table 10 summarizes the mechanisms of action, indications, and common monitoring parameters of various nonbiologic DMARDs. See Rheumatologic Medications and Pregnancy for information on these medications in women of childbearing potential.

Methotrexate

Methotrexate inhibits folic acid metabolism and increases extracellular adenosine levels. It is the recommended initial DMARD for most patients with rheumatoid arthritis and is useful in other disorders, including psoriatic arthritis, vasculitis, and sarcoidosis. Methotrexate is administered weekly along with daily folic acid supplementation, which limits toxicity without affecting efficacy. Potential toxicities include hepatitis and bone marrow suppression (leukopenia, anemia). Patients with liver disease should not receive methotrexate, and limitation of alcohol intake is strongly advised.

Hydroxychloroquine

Hydroxychloroquine is an antimalarial medication that appears to inhibit antigen processing. In systemic lupus erythematosus (SLE), hydroxychloroquine is used to control skin and joint disease, prevent systemic and organ-specific disease flare-ups, and reduce overall mortality. It is also used (alone or in combination with methotrexate and sulfasalazine) to treat undifferentiated connective tissue disease, rheumatoid arthritis, and other forms of inflammatory arthritis. Although its efficacy in arthritis is modest, its excellent side-effect profile makes it a useful adjunctive therapy.

Sulfasalazine

Sulfasalazine exerts systemic effects through its metabolite sulfapyridine and intracolonic effects via the salicylate moiety. Sulfasalazine is moderately effective in rheumatoid arthritis with or without methotrexate. It is also used to treat

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TABLE 10. Nonbiologic Disease-Modifying Antirheumatic Drugs

Agent	Mechanism	Indications	Common Monitoring Parameters
Methotrexate	DHFR inhibition; extracellular adenosine level modification	RA; psoriasis; psoriatic arthritis; DM; PM; vasculitis	Baseline: chest radiography, hepatitis screening, CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine every 3 months[a]
Hydroxychloroquine	Uncertain; appears to involve stabilization of lysosomal vacuoles, leading to inhibition of antigen processing and costimulatory activation	SLE; RA	Baseline: CBC, LCTs, serum creatinine Baseline/periodic ophthalmologic examinations approximately every 12 months to evaluate for hydroxychloroquine deposition, which rarely can lead to visual loss
Sulfasalazine	Antimetabolite; a pro-drug broken down into 5-amino salicylic acid (active metabolite in the gastrointestinal tract) and sulfapyridine (exerts systemic action)	RA; SpA; IBD	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine every 3-6 months
Leflunomide	Blocks dihydroorotase, an enzyme involved in pyrimidine biosynthesis that targets replicating lymphocytes, which lack pyrimidine salvage pathways; antiproliferative	RA	Baseline: chest radiography, hepatitis screening, CBC, LCTs, serum creatinine Thereafter: CBC, serum creatinine every 3 months; LCTs every 8-12 weeks, and leflunomide temporarily or permanently discontinued for significant elevations >2 times normal and additional therapy with cholestyramine for elevations >3 times normal[a]
Azathioprine	Purine analogue; inhibits DNA synthesis essential for proliferating T- and B-lymphocytes	SLE; DM; PM; vasculitis; IBD	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine every 3 months[a]
Cyclophosphamide	Alkylating agent; blocks DNA synthesis and causes cell death	Severe and life-threatening disease in SLE, DM, PM, and vasculitis	Close monitoring clinically and measuring CBC, chemistries, LCTs, urinalysis every 4-8 weeks
Mycophenolate mofetil	Inosine monophosphate inhibition; antiproliferative; mycophenolate is converted into the active metabolite, mycophenolic acid, which inhibits inosine monophosphate dehydrogenase (an enzyme in the purine synthetic pathway) and preferentially inhibits T- and B-lymphocytes	SLE (especially lupus nephritis); vasculitis; DM; PM	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine every 3 months[a]
Cyclosporine	Inhibits calcineurin (a transcription activating factor); preferentially targets T cells	SLE; psoriasis; RA	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine every 2-3 months[a]
Apremilast	Inhibits phosphodiesterase 4	Psoriasis; psoriatic arthritis	Baseline: weight Thereafter: weight, neuropsychiatric effects

CBC = complete blood count; DHFR = dihydrofolate reductase; DM = dermatomyositis; IBD = inflammatory bowel disease; LCTs = liver chemistry tests; PM = polymyositis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SpA = spondyloarthritis.

[a]Recommended monitoring interval is for a stable dose but may be shorter after initiation or in the case of abnormal results and must be individualized to the patient's risk of toxicity.

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spondyloarthritis and inflammatory bowel disease. Toxicities include gastrointestinal upset, headache, agranulocytosis, hepatitis, and reversible oligospermia.

Leflunomide

Leflunomide inhibits lymphocyte activation by blocking the pyrimidine synthesis pathway. It is approved to treat rheumatoid arthritis, in which its efficacy is comparable to methotrexate. Toxicities include gastrointestinal upset, diarrhea, aminotransaminase elevations, cytopenias, infection, and teratogenesis.

Azathioprine

Azathioprine is a purine analogue that inhibits nucleotide synthesis. It is used to treat and/or maintain control of SLE, vasculitis, the inflammatory myopathies, and other autoimmune diseases. Toxicities include gastrointestinal intolerance, bone marrow suppression, hepatitis, and pancreatitis. Coadministration with allopurinol or febuxostat should be avoided because these three drugs compete for the same metabolic pathway, and toxic levels may ensue.

Cyclophosphamide

Cyclophosphamide is a DNA alkylating agent with potent immunosuppressive properties. It is used to treat severe and/or life-threatening manifestations of SLE (including nephritis), systemic sclerosis, the inflammatory myopathies, interstitial lung disease, and vasculitis. Toxicities include bone marrow suppression, leukopenia, anemia, infections, infertility, hemorrhagic cystitis and bladder cancer, and lymphoma and other malignancies. Evaluation of patients with painless hematuria and history of past cyclophosphamide treatment should include cystoscopy to evaluate for bladder cancer.

Mycophenolate Mofetil

Mycophenolate mofetil inhibits the purine pathway of nucleotide synthesis and may be at least as effective as cyclophosphamide for SLE (including nephritis) but with fewer, and milder, side effects. It is also used to treat autoimmune myositis and as a glucocorticoid-sparing agent in systemic vasculitis. Toxicities include diarrhea, cytopenias, and infection.

Cyclosporine

Cyclosporine is both a calcineurin and T-lymphocyte inhibitor that is efficacious in several autoimmune diseases, including rheumatoid arthritis, SLE, autoimmune myositis, psoriasis, and inflammatory bowel disease. Cyclosporine is mainly used as a third-line agent in rheumatologic disease because its potential toxicities (for example, nephrotoxicity, hypertension, tremors, and hirsutism) require close monitoring.

Apremilast

Apremilast was recently approved by the FDA for treatment of psoriasis and psoriatic arthritis. Apremilast inhibits phosphodiesterase 4, resulting in increases in cyclic adenosine monophosphate that inhibit inflammatory responses. Although experience is limited, studies suggest that apremilast is well tolerated and of moderate efficacy.

KEY POINTS

- Methotrexate is the recommended initial disease-modifying antirheumatic drug for most patients with rheumatoid arthritis.
- Hydroxychloroquine is used in patients with systemic lupus erythematosus to control skin and joint disease, prevent systemic and organ-specific disease flare-ups, and reduce overall mortality.
- Cyclophosphamide is used to treat severe and/or life-threatening manifestations of systemic lupus erythematosus, systemic sclerosis, the inflammatory myopathies, interstitial lung disease, and vasculitis.
- Mycophenolate mofetil may be at least as effective as cyclophosphamide for systemic lupus erythematosus but with fewer, and milder, side effects.

Biologic Disease-Modifying Antirheumatic Drugs

Biologic DMARDs are protein-based products that alter the body's natural processes to block immune responses (**Figure 1**). Biologic DMARDs are more specific and typically more effective than nonbiologic DMARDs; however, they are significantly more expensive. Biologic DMARDS are generally administered parenterally; the suffixes of their names indicate their general structure (for example, "mab" for monoclonal antibody and "cept" for receptor derived).

Toxicities of biologic agents relate mainly to the pathways they block. Infection risk is elevated with most biologic agents; therapy should be temporarily interrupted during any significant infection. Biologic agents are frequently used in combination with a nonbiologic DMARD. However, concurrent use of two or more biologic agents is contraindicated because infection rates are increased with minimal, if any, added efficacy. See Vaccination and Screening in Immunosuppression for more details.

Table 11 on page 15 summarizes the structures, targets, indications, and common monitoring parameters of various biologic DMARDs. See Rheumatologic Medications and Pregnancy for information on these medications in women of childbearing potential.

Tumor Necrosis Factor α Inhibitors

Tumor necrosis factor (TNF)-α inhibitors are usually the treatment of first choice for patients with rheumatoid or psoriatic arthritis after inadequate response to nonbiologic DMARDs. TNF-α inhibitors also treat ankylosing spondylitis after failure of NSAIDs. TNF-α inhibitors are effective in 50% to 70% of patients with these diseases. Five TNF-α inhibitors (infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab) are FDA approved to treat rheumatoid arthritis, psoriatic arthritis, and/or ankylosing spondylitis. These agents decrease disease activity and inhibit the progression of

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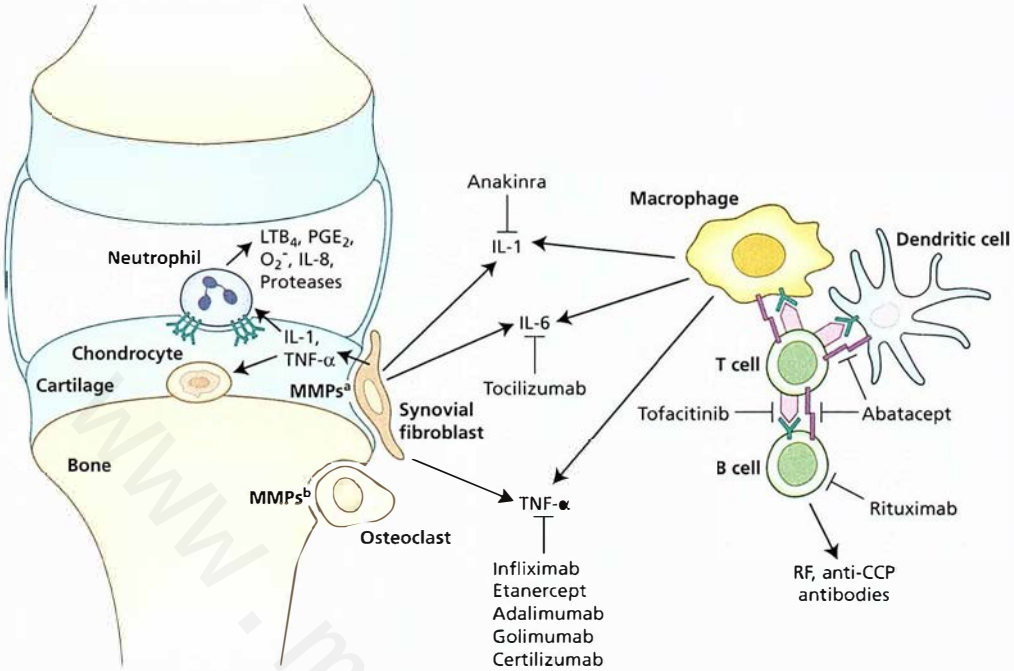

FIGURE 1. Biologic targets in rheumatoid arthritis. Various processes within the rheumatoid joint may be targeted by biologic (and nonbiologic) DMARDs. This figure illustrates the targets of specific biologic agents, described more fully in the text. CCP = cyclic citrullinated peptide; DMARD = disease-modifying antirheumatic drug; IL = interleukin; LTB_4 = leukotriene B_4; MMP = matrix metalloproteinase; O_2 = oxygen; PGE_2 = prostaglandin E_2; RF = rheumatoid factor; TNF = tumor necrosis factor.

[a]Activated synovial fibroblasts secrete MMPs and other enzymes that contribute to the degradation of articular cartilage.

[b]Activated osteoclasts secrete MMPs and other enzymes that contribute to marginal erosions of bone.

CONT.

structural damage in rheumatoid arthritis, most effectively in combination with methotrexate. In psoriasis/psoriatic arthritis, they suppress both cutaneous and articular disease. In ankylosing spondylitis, TNF-α inhibitors improve both axial and peripheral joint symptoms, although radiographic progression of spinal disease may continue. They are also used off-label in uveitis, Behçet syndrome, sarcoidosis, inflammatory bowel disease, and pyoderma syndromes.

Common toxicities include risk of tuberculosis or hepatitis B reactivation as well as fungal (aspergillosis, histoplasmosis, coccidioidomycosis) and bacterial infections. Other potential toxicities include injection site and infusion reactions, leukopenia, induction of autoimmunity (such as drug-induced lupus erythematosus), and heart failure. Rarer toxicities include psoriasiform skin eruption and demyelinating syndromes.

Despite early concerns, overall cancer incidence with use of TNF-α inhibitors does not appear to be increased, with the exception of skin cancer. Nonetheless, TNF-α inhibitors should usually be discontinued if the patient develops any malignancy. In patients with a remote history of malignancy, TNF-α inhibitors have been used cautiously without recurrence in a limited number of patients.

Other Biologic Disease-Modifying Antirheumatic Drugs

Other biologic agents are typically started after failure of one or two TNF-α inhibitors, although some are also approved as first-line therapies.

Abatacept

Abatacept interferes with antigen presentation to T cells and is indicated for moderate to severe rheumatoid arthritis in patients with inadequate response to methotrexate and/or TNF-α inhibition. Abatacept may be administered intravenously or as a subcutaneous injection. Abatacept is associated with increased risk of infection as well as COPD exacerbation. It may also be associated with an increased risk of lymphoma and lung cancer.

Rituximab

Rituximab depletes B cells and is used in combination with methotrexate to treat rheumatoid arthritis in patients who have not adequately responded to a TNF-α inhibitor. Rituximab has recently been shown to be effective in ANCA-associated vasculitis and has been used off-label for SLE and sarcoidosis. Rituximab is administered every 6 months in rheumatoid arthritis or as four weekly infusions for induction of remission in vasculitis. Toxicities include potentially severe infusion reactions; rare cases of progressive multifocal leukoencephalopathy have been reported. Despite depleting B-cell populations, rituximab has not been associated with significant increases in infections.

Tocilizumab

Tocilizumab blocks IL-6 receptors and is used to treat rheumatoid arthritis in patients who have experienced an inadequate response to TNF-α inhibitors. Tocilizumab may be associated

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TABLE 11. Biologic Disease-Modifying Antirheumatic Drugs

Agent	Agent Structure	Target	Indications	Common Monitoring Parameters
Adalimumab	Fully humanized monoclonal antibody	TNF-α	RA; psoriatic arthritis; ankylosing spondylitis; IBD	TB, fungal, and other infections; CBC, serum creatinine, and LCTs at baseline; thereafter every 3-6 months
Etanercept	Soluble p75 TNF-α receptor/IgG Fc segment chimer	TNF-α	RA; psoriatic arthritis; ankylosing spondylitis	TB, fungal, and other infections; CBC, serum creatinine, and LCTs at baseline; thereafter every 3-6 months
Certolizumab pegol	Fab' segment of monoclonal antibody modified by polyethylene glycol strands to reduce immunogenicity	TNF-α	RA; psoriatic arthritis; ankylosing spondylitis	TB, fungal, and other infections; CBC, serum creatinine, and LCTs at baseline; thereafter every 3-6 months
Golimumab	Fully humanized monoclonal antibody	TNF-α	RA; psoriatic arthritis; ankylosing spondylitis	TB, fungal, and other infections; CBC, serum creatinine, and LCTs at baseline; thereafter every 3-6 months
Infliximab	Partially humanized mouse monoclonal antibody	TNF-α	RA; psoriatic arthritis; ankylosing spondylitis; IBD	TB, fungal, and other infections; CBC, serum creatinine, and LCTs at baseline; thereafter every 2-3 months
Abatacept	Soluble CTLA4 receptor/IgG Fc segment chimer	T-cell costimulation	RA	TB, fungal, and other infections; CBC, serum creatinine, and LCTs at baseline; thereafter every 3-6 months
Rituximab	Chimeric (mouse + human) monoclonal antibody	$CD20^+$ B cells	RA; ANCA-associated vasculitis	Infections; IgG levels; CBC, chemistries, and LCTs at baseline and at 2 weeks; thereafter every 3-6 months
Tocilizumab	Humanized monoclonal antibody	IL-6 receptor	RA; JIA; Castleman disease	TB and other infections; CBC, chemistries, and LCTs at baseline and with each infusion or every 2-3 months; lipid profile every 3-6 months
Belimumab	Human monoclonal antibody	BLyS/BAFF	SLE	IgG levels; CBC, chemistries, and LCTs at baseline and 2 weeks; thereafter every 3 months
Tofacitinib	Orally available small molecule agent	JAK	RA	TB and other infections; CBC, chemistries, and LCTs at baseline and every 3 months
Ustekinumab	Human monoclonal antibody	IL-12/IL-23	Psoriasis; psoriatic arthritis	Close monitoring for TB and other infections; CBC, chemistries, and LCTs at baseline and every 3 months
Anakinra	Recombinant receptor antagonist	IL-1β receptor	RA; AOSD; cryopyrin-associated syndromes	CBC at baseline and every 3 months
Rilonacept	Dual IL-1β receptors chimerically attached to IgG Fc segment	IL-1	Cryopyrin-associated syndromes; refractory gout	CBC at baseline and every 3 months
Canakinumab	Fully humanized antibody	IL-1β	Cryopyrin-associated syndromes	CBC at baseline and every 3 months

AOSD = adult-onset Still disease; BAFF = B-cell-activating factor; BLyS = B-lymphocyte stimulator; CBC = complete blood count; IBD = inflammatory bowel disease; IL = interleukin; JAK = Janus kinase; JIA = juvenile idiopathic arthritis; LCTs = liver chemistry tests; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; TB = tuberculosis; TNF = tumor necrosis factor.

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CONT. with elevated liver chemistries, leukopenia, thrombocytopenia, and elevated serum lipid levels. Reactivation of tuberculosis and invasive fungal infections can occur, and rare cases of colon or small bowel perforation have been reported in patients with a history of diverticulitis.

Tofacitinib

Tofacitinib is an oral agent that is FDA approved to treat moderate to severe rheumatoid arthritis in patients who have experienced an inadequate response to methotrexate. In contrast to protein-based biologics, tofacitinib is the first small molecule, specific signal transduction inhibitor to be used in rheumatologic disease and works by inhibiting Janus kinase (JAK) pathway signaling. Tofacitinib may be associated with bone marrow suppression and elevated liver chemistries. Tuberculosis, invasive fungal infections, and bacterial and viral infections can occur. Like tocilizumab, tofacitinib can induce lipid abnormalities and carries a risk of intestinal perforation.

Ustekinumab

Ustekinumab is an anti-IL-12/IL-23 antibody that is FDA approved to treat active psoriatic arthritis and moderate to severe plaque psoriasis. Ustekinumab is administered subcutaneously every 12 weeks. Serious infections are uncommon but have been reported.

Interleukin-1β Inhibitors

Anakinra is FDA approved to treat rheumatoid arthritis but is infrequently used due to limited efficacy. However, anakinra is approved for a cryopyrin-associated periodic fever syndrome (neonatal-onset multisystem inflammatory disease) and is used off-label in similar autoinflammatory syndromes such as Muckle-Wells syndrome, familial cold autoinflammatory syndrome, and adult-onset Still disease. Rilonacept and canakinumab are also beneficial in the treatment of cryopyrin-associated periodic fever syndromes. Anakinra and canakinumab may also be considered for off-label use in severe cases of gout refractory to other therapies.

Belimumab

Belimumab is an anti-BLyS (B lymphocyte stimulator) antibody that is FDA approved to treat active SLE in patients on standard therapy. Belimumab is generally well tolerated, but cytopenias and infection may occur. In one trial, belimumab failed to demonstrate efficacy among black patients with SLE.

KEY POINTS

- Infection risk is elevated with most biologic agents; therapy should be temporarily interrupted during any significant infection.
- Tumor necrosis factor α inhibitors are usually the treatment of first choice for patients with rheumatoid or psoriatic arthritis after inadequate response to nonbiologic disease-modifying antirheumatic drugs.

(Continued)

KEY POINTS *(continued)*

- Other biologic agents are typically started after failure of one or two tumor necrosis factor α inhibitors, although some are also approved as first-line therapies.

Vaccination and Screening in Immunosuppression

Patients with autoimmune diseases are at increased risk for infection, and risk may be significantly increased with the institution of immunosuppressive therapies. Accordingly, patients with rheumatologic disease should be fully vaccinated according to general guidelines; specific recommendations for immunocompromised patients may also apply. Whenever possible, patients should be brought up to date on vaccinations prior to starting immunosuppressive agents because vaccine responses may be diminished when on treatment. Nonetheless, immunosuppressed patients do respond immunologically to vaccines and should not generally be deprived of the opportunity to be vaccinated.

Patients on nonbiologic DMARDs can receive vaccines of all types. Because of a theoretical risk of infection in a higher state of immunosuppression, the use of live attenuated vaccines (for example, herpes zoster vaccine, yellow fever vaccine) is currently contraindicated for patients on biologic therapies. However, such patients may be administered live attenuated vaccines approximately 4 weeks before starting biologic therapy.

Prior to initiating aggressive immunosuppressive therapy, the following recommendations for screening have been suggested:

- Tuberculosis screening with tuberculin skin testing or interferon-γ release assay, particularly for patients initiating most biologic therapies
- Hepatitis B and C serologies, particularly for patients initiating potentially hepatotoxic agents (methotrexate, leflunomide) or TNF-α inhibitor therapy
- HIV screening
- Strongyloidiasis screening if patient is from an endemic area

Patients with latent or active tuberculosis, active hepatitis B, or untreated HIV infection require initiation of infection therapy prior to initiating immunosuppressive therapy. Repeat screening for tuberculosis should be performed annually, with similar repeat screening for hepatitis, HIV, and strongyloidiasis in the presence of ongoing risk.

KEY POINTS

- Whenever possible, patients should be brought up to date on vaccinations prior to starting immunosuppressive therapy.
- Live attenuated vaccines are currently contraindicated for patients on biologic therapies; however, live attenuated vaccines may be administered approximately 4 weeks before starting biologic therapy.

(Continued)

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KEY POINTS *(continued)*

- Prior to initiating aggressive immunosuppressive therapy, screening for infections (tuberculosis, hepatitis B and C, HIV) is indicated; if needed, infection therapy must be started before initiating immunosuppressive therapy.

Urate-Lowering Therapy

The American College of Rheumatology guidelines currently indicate that urate-lowering therapy (ULT) should be initiated in patients with gout who have had two or more attacks within a 1-year period, one attack in the setting of chronic kidney disease of stage 2 or worse, one attack with the presence of tophi visible on examination or imaging, or one attack with a history of urolithiasis. ULT reduces total body uric acid burden; the treatment target is a serum urate level of 6.0 mg/dL (0.35 mmol/L) or less. Over time, urate lowering reduces risk of future gout attacks and promotes regression of tophi. Treatment with ULT is usually life-long.

Anti-inflammatory prophylaxis to prevent gout attacks is recommended when ULT is initiated because of the paradoxical increased risk of acute gout attacks when serum urate levels are rapidly decreased by medication. See Crystal Arthropathies for more information on gout prophylaxis.

Allopurinol

Allopurinol is a first-line agent for serum urate reduction in patients with gout. Allopurinol is a purine analogue that inhibits xanthine oxidase, the final enzyme in the pathway of urate synthesis from purine precursors. Allopurinol is metabolized by the liver and renally excreted; its active metabolite oxypurinol has a half-life of 12 to 17 hours, or longer in patients with kidney disease.

Allopurinol is generally well tolerated and should be initial treatment for patients requiring ULT due to its extensive use history and cost-benefit profile. However, it can very rarely provoke a severe hypersensitivity reaction with fever, lymphadenopathy, widespread erythema, purpura, and skin necrosis and should therefore be discontinued at the first sign of a rash. Allopurinol should be avoided in patients taking other purine analogues such as azathioprine or 6-mercaptopurine because toxic levels of either or both drug may ensue. Patients should be periodically monitored for liver function, kidney function, and complete blood count levels during allopurinol treatment.

Allopurinol is FDA approved for dosing up to 800 mg/d. However, the dose most commonly used in routine practice is 300 mg/d, a dose that is sufficient to achieve the serum urate target in only half the patients treated. Although concern was expressed regarding allopurinol dosing and the risk of hypersensitivity, it appears that gradual dose escalation with careful monitoring is a safe approach, even in patients with kidney disease. The American College of Rheumatology recommends a starting dose of 100 mg/d (50 mg/d in patients with stage 4 or 5 chronic kidney disease) with a urate check and titration upward every 2 to 5 weeks, until a target level of 6.0 mg/dL (0.35 mmol/L) or less is achieved.

Febuxostat

Febuxostat is an alternative first-line therapy for urate lowering. In contrast to the purine analogue allopurinol, febuxostat is a non-purine, non-competitive xanthine oxidase inhibitor that is more specific than allopurinol. Febuxostat is newer and more expensive than allopurinol. It is less likely to cause hypersensitivity reactions and may be used in patients who have had adverse reactions to allopurinol. Febuxostat is excreted via the gastrointestinal tract and kidneys and needs no dose adjustment for patients with mild to moderate chronic kidney disease. Febuxostat should be avoided in patients taking other purine analogues such as azathioprine or 6-mercaptopurine because toxic levels of either or both drug may ensue.

Febuxostat is approved at doses of 40 mg/d or 80 mg/d in the United States and 120 mg/d in Europe. The 40-mg dose is roughly equivalent to 300-mg allopurinol in efficacy, whereas the 80-mg dose is superior to 300-mg allopurinol. To date, studies comparing the efficacy of febuxostat versus higher doses of allopurinol are lacking. Patients should be monitored for liver function during therapy with this agent.

Probenecid

Probenecid is a second-line agent that promotes kidney uric acid excretion (uricosuric effect). Probenecid may also be used in conjunction with a xanthine oxidase inhibitor for synergistic effect. Probenecid has limited efficacy in patients with a creatinine clearance less than 50 mL/min and is relatively contraindicated in patients with kidney stones or hyperuricosuria (indicating uric acid overproduction). Probenecid requires frequent daily dosing and adequate hydration, and it has multiple drug-drug interactions. Kidney function and complete blood count levels should be monitored.

Pegloticase

Humans lack the gene for uricase, which converts uric acid to the more soluble allantoin; therefore, repletion of uricase is a potential strategy for lowering uric acid. Pegloticase is a recombinant pegylated uricase that dramatically lowers serum urate. Pegloticase is indicated for patients with persistent moderate to severe gout who have failed standard ULT. Pegloticase is administered intravenously every 2 weeks; gout flares are common, and infusion reactions may occur. Patients on pegloticase must eschew other ULTs and should have serum urate levels checked before each infusion. Increase of serum urate to greater than 6.0 mg/dL (0.35 mmol/L) suggests failure of the drug due to immunogenicity, which indicates that the patient is at risk for infusion reactions, and requires discontinuation.

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KEY POINTS

- Urate-lowering therapy is indicated for patients with gout who have had two or more attacks within a 1-year period, one attack in the setting of chronic kidney disease of stage 2 or worse, one attack with the presence of tophi visible on examination or imaging, or one attack with a history of urolithiasis.
- Allopurinol and febuxostat are first-line agents for serum urate reduction; allopurinol is less expensive but can rarely cause a severe hypersensitivity reaction and should be discontinued at the first sign of a rash.

Rheumatologic Medications and Pregnancy

Some rheumatologic medications have potentially adverse effects on pregnancy. **Table 12** discusses these agents and their relative risks.

KEY POINTS

- Methotrexate is highly teratogenic and abortifacient and must be discontinued at least 3 months prior to conception.
- Hydroxychloroquine is relatively safe in pregnancy and should not be discontinued.
- Leflunomide is extremely teratogenic and must not be used before/during pregnancy; if leflunomide is inadvertently administered, cholestyramine treatment is required to remove the drug from the body before pregnancy.

Nonpharmacologic and Nontraditional Management

Physical and Occupational Therapy

Physical and occupational therapy are integral to the comprehensive management of many types of arthritis. Physical therapy can help manage pain and functional deficits in arthritis. Overuse injuries related to occupational or recreational activities or loss of strength and flexibility after surgical intervention also respond well to graded exercise. Modalities such as local heat or cold, electrical stimulation, and massage can provide analgesia and may enhance the ability of the patient to exercise.

Occupational therapy refers not only to rehabilitative efforts for enhancing workplace functioning but also to therapy for the hands and upper extremities, including splinting, range of motion exercises, and instruction in joint-sparing techniques.

Complementary and Alternative Medicine

Complementary and alternative medicine (CAM) refers to a diverse group of interventions outside the mainstream of medicine taught in U.S. medical schools. Nearly 40% of Americans use CAM, usually as an adjunct to traditional medical care. Patients with rheumatologic diseases and chronic pain syndromes are more likely to use CAM.

Natural Products

Vitamins, minerals, herbal preparations, and probiotics are labeled as dietary supplements, which permits sale without proof of specific effects or content verification. Although labels on these products commonly make broad statements about particular health benefits, most have not been studied in well-controlled trials.

Glucosamine sulfate and chondroitin sulfate are the most commonly used dietary supplements for arthritis. Earlier trials suggested analgesic benefit, but recent studies have shown little effect on symptoms and/or radiographic disease progression in osteoarthritis, and current guidelines do not recommend their use.

Omega-3 fatty acids present in fish oil inhibit prostaglandin and leukotriene production and reduce inflammation. Clinical trials in rheumatoid arthritis show modest benefit.

Numerous herbal products for arthritis are available over the counter, including ginger, curcumin, bromelain, evening primrose and borage oils, feverfew, willow bark, cat's claw, and *Boswellia*. Although many of these have been shown to have in vitro anti-inflammatory effects, clinical trials are lacking.

Mind-Body Practices

Mind-body practices include tai chi, yoga, acupuncture, meditation, deep-breathing exercises, guided imagery, hypnotherapy, progressive relaxation, and qi gong. Randomized controlled trials support the use of tai chi for reducing pain and enhancing function in patients with osteoarthritis. Some data suggest that yoga may also be beneficial. Acupuncture has been the subject of numerous studies in osteoarthritis, and modest, short-term reductions in pain and improved function have been demonstrated. Few studies have assessed the other modalities.

Role of Surgery

When medications fail to adequately control pain or prevent disability, surgery can be considered. Surgery may be needed acutely or planned electively in chronic circumstances. Osteoarthritis is the most frequent reason for total joint arthroplasty. The knee, hip, and, occasionally, the shoulder are replaced when end-stage joints cause pain at rest or at night or when function is compromised to an unacceptable level. Joint replacements in other locations have less predictable benefit. Arthroscopy is performed primarily for specific indications such as the removal of a loose body or repair of a torn meniscus. Arthroscopy in routine degenerative disease has not been shown to be superior to sham surgery in controlled trials. Arthroscopic synovectomy may be helpful in rheumatoid arthritis when excessive pannus accumulates and does not respond to medical management.

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TABLE 12. Rheumatologic Medications and Pregnancy

Medication/Class	FDA Pregnancy Category[a]	Comments
Anti-Inflammatory Agents		
NSAIDs	Various	May impede implantation and may be associated with a small increased risk of miscarriage when used before 20 weeks' gestation. Use of NSAIDs after 30 weeks' gestation can lead to premature closure of the ductus arteriosus.
Glucocorticoids	Various	In the first trimester, they can increase the risk of cleft palate in the fetus and of gestational diabetes in the mother throughout pregnancy. Nonetheless, they can be useful in the management of active autoimmune disease in pregnancy. Non-fluorinated glucocorticoids (e.g., prednisone, prednisolone, methylprednisolone) have limited ability to cross the placenta and may be preferred, except when treating the fetus (e.g., neonatal lupus erythematosus).
Colchicine	C	Should be used only if the potential benefit justifies the potential risk to the fetus.
Analgesics		
Acetaminophen	B	Generally considered safe at standard dosing, but does cross the placenta.
Opiates	Various	Some opiates/opioids cross the placenta; may cause fetal opioid withdrawal at birth.
Tramadol	C	Should be used only if the potential benefit justifies the potential risk to the fetus; post-marketing reports suggest the possibility of neonatal seizures, withdrawal syndrome, and still birth.
Topical agents	Varies by agent, concentration, and vehicle	Topical use may limit serum levels; individual agents should be reviewed for pregnancy impact prior to use.
Nonbiologic DMARDs		
Methotrexate	X	Highly teratogenic and abortifacient; must be discontinued at least 3 months before pregnancy.
Hydroxychloroquine	C	Despite a C rating, relatively safe in pregnancy and should not be discontinued.
Sulfasalazine	B	Relatively safe during pregnancy.
Leflunomide	X	Extremely teratogenic; must not be used before/during pregnancy; cholestyramine administration is required to remove the drug from the body in all women of childbearing potential upon discontinuation and specifically in those wishing to become pregnant; should be followed up with measurement of leflunomide and its metabolite levels to ensure removal of the drug.
Azathioprine	D	Routine use in pregnancy is not recommended; however, despite a D rating, azathioprine may be safer than some other DMARDs and may be used if an immunosuppressive agent is imperatively needed.
Cyclophosphamide	D	Not used in pregnancy unless absolutely necessary.
Mycophenolate mofetil	D	Teratogenic; should not be used in pregnancy; discontinue for 3 months before attempting pregnancy.
Cyclosporine	C	May be used in pregnancy only if benefits outweigh the risks.
Biologic DMARDs		
TNF-α inhibitors	B	Accumulating retrospective data suggest low risk in pregnancy, but evidence is limited; can be continued if absolutely needed; different agents may have different considerations regarding crossing the placenta.
Ustekinumab, anakinra	B	Should be used only if the potential benefit justifies the undefined risk to the fetus.
Abatacept, rituximab, tocilizumab, belimumab, tofacitinib, rilonacept, canakinumab	C	Should be used only if the potential benefit justifies the potential risk to the fetus; tofacitinib may be teratogenic at high doses.
Urate-Lowering Therapy		
Allopurinol	C	Should be used only if the potential benefit justifies the potential risk to the fetus.
Febuxostat	C	Should be used only if the potential benefit justifies the potential risk to the fetus.
Probenecid	B	No current evidence for adverse impact on pregnancy.
Pegloticase	C	Should be used only if the potential benefit justifies the potential risk to the fetus.

DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor.

[a]See MKSAP 17 General Internal Medicine for information on the FDA pregnancy categories.

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KEY POINTS

- Physical and occupational therapy are integral components of a comprehensive management plan for many types of arthritis.
- When medications fail to adequately control pain or prevent disability, surgery can be considered.

Rheumatoid Arthritis

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder of unknown cause that typically presents as a symmetric inflammatory polyarthritis. Characteristically affected joints include the proximal interphalangeal and metacarpophalangeal joints of the hands and feet and the wrists, but other joints can also be involved. Prolonged morning stiffness is common. RA is also associated with extra-articular manifestations, including inflammation of the skin, eyes, pleura, and pericardium. Early diagnosis and immunomodulation offer the best opportunity to avoid permanent joint damage and multisystem complications.

Epidemiology

RA affects approximately 1% of the population worldwide. Women are affected two to three times more often than men. Onset can occur at any age, with peak incidence between ages 30 and 60 years.

Pathophysiology and Risk Factors

Genetic Factors

The risk of RA is increased in relatives of affected persons, primarily as a result of shared genetic factors. Siblings of those with RA have at least twice the risk of developing RA as unrelated individuals, and offspring of affected persons have about three times the risk. Based on twin studies, the heritability of RA is estimated at 60%, suggesting that genetic factors account for the majority of disease susceptibility within the population.

More than 20 risk alleles have been identified, with the largest contribution coming from genes in the major histocompatibility complex (MHC) region. Alleles encoding the "shared epitope" of the HLA-DRB1 molecule have the strongest association with RA (especially severe articular disease, multisystem disease, and rheumatoid vasculitis). The shared epitope corresponds to a specific amino acid sequence in the antigen-binding site of the MHC molecule, suggesting a possible (but unproven) role in facilitating the presentation of specific but currently unidentified antigens. This association of RA with a gene determining a specific antigen response capacity underscores the relationship of disease to immune dysregulation.

Autoantibodies

Autoantibodies, including rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies, are often present in the peripheral blood and synovial fluid of patients with RA. These autoantibodies typically precede clinical disease by years; their possible role in pathogenesis remains an area of investigation. Although they aid in diagnosis, autoantibodies are neither necessary nor sufficient for diagnosing RA.

Rheumatoid factor, an immunoglobulin directed against the Fc portion of IgG, is associated with increased risk of RA diagnosis as well as erosive and/or more widespread joint disease. However, some patients with RA lack rheumatoid factor, and it is also found in other diseases as well as in healthy persons, limiting its diagnostic specificity.

Anti-CCP antibodies occur less frequently than rheumatoid factor but have more diagnostic specificity. Anti-CCP antibodies are directed against citrullinated proteins, including proteins present in inflamed joint tissues, suggesting that anti-CCP antibodies may play a pathogenic role. Clinically, the presence of anti-CCP antibodies predicts a greater risk of erosive disease and radiographic progression.

Environmental Factors

Several environmental exposures increase the risk of RA in genetically susceptible persons. For individuals carrying the shared epitope, smoking conveys up to a fivefold increase in RA risk (more in the presence of rheumatoid factor or anti-CCP antibodies). Smoking risk may be mediated, in part, by the ability of cigarette smoke to induce protein citrullination in the lungs, which may serve as antigens to drive anti-CCP antibody production.

Occupational exposure to silica or asbestos, as well as occupations involving electrical or carpentry work, has also been associated with increased RA risk.

Infection

Although it has long been hypothesized that infection could trigger RA, no definitive proof of the role of any individual organism exists. Nonetheless, observations about *Porphyromonas gingivalis*, the pathogenic agent in periodontitis, continue to stimulate investigations. The presence of periodontal disease is epidemiologically linked to RA. Furthermore, *P. gingivalis* has the ability to generate citrullinated peptides, suggesting a possible antigenic effect.

More recent studies have focused on a possible role for the intestinal microbiome in promoting immune responses leading to RA.

Hormones

The increased incidence of RA in women is most evident prior to menopause, suggesting a role for sex hormones in the modulation of disease. However, the relationship between RA and hormones is complex. Estrogen levels alone cannot adequately explain the link between gender and RA risk because oral contraceptives and postmenopausal hormone replacement have no predictable effect on disease risk.

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KEY POINTS

- Rheumatoid arthritis typically presents as a symmetric inflammatory polyarthritis affecting small joints and is associated with prolonged morning stiffness and extra-articular manifestations.
- Possible risk factors for rheumatoid arthritis include genetic and environmental factors, autoantibodies, infection, and hormones.

Diagnosis

A careful history, physical examination, and assessment of clinical manifestations are the first steps in the evaluation of a patient with suspected RA. Laboratory and imaging studies are indicated to properly establish the diagnosis. Differential diagnoses, including infection, should be excluded. The American College of Rheumatology classification criteria provide guidelines for identifying patients with RA, with the goal of permitting early diagnosis and management (**Table 13**).

Clinical Manifestations

Patients with RA characteristically present with pain and swelling in multiple (>3) small joints of the hands and/or feet, along with morning stiffness lasting at least 1 hour. Distal interphalangeal joint involvement is distinctly rare. Many patients have 12 or more affected joints. Rarely, only a single joint may be initially involved.

Initial symptoms often worsen gradually over weeks to months; fewer than 10% of patients have an abrupt onset of disease. RA frequently interferes with activities of daily living, including occupational and recreational activities. Constitutional symptoms such as increased fatigue and malaise are common. Depression and myalgia may occur and, less often, fever, anorexia, and weight loss. Musculoskeletal manifestations are listed in **Table 14**.

Physical examination reveals tenderness and swelling of the joints, sometimes with warmth and erythema; symmetric joint involvement is common. Joint symmetry refers to involvement of the same rank of joints on both sides (for example, hand metacarpophalangeal joints), rather than exact

TABLE 13. The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis

Target Population: newly presenting patients	
1) who have at least 1 joint with definite clinical synovitis (swelling)	
2) with synovitis not better explained by another disease (rheumatology consult may be indicated)	
Classification Criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA; score may change over time)	
	Score
A) Joint Involvement (swollen or tender)	
1 large joint (shoulders, elbows, hips, knees, ankles)	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)[a]	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B) Serology (at least 1 test result is needed for classification)	
Negative RF and negative anti-CCP antibodies	0
Low-positive RF or low-positive anti-CCP antibodies (>ULN but ≤3 times ULN)	2
High-positive RF or high-positive anti-CCP antibodies (>3 times ULN)	3
C) Acute Phase Reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D) Duration of Joint Symptoms (by patient self-report)	
<6 weeks	0
≥6 weeks	1

CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis; RF = rheumatoid factor; ULN = upper limit of normal for the laboratory and assay.

[a] "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

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TABLE 14. Musculoskeletal Manifestations of Rheumatoid Arthritis

Feature	Findings	Comments
Joint inflammation	Morning stiffness; joint tenderness; soft-tissue swelling; palpable joint effusion; local warmth; pain on active and passive range of motion	Assess duration of morning stiffness by asking "How long does it take from when you wake up in the morning until you feel as good as you are going to feel for the rest of the day?"
Distribution of joint involvement	Symmetric; initially small joints; progresses proximally to larger joints; commonly involves MCP, PIP, MTP, and wrist joints	DIP joint involvement is uncommon (seen in psoriatic arthritis, osteoarthritis).
Joint damage	Decreased range of motion; contractures; ulnar deviation; subluxation; cervical instability; basilar invagination	Marginal erosions may be evident earliest at the 5th MTP joint. Cartilage degradation causes joint-space narrowing. Ankylosis can occur in long-standing disease.
Periarticular involvement	Bursitis; tenosynovitis; tendinopathy; swan neck and boutonnière deformities; flexion contractures; popliteal (Baker) and ganglion cysts	Olecranon bursitis and rotator cuff tendinopathy are common. Tenosynovitis can cause trigger finger but is less prominent than in spondyloarthritis. Popliteal (Baker) cysts are contiguous with the knee joint.
Muscular weakness	Disuse atrophy; drug-induced myopathy (glucocorticoids and other drugs)	Interosseous and quadriceps muscles are common sites of atrophy from disuse.
Decreased bone quality	Periarticular osteopenia; generalized loss of bone mineral density; increased risk of fracture	Risk of fracture may be underestimated by bone mineral density alone.

DIP = distal interphalangeal; MCP= metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal.

mirroring of involved digits. See **Figure 2** for examples of involvement of the hands in RA.

Because viral and other infections can cause transient symmetric arthritis of small joints, active signs of inflammation for at least 6 weeks should be documented before diagnosis of RA is established.

Laboratory Studies

Laboratory studies, including rheumatoid factor, anti-CCP antibodies, and inflammatory markers, can assist in confirming a diagnosis of RA; however, serologies should never be used as the sole criterion for diagnosis because of limitations in sensitivity and specificity.



FIGURE 2. Involvement of the hands in rheumatoid arthritis. Early rheumatoid arthritis with mild fusiform soft-tissue swelling of the proximal interphalangeal joints (*left panel*). Moderate to severe rheumatoid arthritis with synovitis of the metacarpophalangeal joints and swan neck deformities of the second and third digits (*center panel*). Severe deforming rheumatoid arthritis with ulnar deviation, multiple rheumatoid nodules, and proximal interphalangeal joint subluxations (*right panel*).

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Rheumatoid factor is approximately 70% sensitive for the diagnosis of RA. Approximately 50% of patients with RA have detectable rheumatoid factor at onset, increasing to 60% to 80% in established disease. Conversely, up to 20% of patients with RA lack rheumatoid factor. Moreover, rheumatoid factor occurs in other rheumatologic diseases (Sjögren syndrome, systemic lupus erythematosus, polymyositis, dermatomyositis); cryoglobulinemia due to hepatitis B or C virus infection; primary biliary cirrhosis; subacute bacterial endocarditis; and certain lung diseases (sarcoidosis, B-cell lymphomas). Rheumatoid factor can also be present in healthy persons. Thus, the positive predictive value of rheumatoid factor is poor in populations with a low pretest probability of RA. Testing patients with fibromyalgia, osteoarthritis, or nonspecific aches and pains is therefore not recommended because a positive result is more likely to represent a false positive. Higher titers of rheumatoid factor are more likely to be associated with RA as well as with more severe RA disease, multisystem manifestations, and involvement of more joints. However, fluctuations in rheumatoid factor do not mirror disease activity, and serial testing lacks clinical utility in established disease.

Anti-CCP antibody testing has similar sensitivity but superior specificity compared with rheumatoid factor. Although anti-CCP antibody specificity is reported to be around 95%, anti-CCP antibodies occasionally occur in other rheumatologic diseases, active tuberculosis, and chronic lung disease. The dual presence of rheumatoid factor and anti-CCP antibodies makes a diagnosis of RA substantially more likely. Seronegative RA has an identical clinical appearance as seropositive RA but is more likely to occur in men.

Elevation of inflammatory markers such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) suggests RA disease activity; however, normal levels do not absolutely rule out RA activity.

A normochromic, normocytic anemia and/or thrombocytosis may reflect chronic inflammatory RA disease.

Imaging Studies

More than half of inadequately treated patients with RA develop bone erosions within the first 2 years of disease; therefore, baseline and subsequent radiographs are indicated to aid in the diagnosis and to follow disease progression. Plain radiographs of the hands, wrists, and/or feet may show characteristic findings of periarticular osteopenia and marginal (near the edges of the joint) erosions (**Figure 3**); however, erosive changes may not be evident early in the disease course. The earliest site of RA erosion of the foot is classically at the fifth metatarsophalangeal joint (**Figure 4**). In the presence of long-standing inflammation, relatively uniform joint-space narrowing may occur across the entire affected joint.

Musculoskeletal ultrasonography is increasingly utilized for RA diagnosis and management. It requires specialized training and is operator dependent but is more sensitive than radiography for identifying synovitis and erosions. However, it may not be more specific for RA diagnosis than the standard approach.



FIGURE 3. Hand radiograph showing rheumatoid arthritis. Periarticular osteopenia is present at the metacarpophalangeal joints. Marginal erosions are present at the second proximal interphalangeal and metacarpophalangeal joints, as well as the ulnar styloid. Both are characteristic of rheumatoid arthritis and findings that can aid in diagnosis. Joint-space narrowing (a nonspecific finding) is seen at the second and fifth proximal interphalangeal joints.

MRI is sensitive for identifying erosions, synovitis, and tenosynovitis, but its value in RA diagnosis and management is not established. The American College of Rheumatology Choosing Wisely list questions the utility of routinely ordering MRI of peripheral joints to monitor rheumatoid arthritis. However, MRI can be used in the evaluation of cervical spine involvement if subluxation or myelopathy is suspected.

KEY POINTS

- Patients with rheumatoid arthritis characteristically present with pain and swelling in multiple (>3) small joints of the hands and/or feet and prolonged morning stiffness.
- Rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and inflammatory markers assist in confirming a diagnosis of rheumatoid arthritis; however, serologies should never be used as the sole criterion for diagnosis and should be avoided in patients with low pretest probability for disease due to the high rate of false-positive results. *(Continued)*

HVC

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FIGURE 4. Foot radiograph showing rheumatoid arthritis. Characteristic changes of rheumatoid arthritis are frequently seen in the small joints of the feet, as seen here with severe erosive change at the fifth metatarsophalangeal joint and marginal erosions at the first and second metatarsophalangeal joints and the first interphalangeal joint. Nonspecific cystic changes in bone may be seen in many different forms of arthritis.

KEY POINTS *(continued)*

H/C
- Plain radiography of the hands, wrists, and/or feet is indicated to aid in the diagnosis and to follow progression of rheumatoid arthritis; in contrast, MRI of peripheral joints should not be routinely performed to monitor disease progression.

Complications and Extra-Articular Manifestations

Joints

In the absence of appropriate immunosuppressive therapy, patients can develop increasing numbers of swollen and tender joints, subluxation and malalignment, tenosynovitis and ligamentous laxity, reduced grip strength, loss of range of motion, and loss of function. Permanent joint damage and radiographic abnormalities can occur within the first year.

Skin

RA may affect various organs in addition to joints. The skin is most commonly affected, with rheumatoid nodules being the most frequent manifestation. These firm, subcutaneous masses measure from a few millimeters to several centimeters and may be mobile or adhere to the underlying periosteum. Rheumatoid nodules occur alone or in clusters, often on pressure areas such as the elbows, finger joints, ischial and sacral prominences, occiput, and Achilles tendons (see Figure 2). Although usually in periarticular locations on extensor surfaces, they may appear in any location, including the lungs, heart, and muscle.

Pyoderma gangrenosum is also seen in RA. It usually occurs as a single painful lesion on the lower extremities, beginning as a tender erythematous or violaceous papule and rapidly expanding into a purulent, necrotic, nonhealing ulcer (see MKSAP 17 Dermatology, Cutaneous Manifestations of Internal Disease).

Rheumatoid vasculitis is a late complication of RA that affects small and medium vessels and may involve the skin and other organs. It is most common in seropositive male patients with long-standing disease. Small-vessel involvement presents as purpura, petechiae, splinter hemorrhages, nailfold infarctions, and peripheral neuropathy. In medium-vessel disease, nodules, ulcerations, livedo reticularis, and digital infarcts can occur.

Eyes

The most common eye manifestation of RA is keratoconjunctivitis sicca, as is also seen in Sjögren syndrome and systemic lupus erythematosus. Episcleritis occurs with more severe RA disease activity, appears acutely, and causes eye redness and pain; changes in vision rarely occur. Scleritis, uveitis, ulcerative keratitis, and corneal filamentary keratitis also occur during more severe disease and may lead to visual impairment. See Eye Disorders in MKSAP 17 General Internal Medicine for more information.

Pulmonary Involvement

Pleuritis is the most common RA pulmonary manifestation but is frequently asymptomatic. Exudative pleural effusions may occur. Rheumatoid nodules in the lungs can be difficult to diagnose because they are often peripheral in location and usually measure less than 1 cm in diameter. Interstitial lung disease occurs in up to 10% of patients, particularly in male smokers with long-standing, seropositive disease.

Cardiac Involvement

RA is an independent risk factor for both coronary artery disease and heart failure; patients with severe extra-articular disease are at particularly increased risk of cardiovascular death. Pericarditis is common but is often asymptomatic. Rarely, pericarditis is severe, unresponsive to glucocorticoids, and may be restrictive. Successful treatment with disease-modifying agents appears to reduce cardiac comorbidity.

Other Complications

Felty syndrome is a rare complication occurring in patients with severe, erosive, seropositive, long-standing RA. Felty

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syndrome is characterized by neutropenia (absolute neutrophil count <2000/μL [2.0 × 10^9/L]) and splenomegaly, often accompanied by fever, anemia, thrombocytopenia, and/or vasculitis, and can predispose to recurrent bacterial infections. Felty syndrome has limited responsiveness to disease-modifying drugs and may require use of granulocyte colony-stimulating factor.

Unusual complications of long-standing, severe RA include mesangioproliferative glomerulonephritis, amyloidosis, atlantoaxial subluxation due to erosion of the odontoid process, and peripheral neuropathy.

KEY POINTS

- Extra-articular manifestations of rheumatoid arthritis include rheumatoid nodules, rheumatoid vasculitis, keratoconjunctivitis sicca, pleuritis, and pericarditis.
- Rheumatoid arthritis is an independent risk factor for coronary artery disease and heart failure; patients with severe extra-articular disease are at particularly increased risk of cardiovascular death.

Management

General Considerations

RA management often requires a team approach to comprehensively provide optimal care of the joints and other organs and to address psychosocial needs. The American College of Rheumatology treatment recommendations for early and established RA are presented in **Figure 5** and **Figure 6**, respectively.

Once a diagnosis of RA is established, management with disease-modifying antirheumatic drugs (DMARDs) is mandated to minimize damage and reduce disability. The initial goal of treatment is to rapidly reduce disease activity, but the ultimate goal is remission (absence of signs and symptoms of significant inflammatory activity). This "treat-to-target" approach requires treatment protocols and regular follow-up visits to reassess clinical status and response to changes in medication. Therapy is advanced at each follow-up visit until the therapeutic target is reached. The usual interval of follow-up is every 2 to 3 months to reassess whether goals are being met and toxicity is present. Patients may be seen by rheumatologists more frequently if disease activity is high or less often (for example, every 6 to 12 months) if remission has been achieved. In long-standing refractory disease, low disease activity may be an acceptable alternative target, and response-limiting factors such as the presence of structural damage, functional impairment, medical comorbidities, drug side-effect risks, and other individual patient-related factors must be taken into account.

Disease activity is assessed based on history, physical examination, and the use of composite disease activity scores that incorporate findings such as the number of tender or swollen joints and laboratory studies such as ESR or CRP. Composite scores provide a more comprehensive and standardized assessment that can account for variability between patients and within the course of disease for a single patient. Furthermore, treatment targets can be expressed as a single number facilitating comparisons over time. In clinical trials, the most

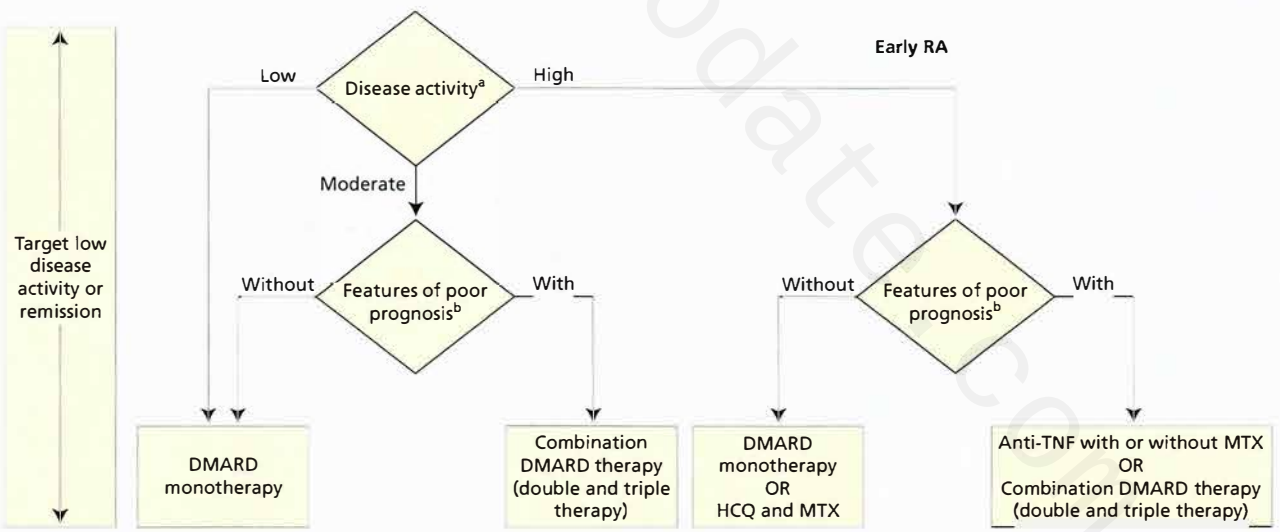

FIGURE 5. 2012 American College of Rheumatology recommendations update for the treatment of early rheumatoid arthritis, defined as a disease duration <6 months. DMARDs include hydroxychloroquine, leflunomide, methotrexate, minocycline, and sulfasalazine. DMARD = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; MTX = methotrexate; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

[a]Definitions of disease activity are available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658) and were categorized as low, moderate, or high.

[b]Patients were categorized based on the presence or absence of 1 or more of the following poor prognostic features: functional limitation (e.g., Health Assessment Questionnaire score or similar valid tools), extra-articular disease (e.g., presence of rheumatoid nodules, RA vasculitis, Felty syndrome), positive rheumatoid factor or anti-cyclic citrullinated peptide antibodies, and bony erosions by radiograph.

Adapted with permission from John Wiley & Sons, from Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64(5):625-639. [PMID: 22473917] Copyright 2012 American College of Rheumatology.

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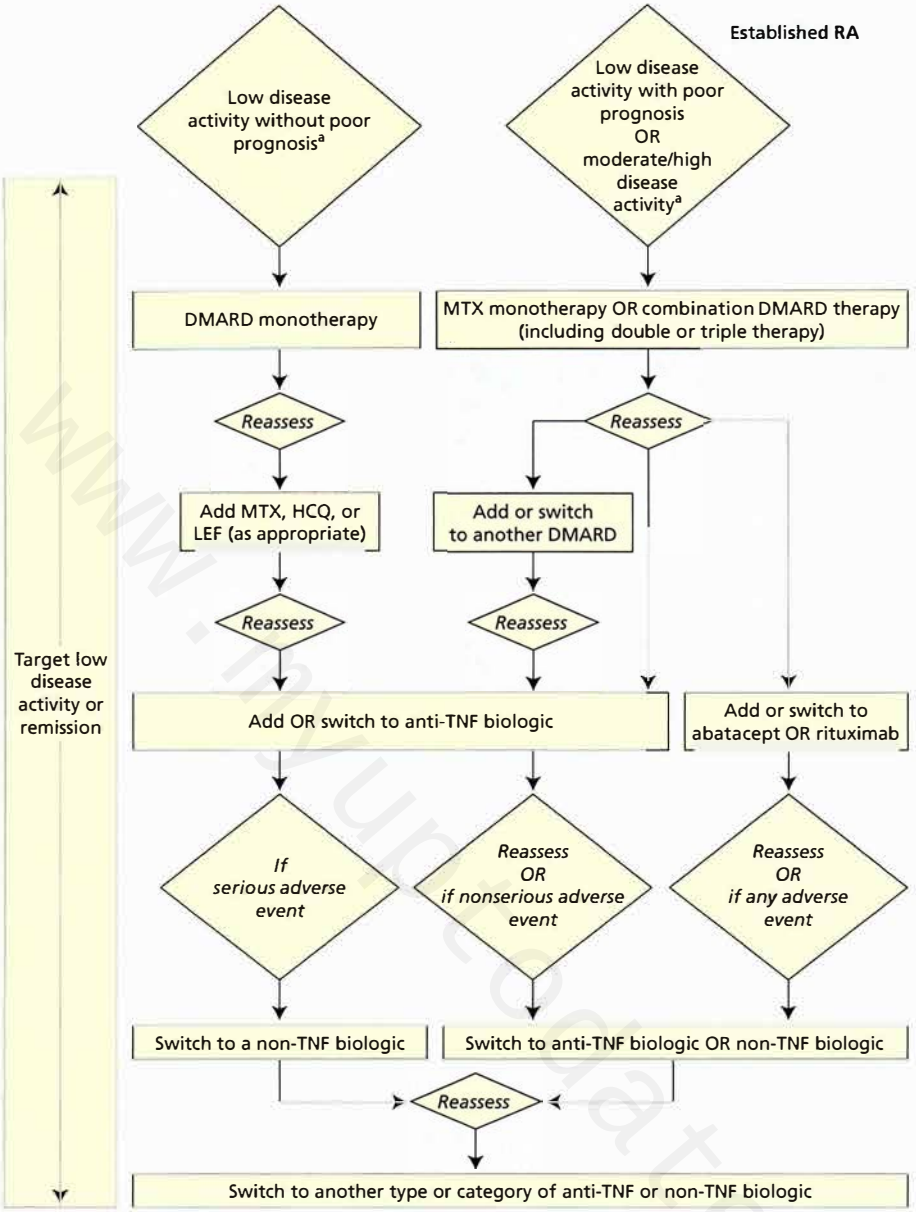

FIGURE 6. 2012 American College of Rheumatology (ACR) recommendations update for the treatment of established rheumatoid arthritis (RA), defined as a disease duration >6 months or meeting the 1987 ACR classification criteria. Depending on a patient's current medication regimen, the management algorithm may begin at an appropriate rectangle in the figure, rather than only at the top of the figure. DMARDs include HCQ, LEF, MTX, minocycline, and sulfasalazine (therapies are listed alphabetically; azathioprine and cyclosporine were considered but not included). DMARD monotherapy refers to treatment in most instances with HCQ, LEF, MTX, or sulfasalazine; in few instances, where appropriate, minocycline may also be used. Anti-TNF biologics include adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab. Non-TNF biologics include abatacept, rituximab, or tocilizumab (therapies are listed alphabetically). DMARD = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

[a]Definitions of disease activity are available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658) and were categorized as low, moderate, or high. Features of poor prognosis included the presence of 1 or more of the following: functional limitation (e.g., Health Assessment Questionnaire score or similar valid tools), extra-articular disease (e.g., presence of rheumatoid nodules, RA vasculitis, Felty syndrome), positive rheumatoid factor or anti-cyclic citrullinated peptide antibodies, and bony erosions by radiograph.

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frequently used disease assessment instrument has been the Disease Activity Score 28 (DAS28), which incorporates the number of tender and swollen joints out of a predetermined set of 28 joints, a weighted ESR or CRP, and a global health assessment. An example of low disease activity based on DAS is ≥2.6 to <3.2 (see Figure 5), and high disease activity based on DAS is >5.1 (see Figure 6). Other disease activity scales to determine the appropriate level of treatment are available.

Patient education is fundamental to managing RA and includes discussing medications and side effects, advising on

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lifestyle choices (diet, weight loss, exercise), and assessing psychosocial needs. Physical and occupational therapy may be appropriate throughout the course of RA. Appropriate exercise can strengthen and protect joints and is an important adjunct in combating fatigue and optimizing function. Smoking cessation is important not only because of its link to disease risk, but also because continued smoking may impair the response to therapy and exacerbate rheumatoid lung disease.

Disease-Modifying Antirheumatic Drugs

Principles, toxicities, baseline evaluation and monitoring, use of vaccinations, and pregnancy issues associated with medications used in RA are discussed in Principles of Therapeutics.

Nonbiologic Disease-Modifying Antirheumatic Drugs

Methotrexate is the recommended initial DMARD for most patients with RA and is appropriate at disease onset as well as in patients whose disease is well established. It is generally continued indefinitely and can be used alone or in combination with biologic DMARDs. Methotrexate is usually well tolerated and has good efficacy, high long-term compliance rates, and relatively low cost but requires regular monitoring. Methotrexate or another nonbiologic DMARD should be tried before initiating therapy with a considerably more expensive biologic DMARD. Generally, the dose of methotrexate is titrated up until the treatment target is achieved. If the response is below target at an oral dose of 25 mg weekly, clinicians may switch to parenteral administration since absorption and efficacy may improve. However, if toxicity or lack of efficacy is encountered at this dose, the use of a biologic agent is indicated.

Hydroxychloroquine and sulfasalazine have long-acting effects and may be used alone, together, or in combination with methotrexate. Triple therapy with these three agents has a reasonable side-effect profile and can be highly efficacious in symptom control and in reducing the risk of structural damage.

Leflunomide may be used with or as a substitute for methotrexate. It is appropriate as a first choice in the treatment of RA or as an alternative to methotrexate if side effects or other considerations limit methotrexate use.

Biologic Disease-Modifying Antirheumatic Drugs

The decision to add a biologic agent should be made based on inadequate response to a nonbiologic DMARD (especially methotrexate) while balancing the patient-specific risks of biologic therapy. Biologic agents are commonly added to methotrexate but are not used in combination with other biologics because of an unacceptable increase in infection without added efficacy.

Tumor necrosis factor (TNF)-α inhibitors are the most widely used biologic agents for RA and are available in both intravenous and subcutaneously administered injections. All TNF-α inhibitors interfere with the actions of TNF-α, a major proinflammatory cytokine in RA pathogenesis. TNF-α stimulates synovial cell proliferation and synthesis of collagenase, leading to cartilage degradation. In addition, TNF-α increases bone resorption, inhibits proteoglycan synthesis, and increases expression of adhesion molecules, thus enhancing inflammatory cell recruitment as well as production of additional proinflammatory cytokines and arachidonic acid metabolites.

TNF-α inhibitors are highly effective for treating RA, leading to rapid (weeks), significant improvement in signs and symptoms for most patients. Their use is associated with increased likelihood of achieving remission in both new-onset and established disease, reduction in radiographic progression, normalization of acute phase reactants, and reduced cardiovascular risk. Their efficacy is enhanced when used in combination with methotrexate.

Other biologic agents target other proinflammatory cytokines and pathways. Tocilzumab is a monoclonal antibody that neutralizes IL-6, a cytokine that activates T cells, B cells, macrophages, osteoclasts, and the hepatic acute phase response. Abatacept blocks necessary second signals between antigen-presenting cells and T cells during antigen presentation, thereby blocking T-cell activation. Rituximab is a monoclonal antibody that depletes B-cell populations, leading to a reduction in B-cell cytokine production, B-cell help for T-cell activation, and the production of a number of autoantibodies, including rheumatoid factor and anti-CCP antibodies. All of these agents have efficacy similar to TNF-α inhibitors.

Tofacitinib is a new oral agent and the first small molecule therapy for RA that specifically targets an intracellular signaling molecule in immune/inflammatory pathways. Tofacitinib inhibits Janus-associated kinases, which signal in response to membrane cytokine receptors to activate STATs (signal transducers and activators of transcription). Tofacitinib appears to have efficacy similar to biologic agents.

Glucocorticoids

Oral or intra-articular glucocorticoids are used as adjunctive therapy in RA. Glucocorticoids act rapidly to control inflammation and joint symptoms and can be useful until slower-acting DMARDs achieve full effect. Glucocorticoids are also used to manage intermittent flares in patients already taking other agents. Regular, frequent use of glucocorticoids should signal the need for increasing the DMARD dose or adding/switching DMARDs. Given their many side effects, glucocorticoids should be employed at the lowest dose and shortest period possible and should never be used as standing monotherapy.

NSAIDs

NSAIDs can ameliorate RA joint symptoms. However, NSAIDs lack disease-modifying activity, do not alter the destructive course of untreated RA, and should never be used as monotherapy.

Surgical Therapy

Surgical interventions are available to patients with RA complications or advanced disease unresponsive to pharmacologic therapy. Large joint (hip, knee) replacement is an option for

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CONT. intractable disease unresponsive to medical management. Patients with pain at rest or night pain are particularly appropriate for total joint replacement. Patients with RA have a higher risk of prosthetic joint infection than patients having total joint arthroplasty for other indications. Repair procedures for tendon ruptures and rotator cuff disease are occasionally needed. Degenerative disk disease may be accelerated in the presence of RA, and spinal procedures such as laminectomy may be indicated. Improvements in pharmacologic management have made surgical approaches to RA increasingly uncommon.

Patients with RA undergoing general anesthesia for any kind of surgery should have cervical spine radiography with flexion and extension views to assess for atlantoaxial subluxation, which rarely can lead to neurologic compromise when the neck is extended during intubation.

KEY POINTS

- Methotrexate is the recommended initial disease-modifying antirheumatic drug for most patients with rheumatoid arthritis.
- The use of tumor necrosis factor α inhibitors or other biologic agents in patients with rheumatoid arthritis can achieve remission in new-onset and established disease, reduce risk of radiographic progression, normalize acute phase reactants, and reduce cardiovascular risk.

Pregnancy and Rheumatoid Arthritis

Nulliparity has been suggested as a risk factor for RA, but data are conflicting. During pregnancy, patients with RA may experience relative disease quiescence, but disease may flare postpartum. There is also evidence that the incidence of RA is increased in the year after delivery, particularly after the first pregnancy. Breastfeeding may decrease the risk.

Methotrexate and leflunomide are absolutely contraindicated in pregnancy and must be discontinued prior to conception. Limited case studies suggest that use of TNF-α inhibitors during pregnancy may be safe, but a relationship to rare birth defects has been raised by a single report. Decisions regarding the use of any biologic agent in pregnancy should incorporate risk-benefit analysis. Both hydroxychloroquine and sulfasalazine are considered relatively safe in pregnancy. Non-fluorinated glucocorticoids such as prednisone, prednisolone, or methylprednisolone have limited ability to cross the placenta and may be preferred. NSAIDs may impede implantation and may be associated with a small increased risk of miscarriage when used prior to 20 weeks' gestation. Use of NSAIDs after 30 weeks' gestation can lead to premature closure of the ductus arteriosus.

See Rheumatologic Disease and Pregnancy in Principles of Therapeutics for more information on these and other medications and their role in pregnancy.

KEY POINTS

- Methotrexate and leflunomide are absolutely contraindicated in pregnancy and must be discontinued prior to conception.
- Both hydroxychloroquine and sulfasalazine are considered relatively safe in pregnancy.

Osteoarthritis

Introduction

Osteoarthritis (OA) is characterized by loss of cartilage accompanied by reactive bony changes, including osteophyte formation, subchondral bony sclerosis, and subchondral cysts. OA typically affects the knees, hips, hands, spine, and feet. Pain and loss of function are the hallmark features; however, OA is variable in its clinical presentation, which can range from asymptomatic radiographic changes to severe and disabling pain and permanent impairment and deformity.

Epidemiology

OA is the most common form of arthritis, affecting at least 30 million persons in the United States. Prevalence increases with age; OA among younger populations is frequently related to a history of recreational or occupational injury in a specific joint or to a strong genetic predisposition. Whereas early OA is slightly more common in men, at older ages women are slightly more frequently affected. Overall, radiographic knee OA is present in about 35% of adults over the age of 60, and radiographic hand OA is present in 55% to 65%. OA is the most common cause of disability in patients over age 65.

Pathophysiology

OA is the consequence of biomechanical and biochemical processes involving the cartilage, synovium, bone, and soft tissues surrounding the joint. These processes can be initiated by a single traumatic event, repeated microtrauma, or genetic, metabolic, or systemic factors affecting the integrity of cartilage. During OA progression, matrix metalloproteinases (MMPs), including collagenase, stromelysin, and gelatinase, are secreted by chondrocytes and degrade cartilage collagen. Inappropriately low levels of tissue inhibitors of metalloproteinases (TIMPs) may reduce the ability of cartilage to resist MMPs.

Inflammatory cytokines such as interleukin (IL)-1β may induce MMP production and suppress collagen production. Ineffective repair responses within the joint may be mediated by insulin-like growth factor and transforming growth factor β,

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leading to abnormal bone growth, including osteophyte formation and subchondral sclerosis.

Risk Factors

Risk factors for OA include advanced age, female gender, obesity, and joint injury caused by repetitive use, trauma, or certain occupations. Joint malalignment, ligamentous laxity, meniscal injury, or surgical meniscectomy can accelerate the onset of OA, as can quadriceps weakness and defects in proprioception, all resulting in abnormal joint forces. Family history may indicate risk; a multitude of genetic variants has been associated with various OA subsets, but no single gene has emerged as definitively predicting onset or severity.

OA risk varies depending on the joint involved. The lifetime risk for symptomatic knee OA is approximately 45%, with a higher risk after job- or sports-related injury or overuse or among those who are obese. Lifetime risk of symptomatic hip OA is approximately 27%, is higher in women, and is less strongly related to obesity and trauma compared with knee OA. Hand OA risk is increased on the basis of genetic predisposition and is more common in women. Manual labor and obesity confer additional risk for hand OA.

KEY POINTS

- Osteoarthritis is characterized by loss of cartilage and the presence of osteophytes, subchondral bony sclerosis, and subchondral cysts.
- Risk factors for osteoarthritis include advanced age, female gender, obesity, and acute or chronic joint injury.

Classification

Primary Osteoarthritis

Primary (idiopathic) OA constitutes most cases of OA, which are designated as such when no specific antecedent event or predisposing disease is present. The designation of primary OA does not exclude the impact of routine factors such as obesity, aging, or a chronic history of significant but non-injurious joint use. Primary OA typically affects the knees, hips, hands, spine, and feet and may be localized (a single or few joints) or generalized (multiple joints). It typically becomes clinically evident around the age of 55 years.

Erosive Osteoarthritis

Erosive OA is a subset of primary OA in which radiographic erosions are seen. Erosive OA typically involves the interphalangeal joints of the fingers and is associated with intermittent flares of swelling and redness of the affected joints. Diagnosis is radiographic, based on the presence of central erosions (contrasting with the marginal erosions of rheumatoid and psoriatic arthritis) and collapse of the subchondral bone in the affected joints. Patients with erosive OA are more likely to have pain and disability than those without erosive features. In contrast to rheumatoid arthritis, erosive OA is common in the distal interphalangeal joints, does not typically affect the wrists or elbows, and is not associated with rheumatoid factor, anti-cyclic citrullinated peptide antibodies, or an elevated erythrocyte sedimentation rate or C-reactive protein level.

Prevalence of erosive OA is approximately 3% in the general population over the age of 55 years and 10% among those with any symptomatic hand OA. Men and women are equally affected.

Secondary Osteoarthritis

Secondary OA indicates joint degeneration in the setting of preexisting joint abnormality. It may occur in the setting of trauma or congenital anatomic abnormalities (such as hip dysplasia). Secondary OA may follow inflammatory arthritis (such as rheumatoid or gouty arthritis or calcium pyrophosphate deposition), avascular necrosis, infectious arthritis, Paget disease, osteopetrosis (congenitally increased bone mass and skeletal fragility), or osteochondritis dissecans (in which a portion of bone and cartilage separates from the surrounding bone). Finally, secondary OA may occur in the setting of metabolic or systemic diseases such as hemochromatosis (iron overload, which is associated with a characteristic OA pattern involving the second and third metacarpophalangeal joints and is diagnosed with the aid of transferrin saturation measurement), ochronosis (excessive accumulation of homogentisic acid), Gaucher disease, hemoglobinopathy, or Ehlers-Danlos syndrome.

Diffuse Idiopathic Skeletal Hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH) is often considered in the same context as OA by virtue of its lack of systemic inflammation, the presence of characteristic bony remodeling changes, a similar epidemiology, and its frequent coexpression with OA. DISH is diagnosed on plain radiograph by the presence of flowing osteophytes involving the anterolateral aspect of four or more contiguous vertebrae most easily detected in the thoracic spine (**Figure 7**). Intervertebral disk spaces are typically preserved; apophyseal or sacroiliac joint inflammatory changes are absent. Peripheral enthesitis and ossification of ligaments in nonvertebral locations may occur. DISH is distinguished from primary OA of the spine (with which it may co-occur) by the manner in which the flowing osteophytes bridge the vertebrae, by its anatomic location, and by the relative preservation of the disk spaces when OA is absent. Complications include dysphagia, unstable spinal fractures, spinal stenosis, postsurgical heterotropic ossifications, difficult intubation, difficult gastroscopy, aspiration pneumonia, and myelopathy. Radiographically, DISH may be difficult to differentiate from ankylosing spondylitis (see Spondyloarthritis).

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FIGURE 7. Diffuse idiopathic skeletal hyperostosis. This disorder is characterized by calcification of the enthesis regions (where the tendons or ligaments insert into bone) and the spinal ligaments. The diagnosis is confirmed on radiograph by the presence of flowing osteophytes along the anterolateral aspect of at least four contiguous vertebral bodies (most easily detected in the thoracic spine), preserved vertebral height, and absent findings typical for ankylosing spondylitis.

The prevalence of DISH increases with age and is approximately 15% in patients over 50 years of age. In contrast to OA, DISH is twice as common in men than in women.

KEY POINTS

- Primary osteoarthritis (OA) constitutes most cases of OA, which are designated as such when no clear antecedent event or predisposing disease is present.
- Erosive hand osteoarthritis is associated with intermittent flares of swelling and redness of the affected joints as well as the presence of central erosions and collapse of subchondral bone in the interphalangeal joints as seen on plain radiographs.
- Secondary osteoarthritis can occur in settings of trauma and metabolic or systemic disease or following joint damage from inflammatory or infectious arthritis.
- Diffuse idiopathic skeletal hyperostosis is characterized by flowing osteophytes involving the anterolateral aspect of four or more contiguous vertebrae most easily detected in the thoracic spine.

Diagnosis

Clinical Manifestations

A thorough history and physical examination are warranted in the initial evaluation of the patient with suspected OA. Patients with symptomatic OA describe pain and stiffness in the affected joint(s). Pain may occur intermittently and be associated with joint use. Patients often report a decline in function associated with the pain. Stiffness may worsen with rest and improve with activity, but typically lasts for only brief periods (less than 30 minutes).

On physical examination, affected joints may be tender, or the patient may report discomfort only when the joint is put through a range of motion (often reduced due to pain and/or deformity). Joint effusions may occur; erythema and warmth are less common than in inflammatory arthritis. More advanced disease may be accompanied by change in the physical appearance of the joints, manifesting as bony enlargement and/or changes in alignment. The most commonly affected joints are the first carpometacarpal and distal and proximal interphalangeal joints of the hands, knees, hips, and apophyseal joints of the spine.

Hand OA typically presents with pain, aching, or stiffness for most days of the prior month. Bony enlargement of a distal interphalangeal joint is termed a Heberden node (**Figure 8**); similar enlargement in a proximal interphalangeal joint is termed a Bouchard node. Occasionally, an individual joint in the hand may be swollen or erythematous (inflammatory or erosive OA), but the presence of multiple swollen joints, particularly proximal joints, should lead to consideration of concomitant calcium pyrophosphate deposition or rheumatoid or psoriatic arthritis.

Diagnosis of knee or hip OA is established in the presence of knee or groin pain for most days of the prior month. Hip involvement can occasionally result in referred pain that is perceived by the patient as knee pain. Crepitus on active joint



FIGURE 8. Heberden nodes in osteoarthritis are bony spurs at the dorsolateral and medial aspects of the distal interphalangeal joints.

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motion, limited range of motion, and morning stiffness lasting less than 30 minutes are typical. Bony enlargement of the knee is common. Knee effusions, which are usually cool, are also common. Chronic effusions may be associated with the formation of popliteal fossa fluid collections (Baker cysts). Knee malalignment is common and may result in a "knocked knee" or "bow-legged" appearance. Long-standing knee OA is associated with quadriceps muscle atrophy.

OA of the spine is a common source of back pain and is often seen in association with degenerative disk disease. Physical examination may demonstrate reduced range of motion and associated muscle spasm; spinal tenderness is rarely present.

Laboratory and Imaging Studies

No specific laboratory abnormalities are associated with primary OA. In most cases, laboratory studies are indicated only when needed to rule out other diagnoses. If NSAID use is contemplated, it is appropriate to first evaluate kidney function. Although arthrocentesis is not mandatory for diagnosing OA, synovial fluid examination should be considered if needed to help rule out inflammatory arthritis (rheumatoid arthritis, crystal-induced disease), hemarthrosis, or infection. Noninflammatory synovial fluid (leukocyte count <2000/μL [2.0×10^9/L]) is typical of OA.

Joint-space narrowing (articular cartilage loss), subchondral sclerosis, and marginal osteophyte formation are the radiographic hallmarks of OA (**Figure 9**); periarticular osteopenia and marginal erosions (as seen in rheumatoid arthritis) are absent. In OA of the knee and hip, joint-space narrowing characteristically occurs mainly on the weight-bearing areas of the joint, distinguishing it from inflammatory arthritis (**Figure 10**). Subchondral sclerosis is seen on plain radiographs as increased bone density subjacent to joint-space narrowing. Both subchondral sclerosis and osteophytes reflect reaction of bone to growth factors stimulated by the mechanical changes driving OA. In erosive hand OA, central erosions are visible on radiograph. However, plain radiography is insensitive for the detection of early OA, and OA severity on plain radiographs is inconsistently associated with pain and other symptoms.

MRI and ultrasonography are currently being investigated as potential tools in OA diagnosis and management.



FIGURE 9. Plain radiograph of hand osteoarthritis showing joint-space narrowing, subchondral sclerosis, and osteophyte formation involving the distal interphalangeal and proximal interphalangeal joints.



FIGURE 10. Plain radiograph of knee medial compartment osteoarthritis showing joint-space narrowing and subchondral sclerosis (*arrow*).

Differential Diagnosis

Polyarthritis of the proximal hand digits may warrant exclusion of rheumatoid arthritis because both OA and rheumatoid arthritis can affect these joints. Whereas rheumatoid arthritis rarely, if ever, affects the distal interphalangeal joints, psoriatic arthritis may affect both proximal and distal joints, but tends to affect these joints more globally than OA. The presence of extensive inflammation and/or morning stiffness, a positive rheumatoid factor, anti–cyclic citrullinated peptide antibodies, elevated erythrocyte sedimentation rate or C-reactive protein, anemia of chronic disease or thrombocytosis without other explanation, or inflammatory synovial fluid also favor the diagnosis of rheumatoid arthritis.

Calcium pyrophosphate deposition can co-occur with OA, may be related to severe presentations of OA, and can promote inflammation that is difficult to distinguish from rheumatoid arthritis when metacarpophalangeal joint and wrist involvement is present. It can be a cause of acute monoarticular or oligoarticular arthritis, particularly in the knee. Joints may be chronically painful or abruptly warm and swollen, and large knee effusions can result.

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KEY POINTS

HVC

- Laboratory studies are indicated only when needed to rule out other diagnoses in patients with primary osteoarthritis (OA); the diagnostic role for MRI and ultrasonography in OA has not been established.
- Joint-space narrowing, subchondral sclerosis, and marginal osteophyte formation are the radiographic hallmarks of osteoarthritis; periarticular osteopenia and marginal erosions (as seen in rheumatoid arthritis) are absent.
- Polyarthritis of the proximal hand digits may warrant exclusion of rheumatoid arthritis because both osteoarthritis and rheumatoid arthritis can affect these joints.

Management

OA management requires a comprehensive, individualized evaluation of symptoms, level of functioning, and patient expectations. Because no single intervention addresses all of the ways in which OA can impact quality of life, a multidisciplinary perspective promotes the best patient outcomes.

Nonpharmacologic Therapy

Exercise (aquatic or land based) is among the most important nonpharmacologic treatments for most patients with OA. Exercise prescriptions should first address acutely symptomatic joints, targeting rehabilitation within the physical capabilities of the patient. Exercise should be repeated regularly and should not overuse the joints or exacerbate symptoms. Exercise should be advanced as the patient improves and can include strengthening, stretching, range of motion, and aerobic activity. Although a physical or occupational therapist is often useful initially and can also provide thermal agents and manual therapy, the goal is to assist patients in incorporating exercise into their daily self-management routine.

Evidence for the efficacy of exercise is most convincing for knee OA. Because excessive weight contributes to both knee OA risk and symptomatology, measures to promote weight loss (exercise, food diaries, support groups, meal planning, nutritional counseling, portion size regulation, evaluation of psychosocial factors and coping strategies) are usually appropriate for overweight patients with knee OA. Obese patients undergoing bariatric surgery may experience reduction in knee OA symptoms.

Properly fitting footwear and/or orthotics can improve ambulation among patients with OA of the feet, ankles, knees, hips, and/or spine. Assistive devices such as canes and walkers can reduce lower extremity symptoms and may permit delay or deferral of surgical intervention. Canes should be held on the side opposite from the affected joint. Short-term use of splints (for example, thumb spica), cushions, and ergonomic supports (for example, in vehicles and at desks and workstations), as well as the use of grab bars and other specialized equipment in bathrooms, can relieve symptoms and enhance functioning. Chronic bracing can be used for severely affected joints that may be unstable, particularly when patients are poor candidates for surgery.

Pharmacologic Therapy

Because no disease-modifying agents are currently available for the treatment of OA, pharmacologic options address the symptoms of OA rather than its underlying cause. Most treatment guidelines suggest the initial use of acetaminophen for pain control, with recognition of potential hepatotoxicity leading to some recommendations limiting the total daily dose to approximately ≤3 g/d. If acetaminophen proves inadequate, an over-the-counter or prescription NSAID should be used. NSAIDs are available in oral, topical, and intravenous forms. Oral preparations are usually first-line NSAID therapy in patients without a contraindication to treatment due to efficacy and cost-effectiveness. Topical NSAIDs are considered to provide similar pain relief OA as oral medications with fewer gastrointestinal effects. Furthermore, the American College of Rheumatology currently recommends topical NSAIDs rather than oral NSAIDs for patients aged 75 years or older. However, they are associated with more skin reactions and are significantly more expensive than oral NSAIDs. NSAIDs can be also be used in combination with acetaminophen. Treatment guidelines suggest using the lowest effective NSAID dose for the shortest time period in order to reduce risk of side effects. However, many patients with OA require years of NSAID use given the prolonged timeframe over which the disease is symptomatic and the limited number of pharmacologic alternatives.

Tramadol is a centrally acting opioid analgesic that weakly inhibits norepinephrine-serotonin reuptake; potential for addiction is lower than for traditional opioids. Tramadol may be useful for managing OA pain when acetaminophen or NSAIDs are ineffective or contraindicated (for example, patients with a history of bleeding peptic ulcer, heart failure, or chronic kidney disease).

Duloxetine is a dual serotonin-norepinephrine reuptake inhibitor indicated for chronic musculoskeletal pain, including pain due to OA. Duloxetine may be used as an adjunct to more rapidly acting analgesics or as a single agent in patients with chronic OA pain.

Traditional opiates may rarely be warranted to control pain in patients with OA who have not responded to other agents or are poor candidates for other interventions to treat painful joints, such as surgery. Patient selection, informed consent, and monitoring of response and for side effects should proceed according to treatment guidelines established for opiate treatment of any chronic pain.

Although early trials suggested an analgesic benefit from glucosamine sulfate and chondroitin sulfate, subsequent studies have shown a minimal effect on symptoms and no moderation in the progression of disease. Therefore, guidelines do not recommend their use.

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See Principles of Therapeutics for a discussion on medication toxicities and side effects.

Intra-articular Injection

When a single symptomatic joint is present, injection directly into the joint may deliver medication to the affected site while minimizing the potential for systemic effects. Intra-articular injections may be used along with or in place of oral or topical analgesics.

Glucocorticoid Injection

Numerous glucocorticoid preparations are available for intra-articular injection, including triamcinolone acetonide, triamcinolone hexacetonide, and methylprednisolone. Glucocorticoids can reduce OA knee pain within days to weeks. When a joint effusion is present, glucocorticoid injections can be particularly helpful after drainage of the excessive joint fluid. Intra-articular facet joint injections may provide pain relief from cervical or lumbar spinal OA, although studies are limited. Local side effects include skin hypopigmentation, subcutaneous tissue atrophy, and joint infection. The frequency of glucocorticoid injections is usually limited to every 3 months due to theoretical concerns about adverse effects on the joint.

Hyaluronic Acid Injection

Although multiple individual trials of hyaluronic acid injection have suggested analgesic benefit for knee OA, recent meta-analyses suggest that any such benefit may be clinically trivial. Functional benefit has also not been demonstrated. However, the possibility that specific patient subsets may obtain benefit from hyaluronic acid injection is not yet determined. Side effects are uncommon but include transient postinjection joint inflammation. The risk of joint infection after hyaluronic acid injection is not currently known.

Surgical Therapy

H When pain or functional impairment cannot be controlled by other means, orthopedic intervention for OA deserves consideration. The decision to proceed with surgery should take into consideration the patient's medical comorbidities and level of preoperative strength and mobility. Radiographic severity alone is an imperfect predictor of symptoms and an inadequate gauge of the need for surgery; decision making should incorporate an appreciation for the likely benefit in terms of quality of life and patient expectations, particularly regarding employment and recreational activities. Pain at rest or that awakens the patient in the middle of the night despite analgesic use is often present in those considering surgery. Preoperative anxiety and depression are associated with worse postoperative outcomes. Morbidly obese patients may experience earlier failure of prostheses and are often advised to lose weight prior to surgery.

For knee and hip OA, the most effective surgical intervention is total joint arthroplasty (removal of the affected articular surfaces followed by replacement with metal and polyethylene prosthetic components). In properly selected patients, arthroplasty can reduce pain, improve function, and enhance quality of life. Patients are transiently anticoagulated to reduce the rate of postoperative deep venous thrombosis to about 1%. Prosthetic joint infection occurs in 1% to 2% of patients undergoing total joint arthroplasty; patients with diabetes mellitus are at increased risk. After 10 years, 85% to 90% of total joint replacements for OA remain functional. However, about 20% of total knee and 10% of total hip arthroplasty patients continue to have some level of persistent pain. H

Arthroscopy may be helpful in knee OA when retrieval of a loose body is required to prevent locking of the joint. However, the routine use of arthroscopic lavage and debridement for OA has fallen out of favor because several studies have demonstrated no benefit of this procedure compared with blinded sham surgery.

KEY POINTS

- A regular exercise program, physical therapy, nutritional counseling, and appropriate footwear, splints, canes, or other assistive devices can benefit patients with osteoarthritis.
- Acetaminophen is the initial choice for osteoarthritis pain control in most instances; if acetaminophen provides inadequate relief, NSAIDs should usually be tried.
- Intra-articular glucocorticoids reduce osteoarthritis knee pain within days to weeks.
- The most effective surgical intervention for knee or hip osteoarthritis is total joint arthroplasty, which can reduce pain, improve function, and enhance quality of life.

Fibromyalgia

Introduction

Fibromyalgia is characterized by chronic widespread pain, tenderness of skin and muscles to pressure, fatigue, sleep disturbance, and exercise intolerance. Patients with fibromyalgia often have coexisting somatic conditions such as pelvic pain, headaches, and temporal mandibular joint pain. Effective treatment addresses both the biologic and psychologic aspects of chronic pain.

Epidemiology

Using the 1990 American College of Rheumatology fibromyalgia classification criteria (widespread body pain, tender points), prevalence in the general population ranges from 0.06% to 10%. Fibromyalgia increases with age up to the sixth decade and declines thereafter. The female-male ratio is 9:1, but this may change with use of newer diagnostic criteria.

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Fibromyalgia may co-occur in patients with inflammatory diseases such as rheumatoid arthritis (25%), systemic lupus erythematosus (30%), and primary Sjögren syndrome (50%). Psychologic distress, mood disorder, victimization, and disordered sleep have also been reported to play contributory roles. The role of physical trauma as an initiator of fibromyalgia is controversial. Importantly, not all patients with fibromyalgia have evidence of psychologic distress or physical trauma, underlining that such factors may contribute to, but do not define, fibromyalgia.

Pathophysiology

Studies suggest that the pain state of fibromyalgia is mediated by aberrant chronic pain reflex arcs centered on the dorsal ganglia of the spine. These arcs function independently but may be exacerbated by acute or chronic pain input such as that seen in arthritis or by the input contributed by psychologic distress. Functional MRI brain studies indicate that pain perception among patients with fibromyalgia is indistinguishable from, but more readily triggered than, pain perception in unaffected individuals. Patients with fibromyalgia demonstrate elevation in pain-facilitating neurotransmitters (glutamate and substance P) and reduction of neurotransmitters that down-regulate pain (norepinephrine, serotonin, and γ-aminobutyric acid). Endogenous opioid levels are paradoxically elevated along with decreased opioid receptor availability, perhaps accounting for the poor response to narcotics seen in those with fibromyalgia.

Diagnosis

The 2010 American College of Rheumatology fibromyalgia diagnostic criteria eliminated the tender point examination, owing to sensitivity biases that resulted in overdiagnosis among women. Current criteria include documentation of self-reported pain for at least 3 months at 19 different body locations (Widespread Pain Index [WPI]) along with a severity score (scale of 0-3) for three reported symptoms: fatigue, waking unrefreshed, and cognitive symptoms (Symptoms Severity Scale [SSS]). The combination of a WPI of ≥7 plus an SSS of ≥5, or a WPI between 3 and 6 plus an SSS of ≥9, establishes a diagnosis of fibromyalgia for the purposes of study enrollment.

In routine clinical practice, the combination of widespread pain ("hurt all over"), waking unrefreshed ("always tired and fatigued"), cognitive fatigue (forgets words or loses track of conversations in mid-sentence), and exercise intolerance ("if I overdo it, I pay for it for several days") are clues to the diagnosis. Previous lack of response to multiple medications, including NSAIDs, is also a diagnostic clue. Cross-sectional data suggest that obstructive sleep apnea may be common. Examination is generally unremarkable except for diffuse tenderness to palpation. The association of fibromyalgia with some inflammatory diseases requires that these disorders be considered when performing a history and physical examination.

Initial laboratory studies include a complete blood count, chemistry panel, thyroid-stimulating hormone, and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). ESR and CRP should be normal; elevated levels should prompt additional evaluation. Antinuclear antibodies, rheumatoid factor, or anti-cyclic citrullinated peptide antibodies should not be obtained unless examination or initial laboratory testing suggests that these are indicated. Muscle enzymes are frequently checked but are useful only in patients who are actually weak on examination.

Management

Patients with fibromyalgia typically benefit from validation of their symptoms by a physician because many patients have previously had their complaints disregarded by caregivers or family. These patients should be reassured that the condition is not an indication of a more serious problem and that additional diagnostic testing is generally unhelpful. Discussing the current understanding of fibromyalgia ("a problem of central pain processing") can be useful when the treatment program is described. The goal is to have the patient actively involved in a program that improves pain processing centrally and increases pain thresholds. Four issues need to be addressed: psychologic distress and/or mood disorder, sleep disturbance (may be tied to the distress), pain, and deactivation. Although patients often avoid aerobic exercise, it is critical for functional improvement. A physical therapist can be useful to discuss daily stretching and a slowly progressive home aerobic exercise program. Sleep hygiene should be reviewed. When another rheumatologic disease or significant psychologic distress is present, referral to a specialist is suggested.

Three drugs are FDA approved for fibromyalgia: the anticonvulsant pregabalin and the dual serotonin-norepinephrine reuptake inhibitors duloxetine and milnacipran. Each provides a modest benefit over placebo, with 30% to 50% of patients experiencing more than 30% reduction in pain. The latter two agents can also address coexisting mood disorder. Off-label therapies that have provided benefit include the tricyclic antidepressants (which have some demonstrated sleep utility), and, to a lesser extent, the selective serotonin reuptake inhibitors, particularly when administered in conjunction with a tricyclic agent.

The combination of medications, reactivation, and a productive lifestyle offers the best chance for significant improvement. Patients should be reassured that the chances of further deterioration are low but should also be aware that there currently is no medical cure for this condition.

KEY POINTS

- Fibromyalgia is a clinical diagnosis characterized by chronic widespread pain, tenderness of the skin and muscles to pressure, fatigue, sleep disturbance, and exercise intolerance.

(Continued)

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KEY POINTS *(continued)*

HVC
- Initial laboratory evaluation of fibromyalgia includes a complete blood count, chemistry panel, thyroid-stimulating hormone, and erythrocyte sedimentation rate or C-reactive protein; routine testing for antinuclear antibodies, rheumatoid factor, anti–cyclic citrullinated peptide antibodies, or muscle enzymes should be avoided.
- Management of fibromyalgia addresses psychologic distress and/or mood disorder, sleep disturbance, pain, and deactivation.
- For patients with fibromyalgia, aerobic exercise is critical for functional improvement.
- Pregabalin, duloxetine, and milnacipran are FDA approved and modestly effective for fibromyalgia.

Spondyloarthritis

Introduction

Spondyloarthritis refers to a group of disorders that share an overlapping set of features, including inflammation of the axial skeleton, tendons, and entheses (insertion of tendon to bone); tendon and enthesis calcification; an association with HLA-B27; and mucocutaneous, gastrointestinal, and ocular inflammation.

The four disorders of spondyloarthritis are ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease (IBD)–associated arthritis, and reactive arthritis (formerly known as Reiter syndrome). Patients who have some of these features but do not meet criteria for one of the four disorders may be designated as having undifferentiated spondyloarthritis.

KEY POINT

- Spondyloarthritis refers to a group of disorders that share an overlapping set of features, including inflammation of the axial skeleton, tendons, and entheses; tendon and enthesis calcification; an association with HLA-B27; and mucocutaneous, gastrointestinal, and ocular inflammation.

Pathophysiology

Genetic Factors

The gene most strongly associated with spondyloarthritis is the class I major histocompatibility complex molecule HLA-B27, which is present in approximately 90% of patients with ankylosing spondylitis. Among first-degree relatives of patients with ankylosing spondylitis, the presence of HLA-B27 confers an increased risk (approximately 10%-30%) of developing the disease. Moreover, ankylosing spondylitis is rare in low HLA-B27 prevalence populations. However, HLA-B27 alone is insufficient to produce spondyloarthritis because most individuals who are positive for HLA-B27 never develop the disease.

Although less strongly associated with other forms of spondyloarthritis, HLA-B27 is present in up to 70% of patients with reactive and/or IBD-associated arthritis. HLA-B27 is also present in 60% to 70% of patients with axial psoriatic arthritis and in 25% of those with peripheral psoriatic arthritis without axial involvement.

Environmental Factors

The strongest evidence that infectious triggers can play a role in spondyloarthritis is found in reactive arthritis, which typically develops after specific gastrointestinal or genitourinary infections. However, the immunobiology underlying infectious triggers remains uncertain, and infectious agents have not been shown to trigger ankylosing spondylitis. A disrupted mucosal barrier between the gut and bloodstream, potentially fostering unopposed interaction of microorganisms with immune tissues, has been hypothesized to promote IBD-associated arthritis.

Reactive arthritis and psoriatic arthritis may be more severe among patients with HIV infection, particularly when HLA-B27 is present. Unexpectedly severe presentations of either disease may warrant evaluation for underlying HIV infection in appropriate cases.

KEY POINTS

- The gene most strongly associated with spondyloarthritis is HLA-B27, which is present in approximately 90% of patients with ankylosing spondylitis.
- The strongest evidence that infectious triggers can play a role in spondyloarthritis is found in reactive arthritis, which typically develops after specific gastrointestinal or genitourinary infections.
- Reactive arthritis and psoriatic arthritis may be more severe among patients with HIV infection, particularly when HLA-B27 is present; unexpectedly severe presentations of either disease may warrant evaluation for underlying HIV infection in appropriate cases.

Classification

Although the disorders comprising spondyloarthritis share common clinical features, each disorder has a greater or lesser tendency to manifest specific features (**Table 15**). However, the features can overlap and the phenotype of each syndrome also varies from patient to patient, making the distinction sometimes challenging.

Ankylosing Spondylitis

Ankylosing spondylitis characteristically affects the axial skeleton and also has extra-articular manifestations (see Table 15). Ankylosing spondylitis is more common in men than women (3:1 ratio), although some studies suggest it is underrecognized in the female population. Peak age of onset is in the second to third decade of life.

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TABLE 15. Clinical Features of Spondyloarthritis

	Ankylosing Spondylitis	Psoriatic Arthritis	IBD-Associated Arthritis	Reactive Arthritis
Musculoskeletal				
Axial involvement	Axial involvement predominates; initially symmetrically involves the SI joints and lower spine, progressing cranially; does not skip regions	May occur at any level; may start in the cervical spine; may skip regions; may be asymmetric	May be asymptomatic but can follow a course similar to ankylosing spondylitis; SI involvement often asymmetric; arthritis does not parallel IBD activity	Less common than in other forms of spondyloarthritis
Peripheral involvement	Enthesitis (e.g., Achilles tendinitis) with or without asymmetric large-joint oligoarthritis; hip involvement can cause significant functional limitation; shoulders can be involved	Various patterns, most commonly polyarticular; DIP involvement is associated with nail involvement; dactylitis; enthesitis; tenosynovitis; arthritis mutilans	Two patterns: mono/oligoarticular large joint lower extremity (parallels IBD activity), and polyarticular small joint upper extremity (does not parallel IBD activity); dactylitis and enthesitis may occur	Enthesitis and asymmetric large-joint oligoarthritis; usually self-limited; nonerosive; some patients experience recurrent or persistent arthritis; may develop features of other forms of spondyloarthritis
Dermatologic	Psoriasis may coexist	Psoriasis typically precedes joint involvement; nail pitting; onycholysis	Pyoderma gangrenosum; erythema nodosum	Keratoderma blennorrhagicum; circinate balanitis
Ophthalmologic	Uveitis (typically anterior, unilateral, recurrent)	Conjunctivitis more common than uveitis (anterior; can be bilateral, insidious, or chronic)	Uveitis (anterior; can be bilateral, insidious, or chronic); conjunctivitis, keratitis, and episcleritis are rare	Conjunctivitis is more common than uveitis
Gastrointestinal	Asymptomatic intestinal ulcerations	—	Crohn disease; ulcerative colitis	Prior GI infection in some patients
Genitourinary	Urethritis (rare)	—	Nephrolithiasis	Prior GU infection in some patients; sterile urethritis; prostatitis; cervicitis; salpingitis
Cardiovascular	Aortic valve disease; aortitis; conduction abnormalities; CAD	Association with traditional CAD risk factors	Thromboembolism	—
Pulmonary	Restrictive lung disease from costovertebral rigidity; apical fibrosis (rare)	—	—	—
Bone quality	Falsely elevated bone mineral density from syndesmophytes; increased risk of spine fracture	Increased risk of fracture; multifactorial	High risk for vitamin D deficiency, low bone density, and fracture	Localized osteopenia

CAD = coronary artery disease; DIP = distal interphalangeal; GI = gastrointestinal; GU = genitourinary; IBD = inflammatory bowel disease; SI = sacroiliac.

Inflammatory low back pain of insidious onset is the hallmark of ankylosing spondylitis, manifesting as pain and stiffness that are worse after immobility and are better with use. Symptoms are prominent in the morning (>1 hour); night pain is characteristic and may awaken the patient. Buttock pain is common and bilateral, and it correlates with sacroiliitis. Early in its course, ankylosing spondylitis almost always affects the lumbar spine; longer and more severe disease may involve the thoracic and cervical regions as well. *Ankylosis* refers to the bony bridging of the vertebrae resulting from chronic inflammation; the calcified ligaments and disk capsules in such cases are read on radiographs as *syndesmophytes*. Fusion of the spine may occur over time, leading to rigidity and kyphosis.

Risk factors for poor prognosis include male gender, early age of onset, tobacco use, and the presence of hip or peripheral arthritis, psoriasis, IBD, iritis, or elevated erythrocyte sedimentation rate (ESR). Mortality is increased, primarily relating

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to increased rates of cardiovascular disease (coronary artery disease, aortic valve regurgitation, aortic aneurysm, conduction disturbance), cancer, and infection.

Psoriatic Arthritis

Psoriatic arthritis is an inflammatory arthritis that is associated with psoriasis (see Table 15). Peak age of onset is between 40 and 60 years; men and women are equally affected. Prevalence of psoriatic arthritis is approximately 1% in the general population. Although estimates of the prevalence of psoriatic arthritis in patients with psoriasis vary, more recent studies using standardized diagnostic criteria indicate that psoriatic arthritis is present in approximately 15% to 20% of those with psoriasis. Psoriasis most commonly precedes the onset of arthritis but may occur with or after arthritis onset.

The most common patterns of joint involvement are an asymmetric lower extremity oligoarthritis (resembling reactive arthritis) or a symmetric polyarthritis involving the distal interphalangeal (DIP), proximal interphalangeal (PIP), and/or metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints (distribution similar to rheumatoid arthritis but includes the DIPs). Less common presentations include DIP involvement only as well as a chronic resorptive arthritis (arthritis mutilans) causing digital shortening and a "telescoping" appearance. Spondylitis (spine or sacroiliac arthritis) may occur; in contrast to ankylosing spondylitis, it is usually asymmetric and may skip regions.

Dactylitis (diffuse swelling of joints, tendons, and/or ligaments of a digit, creating a sausage-like appearance) occurs in approximately 50% of patients with psoriatic arthritis (**Figure 11**). Nail involvement such as pitting or onycholysis (**Figure 12**) is commonly observed concurrent with DIP joint involvement.

The recently developed Classification Criteria for Psoriatic Arthritis (CASPAR) convey a sensitivity and specificity of more than 90% (**Table 16**). Patients with a characteristic pattern of psoriatic joint involvement (especially DIP arthritis and/or dactylitis), but without apparent psoriasis, should undergo a thorough examination for occult psoriatic skin or nail changes. Although patients with psoriatic arthritis are characteristically seronegative, 5% to 10% may demonstrate rheumatoid factor or anti-cyclic citrullinated peptide (CCP) antibodies, possibly owing to overlapping genetic proclivities. Typical radiographic changes of psoriatic arthritis include a combination of marginal joint erosions and new bone formation; classic findings include pencil-in-cup changes (**Figure 13**).

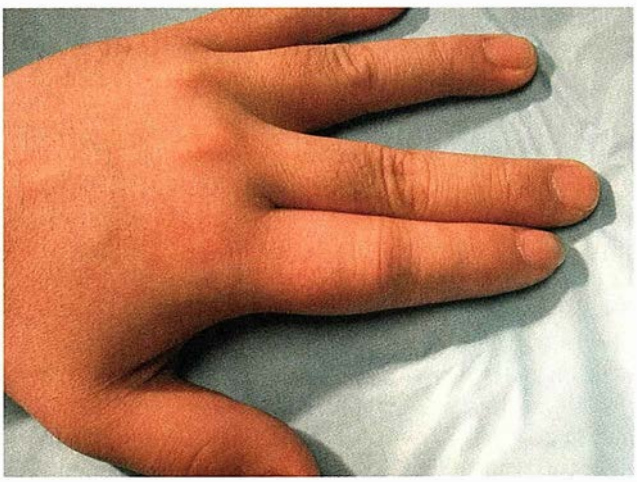

FIGURE 11. Dactylitis ("sausage digit") associated with psoriatic arthritis. Dactylitis manifests as swelling of the entire digit and arises from inflammation of the flexor tendon and adjacent soft tissue.



FIGURE 12. This patient with psoriatic arthritis has onycholysis and onychodystrophy (malformation of a fingernail or toenail).

TABLE 16. Classification Criteria for Psoriatic Arthritis (CASPAR)

Inflammatory articular disease (joint, spine, entheseal)
Plus three or more of the following:
Psoriasis (current, personal history of, family history of)
Psoriatic nail dystrophy
Negative rheumatoid factor[a]
Dactylitis/swelling of entire digit (current, personal history of)
Radiologic evidence of juxta-articular new bone formation (joint of hand or foot)

[a]Five to ten percent of patients may have a positive rheumatoid factor or anti-cyclic citrullinated peptide antibodies; this would not exclude the diagnosis as long as the patient meets sufficient other criteria.

Prognosis of psoriatic arthritis is variable, with studies suggesting a relationship between disease severity and mortality. Severity of skin disease neither predicts nor correlates with severity of arthritis. Elevated ESR and the presence of radiologic joint damage at presentation predict both arthritis progression and mortality; the presence of nail lesions may be protective. Cardiovascular disease is the most common cause of mortality.

Inflammatory Bowel Disease-Associated Arthritis

Inflammatory arthritis is present in 20% to 30% of patients with ulcerative colitis or Crohn disease. IBD-associated arthritis may be axial or peripheral. Peripheral joint involvement

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FIGURE 13. Pencil-in-cup deformity in psoriatic arthritis. Note the erosion and remodeling of the index proximal interphalangeal joint with a cup-like appearance of the distal bone on the ulnar aspect of the joint; the bone proximal to the joint becomes so eroded as to look like a pencil point within the cup.

may be oligoarticular (type 1) or polyarticular (type 2). Only the oligoarticular peripheral arthritis parallels IBD activity. See Table 15 for more information.

Reactive Arthritis

Reactive arthritis is a noninfectious inflammatory arthritis that can occur after specific gastrointestinal or genitourinary infections. Asymmetric monoarthritis or oligoarthritis in the lower extremities is the most common presentation, but up to 20% of patients have polyarthritis. Enthesopathy (including at the Achilles tendon insertion to the calcaneus), dactylitis, and sacroiliitis may occur. Erosive disease is uncommon. See Table 15 for clinical features.

Despite the preceding infection, reactive arthritis is an autoimmune, rather than infectious, arthritis. It is hypothesized that exposure of a susceptible patient to a defined infectious antigen may induce a cross-reaction to a similarly structured, previously tolerated self-antigen (molecular mimicry), resulting in autoimmunity and self-perpetuating inflammation. Therefore, use of antibiotics specifically to treat reactive arthritis has failed to demonstrate benefit.

Gastrointestinal pathogens associated with reactive arthritis include *Yersinia*, *Salmonella*, *Shigella*, *Campylobacter*, and, rarely, *Escherichia coli* and *Clostridium difficile*. The most common genitourinary pathogen is *Chlamydia trachomatis*; cases due to *Ureaplasma urealyticum* have been reported.

Reactive arthritis typically occurs approximately 3 to 6 weeks after the infectious trigger, with a latency range of 2 weeks to 6 months. In a significant minority of cases, the triggering infection may go unrecognized. The presence of HLA-B27 and severity of initial infection may increase the risk of developing reactive arthritis.

Up to 50% of reactive arthritis cases resolve by 6 months, but 20% of patients progress to chronic disease. Recurrent infectious episodes may convey an increased risk of recurrent reactive arthritis.

KEY POINTS

- Inflammatory low back pain of insidious onset is the hallmark of ankylosing spondylitis, manifesting as pain and stiffness that are worse after immobility and are better with use.
- Psoriatic arthritis typically presents as an asymmetric lower extremity oligoarthritis or a symmetric polyarthritis involving the distal interphalangeal, proximal interphalangeal, and/or metacarpophalangeal and metatarsophalangeal joints, often with dactylitis.
- Arthritis of varying patterns may occur in patients with inflammatory bowel disease (IBD); however, only oligoarticular peripheral arthritis parallels IBD activity.
- Reactive arthritis is a noninfectious, autoimmune inflammatory arthritis that can occur after specific gastrointestinal or genitourinary infections and typically presents as asymmetric monoarthritis or oligoarthritis in the lower extremities; enthesopathy, dactylitis, and sacroiliitis may also occur.

Diagnosis

Diagnosis of a specific spondyloarthritis disorder is based on the characteristic history and physical examination, as well as radiographic findings such as sacroiliitis and enthesitis (**Table 17**). The clinical setting may provide a clue to diagnosis. For example, ankylosing spondylitis should be considered in patients with chronic inflammatory back pain who are younger than 45 years old. Peripheral arthritis or tendinitis is less likely to occur in ankylosing spondylitis and should raise suspicion for a different form of spondyloarthritis. Psoriatic arthritis should be considered if there is a prior or current diagnosis of psoriasis, especially along with the characteristic arthritis patterns previously described. IBD-associated arthritis should be considered if there is a prior diagnosis of IBD or current symptoms and signs of possible IBD. Reactive arthritis should be considered if there is a history of preceding infection, especially gastrointestinal or genitourinary infection. Considerable overlap exists between these diseases; for example, a patient with ankylosing spondylitis may also have psoriasis and/or IBD.

Diagnosis may be supported by the presence of HLA-B27 and/or elevated inflammatory markers. Patients lacking laboratory and radiographic evidence of disease may nonetheless have sufficient historical and physical manifestations (characteristic inflammatory arthritis, along with dactylitis, enthesitis, inflammatory eye disease, or psoriasis) to support a

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TABLE 17. Evaluation of Patients with Suspected Spondyloarthritis

History
Inflammatory back and/or joint pain[a]
Family history of SpA or psoriasis
Positive response to NSAIDs
Symptoms consistent with, or existing diagnosis of, psoriasis, IBD, and/or ocular inflammation (iritis, uveitis, conjunctivitis)
Preceding infection
Urethritis symptoms in the absence of ongoing infection
Physical Examination Findings
Spine/SI joint tenderness; limited ROM of spine[b]; tenderness and/or swelling of joints, tendons (dactylitis), and/or tendon insertions to bone (enthesitis, especially Achilles tendon insertion)
Rash and/or nail changes indicative of psoriasis
Ocular inflammation (iritis, uveitis, conjunctivitis)
Laboratory Studies
Positive HLA-B27
Elevated C-reactive protein and/or erythrocyte sedimentation rate
Radiography
Plain radiography of SI joints and/or symptomatic area of spine (lumbar, thoracic, cervical) showing characteristic changes; if plain radiograph is negative, consider MRI of SI joints +/– spine
Plain radiograph of symptomatic peripheral joints to look for erosions and new bone formation suggestive of inflammatory arthritis/enthesitis

IBD = inflammatory bowel disease; ROM = range of motion; SI = sacroiliac; SpA = spondyloarthritis.

[a]Inflammatory joint pain is worse overnight, in the morning, and after immobility; improves with joint use; and is associated with morning stiffness lasting longer than 1 hour.

[b]Schober test, chest expansion, and occiput-wall distance measurements can be useful.

diagnosis. Classification criteria for psoriatic arthritis (CASPAR) and for peripheral and axial spondyloarthritis (Assessment of SpondyloArthritis international Society) have been developed; although these are primarily intended for research purposes, they provide informative paradigms for clinicians diagnosing these disorders.

See **Figure 14** and **Figure 15** for more information on diagnosing spondyloarthritis.

Laboratory Studies

No specific serologic tests are available to diagnose spondyloarthritis. Rheumatoid factor, anti-CCP antibodies, and antinuclear antibodies are usually negative, although low-titer positivity may occasionally be present. Elevated inflammatory markers such as ESR, C-reactive protein, and serum amyloid A protein often correlate with disease activity but may also be normal, especially in patients with ankylosing spondylitis. HLA-B27 testing can define a probability for spondyloarthritis but cannot independently confirm or exclude any specific diagnosis. Although infection has usually resolved by the time of arthritis onset in patients with reactive arthritis, DNA amplification urine testing for *Chlamydia trachomatis* should be performed because some individuals may have asymptomatic persistent infection or carriage of this organism.

Imaging Studies

Conventional radiography of the spine and sacroiliac joints is inexpensive and generally adequate to demonstrate synovitis, axial erosion, or new bone formation in patients with spondyloarthritis, although results may be normal in early disease. With peripheral spondyloarthritis, conventional radiography may detect erosive changes with bony proliferation at the entheses.

Sacroiliitis is usually bilateral and symmetric in ankylosing spondylitis but may be unilateral or absent in other forms of spondyloarthritis. On plain radiographic imaging, sacroiliac erosion initially appears as irregular widening of the joint space, accompanied by sclerotic changes. Later, the joint space narrows, and eventually the sacroiliac joint may fuse. Vertebral plain radiographic findings in ankylosing spondylitis include sclerosis at the attachment of annulus fibrosis to the anterior corner of the vertebral endplate ("shiny corner"), and erosion at the point of contact between the disk and the vertebra. In later disease, vertebrae may lose their normal anterior concavity due to periosteal bone proliferation, resulting in squaring of the vertebral bodies. Calcification of the anterior longitudinal ligament and bridging syndesmophyte formation are late features, leading to ankylosis and a "bamboo" spine appearance (**Figure 16**, on page 41). This may be difficult to differentiate

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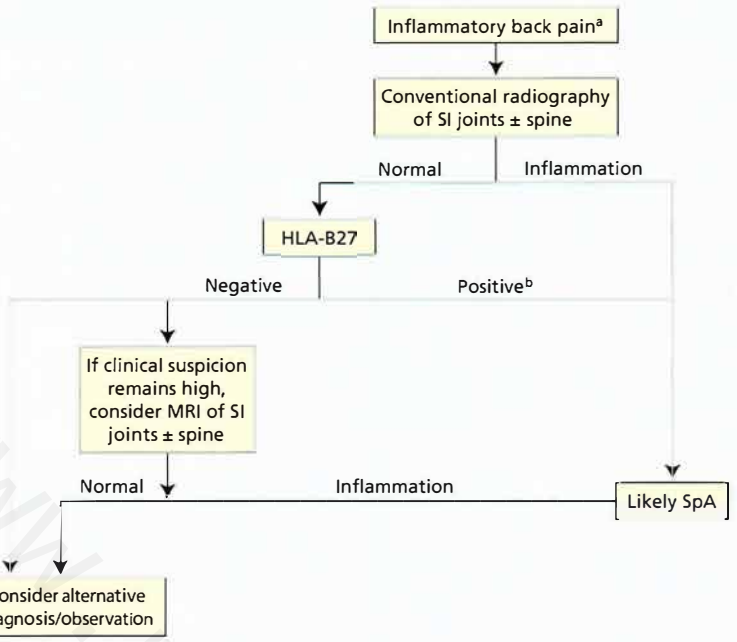

FIGURE 14. Diagnostic evaluation for suspected axial spondyloarthritis. SI = sacroiliac; SpA = spondyloarthritis.

[a]Characterized by pain and stiffness in the spine that is worse after immobility and better with use; prominent morning pain lasting >1 hour; buttock pain is common and typically bilateral.

[b]Particularly if at least one other feature typical of SpA is present: uveitis, enthesitis, dactylitis, psoriasis, inflammatory bowel disease, positive family history of SpA, or elevated inflammatory markers.

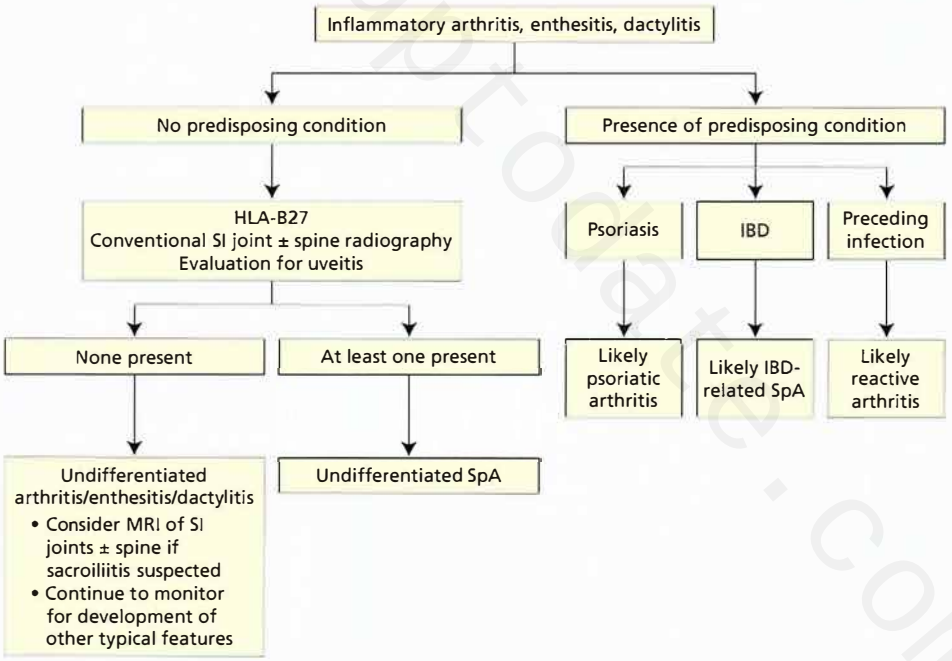

FIGURE 15. Diagnostic evaluation for suspected peripheral spondyloarthritis. IBD = inflammatory bowel disease; SI = sacroiliac; SpA = spondyloarthritis.

from diffuse idiopathic skeletal hyperostosis (DISH); however, the changes in ankylosing spondylitis are usually on both sides of the spine, whereas in DISH they are characteristically right sided. Furthermore, DISH is most commonly thoracic, whereas ankylosing spondylitis starts with sacroiliitis and lumbar arthritis and usually does not skip regions as it ascends.

CT is more sensitive than conventional radiography for detecting bony erosions and may be helpful when disease is suspected but plain radiographs are negative. CT is also useful for detecting subtle vertebral body fractures in patients with ankylosing spondylitis who are at increased risk of spine fractures. However, CT is expensive and conveys increased levels of

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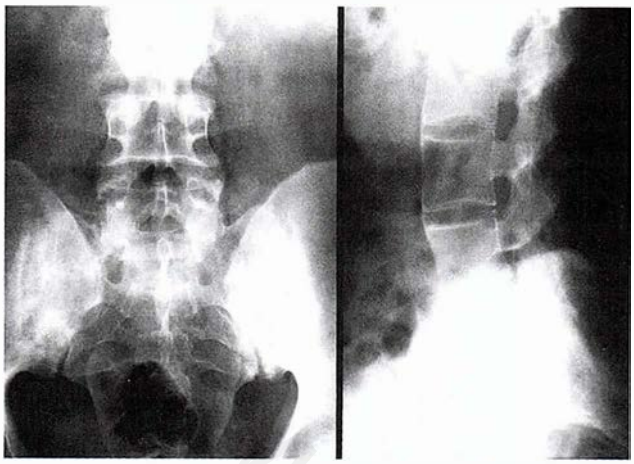

FIGURE 16. The initial radiographic findings of ankylosing spondylitis include irregularities along the margins of the sacroiliac joints leading to eventual ankylosis and fusion. Inflammation of the ligamentous attachments erodes the corners of the vertebral bodies, which produces a squared-off appearance. Over time, ossification of these ligaments leads to the development of a rigid "bamboo spine," named because the shape of the vertebrae resemble bamboo on radiograph.

ionizing radiation exposure. Accordingly, CT is not routinely used to monitor spondyloarthritis disease progression.

MRI can detect early inflammation in the spine and sacroiliac joints, even before bony changes are detected on radiograph or CT. MRI of the sacroiliac joints and/or spine should be obtained if there is high suspicion for spondyloarthritis and conventional radiographs are negative. However, MRI is more expensive and less generally available.

Musculoskeletal ultrasonography can detect peripheral enthesitis and arthritis but has no current role in detecting sacroiliitis or axial involvement.

KEY POINTS

- In patients with spondyloarthritis, rheumatoid factor, anti–cyclic citrullinated peptide antibodies, and antinuclear antibodies are usually negative.
- HLA-B27 testing can support, but cannot independently confirm or exclude, a diagnosis of spondyloarthritis.

HVC
- Conventional radiography of the spine and sacroiliac joints is generally adequate to demonstrate synovitis, axial erosion, or new bone formation in patients with spondyloarthritis; CT should be reserved for identifying occult spine fractures and bony erosions in patients at high risk due to expense and higher level of radiation exposure.

HVC
- In patients with strongly suspected spondyloarthritis, MRI of the sacroiliac joints and/or spine should only be considered if conventional radiographs are negative.

Management

General Considerations

Management of spondyloarthritis should include exercise to preserve spine and peripheral joint strength and range of motion. Glucocorticoid injections may be helpful in providing symptomatic relief, particularly if there are one or two active isolated joints in which a local injection may reduce the need for systemic medication. Pharmacologic therapy is needed for control of symptoms in most forms of spondyloarthritis, although the most effective medication regimen may vary by type of spondyloarthritis present.

A mainstay of pharmacologic therapy is NSAIDs. The various NSAIDs studied are equally effective, but differences exist in individual response to, and tolerance of, a given NSAID; thus, it can be helpful to try a second NSAID if the first has produced an inadequate response. Maximal daily NSAID dosing is generally required to produce a positive response in spondyloarthritis, but the dose may subsequently be reduced depending on patient response and tolerance.

For patients with more serious disease not adequately controlled with NSAIDs or who cannot tolerate NSAIDs, nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs) can be helpful. However, these agents may increase the risk of infection, and certain drugs are extremely expensive or may require parenteral administration.

Patients with severe end-stage joint or soft-tissue damage may need surgery such as tendon repair or joint replacement. Surgery to correct severe spine flexion deformities in ankylosing spondylitis may be considered but can be challenging and risky due to difficulties with intubation for anesthesia, spine fragility, and stabilization.

Ankylosing Spondylitis

Exercise is a particularly important component of ankylosing spondylitis therapy and can help preserve mobility and prevent kyphosis. A physical therapist can assist patients in developing a home exercise routine that can be maintained over time. Glucocorticoid injections to the sacroiliac joints can relieve symptoms and facilitate exercise.

NSAIDs are considered first-line therapy for ankylosing spondylitis. Studies of full-dose NSAIDs demonstrate symptomatic relief as well as reduced sacroiliac and spine inflammation as seen on MRI in some patients. In contrast to their limited effects in modifying the course of almost all other rheumatologic diseases, some studies suggest that daily NSAID use may reduce progression of spine damage caused by ankylosing spondylitis.

Tumor necrosis factor (TNF)-α inhibitors are indicated for patients who have had inadequate responses to NSAIDs. If the first TNF-α inhibitor produces an inadequate response, a different TNF-α inhibitor may be more successful. TNF-α inhibitors demonstrably improve pain and mobility as well as reduce inflammation in axial joints. Although recent reports suggest that they may help slow radiographic disease progression, more studies are needed for confirmation.

Nonbiologic DMARDs such as methotrexate and sulfasalazine are not helpful in treating axial disease but may be helpful in treating accompanying peripheral arthritis.

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Monitoring of patients with ankylosing spondylitis for response to therapy or progression of disease can include patient history, physical examination, and laboratory testing (such as erythrocyte sedimentation rate and C-reactive protein). Serial imaging can also be used to help monitor patients with ankylosing spondylitis, but the 2010 Assessment of SpondyloArthritis international Society/European League Against Rheumatism (ASAS/EULAR) guidelines recommend against repeating spinal radiography more frequently than every 2 years unless absolutely necessary in specific cases.

Psoriatic Arthritis

NSAIDs can improve symptoms of inflammation and are therefore commonly used for pain control but have not been shown to prevent progression of erosions in psoriatic arthritis. Glucocorticoids (systemically or by intra-articular injection) can provide short-term relief, although flare-ups of psoriasis may occur after discontinuation of systemic glucocorticoids.

Nonbiologic DMARDs can treat peripheral arthritis and enthesitis but are unlikely to improve axial disease. Methotrexate has demonstrated efficacy in psoriatic arthritis and also helps psoriasis. Sulfasalazine and hydroxychloroquine can be useful for the arthritis, although there are reports of hydroxychloroquine-induced exacerbation of psoriasis in some patients.

Several biologic agents are highly efficacious in psoriatic arthritis and should be considered for more severe disease, when nonbiologic DMARDs have provided inadequate benefit, and/or in the presence of radiographic evidence of bony damage. TNF-α inhibitors can prevent progression of joint damage and are also effective for treating the accompanying psoriasis. Combination therapy with methotrexate and a TNF-α inhibitor may be more helpful than monotherapy for some patients. Paradoxical worsening of psoriasis has been reported in some patients receiving TNF-α inhibitors. Ustekinumab, a biologic agent that targets interleukin (IL)-12 and IL-23, is FDA approved for use in both severe psoriasis and psoriatic arthritis. Ustekinumab can slow progression of radiographic disease and can be used in combination with methotrexate.

Inflammatory Bowel Disease-Associated Arthritis

NSAIDs may be contraindicated in patients with IBD due to risk of bowel flare-up, limiting their usefulness in IBD-associated arthritis. Glucocorticoids, systemically or by local injection, may provide short-term relief.

Methotrexate may ameliorate IBD-associated arthritis and can also treat the underlying bowel disease, especially Crohn disease. Similarly, sulfasalazine may also be effective for both IBD and IBD-related arthritis.

With the exception of etanercept (a receptor-based rather than antibody-based biologic agent), TNF-α inhibitors are effective treatments for IBD-associated arthritis that can be used when nonbiologic agents fail. However, paradoxical worsening of IBD has been reported in some patients receiving these agents.

Reactive Arthritis

Reactive arthritis is usually self-limited, with symptoms resolving within 6 months; in most cases, symptom-based treatment is sufficient. NSAIDs provide symptomatic relief, and intra-articular glucocorticoid injections may provide local benefit. In patients who progress to severe and/or chronic disease, DMARDs such as sulfasalazine, methotrexate, or leflunomide should be tried, although data for this indication are limited. A few case reports of benefit from TNF-α inhibitors have been published, but more studies are needed.

Antibiotic therapy has not been shown to be effective in reactive arthritis except in rare cases of demonstrated persistent infection.

KEY POINTS

- Management of spondyloarthritis generally includes exercise to preserve strength and range of motion, glucocorticoid injections for symptomatic relief, and pharmacologic therapy.
- NSAIDs are first-line therapy for ankylosing spondylitis; tumor necrosis factor α inhibitors are used when patients have had inadequate response to NSAIDs.
- In patients with psoriatic arthritis, NSAIDs are typically used to control inflammatory symptoms; nonbiologic disease-modifying antirheumatic drugs can treat peripheral arthritis and enthesitis, and biologic agents should be considered for more severe disease.
- Methotrexate or sulfasalazine can be used to treat both the arthritis and bowel disease associated with inflammatory bowel disease–associated arthritis; tumor necrosis factor α inhibitors other than etanercept can be tried when nonbiologic agents fail.
- Antibiotic therapy has not been shown to be effective in reactive arthritis except in rare cases of demonstrated persistent infection.

Systemic Lupus Erythematosus

Introduction

Systemic lupus erythematosus (SLE) is characterized by multiorgan involvement and the presence of autoantibodies, including antibodies directed at intranuclear antigens.

Pathophysiology

SLE demonstrates a polygenic inheritance pattern. Clinical disease results from the interaction of genes, environment, and random effects, resulting in loss of tolerance to self-antigens and active autoimmunity.

Patients with SLE have abnormalities in how dying cells are handled by the immune system. The nuclear material of dying cells may be inadequately cleared, engendering an

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immune response, and promoting up-regulation of autoreactive T and B cells and autoantibodies directed against nuclear and other antigens. Recent studies suggest a role for type 1 interferons in SLE induction. Single gene mutations causing deficiencies of the complement components C1q, C2, or C4 can promote SLE, possibly by impairing clearance of immune complexes and/or apoptotic cell debris.

Epidemiology

Approximately 90% of patients with SLE are women, with disease risk dramatically increasing with the appearance of female sex hormones; the female-to-male ratio is 1:1 in childhood versus 9:1 in adulthood. The disease is more common, and often more severe, among women of African American, Chinese, and Hispanic backgrounds.

KEY POINTS

- Systemic lupus erythematosus is characterized by multiorgan involvement and the presence of autoantibodies, many directed at intranuclear antigens.
- Approximately 90% of patients with systemic lupus erythematosus are women, with disease risk dramatically increasing with the appearance of female sex hormones.

Clinical Manifestations

Mucocutaneous Involvement

Skin and/or mucous membranes are affected in 80% to 90% of patients with SLE; skin manifestations are classified as acute, subacute, or chronic.

The characteristic SLE skin manifestation is acute cutaneous lupus erythematosus (ACLE), also known as malar or butterfly rash, which affects 40% to 50% of patients (**Figure 17**). ACLE consists of erythema and edema over the cheeks and bridge of the nose and potentially the forehead and chin; it characteristically spares the nasolabial folds. A more generalized form of ACLE can also involve the dorsum of the arms and hands, including the areas between the fingers but sparing the knuckle pads. Skin sequelae such as atrophy are not seen.

Subacute cutaneous lupus erythematosus (SCLE) is a photosensitive rash that occurs over the arms, neck, and face (**Figure 18**). It consists of erythematous, annular, or polycyclic lesions, often with a fine scale. SCLE may leave postinflammatory changes (hypo- or hyperpigmentation) but does not cause atrophy. Anti-Ro/SSA autoantibodies are present in 70% of patients with SCLE.

The most common chronic cutaneous manifestation is discoid lupus erythematosus (DLE) (**Figure 19**). DLE occurs in



FIGURE 17. Malar (butterfly) rash. This patient has a classic acute cutaneous lupus erythematosus rash in a butterfly distribution that spares the nasolabial folds. It is erythematous and raised, with a very slight scale. This rash will resolve completely with treatment without leaving any skin atrophy.



FIGURE 18. Rash in subacute cutaneous lupus erythematosus. This patient has an annular polycyclic rash characterized by scaly erythematous circular plaques with central hypopigmentation.



FIGURE 19. Chronic cutaneous lupus erythematosus consists of chronic, slowly progressive, scaly, infiltrative papules and plaques or atrophic red plaques on sun-exposed skin surfaces, most commonly the face, neck, and scalp. Healed lesions result in depressed scars, atrophy, telangiectasias, and hyperpigmentation or hypopigmentation.

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20% of patients with SLE but more commonly occurs as an isolated, nonsystemic finding; patients with isolated DLE usually do not go on to develop SLE. DLE usually affects the scalp and face and presents as hypo- or hyperpigmented, possibly erythematous, patches or thin plaques that may be variably atrophic or hyperkeratotic. In contrast to ACLE and SCLE, DLE can cause scarring, atrophy, and permanent alopecia.

Painless oral or nasopharyngeal ulceration occurs in 5% of patients with SLE. Nonscarring alopecia is a common feature of active SLE, with hair regrowth a sign of disease control. Raynaud phenomenon occurs in 60%, reflecting arterial vasospasm of the digits.

Musculoskeletal Involvement

Joint involvement occurs in 90% of patients with SLE, with inflammatory polyarthralgia the most common presentation. Frank arthritis occurs in 40% of patients with SLE. Both small and large peripheral joints can be affected; the synovial fluid is only mildly inflammatory. SLE arthritis is nonerosive. However, persistent periarticular inflammation can damage joints supporting soft-tissue structures, resulting in reducible subluxation of the digits, swan neck deformities, and ulnar deviation (Jaccoud arthropathy).

Pain or limitation of motion of the large joints, especially the hips, should raise concern for possible osteonecrosis. Up to 37% of patients with SLE develop osteonecrosis by serial MRI scan of the hips, but less than 10% become symptomatic. Large necrotic areas (for example, >20% of the femoral head) may progress to bony collapse, whereas smaller lesions often resolve without structural perturbation. The occurrence of osteonecrosis is attributable to glucocorticoid use and other factors, including Raynaud phenomenon and lupus vasculitis, which may disrupt the blood supply to vulnerable bone volumes. Prednisone doses greater than 20 mg/d and cushingoid facial features are markers of risk. Patients with osteonecrosis have night pain and use pain. Early diagnosis is by MRI, with more advanced disease visible on radiograph.

Myalgia is reported by up to 85% of patients with SLE, but frank myositis occurs in only about 10%. Histologically and clinically, SLE myositis resembles polymyositis. Medications such as antimalarials and glucocorticoids can cause drug myopathies that must be ruled out in SLE patients with weakness. Fibromyalgia co-occurs in 30% of patients with SLE and is important to diagnose to avoid unnecessary use of immunosuppressive medications.

Kidney Involvement

Lupus nephritis occurs in up to 70% of patients with SLE; the presence of anti–double-stranded DNA antibodies is a marker for risk. All patients with SLE should be evaluated for possible nephritis with baseline serum creatinine, urine protein-creatinine ratio for proteinuria, and urinalysis with microscopic evaluation. Minor abnormalities (proteinuria <500 mg/24 h, minimal hematuria, no casts) should be monitored regularly (3-month intervals), whereas significant initial abnormalities (especially cellular casts) require immediate further evaluation. Patients with inadequately treated lupus nephritis may progress to need dialysis or transplant. Signs and symptoms defining more severe lupus nephritis include hypertension, lower extremity edema, active urine sediment (proteinuria, hematuria, cellular casts), and elevated serum creatinine. Kidney biopsy is frequently warranted to define the histological subtype and the degree of disease activity and chronicity essential for planning appropriate therapy. Indications for kidney biopsy are as follows: increasing serum creatinine without explanation, proteinuria >1000 mg/24 h, proteinuria >500 mg/24 h with hematuria, and proteinuria >500 mg/24 h with cellular casts.

SLE patients with hypercoagulable states (for example, the antiphospholipid antibody syndrome, the nephrotic syndrome) may be at risk for renal artery or vein thrombosis.

See Glomerular Diseases in MKSAP 17 Nephrology for more information on the six classes and treatment of lupus nephritis.

Neuropsychiatric Involvement

The American College of Rheumatology 1999 SLE classification criteria recognize 19 possible manifestations attributable to neuropsychiatric systemic lupus erythematosus (NPSLE) (**Table 18**). The most common manifestations are headache,

TABLE 18. Neuropsychiatric Manifestations of Systemic Lupus Erythematosus

Central Nervous System
Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache
Movement disorder (such as chorea)
Seizure disorder
Myelopathy
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis
Peripheral Nervous System
Acute inflammatory demyelinating polyradiculoneuropathy (such as Guillain-Barré syndrome)
Autonomic neuropathy
Mononeuropathy (single or multiplex)
Myasthenia gravis
Cranial neuropathy
Plexopathy
Polyneuropathy

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cognitive dysfunction, and mood disorder. NPSLE prevalence is as high as 75%; prevalence of more acute presentations (for example, seizures and psychosis) is significantly lower. In addition to central manifestations, peripheral neuropathy occurs in up to 14% of SLE patients, with the majority due to the disease itself and the remainder due to non-SLE causes (medications, other diseases such as diabetes mellitus, spinal radiculopathies).

NPSLE pathophysiology may include vascular inflammation and/or occlusion, the effects of cytokines on neuronal function, or antibodies directed against various neuronal or glial components. The blood-brain barrier generally prevents passage of antibodies into the central nervous system (CNS) but with inflammation becomes permeable. Some of the antibodies/cytokines in NPSLE may also be produced within the CNS itself.

The general approach to suspected NPSLE is to first exclude an infection or medication effect. Evaluation of more severe manifestations such as seizures or meningitis requires CNS imaging, cerebrospinal fluid (CSF) analysis, and measurement of NPSLE-associated autoantibodies. Autoantibodies that may be found in the serum and/or CSF in patients with NPSLE include antineuronal, anti-NMDA receptor, antiribosomal P, and antiphospholipid antibodies/lupus anticoagulant (APLA/LAC). For patients with suspected peripheral neuropathies, electromyography (EMG) and nerve conduction studies (NCS) are useful in the diagnosis and potential cause of the neuropathy. EMG/NCS should be able to distinguish a spinal radiculopathy (non-SLE cause) from a mononeuritis (likely associated with SLE), for example.

Imaging of the patient with NPSLE should be influenced by the clinical manifestations and is often done to rule out other possibilities. Imaging may include CT to rule out CNS bleeding or stroke; MRI to identify infection, white matter lesions, or myelopathy in a patient with suspected transverse myelitis; and PET to evaluate functional abnormalities in patients with cognitive impairment. Neuropsychologic testing may help identify organic versus functional cognitive changes.

Cardiovascular Involvement

Up to 40% of patients with SLE experience pericarditis, which is often asymptomatic. Pericarditis may be associated with a neutrophilic pericardial effusion that can rarely lead to tamponade. Antinuclear antibodies (ANA), anti-double-stranded DNA antibodies, and so-called lupus erythematosus cells (neutrophils engulfing extruded cell nuclei) can be detected in the fluid but rarely alter diagnosis or management. Constrictive pericarditis may also occur. Pericardial disease can be demonstrated by CT or MRI.

Myocarditis occurs in 5% to 10% of patients with SLE, more commonly among black patients. Presentations can be dramatic, with acute onset of heart failure. Echocardiogram-measured ejection fractions of less than 20% are not uncommon. Rapid response to high-dose glucocorticoids supports a pathogenic role for SLE inflammation/autoimmunity. Cardiac MRI is increasingly used to detect myocardial inflammation.

Cardiac valves are abnormal on transesophageal echocardiogram in many patients with SLE, most characteristically those with APLA/LAC. Thickening of the mitral and aortic valve leaflets are the most common abnormalities, but vegetations, regurgitation, and stenosis also occur. Libman-Sacks endocarditis, the classic designation for noninfectious verrucous vegetations, favors the mitral valve. These verrucous masses can embolize, leading to downstream occlusion.

Patients with SLE have a 2- to 10-fold increased prevalence of ischemic heart disease, the most common cause of death among older patients with SLE. Severe SLE disease activity and prednisone doses of more than 20 mg/d are independent risk factors for early myocardial infarction. Traditional risk factors such as hypertension and total cholesterol levels also play a role and require clinical management.

Pulmonary Involvement

Pleuritis occurs in 45% to 60% of patients who have SLE, with or without pleural effusion. When present, effusions are exudative, and lupus erythematosus cells and ANA may be present.

Parenchymal lung involvement is relatively uncommon in SLE; lung infiltrates are more likely to be infectious than directly associated with SLE. Nonetheless, interstitial lung disease occurs in 3% to 8% of patients with SLE. Acute lupus pneumonitis is a potentially serious inflammatory airway disease characterized by fever, cough, shortness of breath, hypoxemia, and pleuritic chest pain. Chest radiograph may show unilateral or bilateral infiltrates. Mortality rates approach 50%, and aggressive respiratory support combined with immunosuppression is required. An even rarer manifestation is diffuse alveolar hemorrhage, which typically presents with shortness of breath, hypoxemia, diffuse alveolar infiltrates on chest radiograph, a dropping hematocrit, and a high DLCO on pulmonary function tests, all in the setting of active SLE. Bronchoscopy with bronchoalveolar lavage and biopsy is used to demonstrate hemorrhage and rule out infection. Chest MRI may detect blood as changes on T2-weighted images. Aggressive immunosuppressive therapy and respiratory support are required, but mortality rates are as high as 50% to 90%.

When evaluating a patient with SLE who has pulmonary infiltrates, it is usually prudent to treat empirically for a possible infectious cause. Antibiotics and immunosuppressive therapy are generally started simultaneously and modified in response to additional diagnostic data. Opportunistic infections should be considered in a patient who is immunosuppressed and/or not responding appropriately to therapy.

Shrinking lung syndrome is characterized by pleuritic chest pain and shortness of breath, with progressive decrease in lung volumes on chest radiograph and pulmonary function tests. Aggressive immunosuppression may reverse the process. The cause is uncertain, but pleuropulmonary disease or diaphragmatic dysfunction is believed to contribute.

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Hematologic Involvement

CONT.

All three bone marrow cell lines can be affected in SLE. Leukopenia occurs in 50% of patients, with lymphopenia predominating. Whereas hemolytic anemia with direct antiglobulin (Coombs) test positivity is seen in only 10%, up to 80% of patients with SLE have normocytic, normochromic anemia of chronic disease. Thrombocytopenia occurs in 30% to 50% and is generally mild. Severe thrombocytopenia (<50,000/μL [50 × 10^9/L]) occurs in 10% of SLE patients in isolation or in conjunction with hemolytic anemia (Evans syndrome); isolated idiopathic thrombocytopenic purpura may be a clue to underlying SLE. APLA/LAC is also associated with thrombocytopenia. In patients with quiescent SLE, mild cytopenias do not require intervention.

SLE cytopenias are driven by both immune and nonimmune mechanisms. Immune-mediated hematologic conditions seen in SLE include autoimmune hemolytic anemia, Evans syndrome, aplastic anemia, and pure red cell aplasia. Nonimmune causes include chronic SLE inflammation, infections, medications, myelodysplasia, and myelofibrosis. It may be difficult to distinguish disease activity from drug effect, and empiric withdrawal of a drug may be required. Indications for bone marrow biopsy include the following: no obvious explanation for cytopenia, elevated serum iron, elevated mean corpuscular volume unexplained by medication effect, serum monoclonal spike, and the antiphospholipid antibody syndrome.

APLA/LAC antibodies are detected in 40% of patients with SLE, but fewer than 40% of these patients are clinically affected. The APLA/LACs are autoantibodies that interact with endothelial cells, monocytes, platelets, and complement to cause a prothrombotic state. The common clinical manifestations include venous and arterial thrombosis, miscarriage (especially second trimester), livedo reticularis, cytopenias, and cardiac valve thickening/vegetations. LAC carries a higher risk of thrombosis than other APLAs; however, the highest risk is in patients who are triple positive for LAC, anti-β_2-glycoprotein I, and anticardiolipin antibodies, who have a 30% rate of thrombosis. Patients with SLE are at increased risk for thrombosis even in the absence of detectable APLA/LAC.

See Thrombotic Disorders in MKSAP 17 Hematology and Oncology for a discussion on the antiphospholipid antibody syndrome.

Gastrointestinal Involvement

Gastrointestinal disease occurs in 25% to 40% of patients with SLE and may be underrecognized. Esophageal dysmotility and/or reflux occurs in 5% of patients, especially those with Raynaud phenomenon and anti-U1-ribonucleoprotein antibodies. Sterile peritonitis is a potential cause of abdominal pain. Mesenteric vasculitis can occur, often accompanied by cutaneous vasculitis. Mesenteric thrombosis can occur in patients with the antiphospholipid antibody syndrome. Hepatic involvement occurs in 10% and is distinguished from primary autoimmune hepatitis by lower aminotransferase levels, lack of autoimmune hepatitis-associated autoantibodies (anti-smooth muscle, anti-liver/kidney microsomal), different histology on biopsy, and the presence of antiribosomal P antibodies in SLE hepatitis. Very rarely, pancreatitis associated with SLE has been reported due to thrombosis, vasculitis, or medication complications. H

Malignancy

In patients with SLE, there is a sevenfold increased risk of non-Hodgkin lymphoma, especially diffuse large B-cell lymphoma, compared with the general population. This increased risk may relate to chronic B-cell activation and/or use of medications (for example, azathioprine or cyclophosphamide) that promote hematologic malignancies. Hodgkin lymphomas and leukemias are also more common in SLE, presumably for similar reasons. Lung cancer rates are increased by 1.4 times the general population risk, and patients with SLE who develop lung cancer are invariably smokers. H

Cervical cancer risk is increased and associated with both immunosuppressive (cyclophosphamide) use and increased prevalence of human papillomavirus in women with SLE. Women with SLE are less likely to undergo cervical screening than women in the general population, possibly related to care by specialists who are less likely to provide such screening. Certain solid organ tumors, notably breast, endometrial, prostate, and ovarian, may be less common in patients with SLE.

KEY POINTS

- The characteristic skin manifestation of systemic lupus erythematosus is acute cutaneous lupus erythematosus (also known as malar or butterfly rash), which is characterized by erythema and edema over the cheeks and bridge of the nose.
- Musculoskeletal involvement, including joint manifestations (most commonly inflammatory polyarthralgia) and myalgia, is common in patients with systemic lupus erythematosus.
- All patients with systemic lupus erythematosus should be evaluated for nephritis with baseline serum creatinine, urine protein-creatinine ratio, and urinalysis with microscopic evaluation.
- The most common neuropsychiatric manifestations of systemic lupus erythematosus are headache, cognitive dysfunction, and mood disorder.
- Pericarditis is the most common acute cardiac manifestation of systemic lupus erythematosus (SLE); ischemic heart disease is the most common cause of death for older patients with SLE.

Diagnosis

SLE should be considered in any patient who presents with unexplained multisystem disease. The most common early SLE manifestations include constitutional symptoms (fever, weight loss, or severe fatigue), arthralgia/arthritis, and skin disease. SLE should be included in the differential of a patient (especially a young woman) with any of the following manifestations: persistent rash, particularly if it is photosensitive; polyarticular

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arthritis; pleuritis; pericarditis; unexplained cytopenias, especially lymphopenia; a nephritic urine sediment; or thromboembolic disease. The American College of Rheumatology has defined 11 criteria, with the presence of any 4 serially or simultaneously sufficient to support the diagnosis of SLE, typically including a positive ANA (**Table 19**). Myalgia, arthralgia, and fatigue are insufficient reasons to test for ANA unless accompanied by objective SLE findings. Patients with these nonspecific symptoms should first be evaluated for more common conditions such as anemia, thyroid disease, and fibromyalgia. If unexplained findings such as cytopenias or organ involvement are found, SLE should then be added to the differential diagnosis.

Laboratory Studies

Initial laboratory studies for SLE include an ANA test to screen for nuclear-directed autoantibodies. The traditional indirect immunofluorescence ANA is highly sensitive (95%) for SLE and may convey additional information based on the immunofluorescence pattern observed, but its specificity is limited because it can be positive in patients with other autoimmune diseases or in those without clinical autoimmune disease (usually at low titer). Therefore, ANA should always be interpreted in the context of pretest probability.

If ANA is positive, SLE-specific autoantibodies (anti-double-stranded DNA, anti-Smith, anti-U1-ribonucleoprotein, and anti-La/SSB), as well as tests for other autoimmune diseases under consideration, should be obtained to further characterize the disease (**Table 20**). Anti-Ro/SSA antibody testing may simultaneously occur because a small percentage of patients with SLE are negative for ANA but positive for anti-Ro/SSA antibodies. Conversely, a negative ANA plus a negative anti-Ro/SSA essentially rules out SLE. In many commercial

TABLE 19. American College of Rheumatology Criteria for the Diagnosis of Systemic Lupus Erythematosus

Criteria[a]	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences
Discoid rash	Erythematous, circular, raised patches with keratotic scaling and follicular plugging; atrophic scarring may occur
Photosensitivity	Rash after exposure to ultraviolet light
Oral ulcers	Oral and nasopharyngeal ulcers (observed by physician)
Arthritis	Nonerosive arthritis of ≥2 peripheral joints, with tenderness, swelling, or effusion
Serositis	Pleuritis or pericarditis (documented by electrocardiogram, rub, or evidence of effusion)
Kidney disorder	Urinalysis: 3+ protein or urine protein >500 mg/24 h; cellular casts
Neurologic disorder	Seizures or psychosis (without other cause)
Hematologic disorder	Hemolytic anemia or leukopenia (<4000/μL [4.0 × 10^9/L]) or lymphopenia (<1500/μL [1.5 × 10^9/L]) or thrombocytopenia (<100,000/μL [100 × 10^9/L]) in the absence of offending drugs
Immunologic disorder	Anti-double-stranded DNA, anti-Smith, and/or antiphospholipid antibodies
ANA	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in the absence of drugs known to induce ANA

ANA = antinuclear antibodies.

[a]Any combination of 4 or more of the 11 criteria, well documented at any time during a patient's history, makes it likely that the patient has systemic lupus erythematosus (specificity and sensitivity are 95% and 75%, respectively).

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TABLE 20. Common Autoantibodies in Systemic Lupus Erythematosus

Autoantibody	Frequency in SLE	Comments
Antinuclear	95%	Useful as an initial screening test
Anti-double-stranded DNA	50%	Found in more severe disease, especially kidney disease; antibody levels commonly follow disease activity and are useful to monitor
Anti-Ro/SSA	40%	Associated with photosensitive rashes, discoid lupus, and neonatal SLE, including congenital heart block; also common in Sjögren syndrome
Anti-U1-ribonucleoprotein	35%	Associated with Raynaud phenomenon and esophageal dysmotility; also seen in MCTD
Anti-Smith	25%	Specific for SLE; often associated with more severe disease
Anti-La/SSB	15%	Common in Sjögren syndrome; less common in SLE and neonatal SLE
Antiribosomal P	15%	Associated with CNS lupus and lupus hepatitis

CNS = central nervous system; MCTD = mixed connective tissue disease; SLE = systemic lupus erythematosus.

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laboratories, the sequential testing of autoantibodies has recently been automated. Although these new test sequences may simplify physician assessment, they often use a different method for assessing the initial ANA (ELISA rather than indirect immunofluorescence) that may have reduced sensitivity and specificity.

A complete blood count, chemistry panel, and urinalysis (including microscopy) should be ordered, along with an erythrocyte sedimentation rate (ESR) and potentially a C-reactive protein level (CRP). ESR is preferred over CRP initially because some patients with SLE do not generate CRP during SLE flares. However, monitoring CRP in patients with SLE and defining those who do or do not generate CRP during flares may be helpful in distinguishing flares from infection. Complements should also be assessed (most commonly, C3 and C4) because these levels are reduced during SLE activity, reflecting immune complex formation that provokes complement activation. These studies may help define the presence of organ involvement and the level of inflammation as well as provide a baseline for following disease activity.

Differential Diagnosis

The differential diagnosis of SLE includes other autoimmune multisystem diseases, many of which are similarly more common in women: ANCA-associated vasculitis, rheumatoid arthritis, adult-onset Still disease, dermatomyositis, Sjögren syndrome, and mixed connective tissue disease. Severe viral infection can also mimic SLE (fever, myalgia, rash, cytopenias).

Drug-Induced Lupus Erythematosus

Drug-induced lupus erythematosus (DILE) occurs when a medication triggers immune-mediated disease with manifestations mimicking SLE. Common symptoms include malaise, fever, arthritis, and rash; kidney and CNS disease are uncommon. ANA is often transiently positive, along with antihistone antibodies. Diagnosis is confirmed when symptoms resolve after discontinuing the offending agent. Patients with SLE are at no more risk of DILE than the general population.

High-risk medications for DILE include procainamide, methyldopa, quinidine, and hydralazine; all but hydralazine are now rarely used in current practice. Some drugs are lower risk (for example, minocycline), but because of frequent use, more cases develop. **Table 21** lists medications associated with DILE, the autoantibodies detected, and clinical manifestations.

Undifferentiated Connective Tissue Disease

Undifferentiated connective tissue disease (UCTD) refers to syndromes with objective abnormalities that do not meet sufficient criteria to be categorized as SLE or another specific connective tissue disease. Patients who have two or three criteria for SLE can be diagnosed as having UCTD or alternatively may be designated as having incomplete SLE.

KEY POINTS

- The most common early manifestations of systemic lupus erythematosus include constitutional symptoms, arthralgia/arthritis, and skin disease.
- Initial testing for systemic lupus erythematous (SLE) begins with antinuclear antibodies; if positive, SLE-specific autoantibodies (anti–double-stranded DNA, anti-Smith, anti-U1-ribonucleoprotein, and anti-La/SSB) should be obtained to further characterize the disease.
- In addition to antinuclear antibody and other autoantibody testing, laboratory studies for evaluating systemic lupus erythematosus include a complete blood count, chemistry panel, complement levels, erythrocyte sedimentation rate, and urinalysis.

(Continued)

TABLE 21. Medications Commonly Associated with Drug-Induced Lupus Erythematosus

Medication	Antibodies Detected	Comments
Procainamide	ANA; antihistone	75% ANA positive; 20% develop DILE; fever; arthritis; serositis
Hydralazine	ANA; antihistone	20% ANA positive; 5%-8% develop DILE; fever; arthritis; rare vasculitis and kidney disease
Minocycline	ANA; ANCA; anti-dsDNA rare	Arthritis; vasculitis; autoimmune hepatitis
Antithyroid drugs	ANA; ANCA; antihistone	Vasculitic rash; rare pulmonary and kidney disease
Statins	ANA; antihistone; anti-dsDNA	SLE, SCLE, dermatomyositis, and polymyositis all reported
Calcium channel blockers	ANA; anti-Ro/SSA; antihistone rare	SCLE
Thiazide diuretics	ANA; anti-Ro/SSA; antihistone rare	SCLE
ACE inhibitors	ANA; anti-Ro/SSA; antihistone rare	SCLE
TNF-α inhibitors	ANA in 23%-57%; chromatin and anti-dsDNA common; antihistone rare	DILE most common with infliximab, uncommon for etanercept; SLE, SCLE, DLE all reported

ANA = antinuclear antibodies; DILE = drug-induced lupus erythematosus; DLE = discoid lupus erythematosus; dsDNA = double-stranded DNA; SCLE = subacute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus; TNF = tumor necrosis factor.

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KEY POINTS (continued)

- Drug-induced lupus erythematosus occurs when a medication triggers immune-mediated disease with manifestations mimicking systemic lupus erythematosus; treatment includes discontinuing the offending agent.
- Undifferentiated connective tissue disease refers to syndromes with objective abnormalities that do not meet sufficient criteria to be categorized as systemic lupus erythematosus or another specific connective tissue disease.

Management

In virtually all cases, SLE management requires pharmacologic therapy (**Table 22**). Serial monitoring of disease-responsive laboratory studies (complete blood count, ESR, anti–double-stranded DNA antibodies, complements [C3 and C4], urinalysis, and urine protein-creatinine ratio) is mandatory to track disease activity, identify warning signs of disease flare, and monitor response to therapy. Frequency of monitoring depends upon current level of disease activity. Modification of therapy should generally be done with input from the patient's rheumatologist and/or nephrologist.

Hydroxychloroquine is an anchor drug for SLE and should be initiated in every patient with SLE who can tolerate the medication. This agent can prevent SLE flares, improve outcomes in high-risk pregnancies, reduce the risk of thrombosis and myocardial infarction, reduce disease-associated damage in general, and improve survival. It is particularly useful for arthritis and the skin manifestations. Hydroxychloroquine may be the only medication needed for mild disease.

For many acute manifestations of SLE, glucocorticoids are the initial treatment based on their efficacy and rapid onset of action. Glucocorticoid dose should be appropriate to the disease severity and the organs involved. For SLE-related arthritis, rash, pleuritis, pericarditis, or mild cytopenias, a dose of 20 to 40 mg/d of prednisone may be appropriate. Patients with more severe disease (for example, class II-IV nephritis, more severe cytopenias, or severe pleural or pericardial disease) may require high-dose glucocorticoids (40 to 60 mg/d of prednisone). The most severe manifestations (for example, rapidly progressive class III-IV nephritis, psychosis, seizures, diffuse alveolar hemorrhage, or myocarditis) should generally be treated in the hospital with high-dose intravenous glucocorticoids (1000 mg/d for 3 days) followed by 40 to 60 mg/d of oral prednisone. Given the many adverse effects associated with glucocorticoid use, glucocorticoids alone are generally not used for chronic therapy, and additional therapy is quickly added for disease control and glucocorticoid sparing. Prednisone is generally tapered as tolerated after the first month of therapy with the goal of reducing the dose to less than 10 mg/d by 3 months.

For severe SLE, the goal is to control autoimmunity and inflammation and induce disease remission with potent medications, then substitute with less potent and less toxic therapy to maintain the remission. For active lupus nephritis, mycophenolate mofetil is currently the preferred oral agent; dosage is 2000 to 3000 mg/d and may take 4 to 6 weeks to reach full efficacy. For the most severe disease (severe active nephritis, acute CNS lupus, pulmonary hemorrhage, myocarditis), intravenous cyclophosphamide in a dosage of 500 mg every 2 weeks for 6 doses or 750 mg/m² every month for 6 months is usually used to induce remission, followed by mycophenolate mofetil or possibly azathioprine as maintenance therapy. The biologic agent belimumab is approved for

TABLE 22. Medications Commonly Used to Treat Systemic Lupus Erythematosus

Medication	Common Uses in SLE	Important Side Effects
NSAIDs	Painful, non-organ-threatening manifestations such as arthritis	Hypertension; GI bleeding; AKI
Prednisone	Used for all manifestations in varying doses	Hypertension; glucose intolerance; weight gain; infection; osteonecrosis
Hydroxychloroquine	Used for mild to moderate disease; especially useful for skin involvement and to prevent disease flares	Rash; retinopathy; vacuolar myopathy
Mycophenolate mofetil	Moderate to severe disease; as effective as cyclophosphamide for remission induction for nephritis	Bone marrow suppression; elevation of liver enzymes; infection
Azathioprine	Moderate to severe disease	Bone marrow suppression; elevation of liver enzymes; hematologic malignancy
Cyclophosphamide	Severe organ or life-threatening disease	Bone marrow suppression; hemorrhagic cystitis; infection; malignancy
Belimumab	Add-on therapy for moderate to severe disease	Infusion reactions; infections

AKI = acute kidney injury; GI = gastrointestinal; SLE = systemic lupus erythematosus.

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CONT.

patients with incomplete responses to conventional treatments. See Glomerular Diseases in MKSAP 17 Nephrology for details on the treatment of lupus nephritis.

NSAIDs can be useful for management of patients with arthritis, pleuritis, or pericarditis. These agents should be avoided in patients with kidney disease and/or uncontrolled hypertension. H

See Principles of Therapeutics for additional information on SLE medication toxicities, monitoring parameters, and more.

KEY POINTS

- Serial monitoring of disease-responsive laboratory studies (complete blood count, erythrocyte sedimentation rate, anti-double-stranded DNA antibodies, complements, urinalysis, and urine protein-creatinine ratio) is mandatory to track disease activity, identify warning signs of disease flare, and monitor response to therapy.
- Hydroxychloroquine should be initiated in every patient with systemic lupus erythematosus who can tolerate the medication.
- Glucocorticoids are usually the initial therapy for acute manifestations of systemic lupus erythematosus, with dosing based on disease severity.
- For severe systemic lupus erythematosus, the goal is to control autoimmunity and inflammation and induce disease remission with potent medications, then substitute with less potent and less toxic therapy to maintain the remission.

Pregnancy and Childbirth Issues

Women with SLE experience miscarriage, stillbirth, and premature delivery two to five times more often than women without the disease. SLE pregnancies are at an eightfold risk for intrauterine growth retardation. Active disease, especially nephritis, and the presence of anti-Ro/SSA and/or APL antibodies are risk factors for fetal morbidity and mortality. Conception should ideally be deferred until SLE disease is quiescent.

Proteinuria may increase during pregnancy in patients with SLE, rendering differentiation from preeclampsia/eclampsia a challenge. Increases in anti-double-stranded DNA antibody levels or the acute development of an active urine sediment implicates SLE as the cause. In contrast, serum urate rises in preeclampsia but not during lupus flares.

Fetuses of mothers who are positive for anti-Ro/SSA or anti-La/SSB antibodies are at risk for developing neonatal lupus erythematosus. Arthritis and rash are common manifestations; in 2% of these pregnancies, congenital heart block may occur and cause mortality or require permanent pacing. Risk of neonatal lupus erythematosus rises to 12% after a first child born with the condition. Recent studies suggest that maternal hydroxychloroquine use may reduce the risk of neonatal lupus erythematosus.

Medications that are safe for use during SLE pregnancies include hydroxychloroquine, prednisone, and azathioprine (if an immunosuppressive agent is absolutely needed). Cyclophosphamide-induced infertility is age- and dose-dependent and should be discussed with female patients of reproductive age before administering this medication. See Principles of Therapeutics for more information on medications and pregnancy.

KEY POINTS

- Women with systemic lupus erythematosus (SLE) experience miscarriage, stillbirth, and premature delivery two to five times more often than women without the disease; furthermore, SLE pregnancies are at an eightfold risk for intrauterine growth retardation.
- Fetuses of mothers who are positive for anti-Ro/SSA or anti-La/SSB antibodies are at risk for developing neonatal lupus erythematosus.

Prognosis

SLE prognosis has improved significantly from the 1960s (50% 5-year survival rate) to the present (>90% 5-year survival rate). Nonetheless, there continues to be a bimodal mortality for SLE, with early deaths related to SLE and infections and late mortality associated with cardiovascular disease. Factors adversely affecting survival include myocarditis, nephritis, low socioeconomic status, male gender, and age over 50 years at diagnosis.

A complete 5-year remission in SLE is uncommon, occurring in only 2% of patients. Current data suggest 20% to 40% of patients have an incomplete response to available therapies, indicating the need for better therapeutic approaches.

KEY POINT

- Factors adversely affecting survival of patients with systemic lupus erythematosus include myocarditis, nephritis, low socioeconomic status, male gender, and age over 50 years at diagnosis.

Sjögren Syndrome

Introduction

Sjögren syndrome is an immune-mediated disease of unknown cause manifesting as infiltrative inflammation that damages exocrine glands, including the major and minor salivary glands, lacrimal glands, and, less commonly, other exocrine glands such as the pancreas.

Pathophysiology

Biopsied glandular tissue from patients with Sjögren syndrome reveals inflammatory infiltrates composed of

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CD4-positive T lymphocytes, accompanied by lesser populations of B and plasma cells. Immune system dysregulation, including B-cell hyperactivity and hypergammaglobulinemia, is commonly reported.

Epidemiology

The prevalence of Sjögren syndrome ranges from 0.19% to 1.39%, depending upon the classification criteria used. However, Sjögren syndrome may be underdiagnosed, such that its prevalence may be higher than reported. Incidence peaks around the fifth decade, and there is a female predominance (9:1 ratio).

Clinical Manifestations

The prominent clinical feature of Sjögren syndrome is sicca, or dryness, particularly of the eyes (keratoconjunctivitis sicca) and mouth (xerostomia). Keratoconjunctivitis sicca can result in corneal damage and visual impairment. Xerostomia can result in dental caries due to loss of antibacterial features of saliva. Dryness of mucosal surfaces (such as the vagina, skin, or bronchi) and exocrine gland hypertrophy are common findings. Sjögren syndrome can also cause extraglandular manifestations as a result of autoimmune/inflammatory mechanisms (**Table 23**).

Presumably because of preexisting lymphocyte activation, patients with Sjögren syndrome have an increased risk of lymphoma, with diffuse large B-cell and mucosa-associated lymphoid tissue (MALT) lymphomas being the most common (See MKSAP 17 Hematology and Oncology). Sjögren syndrome lymphoma risk is 16- to 44-fold that of the general population. Hypocomplementemia and lymphopenia at the time of Sjögren diagnosis may predict lymphoma development. New and persistent adenopathy or other symptoms suggestive of lymphoma should prompt further evaluation with lymph node biopsy.

TABLE 23. Extraglandular Clinical Manifestations of Sjögren Syndrome

Site/Organ	Manifestation/Frequency
General	Fatigue (70%), fever (6%)
Skin	Rash, cutaneous vasculitis: 10%-16%
Joint	Arthralgia/arthritis: 36%
Lung	Interstitial pneumonitis: 5%-9%
Kidney	Interstitial nephritis, distal (type 1) renal tubular acidosis, glomerulonephritis: 5%-6%
Neurologic	Central nervous system (CNS): demyelinating disease, myelopathy, cranial nerve neuropathy
	Peripheral nervous system: small-fiber neuropathy, mononeuritis multiplex, peripheral neuropathy: 8%-27% (for CNS and peripheral)
Gastrointestinal	Autoimmune hepatitis, primary biliary cirrhosis: 3%-20%
Hematologic	Lymphoma, cytopenia: 2%
Other	Systemic vasculitis (7%), cryoglobulinemia (4%-12%), Raynaud phenomenon (16%), thyroid disease (10%-15%)

Diagnosis

Diagnosis of Sjögren syndrome is based primarily on typical sicca symptoms as well as glandular (enlarged lacrimal and/or parotid glands) and extraglandular manifestations. It is helpful to confirm eye and mouth dryness in an objective manner, for example, by documenting reduced tear production utilizing the Schirmer test (decreased wetting of tear test strips) or with special stains and slit-lamp examination. Rarely, gallium scanning or sialography may be warranted to characterize the exocrine gland involvement.

Laboratory findings include positive autoimmune serologies (rheumatoid factor, antinuclear, anti-Ro/SSA, and anti-La/SSB antibodies) and hypergammaglobulinemia. Anti-Ro/SSA and anti-La/SSB antibodies are characteristic for Sjögren syndrome but are also common in patients with systemic lupus erythematosus, mothers of infants with neonatal lupus, and, occasionally, healthy persons. Rheumatoid factor levels are typically higher than those seen in rheumatoid arthritis. In the presence of classic historical and physical findings, the presence of anti-Ro/SSA and anti-La/SSB antibodies may be sufficient to diagnose Sjögren syndrome. In unclear cases, a lip biopsy demonstrating minor salivary gland inflammation is considered the gold standard for diagnosis.

Other autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and autoimmune thyroiditis, are commonly associated with Sjögren syndrome. This has traditionally been called secondary Sjögren syndrome, although recent classification criteria do not make this distinction. Conditions that mimic Sjögren syndrome include IgG4-related disease, graft versus host disease, amyloidosis, sarcoidosis, AIDS (diffuse infiltrative lymphocytosis syndrome), hepatitis C virus infection, and history of head and neck irradiation. Many of these conditions share with Sjögren syndrome a predilection for infiltration of exocrine glands, sicca symptoms, and/or positive antinuclear antibodies or rheumatoid factor, rendering diagnosis difficult.

Management

Management of Sjögren syndrome consists of symptomatic, local, and systemic approaches (**Table 24**). Sicca symptoms are treated with hydration and lubrication, although other local measures and medications may be helpful. Avoidance of medications that worsen sicca (for example, anticholinergic agents) is recommended. Immunosuppressive therapy does not alleviate sicca symptoms but may suppress extraglandular

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TABLE 24. Management of Sjögren Syndrome

Symptom	Therapy
Ocular sicca	Artificial tears; glasses with side panels to reduce exposure; punctal plugs/ occlusion; topical cyclosporine
Oral sicca	Artificial saliva; sugar-free lozenges to promote salivation; good dental hygiene; muscarinic cholinergic receptor stimulators (e.g., pilocarpine, cevimeline)
Vaginal/Skin sicca	Topical lubrication
Extraglandular	Mild symptoms (e.g., arthralgia or rash): NSAIDs; hydroxychloroquine; topical or low-dose glucocorticoids
	Moderate to severe symptoms (e.g., lung, kidney, or nervous system involvement; vasculitis): high-dose glucocorticoids; immunosuppressive therapy such as methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, or rituximab

manifestations. Biologic agents have not been proven to treat Sjögren syndrome, although some reports suggest responsiveness to the anti-B-cell antibody rituximab.

Prognosis

Most patients with Sjögren syndrome do not progressively worsen over time, and their mortality rate is similar to the general population. Increased mortality is associated with lymphoproliferative malignancy and/or other associated autoimmune disease. Low complement levels, lymphocytopenia, and cryoglobulinemia at diagnosis are predictive of unfavorable outcome due to lymphoma, severe disease manifestations (such as vasculitis), and premature death.

KEY POINTS

- Sjögren syndrome manifests as infiltrative inflammation of exocrine glands, characterized by dry eyes and dry mouth.
- Patients with Sjögren syndrome have a 16- to 44-fold increased risk of lymphoma, most commonly from diffuse large B-cell and mucosa-associated lymphoid tissue lymphomas.
- In patients with classic historical and physical findings, the presence of anti-Ro/SSA and anti-La/SSB antibodies may be sufficient to diagnose Sjögren syndrome; in unclear cases, a lip biopsy demonstrating minor salivary gland inflammation is considered the gold standard for diagnosis.
- Autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and autoimmune thyroiditis, are commonly associated with Sjögren syndrome.

Mixed Connective Tissue Disease

Introduction

Mixed connective tissue disease (MCTD) is an overlap syndrome that includes features of systemic lupus erythematosus (SLE), systemic sclerosis, and/or polymyositis in the presence of anti-U1-ribonucleoprotein (RNP) antibodies.

Epidemiology

MCTD is rare (1:1,000,000). Age at onset is between 30 and 50 years, with a 9:1 female predominance. Most patients have no known risk factors.

Clinical Manifestations and Diagnosis

More than 50% of patients with MCTD have hand edema and synovitis at disease onset. About one third develop myositis, and nearly half develop decreased esophageal motility and fibrosing alveolitis. Pulmonary arterial hypertension occurs in 20%, with fatigue often the initial symptom. Patients suspected of having MCTD should undergo high-resolution CT of the chest, echocardiography, and pulmonary function testing. Clinical findings may evolve, such that a patient who initially appears to have a single disease (for example, SLE) may accrue features to support an MCTD diagnosis.

Skin manifestations include sclerodactyly, scleroderma, calcinosis, telangiectasias, photosensitivity, malar rash, and Gottron rash. Pleuropericarditis occurs in up to 60% of patients, and sicca symptoms in up to 50%. Trigeminal neuralgia occurs in up to 25% of patients. Kidney involvement occurs in 25% of patients, typically as membranous nephropathy.

In addition to overlapping features of SLE, systemic sclerosis, and/or polymyositis, MCTD diagnosis requires the presence of anti-U1-RNP antibodies. Laboratory studies may additionally show leukopenia, thrombocytopenia, and an elevated erythrocyte sedimentation rate. Antinuclear antibodies may be present, with a very high titer (≥1:1200) in a speckled pattern. The presence of anti-Smith or anti-double-stranded DNA antibodies should suggest SLE rather than MCTD.

Management

MCTD management is determined by the manifestations of the individual patient. Glucocorticoids, azathioprine, and methotrexate can be used for arthritis and myositis. Symptoms associated with Raynaud phenomenon may benefit from calcium channel blockers; patients with esophageal dysmotility should receive proton pump inhibitors. Cyclophosphamide may be tried for interstitial lung disease and phosphodiesterase inhibitors and/or anti-endothelin therapies for pulmonary arterial hypertension.

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Prognosis

The course of MCTD is variable; the likelihood of developing interstitial lung disease, pulmonary arterial hypertension, and/or cardiovascular disease increases with disease duration. MCTD mortality is increased compared with SLE, mainly as a consequence of pulmonary arterial hypertension. Renovascular disease as seen in systemic sclerosis may uncommonly contribute to morbidity and mortality.

KEY POINTS

- Mixed connective tissue disease is an overlap syndrome that includes features of systemic lupus erythematosus, systemic sclerosis, and/or polymyositis in the presence of anti-U1-ribonucleoprotein antibodies.
- Typical findings of mixed connective tissue disease include hand edema, synovitis, myositis, decreased esophageal motility, and fatigue.
- Treatment for mixed connective tissue disease is determined by the manifestations of the individual patient.

Crystal Arthropathies

Introduction

In crystal arthropathies, metabolic abnormalities promote the formation and deposition of crystals that stimulate inflammation. This chapter discusses gout, calcium pyrophosphate deposition, and basic calcium phosphate deposition.

Gout

Gout is characterized by intermittent painful inflammatory joint attacks, resulting from crystallization of excessive levels of uric acid (hyperuricemia).

Epidemiology

Gout is the most common inflammatory arthritis in the United States (prevalence, 4%). Serum urate levels rise after puberty in men and after menopause in women; premenopausal women are therefore protected from gout except in cases of underlying disease or strong genetic factors. Gout becomes increasingly common among older individuals owing to accumulation of additional hyperuricemia risk factors (for example, chronic kidney disease). Approximately 13% of patients over the age of 80 years are affected.

Gout is typically associated with multiple comorbidities (hypertension, obesity, diabetes mellitus, chronic kidney disease, vascular disease, dyslipidemia, and nephrolithiasis) that may complicate treatment, either by posing contraindications to specific therapies or because treating some comorbid conditions can worsen hyperuricemia (for example, using diuretics to treat hypertension).

Despite important advances in understanding and treating gout, it remains a disease that is often suboptimally managed.

Pathophysiology

Uric acid is the end product of purine metabolism in humans. Free purines arise from nucleic acid breakdown during cell turnover, from adenosine triphosphate metabolism, and through dietary intake. Xanthine oxidase is the terminal enzyme in human uric acid synthesis. In contrast to most mammals, humans lack the enzyme uricase, which processes urate to the more soluble allantoin (**Figure 20**).

At physiologic conditions (pH, 7.4), uric acid exists primarily as its ionized form, urate; therefore, hyperuricemia technically refers to elevated serum urate. The saturation concentration of urate is 6.8 mg/dL (0.40 mmol/L), with monosodium urate crystals unlikely to form at concentrations below this level; hyperuricemia is therefore defined based on this physiologic parameter. Urate is cleared by the kidneys via both glomerular filtration and active urate secretion in the proximal tubule; resorption by other proximal tubule transporters occurs concurrently.

The most common risk factor for hyperuricemia is underexcretion of urate by the kidneys due to impaired glomerular filtration and/or defects of urate handling in the renal proximal tubule (**Table 25**). Alternatively, about 10% of patients with gout have genetic aberrancies causing excessive uric acid production. Hyperuricemia in the adult population is common (up to 20%) but usually asymptomatic; measurement of serum urate is therefore not a useful screening tool for gout in the absence of appropriate clinical signs and symptoms.

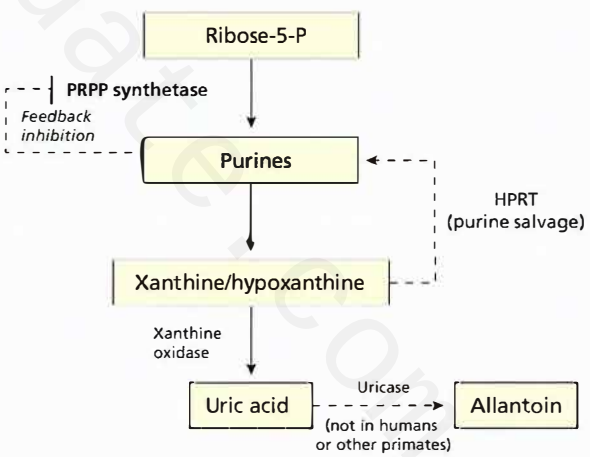

FIGURE 20. Purine biosynthesis and metabolism to uric acid. De novo purine synthesis can occur in human cells. Rarely, hereditary overactivity of phosphoribosylpyrophosphate (PRPP) synthetase results in excessive purine production. Purine salvage (to recover purines from the breakdown of nucleic acids for reuse) occurs through hypoxanthine-guanine phosphoribosyltransferase (HPRT); HPRT deficiency results in purine depletion and thus increased uric acid synthesis due to lack of negative feedback (as in Lesch-Nyhan syndrome). Humans lack the gene for uricase; in most other mammals, this enzyme converts uric acid to the more soluble allantoin and results in much lower urate levels.

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TABLE 25. Causes of Hyperuricemia

Primary renal uric acid underexcretion (hereditary, renal tubular basis)
Chronic kidney disease of any cause (secondary uric acid underexcretion)
Uric acid overproduction due to primary defect in purine metabolism: PRPP synthetase overactivity; HPRT deficiency
Conditions of cell turnover leading to purine/urate generation: leukemia/lymphoma; psoriasis; hemolytic anemia; polycythemia vera
Drug-induced hyperuricemia (agents reducing renal glomerular filtration and/or tubular urate excretion): thiazide and loop diuretics; cyclosporine; low-dose salicylates; ethambutol; pyrazinamide; lead ingestion/toxicity
Diet-induced hyperuricemia (agents high in purines or inducing purine/urate biosynthesis): alcohol; shellfish; red meat; high-fructose corn syrup-sweetened beverages and foods

HPRT = hypoxanthine-guanine phosphoribosyltransferase; PRPP = phosphoribosylpyrophosphate.

Nonetheless, hyperuricemia is the primary risk factor for gout, with increasing incidence of gout in patients with higher serum urate levels. The mechanisms leading to urate crystallization are incompletely elucidated but depend on temperature, pH, and other physicochemical factors.

Once crystals form, resident tissue macrophages phagocytose them to initiate an inflammatory cascade. Interleukin (IL)-1β production fuels the process and promotes synthesis of additional cytokines (for example, tumor necrosis factor α, IL-6). Additionally, complement activation on the crystal surface generates split products that stimulate and attract neutrophils. Collectively, these signals promote neutrophil infiltration, the hallmark of an established gout attack.

Clinical Manifestations

Gout can be considered as having three phases: acute gouty arthritis, intercritical gout, and chronic recurrent or tophaceous gout (also known as chronic tophaceous gouty arthropathy).

Acute Gouty Arthritis

The classic gout presentation is podagra, in which the metatarsophalangeal joint of the great toe becomes painful, red, and swollen over 12 to 24 hours. First gout attacks typically are monoarticular and begin at night. Approximately 90% of first attacks present in this manner. First attacks in women are less likely to fit this classic picture.

Recurrent attacks can occur in nearly any joint, with either monoarticular or polyarticular presentation. Attacks in bursae also occur. In poorly controlled disease, flares become more frequent and involve an increasing number of joints. Systemic inflammation is common, including fever (typically <38.9 °C [102.0 °F]), peripheral leukocytosis (up to 13,000/μL [13 × 10^9/L]), and elevated inflammatory markers (C-reactive protein and erythrocyte sedimentation rate). Systemic findings tend to correlate with the severity of the attack and normalize rapidly with treatment.

Soft tissues adjacent to the joints can be affected during acute flares, becoming red, painful, and edematous. Soft-tissue inflammation can mimic cellulitis, tenosynovitis, or dactylitis, rendering the diagnosis of gout challenging.

Although a chronically elevated serum urate level is a hallmark of gout, serum urate levels can occasionally be low during acute attacks, possibly because cytokines promote renal urate excretion. Thus, when there is reasonable clinical suspicion for gout, treatment is indicated even with a normal serum urate level. The serum urate level should be reassessed after the flare has resolved for a more accurate characterization.

Intercritical Gout

The period between gout attacks is referred to as the intercritical phase, during which the patient is typically asymptomatic. Early in the course of disease, attacks tend to be infrequent, but most patients experience a recurrent attack within 2 years of their first attack. In long-standing or poorly controlled gout, the time between attacks tends to diminish.

Chronic Recurrent and Tophaceous Gout

Chronic recurrent gout refers to a disease state in which poorly controlled gout results in frequent flares and/or chronic gouty arthropathy, in which synovitis persists between acute attacks. Chronic recurrent gout is usually the consequence of ineffective therapy, medication noncompliance, or undertreatment. Chronic recurrent gout poses a significant economic burden in terms of health care costs and lost time from work. Patients with this degree of gout severity should be referred to a rheumatologist for management.

Tophi (stone-like deposits of monosodium urate surrounded by a fibrous and inflammatory rind) may form in the joints and soft tissues (**Figure 21**). Tophi can form in any joint,



FIGURE 21. Numerous, bulky deposits of monosodium urate crystals form tophi, a sign of late-stage gout that has not been adequately treated with urate-lowering therapy.

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leading to bone erosion, chronic joint damage, skin ulceration, infection, disability, and impaired quality of life.

Diagnosis

Gout should be suspected in the setting of acute monoarticular or polyarticular inflammation in an at-risk patient (see Epidemiology). Infectious arthritis must be actively excluded, given its high rate of morbidity and mortality. The differential diagnosis of acute gout is listed in **Table 26**. A high C-reactive protein and/or erythrocyte sedimentation rate support an inflammatory process but are nonspecific. A high serum urate level supports the potential for gout, but most patients with hyperuricemia do not have gout, and serum urate may be low during some acute attacks.

The gold standard for diagnosing gout is joint aspiration and synovial fluid analysis. Synovial fluid analysis permits definitive diagnosis and can rule out other, clinically indistinguishable conditions. Under polarized light, monosodium urate crystals are needle shaped and negatively birefringent (yellow when parallel, blue when perpendicular to the polarizing axis). Synovial fluid leukocyte count should also be measured; gout fluid is typically inflammatory (2000/μL to >100,000/μL [2.0-100 × 10^9/L], neutrophil predominance of ≥50%). Whereas extracellular crystals confirm a chronic gout diagnosis, crystals within neutrophils define active, gout-induced inflammation. Gram stain and cultures must be obtained to exclude infection. Acute gout and joint infection occasionally coexist.

Because joint aspiration is not always feasible or successful, diagnosis is occasionally made on clinical grounds alone. However, a clinical diagnosis does not permit the definite exclusion of infection or other inflammatory arthritis. The American College of Rheumatology preliminary classification criteria for acute gout serve as a helpful, albeit imperfect, tool for diagnosing gout (**Table 27**). Importantly, infection of the first metatarsophalangeal joint is uncommon.

Radiography is of limited utility in early gout but may be warranted to exclude fracture or other non-gout etiologies. In severe or long-standing gout, radiographs can demonstrate classic gouty erosions described as punched-out lesions, often with overhanging edges where the bones have been eaten away by tophaceous deposits (**Figure 22**).

TABLE 26. Differential Diagnosis of Acute Gouty Arthritis

Condition	Comments
Infectious arthritis	Presentation may be identical to gout. Infectious arthritis is usually monoarticular but can be polyarticular. Gout and infectious arthritis can also coexist.
Acute calcium pyrophosphate crystal arthritis (also known as pseudogout)	Pseudogout is less likely to present in the great toe (podagra), but acute presentations may still be identical to gout. Synovial fluid analysis can distinguish these entities.
Basic calcium phosphate deposition	Because of their small size, basic calcium phosphate crystals are unlikely to be seen in synovial fluid on light microscopy except as aggregates stained with alizarin red.
Trauma	Trauma can lead to local pain and swelling, with or without a fracture, and can also trigger a gout attack.
Other forms of inflammatory arthritis (e.g., reactive arthritis, rheumatoid arthritis, psoriatic arthritis, acute rheumatic fever)	Clinical context, affected joints, and pattern of arthritis are all helpful in distinguishing these entities. Synovial fluid analysis is particularly important when there is diagnostic uncertainty.

Management

Gout management centers on two fundamental principles: 1) control of inflammation to treat or prevent acute gout attacks and 2) reduction of serum urate to treat the underlying hyperuricemia that leads to inflammatory disease. Both are essential for proper gout management.

Treatment of Acute Gouty Arthritis

Acute gout flares should be treated with pharmacologic intervention, ideally within 24 hours of onset to maximize treatment efficacy. In patients with classic podagra or other mild to moderate presentations, monotherapy with colchicine (1.2 mg followed by 0.6 mg 1 hour later), full-dose NSAIDs (such as naproxen 500 mg twice daily), or glucocorticoids (for

TABLE 27. American College of Rheumatology Criteria for the Classification of Acute Arthritis of Primary Gout

Criteria
The presence of six of the following clinical, laboratory, and radiographic findings, even in the absence of crystal identification:
More than one attack of acute arthritis
Maximum inflammation developed within 1 day
Monoarthritis attack
Redness observed over joints
First metatarsophalangeal joint painful or swollen
Unilateral first metatarsophalangeal joint attack
Unilateral tarsal joint attack
Tophus (suspected)
Hyperuricemia
Asymmetric swelling within a joint visible on physical examination or radiography
Subcortical cysts without erosions visible on radiography
Monosodium urate monohydrate microcrystals in joint fluid during attack
Joint fluid culture negative for organisms during attack

Adapted with permission from John Wiley & Sons, from Wallace SL, Robinson H, Masi AT, et al. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum. 1977;20(3):895-900. [PMID: 856219] Copyright 1977 American College of Rheumatology.

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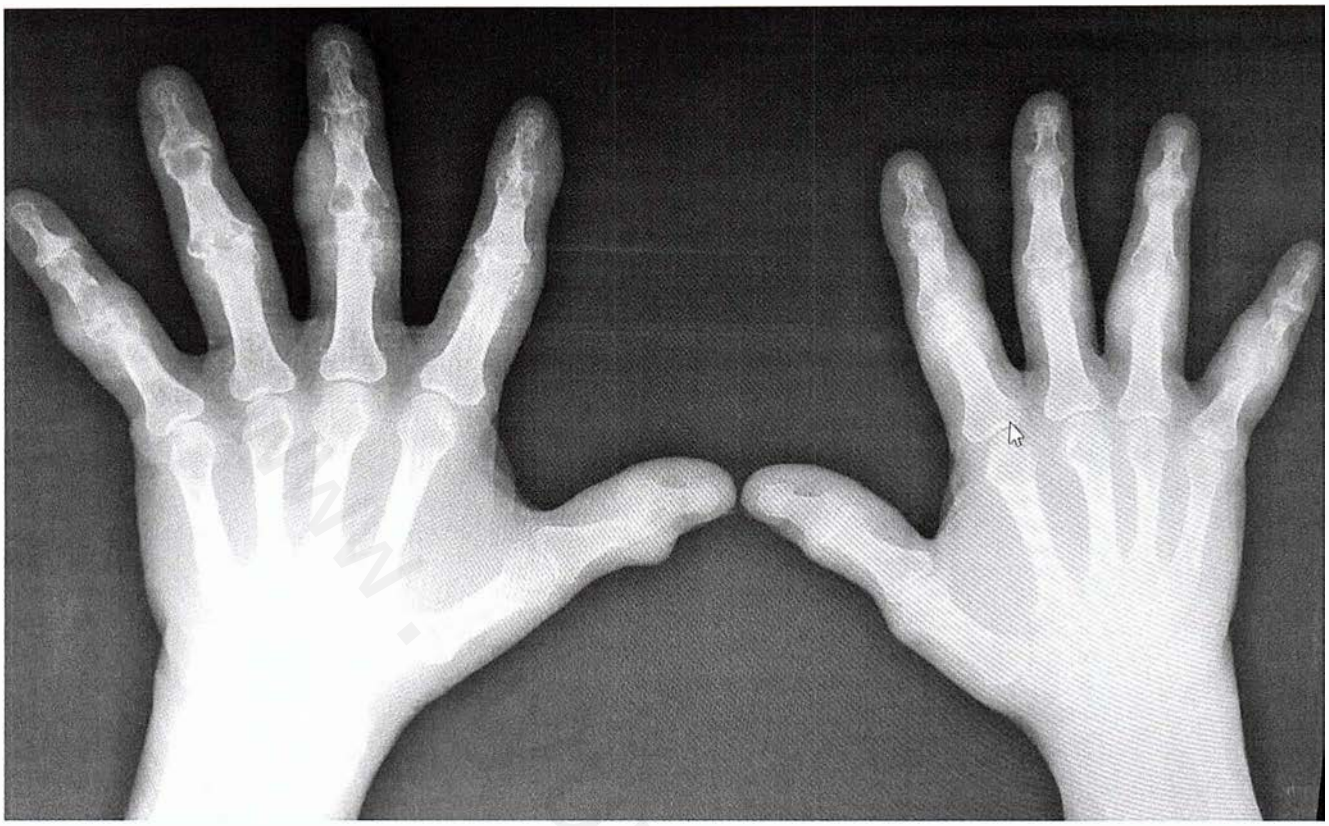

FIGURE 22. Punched-out bone lesions and erosions with overhanging edges associated with severe or long-standing gout.

Courtesy of Elaine Karis, MD.

CONT.

example, prednisone, 0.5 mg/kg) are all recommended. Selection should account for patient preferences, comorbidities, and concomitant medication use. Any NSAID, including selective cyclooxygenase-2 inhibitors, may be employed. Intra-articular glucocorticoid injection is an excellent option for monoarticular attacks, with fewer systemic toxicities than oral glucocorticoids, but requires expertise and prior synovial fluid assessment to rule out infection. Ice can reduce pain and swelling, particularly in flares involving one or two joints.

In refractory cases, switching to a different anti-inflammatory class may be attempted. For severe and/or polyarticular flares, combination therapy with two anti-inflammatory classes may be needed, but additive toxicities should be considered. Off-label use of the interleukin-1β inhibitors anakinra or canakinumab can be considered in severe cases when standard therapies are ineffective, contraindicated, or not tolerated. Patients already taking urate-lowering therapy should continue at the same dose throughout a flare because changes in serum urate can exacerbate attacks.

Urate-Lowering Therapy and Prophylaxis

All patients with gout should be educated on lifestyle modifications to reduce serum urate, including weight loss if appropriate (see Table 25). Intake of high-purine (for example, meat and seafood) and high-fructose (for example, soft drinks and processed foods with added high-fructose corn syrup) foods as well as alcoholic beverages (especially beer) should be limited because all contribute to increased serum urate levels. Dairy intake may lower urate through uricosuric effects, and low-fat dairy products may thus offer benefit to patients with gout. Hydration and substitution of urate-lowering for urate-raising medications can further reduce baseline urate. For example, use of a calcium channel blocker or losartan instead of a diuretic for hypertension can promote decreased serum urate; notably, the former two agents should be used preferentially to treat hypertension in patients at risk for gout attacks.

The American College of Rheumatology (ACR) guidelines currently indicate that urate-lowering therapy should be initiated in patients with gout who have had two or more attacks within a 1-year period, one attack in the setting of chronic kidney disease of stage 2 or worse, one attack with the presence of tophi visible on examination or imaging, or one attack with a history of urolithiasis. Urate-lowering therapy should usually be initiated during the intercritical phase to avoid exacerbating active attacks. Treatment to a target serum urate level of less than 6.0 mg/dL (0.35 mmol/L) is mandatory; still lower targets may be needed to improve symptoms or signs of gout or to resolve tophi. First-line therapy for urate lowering is typically the xanthine oxidase inhibitor allopurinol. An appropriate alternative is the newer xanthine oxidase inhibitor, febuxostat, which is equally or more efficacious (and causes less hypersensitivity) but significantly more expensive.

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The uricosuric agent probenecid blocks renal uric acid resorption and may be added to, or substituted for, a xanthine oxidase inhibitor if xanthine oxidase monotherapy is inadequate or not tolerated; however, probenecid may raise the risk of kidney stones and has limited efficacy in patients with impaired kidney function. In chronic refractory gout or when patients experience severe gout disease burden and standard urate-lowering therapy has been unsuccessful or not tolerated, the potent intravenous agent pegloticase is a treatment option. Pegloticase provides uricase activity, enzymatically converting urate to the more soluble compound allantoin. See Principles of Therapeutics for more information on urate-lowering therapy.

Gout flare prophylaxis should be initiated along with urate-lowering therapy because urate reduction can provoke attacks (owing to sloughing of microcrystals within the joint). Prophylaxis should continue in the presence of any active disease. In the absence of active disease, the ACR currently recommends that prophylaxis should be continued for the greater of the following: 6 months; 3 months after achieving the target serum urate level for a patient without tophi; or 6 months after achieving the target serum urate level where there has been resolution of tophi. First-line options for gout prophylaxis include colchicine, 0.6 mg (or 0.5 mg) once or twice daily, adjusting for kidney function and consideration of drug-drug interactions (see Principles of Therapeutics). Low-dose NSAIDs (such as naproxen, 250 mg twice daily) are an equally recommended alternative, but the gastrointestinal and cardiac toxicity of NSAIDs must be considered. Current guidelines endorse ≤10 mg of daily prednisone as an acceptable second-line prophylactic agent, with monitoring for the side effects of chronic glucocorticoid use.

KEY POINTS

- Gout is characterized by intermittent painful inflammatory joint attacks resulting from crystallization of excessive levels of uric acid (hyperuricemia).
- In patients with suspected gout, synovial fluid analysis is used to identify monosodium urate crystals, and Gram stain and cultures are ordered to exclude infection.
- Treatment of acute gouty arthritis involves control of inflammation using colchicine, NSAIDs, or glucocorticoids.
- Urate-lowering therapy should be initiated in patients with gout who have had two or more attacks within a 1-year period, one attack in the setting of chronic kidney disease of stage 2 or worse, one attack with the presence of tophi visible on examination or imaging, or one attack with a history of urolithiasis.
- Gout flare prophylaxis should be initiated along with urate-lowering therapy because urate reduction can transiently provoke attacks; first-line options include colchicine and NSAIDs.

Calcium Pyrophosphate Deposition

Calcium pyrophosphate (CPP) crystals are a common cause of calcification in connective tissues in and near joints. Calcium pyrophosphate deposition (CPPD) is associated with four distinct clinical presentations. There has been inconsistency in the literature and in practice surrounding the terminology for these entities. The European League Against Rheumatism (EULAR) recently published guidelines to clarify the terminology, although these have not been universally adopted. EULAR advocates for using "calcium pyrophosphate deposition" or "CPPD" as a broad term to refer to all instances of calcium pyrophosphate deposition and redefines the terminology for the various presentations of CPPD. Here we use the EULAR terminology but also mention the common terms used to describe the subtypes of CPPD.

The four clinical presentations are cartilage calcification (also known as chondrocalcinosis), acute CPP crystal arthritis (also known as pseudogout), chronic CPP crystal inflammatory arthritis, and osteoarthritis with CPPD.

Pathophysiology

The pathophysiology of CPPD is poorly characterized. CPPD in the joints may result from excessive body calcium or other metabolic derangements, overproduction of pyrophosphate by cartilage chondrocytes, or other local factors. Risk factors for CPPD include previous joint injury and familial predisposition. Particularly in a young person, a diagnosis of CPPD should prompt an evaluation for diseases associated with CPPD, including hyperparathyroidism, hemochromatosis, hypomagnesemia, and hypothyroidism.

The mechanism of chronic low-grade joint damage seen in some patients with cartilage calcification is not fully elucidated. In contrast, acute CPP crystal arthritis is known to induce inflammation via pathways similar to those induced by monosodium urate crystals in acute gout, triggering interleukin-1β production by macrophages and leading to additional inflammation and neutrophil recruitment.

Clinical Manifestations

Cartilage Calcification

Cartilage calcification (also known as chondrocalcinosis) is a radiographic finding that is usually the result of CPPD. Cartilage calcification is typically asymptomatic but may be associated with acute CPP crystal arthritis and/or pyrophosphate arthropathy. In the knee, cartilage calcification is seen as a linear density within and parallel to the surface of the cartilage (**Figure 23**); in the wrist, it is often seen in the triangular fibrocartilage distal to the ulna. Cartilage calcification can be an isolated finding or can occur in association with osteoarthritis. Prevalence increases with age, with a prevalence of approximately 50% in patients aged ≥85 years.

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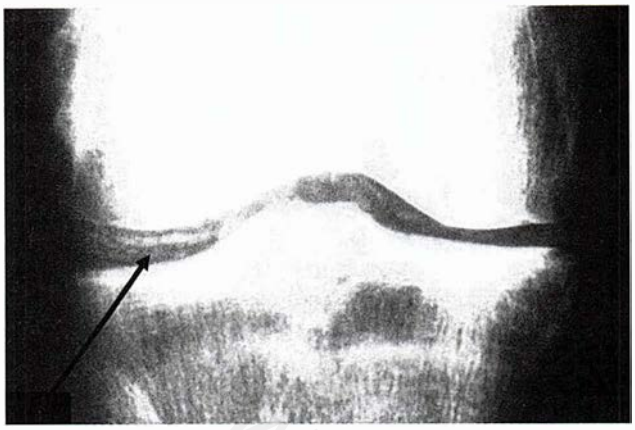

FIGURE 23. Cartilage calcification (also known as chondrocalcinosis) of the knee. This radiograph shows linearly arranged calcific deposits in the articular cartilage (*arrow*).

Acute Calcium Pyrophosphate Crystal Arthritis

Acute CPP crystal arthritis (also known as pseudogout) is characterized by painful inflammatory arthritis attacks reaching maximum intensity within 24 hours. The knee, wrist, and shoulder are typically affected; podagra is uncommon. Acute CPP crystal arthritis is generally indistinguishable from a gout flare; synovial fluid analysis is needed to make a definitive diagnosis (coexistence of the two diseases is possible). In contrast to monosodium urate crystals, CPP crystals are rhomboid shaped and positively birefringent. Cartilage calcification on radiograph suggests that an acute arthritis may be due to CPP crystals but is nondiagnostic. Acute CPP crystal arthritis occurs most commonly in patients over 65 years of age.

Pyrophosphate Arthropathy

Pyrophosphate arthropathy is a general term for joint damage attributed to CPPD and may present in two distinct patterns: chronic CPP crystal inflammatory arthritis and osteoarthritis with CPPD (both terms advocated by EULAR). In chronic CPP crystal inflammatory arthritis, there is ongoing inflammation with a pattern of joint involvement often resembling rheumatoid arthritis ("pseudo-rheumatoid arthritis"). In osteoarthritis with CPPD, patients exhibit accelerated osteoarthritis findings in joints not commonly involved with simple osteoarthritis (for example, wrist, metacarpophalangeal, or shoulder joints), with or without superimposed acute CPP crystal arthritis flares. It is presumed in these cases that the presence of crystals within the cartilage promotes a degenerative process not otherwise distinguishable from osteoarthritis.

Management

Management of CPPD centers on controlling symptoms and reducing inflammation (**Table 28**). In contrast to gout, no therapy is currently available to eliminate the pathogenic CPP crystals. Nonetheless, any underlying metabolic disorder that may contribute to CPPD should be addressed.

KEY POINTS

- Calcium pyrophosphate deposition can be associated with hyperparathyroidism, hemochromatosis, hypomagnesemia, and hypothyroidism.
- Acute calcium pyrophosphate crystal arthritis is generally indistinguishable from an acute gout flare; synovial fluid analysis is used to make a definitive diagnosis based on the characteristic rhomboid shape and positive birefringence of calcium pyrophosphate crystals.
- Management of calcium pyrophosphate deposition centers on control of symptoms and reduction of inflammation; any underlying metabolic disorder that may contribute should also be addressed.

Basic Calcium Phosphate Deposition

Basic calcium phosphate (BCP) crystals (including hydroxyapatite) are a common cause of cartilage calcification and may be radiographically indistinguishable from CPPD. Unlike CPP crystals, BCP crystals also commonly deposit in periarticular tendons, bursae, and other soft tissues. Patients are often

TABLE 28. Management of Calcium Pyrophosphate Deposition

Clinical Presentation	Treatment/Comments
Cartilage calcification (also known as chondrocalcinosis)	No specific treatment
Acute calcium pyrophosphate crystal arthritis (also known as pseudogout)	Local treatment: joint aspiration; intra-articular glucocorticoid injection; joint immobilization; ice packs
	Systemic treatment: NSAIDs; colchicine; glucocorticoids (oral or parenteral)
	Prophylaxis if recurrent attacks (three or more annual attacks): low-dose colchicine or daily NSAIDs (with gastrointestinal protection)
Chronic calcium pyrophosphate crystal inflammatory arthritis	Low-dose colchicine or daily NSAIDs (with gastrointestinal protection); low-dose glucocorticoids; methotrexate; hydroxychloroquine
Osteoarthritis with calcium pyrophosphate deposition (CPPD)	Same treatment as osteoarthritis without CPPD (e.g., physical therapy; pain control; local glucocorticoids)

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asymptomatic, but BCP crystals can cause destructive arthropathy. Although not always visible on radiographs, BCP crystals have been identified as a common feature of degenerative joint disease in osteoarthritis (on histological examination). BCP crystals also can stimulate inflammation via pathways similar to monosodium urate and CPP crystals. BCP deposition can cause Milwaukee shoulder syndrome, a painful, swollen, and often destructive process of the glenohumeral joint and rotator cuff; this condition typically occurs in women over the age of 70 years.

Diagnosis of BCP deposition is made clinically or by joint aspiration. The synovial fluid is characteristically noninflammatory (<2000/μL [2.0×10^9/L]). BCP crystals are not visible on polarized microscopy but may be visualized on electron microscopy or under light microscopy as nonbirefringent clumps that stain with alizarin red. Treatment for symptomatic BCP deposition includes NSAIDs, joint aspiration and tidal lavage, and intra-articular glucocorticoid injection.

KEY POINTS

- Basic calcium phosphate deposition can cause Milwaukee shoulder syndrome, which presents with a painful, swollen shoulder; is often associated with significant destruction of the glenohumeral joint and rotator cuff; and typically occurs in women over the age of 70 years.
- Diagnosis of basic calcium phosphate deposition is made clinically and/or by joint aspiration and staining with alizarin red.
- Management of symptomatic basic calcium phosphate deposition includes NSAIDs, joint aspiration and tidal lavage, and intra-articular glucocorticoid injection.

Infectious Arthritis

Introduction

Infectious arthritis is caused by bacteria, fungi, or viruses and should be considered in any patient with one or more inflamed joints. Significant morbidity and mortality can result from inadequate or delayed management.

Pathophysiology

Bacterial or fungal joint infections arise from hematogenous seeding (most cases), direct inoculation (for example, with surgery or, rarely, glucocorticoid injection), or contiguous spread from neighboring osteomyelitis, cellulitis, or septic bursitis. Some bacteria produce toxins or enzymes that directly damage tissues. Bacteria also trigger inflammatory responses characterized by neutrophilic infiltration into the joint space. If unresolved, these processes can rapidly progress to joint damage or destruction.

In some forms of viral-induced and other infectious arthritis, joint inflammation may develop as a consequence of immune complexes elicited by the pathogen, rather than direct infection.

Diagnosis

Infection should be considered in the differential diagnosis of any acutely or chronically inflamed joint. Joint infection should be suspected based on clinical history, presence of risk factors (**Table 29**), and initial laboratory studies. Although elevated inflammatory markers (leukocyte count, erythrocyte sedimentation rate [ESR], and C reactive protein [CRP]) may suggest infectious arthritis, they cannot confirm the diagnosis or exclude other inflammatory causes.

Clinical Manifestations

The hallmarks of a joint infection are warmth, erythema, pain, and swelling. The typical bacterial infectious arthritis develops over days; onset is more indolent for fungal or mycobacterial infections. Joint infections are commonly limited to a single joint; the knee is the most common site, but the hip, wrist, and ankle are also commonly affected. In approximately 20% of cases, bacterial or fungal arthritis presents with polyarthritis

TABLE 29. Risk Factors for Infectious Arthritis

General Risk Factors
Age >80 years or very young children
Alcoholism
Cutaneous ulcers or other skin infections
Diabetes mellitus
End-stage kidney disease
History of intra-articular glucocorticoid injection
Injection drug use
Low socioeconomic status
Patients receiving immunosuppressive agents
Prosthetic joint or recent joint surgery
Sickle cell disease
Underlying malignancy
Risk Factors for Gonococcal Infection
Younger, sexually active patients
Risk Factors for Lyme Arthritis
Travel or residence in an endemic area
Documented tick bite or erythema chronicum migrans
Risk Factors for Mycobacterial or Fungal Infection
Patients with HIV infection or other immunosuppression
Patients receiving tumor necrosis factor α inhibitors
Travel or residence in an endemic area

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and a worse prognosis. Fever and rigors may occur but are not universally present (60% of patients); absence of fever therefore does not exclude an infected joint.

Laboratory Studies and Imaging

When infectious arthritis is suspected, the synovial fluid must be aspirated and assessed for leukocyte count, Gram stain, culture (bacterial and, depending on index of suspicion, mycobacterial and fungal), and crystal analysis (to rule out alternative or concomitant etiologies). Joint aspiration should be performed before initiating antibiotics whenever possible to maximize the likelihood of positive cultures. In bacterial infection, the synovial fluid leukocyte count is markedly increased (usually >50,000/μL [50 × 10^9/L] with neutrophil predominance). Because synovial fluid cultures have a sensitivity of approximately 80% and may be negative due to antibiotics, a fastidious organism, or other reasons, clinical assessment must ultimately guide treatment.

Cultures of blood and other possible sources of infection (such as urine or sputum) should be obtained if infectious arthritis is under consideration, ideally before starting antibiotics. Peripheral leukocyte count, ESR, and CRP should be measured.

Radiographs are nonspecific early in infectious arthritis but may reveal local swelling or joint destruction if the infection has been left untreated, whether in bacterial, mycobacterial, or fungal infections. MRI, CT, and ultrasonography are not routinely indicated but may help identify early erosions, concurrent osteomyelitis, or joint effusions that are difficult to assess on examination (for example, in the hip). Imaging may also help guide arthrocentesis.

Cultures of the genitourinary tract, rectum, and/or pharyngeal sites should be obtained when disseminated gonococcal infection is suspected. Diagnosis of Lyme disease and viral infections relies on serologic testing. H

KEY POINTS

- Infectious arthritis is caused by bacteria, fungi, or viruses and should be considered in any patient with one or more inflamed joints.
- The hallmarks of a joint infection are warmth, erythema, pain, and swelling.
- Diagnosis of infectious arthritis is confirmed by joint aspiration and aided by clinical history, physical examination, and laboratory studies.
- In bacterial infection, the synovial fluid leukocyte count is markedly increased (usually >50,000/μL [50 × 10^9/L] with neutrophil predominance).

Causes

Common causes of infectious arthritis are discussed in the following sections. For more information on the specific infections/diseases, refer to MKSAP 17 Infectious Disease.

Infection with Gram-Positive Organisms

H

Gram-positive organisms are the most common causes of infectious arthritis in adults. *Staphylococcus aureus* is the most common infecting organism, regardless of age or risk factors. *S. aureus* damages joints directly via toxic effects and indirectly via inflammatory responses. Symptoms develop rapidly and escalate within hours to days. The emergence of methicillin-resistant *S. aureus* poses treatment challenges. *Streptococcus pneumoniae* is another common pathogen. Polymicrobial infections occur uncommonly but may indicate a worse prognosis.

Infection with Gram-Negative Organisms

Nongonococcal Gram-Negative Organisms

Nongonococcal gram-negative bacterial arthritis is more common in patients who are immunosuppressed, are elderly, or have a history of injection drug use, recent trauma, or gastrointestinal infection. *Escherichia coli* and *Pseudomonas aeruginosa* are the most common gram-negative organisms to infect the joints. Injection drug users are at particular risk for *Pseudomonas*. Patients with sickle cell anemia are predisposed to *Salmonella* infection. *Haemophilus influenzae*, previously a common cause of infectious arthritis, has declined due to *H. influenzae* vaccine. Gram-negative bacterial joint infections cause rapid onset of symptoms and potential joint destruction if not promptly and appropriately treated.

Disseminated Gonococcal Infection

Disseminated gonococcal infection occurs in up to 3% of patients with *Neisseria gonorrhoeae* and can cause two distinct clinical presentations. Risk is highest in young, sexually active adults.

Patients with disseminated gonococcal infection and bacteremia present with vesiculopustular or hemorrhagic macular skin lesions (**Figure 24**), fever, chills, and polyarthralgia. Knees,



FIGURE 24. Disseminated gonococcal infection presents as a febrile arthritis-dermatitis syndrome with migratory polyarthralgia evolving into frank arthritis with or without tenosynovitis that involves one or more joints. Skin lesions are found in approximately 75% of cases, classically presenting as a small number of necrotic vesicopustules on an erythematous base.

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elbows, and distal joints are typical sites of involvement. Tenosynovitis of the dorsa of the hands and/or feet is a characteristic feature. Synovial fluid leukocyte counts are lower than in other bacterial infections (<25,000/μL [25 × 10^9/L]). Blood cultures or cultures of the genitourinary tract (for example, cervical or urethral specimens), rectum, or pharynx are often positive, but synovial fluid cultures are usually negative. Special media are required to culture *N. gonorrhoeae*.

Gonococcal infection can also present as a purulent arthritis without the rash or other features of bacteremia. In this case, one or two joints are typically involved, most commonly the knee followed by the wrist, ankle, and elbow. Synovial fluid cultures are more often positive for *N. gonorrhoeae* in this setting.

Lyme Arthritis

Lyme disease is caused by infection with *Borrelia* species. There are three phases of Lyme disease: early localized, early disseminated, and late. Although arthralgia is common in early Lyme disease, Lyme arthritis generally refers to frank inflammation of the joints as a manifestation of late Lyme disease. Late Lyme arthritis frequently causes impressively large effusions, most often a knee monoarthritis with prominent stiffness but relatively little pain. Asymmetric oligoarticular presentations also occur. Lyme arthritis can occur as a transient event, follow an intermittent pattern, or develop into a chronic arthritis. Diagnosis is made by serologic testing (enzyme-linked immunosorbent assay followed, if positive, by Western blot) indicating an immune response to *Borrelia burgdorferi*. Joint aspiration demonstrates a moderately inflammatory synovial fluid (leukocyte count typically 20,000-25,000/μL [20-25 × 10^9/L], neutrophil predominant). Synovial fluid cultures are negative, but *B. burgdorferi* DNA can be detected by polymerase chain reaction. Permanent joint damage is less common than in gram-positive or gram-negative pyogenic infections.

Mycobacterial Infections

Several mycobacterial species can affect the musculoskeletal system, the most important being *Mycobacterium tuberculosis*.

Mycobacterium tuberculosis

Mycobacterium tuberculosis infection exhibits extrapulmonary symptoms in nearly 20% of patients, with bone or joint involvement occurring in approximately 2% overall. Patients at particular risk include persons who have lived in or visited an endemic area, patients with untreated HIV infection, and patients with immunosuppression for any other reason, including biologic therapy for autoimmune diseases. Musculoskeletal *M. tuberculosis* can develop early after infection or after an extended latency, with reactivation often triggered by immunocompromise. Patients with musculoskeletal *M. tuberculosis* infection typically manifest a chronic, indolent course, often without constitutional symptoms. Musculoskeletal *M. tuberculosis* infection most commonly presents as spondylitis (Pott disease) or vertebral osteomyelitis. Tuberculous osteomyelitis of almost any other bone is also possible.

Arthritis caused by *M. tuberculosis* is usually monoarticular, often involving the hip or knee. Joint destruction is possible but occurs slowly. Synovial fluid analysis usually suggests a nonspecific inflammatory process; imaging may be normal or show erosions that cannot be readily distinguished from other infections. Acid-fast smears of synovial fluid are positive only in a minority of cases; synovial fluid culture or synovial biopsy with granuloma identification are more likely to be diagnostic. Tuberculin skin tests are not uniformly positive, especially in immunosuppressed individuals; therefore, a negative test does not definitively exclude infection. Although signs of pulmonary tuberculosis or tuberculosis of other sites should be sought, many patients present with isolated musculoskeletal disease.

Mycobacterium marinum

Mycobacterium marinum is a freshwater and saltwater organism that enters the skin through breaks or abrasions. Common scenarios include anglers and aquarium hobbyists with bare hand exposure to water. *M. marinum* infections typically begin as red or violaceous plaques, nodules, or abscesses in the skin, and may spread locally to involve the hand joints. Therapy requires multidrug regimens such as rifampin and ethambutol.

Fungal Infections

Fungal infections are a rare cause of infectious arthritis but are important to consider, particularly in immunocompromised patients and/or endemic areas. Fungal arthritis is most likely to be caused by *Coccidioides* (endemic in the southwestern United States), *Sporothrix* (found in farm and garden soil), *Cryptococcus*, *Blastomyces* (endemic in the central United States), and *Candida*. Infections are typically monoarticular, follow an indolent course, and derive most often from hematogenous spread. Direct inoculation of the joint due to trauma or extension from a nearby site of infection is also possible. Both arthritis and osteomyelitis can occur. Diagnosis is often challenging. Synovial fluid analysis typically reveals inflammatory fluid with negative bacterial cultures. Appropriate fungal cultures or synovial biopsy may yield a diagnosis.

Viral Infections

Various viral infections can lead to musculoskeletal symptoms. Symptoms may occur via direct invasion, immune complex deposition, or less well-defined mechanisms.

Hepatitis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections frequently cause musculoskeletal symptoms. Acute HBV infection causes symmetric polyarthritis (especially in the hands and knees) during the prodromal stage of disease, often accompanied by rash; joint pain lasts days or weeks and then

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resolves. In chronic HBV, arthritis may persist, possibly due to immune complex formation. Chronic HCV causes a wide array of musculoskeletal symptoms ranging from arthralgia to arthritis (oligoarticular or polyarticular presentations). Both HBV and especially HCV infection may provoke cryoglobulinemia, resulting in arthritis, glomerulonephritis, and other signs of vasculitis such as palpable purpura. Diagnosis of HBV and HCV is by serologic and polymerase chain reaction testing.

Parvovirus B19

Parvovirus B19, which causes the childhood condition known as fifth disease (also known as erythema infectiosum), is a DNA virus with a tropism for erythrocyte precursors. Adults usually contract the virus from children; individuals at risk include school workers and parents. Infection may be asymptomatic or produce a flu-like illness. As the host mounts a response, a classic "slapped cheek" rash and arthritis may occur. In adults, the rash may be absent or atypical. The arthritis begins acutely, with symmetric swelling and stiffness of the small joints of the hands and feet, as well as wrists and knees, often mimicking rheumatoid arthritis. Parvovirus B19 arthritis typically lasts for several weeks, but occasionally many months, before resolving. The presence of circulating anti-parvovirus IgM antibodies provides evidence of active disease; IgG antibodies indicate prior infection and are found in many healthy persons. Management is supportive, using anti-inflammatories (such as NSAIDs) and analgesics.

Rubella

Rubella (German measles) has become uncommon in countries with vaccine programs; nonvaccinated populations remain at risk. Infection can cause rash, fever, and lymphadenopathy. A polyarthritis of sudden onset may occur, affecting medium and small joints (hands, wrists, knees), usually resolving within 2 weeks. Synovial fluid is inflammatory. Diagnosis is made by documenting IgM anti-rubella antibodies or by isolating the virus from synovial fluid or the nasopharynx. Arthritis can also occur in response to the rubella vaccine.

Chikungunya

Chikungunya virus is an alphavirus endemic to Asia and Africa, where it is transmitted by mosquito vectors; however, cases are increasingly seen in the United States secondary to travel to endemic countries. Chikungunya virus causes fever, rash, and myalgia, along with thrombocytopenia and/or leukopenia. Chikungunya arthritis is self-limited, but severe polyarthritis/tenosynovitis can persist for as long as 6 months. Diagnosis is by clinical context, travel history, and identification of IgM anti-Chikungunya antibodies and/or viral isolation by polymerase chain reaction. Treatment is supportive.

Prosthetic Joint Infections

Prosthetic joint infection is a rare but serious complication of joint replacement. Infection rates are highest in knee replacements (up to 2%) and lower in hip and shoulder replacements. Coagulase-negative staphylococci (for example, *Staphylococcus epidermidis*) are common infecting organisms. Risk factors include superficial surgical site infection, malignancy, revision arthroplasty, inflammatory arthritis, immunosuppression, obesity, and chronic illness. Infections are most likely to occur within the first 2 years after surgery. Infections may be of early (<3 months after surgery), delayed (3-12 months), or late (>12 months after surgery) onset. Early and delayed onset infections are acquired during prosthesis implantation, whereas late-onset infections arise de novo from hematogenous seeding of the joint. Prosthetic joint infection is promoted by the development of a biofilm (coalescence of bacteria) on the artificial joint surface; biofilms are resistant to treatment both because of lack of perfusion and because biofilm bacteria develop antimicrobial resistance as a consequence of their limited exposure to treatment agents.

Early-onset infections present with joint swelling, erythema, wound drainage, and/or fever. Delayed-onset infections present insidiously with prolonged joint pain, often without fever. Late-onset infections may present as acute pain and swelling, often after hematogenous seeding from a vascular catheter or a site of infection distant from the affected joint.

Prompt orthopedic consultation should be sought for patients with suspected prosthetic joint infection because treatment nearly always requires surgical intervention (in addition to antibiotics). ESR and CRP are typically elevated. Plain radiographs are mandatory and may show erosion or loosening around the implantation site. Aspiration of the affected joint can confirm the diagnosis but may be deferred if surgical intervention is imminent. Synovial fluid cultures and blood cultures should always be obtained prior to antibiotic initiation in a stable patient. Surgical options include debridement, primary replacement of the affected hardware, or complete removal of the artificial joint and replacement after the infection is fully resolved.

Infections in Previously Damaged Joints

Joints that have been previously damaged by trauma, inflammatory arthritis, degenerative arthritis, surgical procedures, or other causes are inherently more susceptible to infection. In patients with a history of joint damage or radiographic evidence of prior damage, acute pain and swelling in a joint should raise suspicion for the possibility of an infected joint.

KEY POINTS

- Gram-positive organisms are the most common causes of infectious arthritis in adults, with *Staphylococcus aureus* being the most common infecting organism.
- Patients with disseminated gonococcal infection present with one of two syndromes: arthritis, tenosynovitis, and dermatitis or a purulent monoarthritis or oligoarthritis.
- Nongonococcal gram-negative bacterial arthritis is more common in patients who are immunosuppressed, are elderly, or have a history of injection drug use, recent trauma, or gastrointestinal infection.

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KEY POINTS *(continued)*

- Musculoskeletal *Mycobacterium tuberculosis* typically presents as a chronic, indolent process, often without constitutional symptoms and most commonly as spondylitis, vertebral osteomyelitis, or hip or knee arthritis.
- Prompt orthopedic consultation should be sought for patients with suspected prosthetic joint infection because treatment typically requires surgical intervention.

Management

Pharmacologic Therapy

Pharmacologic therapy is the cornerstone of treatment for infectious arthritis. Bacterial or fungal joint infections require antimicrobial or antifungal agents (**Table 30**). Particularly for bacterially infected joints, antibiotic therapy should be initiated rapidly to prevent joint damage and other adverse outcomes. Whenever possible, synovial fluid culture

TABLE 30. Infectious Arthritis Treatment Based on the Suspected Pathogen

Likely or Identified Pathogen	First-Line Therapy	Second-Line Therapy	Comments
Gram-Positive Cocci			
If MRSA is a concern (risk factors or known MRSA carrier)	Vancomycin or linezolid	Clindamycin, daptomycin	—
MSSA	Oxacillin/nafcillin or cefazolin	—	Narrow treatment to MSSA coverage based on sensitivity data.
Gram-Negative Bacilli			
Enteric gram-negative bacilli	3rd generation cephalosporin (e.g., ceftriaxone or cefotaxime)	Fluoroquinolones	—
Pseudomonas aeruginosa	Ceftazidime with an aminoglycoside (e.g., gentamicin)	Carbapenems, cefepime, piperacillin-tazobactam, fluoroquinolones	—
Gram-Negative Cocci			
Neisseria gonorrhoeae	IV ceftriaxone × 7-14 days	Fluoroquinolones (only if culture sensitivities support this)	If suspected gonococcal arthritis, treat for co-infection with chlamydia empirically (azithromycin or doxycycline); in the absence of specific culture sensitivity data, "stepping down" to oral therapy of any type is no longer recommended due to increasing resistance of *N. gonorrhoeae* to commonly used oral agents.
Gram Stain Unavailable or Inconclusive			
Likely pathogen depends on patient risk factors: consider MRSA, and gram-negative organism if immunocompromised, at risk for gonococcal infection, or with joint trauma	E.g., vancomycin, or vancomycin + 3rd generation cephalosporin	—	Appropriate to start with broad antibiotic coverage and narrow coverage if culture data become available.
Borrelia burgdorferi (Lyme arthritis)	Oral doxycycline or amoxicillin × 28 days	—	If concurrent neurologic findings, IV ceftriaxone × 28 days.
Mycobacterium tuberculosis	3- to 4-drug treatment (e.g. isoniazid, pyrazinamide, rifampin, ethambutol, streptomycin)	—	Duration may vary from 6 months or longer depending on drug regimen (shorter treatment if rifampin is used).
Fungal infections	Amphotericin B, azoles (fluconazole, itraconazole, voriconazole, posaconazole), depending on suspected organism or culture data	—	Prolonged treatment courses of several months may be needed; maintenance therapy may be required in high-risk patients.

IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.

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results should guide treatment. However, if the patient is unstable or culture data are unavailable, empiric therapy should be initiated. Duration of treatment for bacterial arthritis is variable. Commonly, 2 weeks of intravenous therapy is followed by 2 weeks of oral therapy. However, patient response, organism sensitivities, and severity of infection (number of joints involved, associated bacteremia) may alter the treatment course.

Management of arthritis due to viral infections is usually supportive, awaiting resolution of the underlying infection. Arthritis due to HCV (with or without cryoglobulinemia) may improve with antiviral treatment.

Surgical Therapy

Drainage of purulent fluid from a bacterially infected native joint is a critical component of successful treatment. Infected native joints that can be drained fully with aspiration can be managed with either serial (usually daily) arthrocentesis or surgical drainage. For joints that are less easily accessed (such as the hip) or when needle drainage proves inadequate, arthroscopic or open surgical drainage is required. Surgical management of prosthetic joint infections is discussed in Prosthetic Joint Infections. H

KEY POINTS

- For bacterially infected joints, antibiotics should be initiated promptly to prevent joint damage.
- Synovial fluid culture results should guide treatment of bacterial or fungal infections; however, if the patient is unstable or culture data are unavailable, empiric therapy should be initiated.
- Management of viral arthritis is generally supportive, awaiting resolution of the underlying infection.
- Drainage of purulent fluid from a bacterially infected native joint is a critical component of successful treatment.

Idiopathic Inflammatory Myopathies

Introduction

The idiopathic inflammatory myopathies (IIMs) are characterized by autoimmunity and inflammatory involvement of muscle fibers (frequently termed *myositis*), resulting in muscle weakness. The three IIMs are polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM).

Pathophysiology

Although all three IIMs cause muscle weakness, they have different underlying immunologic mechanisms. PM is a CD8-positive T-cell–mediated immune disease with direct myocyte injury. DM is considered an immune complex disease with vascular inflammation in muscle and subsequent muscle damage. IBM is most likely a myodegenerative disorder with vacuolar inclusions and a related T-cell response.

Epidemiology

The IIMs are rare (prevalence, 5-22/100,000). Overall female-to-male ratio is 2:1. DM has a bimodal distribution of onset, with the highest incidence in the second and fourth decades. PM incidence peaks in the fourth decade. IBM typically affects men older than 50 years of age.

KEY POINT

- The idiopathic inflammatory myopathies include polymyositis, dermatomyositis, and inclusion body myositis and are associated with inflammatory involvement of muscle fibers and resultant weakness.

Clinical Manifestations

The IIMs affect various sites and organs. PM and DM may also be associated with systemic symptoms (fever, fatigue, weight loss), Raynaud phenomenon, and arthritis. About 30% of patients with DM and PM may present with an acute onset of significant constitutional symptoms and a constellation of features called the antisynthetase syndrome. This syndrome is defined by the presence of autoantibodies to aminoacyl-transfer (t)RNA synthetase enzymes (such as anti-Jo-1) plus two of the following clinical features: inflammatory myositis, interstitial lung disease, Raynaud phenomenon, nonerosive inflammatory arthritis, and mechanic's hands.

IBM is rarely associated with extramuscular manifestations.

Muscular Involvement

Symmetric painless proximal weakness of the arms and legs is the classic feature of DM and PM. Onset is acute or subacute, with disease progressing over weeks. The deltoids, arm/hip flexors, and neck flexors are characteristically involved. Patients report difficulty combing hair, rising from a chair, and climbing stairs (classic triad of hair, chair, stair), and difficulty with routine activities such as cooking, cleaning, and shopping. Muscle atrophy is absent initially but may occur in long-standing disease.

In contrast to DM and PM, muscle weakness in IBM characteristically affects both distal and proximal muscles. Although typically symmetric, IBM muscle involvement may be asymmetric in up to 15% of patients. Onset is insidious and slowly progressive, often over years.

Cutaneous Involvement

DM is associated with multiple cutaneous manifestations. Gottron sign/papules are symmetric erythematous/violaceous macules, patches, or papules located on the extensor surfaces of the metacarpophalangeal joints (**Figure 25**).

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FIGURE 25. Gottron papules. Erythematous papular and patchy eruption with overlying scaling on the extensor surface of metacarpophalangeal joints in a patient with dermatomyositis.

Common rashes include heliotrope rash (edematous lilac discoloration of periorbital tissue) (**Figure 26**) as well as photodistributed rashes such as the shawl sign (upper back) (**Figure 27**) and V sign (neck/upper chest) (**Figure 28**). Poikiloderma (mottled pigmentation, epidermal atrophy, and telangiectasia) can occur in both sun-exposed and unexposed



FIGURE 26. Heliotrope rash. Violaceous erythematous papular eruption with hyperkeratosis on the upper eyelids in a patient with dermatomyositis.



FIGURE 27. Shawl sign. Poikilodermatous (demonstrating a variety of different shades) erythematous patchy rash on the upper back in a patient with dermatomyositis.



FIGURE 28. V sign. Violaceous erythema and redness present on the neck and upper chest in a patient with dermatomyositis.

areas. Gottron sign/papules and heliotrope rash are considered pathognomonic for DM. Nail changes such as cuticular hypertrophy or nailfold capillary abnormalities can occur. Amyopathic DM refers to classic cutaneous findings occurring in the absence of muscle involvement. Mechanic's hands, characterized by hyperkeratotic fissuring of the palmar and lateral surfaces of the fingers, is seen in both DM and PM (**Figure 29**). See MKSAP 17 Dermatology for more information on the cutaneous manifestations of DM.

The skin is generally uninvolved in PM and IBM.

Cardiopulmonary Involvement

Interstitial lung disease (ILD) is common in DM and PM. ILD is symptomatic in 10% to 25% of patients with DM and PM and



FIGURE 29. Mechanic's hands. Hyperkeratotic, fissured skin on the palmar and lateral aspects of fingers, seen in patients with polymyositis and dermatomyositis.

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CONT. can be recognized in up to 65% of patients screened with high-resolution CT. ILD may precede muscle symptoms, may be asymptomatic, and is associated with poor prognosis. ILD occurrence is often associated with antisynthetase antibodies, including anti-Jo-1, and may cause rapidly progressive respiratory failure and death. Routine screening for ILD with imaging such as chest radiography or CT is appropriate in asymptomatic patients in the presence of antisynthetase antibodies. ILD is not commonly seen in IBM.

All of the IIMs can cause chest wall and diaphragm muscle weakness, resulting in shortness of breath and, occasionally, respiratory failure. Pharyngeal muscle involvement can lead to aspiration pneumonia, which can worsen ILD.

Symptomatic cardiac disease is uncommon, but minor electrocardiogram changes (arrhythmias and conduction abnormalities), presumably due to subclinical myocarditis, are commonly observed.

Gastrointestinal Involvement

Weakness of the striated muscle of the upper esophagus and/or oropharynx is common in IIM and can lead to dysphagia, aspiration, regurgitation, and associated pneumonitis. Esophageal disease is more common among older patients and those with IBM. Gastrointestinal hypomotility may occur and promote malabsorption. H

KEY POINTS

- Symmetric painless proximal muscle weakness of the arms and legs is the classic feature of dermatomyositis and polymyositis; onset is acute or subacute.
- The muscle weakness associated with inclusion body myositis affects both distal and proximal muscle groups; onset is insidious and slowly progressive.
- Dermatomyositis is associated with Gottron papules/sign, heliotrope rash, photodistributed rashes, and nail-fold changes; skin is generally spared in polymyositis and inclusion body myositis.
- Interstitial lung disease in patients with dermatomyositis or polymyositis may be asymptomatic, may precede muscle symptoms, is often associated with antisynthetase antibodies, including anti-Jo-1, and is associated with poor prognosis.

Association with Malignancy

Increased malignancy rates are seen in both DM and PM. Relative risk for malignancy is 2.4 to 7.7 for DM and 1.7 to 2.1 for PM, compared with the general population. Malignancy risk is highest during the first year after DM/PM diagnosis and declines thereafter but remains elevated even after 5 years. Cutaneous necrosis, vasculitis, and older age at diagnosis may be risk factors.

Cancers associated with DM and PM are similar to those seen in the general population, including adenocarcinomas of the bladder, cervix, lung, ovaries, pancreas, and stomach. Ovarian cancer risk may be especially increased. Age-appropriate screening is recommended for all patients with PM or DM, with consideration of additional testing for ovarian cancer using imaging such as transvaginal pelvic ultrasonography. Routine additional testing is not cost effective, but chest and abdominal CT and/or PET scanning should be considered if there is strong suspicion or additional risk factors are present.

Any relationship between malignancy and IBM remains poorly defined.

KEY POINT

- Age-appropriate cancer screening is recommended for patients with dermatomyositis or polymyositis, with consideration of additional testing for ovarian cancer; additional CT or PET scanning to look for underlying malignancy is not cost effective unless the patient has additional risk factors. HVC

Diagnosis

IIM is a clinical diagnosis supported by tissue and laboratory studies. The unifying feature is muscle weakness; the pattern of muscle and extramuscular involvement suggests the specific type. Once IIM is suspected, muscle enzyme and autoantibody studies, as well as electromyography and/or imaging studies, are performed. Muscle biopsy should be performed in most patients. **Table 31** lists common and differentiating features of the IIMs.

Muscle-Related Enzymes

Muscle enzyme elevations occur in more than 90% of patients with DM and PM, especially during active disease. Creatine kinase and aldolase are the most important, but others (for example, lactate dehydrogenase and aspartate aminotransferase) also may be elevated. In DM and PM, muscle enzyme elevation is dramatic (usually 10- to 50-fold the upper limit of normal) but may or may not correlate with degree of weakness. Normal muscle enzymes may be present in 5% to 10% of patients with DM or PM, particularly in chronic disease with loss of muscle mass. Amyopathic DM refers to DM with cutaneous involvement and normal muscle enzyme levels in the absence of muscle manifestations.

Patients with IBM typically have mildly elevated levels of muscle enzymes, in the range of one to threefold the upper limit of normal.

Autoantibodies

A number of characteristic autoantibodies are seen in DM and PM. Antinuclear antibodies (ANA) are detected in approximately 80% of patients with DM and PM.

Myositis-specific autoantibodies (MSA) are found in approximately 30% of patients with PM and/or DM and include antibodies to aminoacyl-transfer (t)RNA synthetases

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TABLE 31. Features of the Idiopathic Inflammatory Myopathies

	Dermatomyositis	Polymyositis	Inclusion Body Myositis
Epidemiology			
Sex	Childhood: female = male; Adult: female > male	Female > male	Male > female
Age of onset	All	<50 years	>50 years
Familial association	No	No	Yes
Clinical Presentation			
Onset of symptoms	Acute or subacute	Acute or subacute	Insidious
Weakness	Proximal	Proximal	Proximal and distal
Course	Rapid	Rapid	Slowly progressive
Skin rash	Yes	No	No
Diagnostic Findings			
Muscle enzymes	>10 times normal	>10 times normal	<10 times normal
Electromyography	Myopathic	Myopathic	Myoneuropathic
Muscle biopsy	Microinfarctions; myofibril grouping	Myofibril necrosis	Rimmed vacuoles; inclusions
Treatment			
Response	Good	Good	Poor

(antisynthetase antibodies, including anti-Jo-1), antibodies to signal recognition particle (SRP), and antibodies to Mi-2, a nuclear helicase.

Myositis-associated autoantibodies (MAA), commonly anti-PM-Scl, anti-Ku, anti-Ro/SSA, anti-La/SSB, and anti-U1-ribonucleoprotein (RNP) antibodies, are found in approximately 30% of patients with PM and/or DM.

In clinical practice, ANA testing is usually done initially during diagnostic work-up. Positive ANA supports the diagnosis of IIM, although negative tests do not exclude it. MSA testing is usually performed during initial diagnostic evaluation or once diagnosis is established because MSA may be associated with particular clinical syndromes, patterns of organ involvement, certain histopathologic findings, and prognosis. MAA testing is usually ordered if previous testing has been inconclusive. Positive anti-U1-RNP antibodies suggest an overlap syndrome with mixed connective tissue disease.

To date, no autoantibodies characteristic of IBM have been identified.

Imaging Studies

Imaging studies are sensitive but nonspecific for the IIMs and cannot definitively differentiate among inflammatory, metabolic, traumatic, and other myopathies. Muscle imaging can identify affected sites for biopsy, aid in clinical diagnosis, and help follow the response to treatment and course of disease. MRI is usually the preferred modality and can show active inflammation of muscle and follow its course; edema, active myositis, fibrosis, and calcification in advanced disease can also be detected. Because of limited specificity, the pattern of muscle involvement on MRI is usually reported as either consistent or likely inconsistent with IIM.

Electromyography

Electromyography (EMG) is obtained in most patients with IIM due to almost universal availability and high sensitivity. EMG can identify characteristic abnormalities and exclude neuropathic disease. The characteristic triad of EMG findings includes short duration small, low-amplitude polyphasic potentials; fibrillation potentials at rest; and bizarre, high frequency, repetitive discharges. As with MRI, these findings are not adequately specific for definitive diagnosis alone because they may also be seen in infectious, toxic, or metabolic myopathies.

Muscle Biopsy

Biopsy of an affected muscle is the gold standard for diagnosis and should be obtained initially in most patients to distinguish between DM, PM, and IBM as well as nonimmune, noninflammatory myopathic disorders. Muscle biopsy is also sometimes needed during the course of disease to evaluate treatment response or rule out a new or alternative cause of weakness.

DM is typically associated with a mixed B and CD4-positive T-cell perivascular infiltrate, vasculitis with microinfarction and grouping of muscle fibers, and perifascicular muscle atrophy. PM infiltrates primarily consist of CD8-positive T cells, involving all layers of muscle fibers with invasion and myophagocytosis. The primary target seems to be the

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vascular endothelium in DM and the myofibrils themselves in PM. IBM demonstrates a mild T-cell predominant inflammatory infiltrate (similar to PM), along with the presence of rimmed vacuoles and eosinophilic and basophilic inclusions within muscle fibers. Filamentous tubules seen on electron microscopy are highly specific for IBM.

KEY POINTS

- Dermatomyositis and polymyositis are associated with elevation of muscle enzymes such as creatine kinase and aldolase as well as autoantibodies such as antinuclear antibodies, myositis-specific autoantibodies, and myositis-associated autoantibodies.
- In the idiopathic inflammatory myopathies, muscle imaging can identify sites for biopsy, aid in clinical diagnosis, and help assess the response to treatment.
- Biopsy of an affected muscle is the gold standard for diagnosis to distinguish between dermatomyositis, polymyositis, and inclusion body myositis as well as nonimmune, noninflammatory myopathic disorders.

Differential Diagnosis

The differential diagnosis for myopathy is broad (**Table 32**) and includes hereditary diseases, infection, and endocrine and drug-induced myopathies. Colchicine and hydroxychloroquine, both used frequently in rheumatologic disease, may cause myopathy. Glucocorticoids, used in treating IIMs, can themselves cause muscle weakness that may require withdrawal of therapy. Statins are a frequent cause of myalgia and/or asymptomatic creatine kinase elevations; many cases are mild, and not all will require discontinuation. Rarely, statin use can result in an autoimmune myopathy associated with antibodies to the enzyme HMG-CoA reductase. See MKSAP 17 Neurology for more information on myopathy.

KEY POINT

- The differential diagnosis of the idiopathic inflammatory myopathies includes other myopathies that present with muscle weakness, toxic myopathies, and disorders that present with weakness but without muscle involvement.

Management

IIM management requires a comprehensive approach combining aggressive pharmacotherapy, physical therapy to maintain muscle strength, and supportive interventions. Glucocorticoids, initiated at high doses and tapered once serum muscle enzymes normalize, are the mainstay treatment for PM and DM. Clinical symptoms may take months to improve.

TABLE 32. Differential Diagnosis of Myopathy

Myopathy[a]	Common Examples	Comments
Idiopathic inflammatory myopathies	Dermatomyositis (DM); polymyositis (PM); inclusion body myositis (IBM)	DM and PM: acute/subacute, symmetric proximal weakness, pathognomic rash in DM; IBM: insidious, proximal and distal weakness
Connective tissue disease	Systemic lupus erythematosus; mixed connective tissue disease; systemic sclerosis	Prominent extramuscular features typical of underlying disorder
Endocrine disease	Hypothyroidism; Addison disease; vitamin D deficiency	Subtle extramuscular features; routine testing to evaluate
Infection-induced myopathies	Bacterial: Lyme disease; pyomyositis Viral: influenza; HIV; hepatitis B; hepatitis C Parasitic: toxoplasmosis; trichinosis	Detailed history and physical usually gives clue; difficult to diagnose
Drug- or toxin-induced myopathies	Glucocorticoids; ethanol; statins; colchicine; hydroxychloroquine	Lack of typical symptoms; muscle biopsy is useful
Metabolic myopathies	Acid maltase deficiency; McArdle disease	Typical history; associated with exercise/exertion; ischemic forearm testing
Mitochondrial myopathies	Kearns-Sayre syndrome; Leigh syndrome	Difficult to diagnose; muscle biopsy needed to evaluate
Muscular dystrophies	Duchenne dystrophy; Becker dystrophy	Suggestive history; onset typically in young adulthood
Neurologic and neuromuscular disorders	Amyotrophic lateral sclerosis; myasthenia gravis; Guillain-Barré syndrome; cerebrovascular accident; multiple sclerosis	Suggestive history; some are weakness mimickers (lack of direct involvement of muscle)

[a]Asymptomatic elevation in serum muscle enzymes, especially creatine kinase, is fairly common, may occur without any underlying disease, and is more frequent in black persons. Although usually benign, it must be distinguished from an actual myopathic disorder if weakness and other suggestive features are present.

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Immunosuppressive therapy with methotrexate or azathioprine is used for glucocorticoid-resistant disease or glucocorticoid sparing; it is also used in poor prognosis groups and patients with extramuscular disease such as ILD. Other immunosuppressive agents (such as mycophenolate mofetil and leflunomide) have also been used. Intravenous immune globulin (IVIG) therapy is recommended as an alternative treatment for DM.

IBM is generally resistant to pharmacotherapy, although glucocorticoids, methotrexate, and/or IVIG are often tried.

KEY POINTS

- Management of the idiopathic inflammatory myopathies combines pharmacotherapy, physical therapy to maintain muscle strength, and supportive interventions.
- Glucocorticoids are the mainstay therapy for dermatomyositis and polymyositis, with high doses used until serum muscle enzymes normalize.
- In dermatomyositis and polymyositis, immunosuppressive therapy is used for glucocorticoid-resistant disease and for glucocorticoid sparing; it is also used in poor prognosis groups or in patients with severe extramuscular disease such as interstitial lung disease.
- Inclusion body myositis is generally resistant to treatment, although glucocorticoids, methotrexate, and/or intravenous immune globulin are often tried.

Prognosis

DM and PM are responsive to early aggressive treatment, with symptomatic and histologic improvement in most cases and a 5-year survival rate of 95%. Older age, underlying malignancy, pulmonary fibrosis, and esophageal dysmotility are associated with poorer prognosis; the most common causes of death are malignancies, infections (particularly aspiration pneumonia), profound muscle weakness, cardiovascular disease, and respiratory failure.

Patients with IBM tend to experience a long slow decline of muscle function regardless of therapy, with a large impact on daily activities but little impact on overall survival.

KEY POINT

- The most common causes of death in patients with polymyositis and dermatomyositis are malignancies, infections, profound muscle weakness, cardiovascular disease, and respiratory failure.

Systemic Vasculitis

Introduction

Vasculitis refers to inflammation of arteries, veins, or capillaries. Involved vessels may be large, intermediate, or small. Vasculitis can be idiopathic, or secondary to an antigen trigger or other autoimmune condition (**Table 33**). Vasculitis can mimic, or be mimicked by, other systemic conditions (**Table 34**). Discussion here is limited to diseases in which vasculitis is the primary disorder.

Large-Vessel Vasculitis

Giant cell arteritis (GCA) and Takayasu arteritis (TA) constitute the large-vessel vasculitides. Although not a vasculitis,

TABLE 33. Causes of Secondary Vasculitis

Medications
Antimicrobial agents
Vaccines
Antithyroid agents
Anticonvulsant agents
Antiarrhythmic agents
Diuretics
Other cardiovascular drugs
Anticoagulants
Antineoplastic agents
Hematopoietic growth factors
NSAIDs
Leukotriene inhibitors
Psychotropic drugs
Sympathomimetic agents
Allopurinol
Tumor necrosis factor modulatory agents
Interferon alfa
Infections
Hepatitis A, B, and C virus
HIV
Bacterial endocarditis
Parvovirus B19
Neoplasms
Hairy cell leukemia (associated with polyarteritis nodosa)
Other hematologic and solid malignancies
Autoimmune Diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Sjögren syndrome
Inflammatory myopathies
Systemic sclerosis
Relapsing polychondritis
Inflammatory bowel disease
Primary biliary cirrhosis

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TABLE 34. Differential Diagnosis of Vasculitis

Disease	Comments
Infection (sepsis, endocarditis, hepatitis)	Heart murmur, rash, and/or musculoskeletal symptoms can occur in bacterial endocarditis or viral hepatitis.
Drug toxicity/poisoning	Cocaine, amphetamines, ephedra alkaloids, and phenylpropanolamine may produce vasospasm, resulting in symptoms of ischemia.
Coagulopathy	Occlusive diseases (disseminated intravascular coagulation, the antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura) can produce ischemic symptoms.
Malignancy	Paraneoplastic vasculitis is rare. Any organ system may be affected, but the skin and nervous system are the most common. Vasculitic symptoms may precede, occur simultaneously with, or follow diagnosis of cancer. Lymphoma occasionally may involve the blood vessels and mimic vasculitis. Consider malignancy in patients with incomplete or no response to therapy for idiopathic vasculitis.
Atrial myxoma	Classic triad of symptoms: embolism, intracardiac obstruction leading to pulmonary congestion or heart failure, and constitutional symptoms (fatigue, weight loss, fever). Skin lesions can be identical to those seen in leukocytoclastic vasculitis. Atrial myxomas are rare but are the most common primary intracardiac tumor. Myxomas also can occur in other cardiac chambers.
Multiple cholesterol emboli	Typically seen in patients with severe atherosclerosis. Embolization may occur after abdominal trauma, aortic surgery, or angiography. May also occur after heparin, warfarin, or thrombolytic therapy. Patients may have livedo reticularis, petechiae and purpuric lesions, and localized skin necrosis.

polymyalgia rheumatica (PMR) is discussed here because of its close association with GCA.

Giant Cell Arteritis

Epidemiology and Pathophysiology

GCA is the most common primary vasculitis (10 cases/100,000). GCA is most common among white persons, especially northern Europeans. Women are affected more often than men (2:1 ratio). Median age of onset is 70 years; GCA in patients under age 50 is rare.

GCA characteristically affects the second- to fifth-order branches of the aorta. Affected arteries include the external carotids, temporal arteries (hence the alternative designation *temporal arteritis*), and ciliary and ophthalmic arteries. Subclavian and brachial arteries can be affected. Uncommonly, intracranial arteritis may occur.

In GCA, dendritic cells in the vessel adventitia become activated and recruit T cells and monocytes into the vessel wall. Within the media, macrophages coalesce into multinucleated giant cells and secrete metalloproteinases, disrupting the internal elastic lamina. Simultaneously, intimal proliferation can reduce blood flow and induce partial or complete ischemia of the affected tissue bed.

Clinical Manifestations and Diagnosis

Patients with GCA classically report scalp pain, headache, or tenderness over the temporal artery, which is usually unilateral. Systemic inflammation results in malaise, weight loss, and low-grade fever. Patients may experience pain in the muscles of mastication during chewing (jaw claudication). The most feared outcome is blindness, caused by ophthalmic and/or posterior ciliary artery occlusion. Blindness can be sudden or preceded by transient visual loss (amaurosis fugax). Diplopia is common. In some patients, brachial artery involvement causes decreased pulses and hand or forearm ischemia. Aortic aneurysm is a potential complication as is aortic dissection, which may occur with or without preceding aneurysm formation. Of patients with GCA, 30% to 50% concurrently have PMR (see Polymyalgia Rheumatica).

GCA should be considered in any individual ≥50 years of age with temporal or other atypical headache, jaw claudication, or visual changes, with or without PMR. Nearly all patients with GCA have a markedly elevated erythrocyte sedimentation rate (ESR), which is typically elevated to greater than 50 mm/h. On examination, the temporal artery may be erythematous, swollen, and tender. Definitive diagnosis should be pursued whenever possible via biopsy of a temporal artery segment. However, the presence of skip lesions and the need for expert examination of the biopsied specimen may sometimes lead to false-negative results. In such cases, biopsy of the contralateral artery may be warranted. Angiography of the arms is indicated in patients with peripheral vascular insufficiency.

Management

Treatment of suspected GCA should never be deferred pending biopsy because 1) treatment is rapidly effective and prevents blindness, and 2) biopsy specimens remain interpretable for at least 2 weeks after treatment initiation. In virtually all instances, patients with GCA should receive oral prednisone (60 mg/d [or 1 mg/kg/d]). In patients with visual loss, intravenous (IV) pulse glucocorticoids (typically methylprednisolone, 1000 mg/d for 3 days) may be tried, although restoration of vision should not be anticipated. Prednisone should generally be administered for approximately 1 month (or until resolution of signs and symptoms), with subsequent dose reduction at a rate of about 10% every few weeks. The ESR usually responds rapidly and can then serve as a marker of disease activity.

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Patients should be monitored for relapse, in which case prednisone should be transiently increased; treatment duration may range from 6 to 18 months. Data from observational studies support that the coadministration of low-dose aspirin (80 mg/d) further reduces the risk of blindness and deserves consideration.

When prednisone is contraindicated or in cases where GCA has failed to respond to glucocorticoid therapy, methotrexate, the anti–interleukin-6 agent tocilizumab, and cyclophosphamide have been used, although evidence of their effectiveness is limited.

The long-term outcomes of adequately treated GCA are good, with recurrences uncommon.

Polymyalgia Rheumatica

Epidemiology and Pathophysiology

PMR is not a vasculitis but is discussed here because of its relationship with GCA; most experts consider that GCA and PMR exist on a spectrum of a single unifying disease. Of patients with GCA, 30% to 50% have concurrent PMR; conversely, 10% to 15% of patients with PMR, but no clinical GCA, show occult GCA on blind temporal artery biopsy. PMR epidemiology is similar to GCA, but PMR is 2 to 3 times more common.

Clinical Manifestations and Diagnosis

Patients with PMR experience symmetric pain and stiffness in the shoulder, neck, and hip regions, without actual joint arthritis. Common symptoms include the inability to comb hair or rise from a chair unassisted. In some cases, mild synovitis occurs in the wrists and hands. Strength and muscle enzymes (creatine kinase, aldolase) are generally normal.

PMR is a clinical diagnosis based on the characteristic symptoms in a patient older than 50 years. Patients with PMR demonstrate systemic inflammation (for example, elevated ESR), along with low-grade fever, malaise, and fatigue. In the absence of GCA signs and symptoms, temporal artery biopsies are not routinely performed.

Management

In contrast to GCA, PMR responds well to low-dose prednisone (10-20 mg/d). Most patients respond with dramatic improvement in their symptoms within 3 days, and failure to do so suggests an alternative diagnosis. Patients with PMR frequently experience partial relapses during prednisone tapering, requiring transient up-titration. PMR treatment is therefore commonly of long duration; some patients need several years to completely discontinue prednisone, whereas others remain on prednisone indefinitely.

Takayasu Arteritis

Epidemiology and Pathophysiology

In Takayasu arteritis (TA), the affected arteries are primarily the aorta (ascending, descending thoracic, and abdominal aorta) and its major branches. In contrast to GCA, TA is rare (2 cases/million patient-years) and mainly affects young women (9:1 ratio) with a typical age at onset between 15 and 25 years.

Histologically, the pathophysiologic processes of TA and GCA are similar, with infiltration of T cells, macrophages, and giant cells in the vessel wall.

Clinical Manifestations and Diagnosis

Clinical manifestations of TA result from inflammation and/or the consequences of large artery disease. Fever, fatigue, malaise, and weight loss, along with arthralgia and myalgia, often precede the onset of specific signs and symptoms. Patients may have diminished or absent pulses in the brachial, femoral, axillary, carotid, ulnar, and radial distributions, often accompanied by bruits. Blood pressure measurements may differ on the left and right sides. Aortic coarctation may cause decreased kidney perfusion, compensatory renin/angiotensin release, and hypertension. Wall weakness may lead to aneurysms of the aorta and other vessels; aortic root aneurysm can result in aortic valve incompetence. Central nervous system involvement is uncommon but can lead to syncope, stroke, and ocular findings.

TA should be suspected in patients younger than 40 years with unexplained systemic inflammation and/or signs and symptoms of large-vessel impairment. Angiogram demonstrates focal arterial narrowing and/or aneurysms (**Figure 30**). Laboratory testing is nonspecific but typically reveals an elevated ESR.



FIGURE 30. Takayasu arteritis. This angiogram of the aorta demonstrates high-grade stenosis of the proximal right subclavian artery (*white arrow*) as well as the left subclavian artery just below the origin of the left vertebral artery (*black arrow*). Incidentally noted is anatomic variation with a common origin of the right brachiocephalic artery and the left common carotid artery.

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Management

Untreated TA conveys significant morbidity and mortality; early recognition and management are therefore critical. Standard TA treatment is high-dose prednisone (1 mg/kg/d), followed by taper. Patients with structural damage to affected vessels may require angioplasty to improve blood flow, or, in severe cases, arterial bypass or reconstruction.

KEY POINTS

- Giant cell arteritis should be considered in any individual older than age 50 years with temporal or other atypical headache, jaw claudication, or visual changes.
- Although temporal artery biopsy is indicated to make a definitive diagnosis of giant cell arteritis, initiation of prednisone should not be delayed; treatment can prevent blindness, and biopsy specimens remain interpretable for at least 2 weeks after treatment initiation.
- Patients with polymyalgia rheumatica experience symmetric pain and stiffness in the shoulders, neck, and hips, along with low-grade fever, malaise, and fatigue; standard treatment is low-dose prednisone.
- Takayasu arteritis should be suspected in patients younger than age 40 years with unexplained systemic inflammation and/or signs and symptoms of large-vessel impairment; standard treatment is high-dose prednisone.

Medium-Vessel Vasculitis

Polyarteritis Nodosa

Epidemiology and Pathophysiology

Polyarteritis nodosa (PAN) is rare (5-10 patients/million); men and women are affected equally. In approximately 30% of cases, PAN is associated with hepatitis B virus infection; hepatitis B vaccination reduces PAN incidence. The remainder of cases are idiopathic. PAN characteristically affects medium and small arteries; arterial inflammation results in vessel narrowing and, characteristically, aneurysms and microaneurysms. The classic features of PAN result from ischemia and/or aneurysm rupture. Organs typically affected include the kidneys, gastrointestinal tract (especially the mesenteric artery and small intestine), peripheral nervous system, and skin. Involvement of the testicles, ovaries, and breasts can occur. Coronary arteries can also be affected.

Clinical Manifestations and Diagnosis

Patients with PAN usually present with nonspecific inflammatory symptoms (fatigue, malaise, fever, myalgia, arthralgia). Renal artery vasculitis can cause decreased kidney blood flow, resulting in decreased glomerular filtration, renin/angiotensin overproduction, and hypertension. Glomerulonephritis does not occur. Abdominal symptoms include chronic or intermittent ischemic pain, especially after eating (abdominal angina); bowel infarction may ensue. Neurologic involvement commonly takes the form of mononeuritis multiplex. Skin findings include livido reticularis, purpura, and painful subcutaneous nodules.

Elevated inflammatory markers are typically present, and hepatitis B antigenemia is detectable in infected patients. Vascular imaging studies are most useful for diagnosis. Mesenteric and/or renal artery imaging with either angiography or CT angiography reveals medium-sized artery aneurysms and stenoses.

Management

PAN carries significant potential for poor outcome, including kidney disease and mortality. Treatment is aggressive, including high-dose prednisone and cyclophosphamide. Other disease-modifying antirheumatic drugs (methotrexate, azathioprine, mycophenolate mofetil) may be considered for milder disease or as maintenance therapy. Patients with hepatitis B should receive plasma exchange and antiviral therapy whenever feasible.

Primary Angiitis of the Central Nervous System

Epidemiology and Pathophysiology

Primary angiitis of the central nervous system (PACNS) is exceedingly rare (2.4 cases/million person-years). Median age of onset is 50 years, with men affected twice as often as women. Progression may be insidious. Vascular involvement is limited to intracerebral vessels; a necrotizing granulomatous vasculitis is typical.

Clinical Manifestations and Diagnosis

The most common features of PACNS are recurrent headaches and progressive encephalopathy. Strokes, transient ischemic attacks, visual field defects, and seizures also occur. Systemic vasculitis is absent, and systemic inflammatory markers are not elevated. Diagnosis requires a high index of suspicion and aggressive evaluation, including lumbar puncture, MRI, cerebral angiography, and brain biopsy. Cerebrospinal fluid analysis reveals lymphocytosis and elevated protein. MRI reveals multiple diffuse and focal abnormalities but is nonspecific. Intracranial angiography typically reveals areas of ectasia and stenosis, but other entities (atherosclerosis, vasospasm) may produce similar pictures. The definitive test is a brain biopsy revealing granulomatous vasculitis. Brain biopsy also permits identification and/or elimination of other important diagnoses, including infection and malignancy. Because vascular involvement in PACNS is patchy, a normal biopsy may sometimes represent a false negative. Nonetheless, brain biopsy is nearly always necessary.

Management

PACNS can lead inexorably to cognitive decline, dementia, and death. Management is aggressive and includes high-dose glucocorticoids and daily oral cyclophosphamide.

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Kawasaki Disease

Epidemiology and Pathophysiology

Kawasaki disease (KD) is a medium-vessel vasculitis of infants and children, most commonly boys of Asian origin. A seasonal predominance (late winter-spring) suggests an as-yet unidentified infectious trigger.

Clinical Manifestations and Diagnosis

Symptoms of KD include high spiking fevers, conjunctivitis, and mucositis of the lips and oral cavity, including a strawberry-like tongue. A polymorphous truncal rash is accompanied by palmar and plantar erythema, induration, and desquamation. Cervical lymphadenopathy is common. Most concerning is vasculitic involvement of the coronary arteries, resulting in coronary artery aneurysms and/or thrombosis, and potentially myocardial infarction and mortality. Other cardiac manifestations include myocarditis and pericarditis.

Management

Standard KD treatment consists of intravenous immune globulin (2 g/kg) plus aspirin (30-100 mg/kg/d). This regimen reduces inflammation and the risk of coronary aneurysms. Patients who develop medium-large coronary artery aneurysms during the acute phase of the illness are at increased risk of coronary artery stenosis and require close follow-up with periodic testing that may include electrocardiography, echocardiography, and ischemic stress testing.

KEY POINTS

- In approximately 30% of cases, polyarteritis nodosa (PAN) is associated with hepatitis B virus infection; hepatitis B vaccination reduces PAN incidence.
- Treatment of polyarteritis nodosa includes high-dose prednisone and cyclophosphamide.
- Primary angiitis of the central nervous system presents with recurrent headaches and progressive encephalopathy.
- Kawasaki disease occurs in infants and young children; symptoms include high spiking fevers, conjunctivitis, rash, and mucositis of the lips and oral cavity.

Small-Vessel Vasculitis

Small-vessel vasculitis affects post-capillary venules, arterioles, and capillaries. Because these vessels are ubiquitous, small-vessel vasculitides present with a wide range of manifestations. Two major categories of small-vessel vasculitis are discussed here: ANCA-associated vasculitis and immune complex-mediated vasculitis.

ANCA-Associated Vasculitis

ANCA-associated vasculitis constitutes three diseases: granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome). In addition, rapidly progressive glomerulonephritis may sometimes present as an ANCA-associated process (see MKSAP 17 Nephrology, Glomerular Diseases). ANCAs were first recognized when sera from patients with vasculitis were noted to bind to fixed neutrophils in vitro in two distinct patterns—either perinuclear (p-ANCA) or diffusely throughout the cytoplasm (c-ANCA). These patterns were found to reflect distinct antibody types, with p-ANCA mainly directed toward the neutrophil enzyme myeloperoxidase (MPO), and c-ANCA toward the neutrophil proteinase 3 (PR3). These antibodies are now specifically identified using enzyme-linked immunosorbent assays.

Specific ANCA-associated diseases are classically associated with one or the other, but not both, ANCA types. Although the clinical pictures of c-ANCA and p-ANCA vasculitides differ, investigators have proposed a common process through which all ANCA may promote vasculitis (**Figure 31**). Based on the proposed model, the extent of ANCA deposition need not be large to cause disease. Thus, on immunofluorescence of histopathologic specimens, little antibody staining is seen, leading

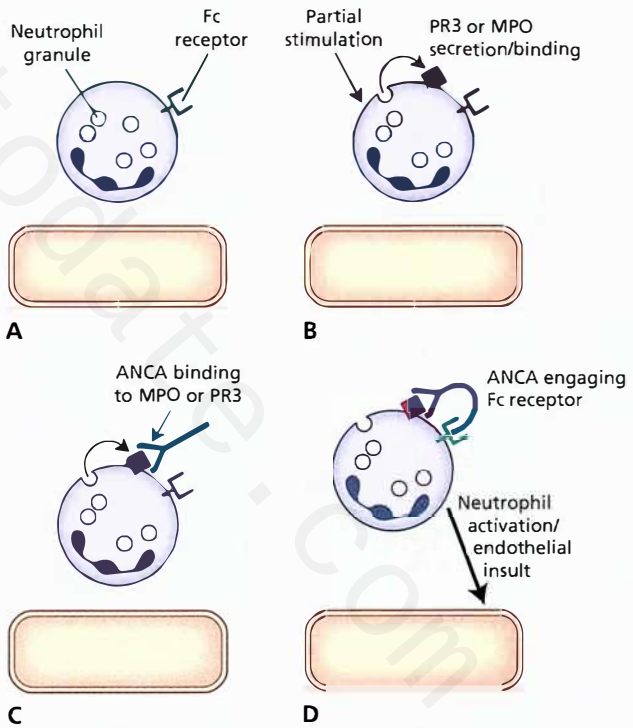

FIGURE 31. Model of presumed ANCA activity in promoting vasculitis. A, Quiescent neutrophil and adjacent endothelial cell. B, Low-level activation of the neutrophil ("priming") results in early partial neutrophil degranulation (release of granule contents to the extracellular environment), allowing de novo exposure of MPO and/or PR3, which result in humoral immunity and the formation of anti-MPO or anti-PR3 autoantibodies. C, Adherence of secreted MPO/PR3 on the neutrophil surface permits ANCA binding to the neutrophil. D, ANCA bound to neutrophil surface engages the neutrophil Fc receptor, fully stimulating the neutrophil and leading to release of enzymes such as metalloproteinases, as well as toxic oxygen radicals, that damage the endothelium. MPO = myeloperoxidase; PR3 = proteinase 3.

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CONT. to the designation of ANCA vasculitides as *pauci-immune*. In all ANCA vasculitides, fever, malaise, weight loss, myalgia, and arthralgia are common.

Granulomatosis with Polyangiitis

Epidemiology and Pathophysiology

Granulomatosis with polyangiitis (GPA) is the most common ANCA-associated vasculitis (8-10 cases/million). GPA typically affects middle-aged to older patients (mean age, approximately 55 years). White persons, typically northern Europeans, are more commonly affected. Of note, 80% to 90% of patients with GPA demonstrate a c-ANCA pattern and anti-PR3 antibody positivity.

Clinical Manifestations and Diagnosis

Classic GPA affects the upper respiratory tract (including sinuses and ears), lungs, and kidneys. Nasal and/or sinus pain and stuffiness, rhinitis, and/or epistaxis are common. Nasal inflammation can cause cartilage damage and collapse (saddle nose deformity). Hearing loss may occur, usually due to eustachian tube damage. Inflammation can damage the trachea, causing airway narrowing and obstruction. Ocular inflammation may lead to blindness. In the lungs, nodules and infiltrates occur (**Figure 32**); capillaritis may result in alveolar hemorrhage and hemoptysis. In the kidneys, rapidly progressive crescentic glomerulonephritis may ensue. Other organ systems commonly involved include the skin (painful cutaneous nodules, palpable purpura, urticarial and ulcerative lesions) and peripheral nerves.

Diagnosing GPA requires the appropriate clinical and serological picture. In the setting of a classic GPA picture, positivity for c-ANCA/anti-PR3 is considered by many rheumatologists to be adequate to initiate treatment. However, because all effective treatments have toxicity, most experts recommend that a tissue diagnosis is essential in all but the most clear-cut cases. Tissues available for biopsy include skin, lung, sinuses, sural nerve, and kidneys. Lung biopsy is invasive but most reliably provides the characteristic histopathologic findings, including both vasculitis and necrotizing granulomas (characteristic of GPA but not the other ANCA diseases). Kidney biopsy is high yield when kidney involvement is apparent, but because granulomas are absent, the biopsy will not distinguish GPA from the other ANCA conditions. Skin biopsies are less often nondiagnostic but are readily obtained.

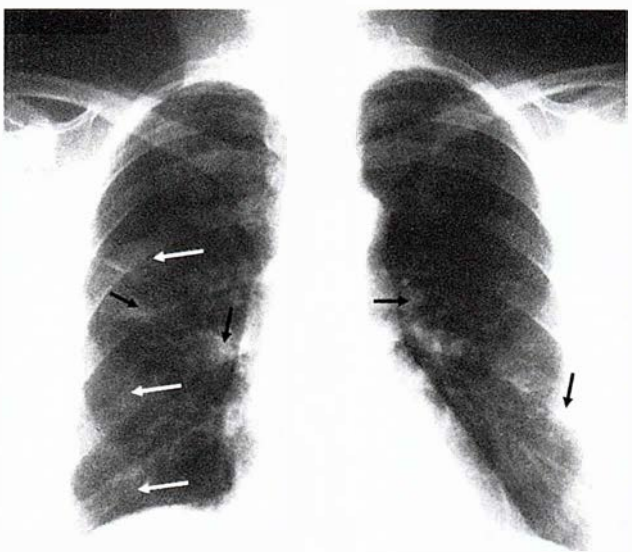

FIGURE 32. A frontal chest radiograph showing both patchy alveolar infiltrates (*white arrows*) and nodules (*black arrows*) in a patient with granulomatosis with polyangiitis (formerly known as Wegener granulomatosis).

Management

For severe or generalized disease, treatment of GPA consists of high-dose glucocorticoids plus cyclophosphamide for approximately 6 months, followed by maintenance therapy with methotrexate, azathioprine, or mycophenolate mofetil. Glucocorticoids alone are insufficient to control GPA. Recent studies suggest that the anti-B-cell antibody rituximab is as efficacious as cyclophosphamide, possibly with less toxicity. For limited disease (no kidney disease and only mild lower airway disease), methotrexate and glucocorticoids alone may be sufficient; such patients should be carefully monitored for treatment failure necessitating the more aggressive regimen. Using these approaches, GPA mortality has declined from 90% to around 10%.

Microscopic Polyangiitis

Epidemiology and Pathophysiology

Microscopic polyangiitis (MPA) shares features with GPA but differs with regard to organ involvement and autoimmunity. MPA occurs about half as frequently as GPA. Men are affected more commonly than women (2:1 ratio). Patients tend to develop MPA in their fourth to fifth decades, but earlier and later cases occur. Patients with MPA classically express p-ANCA and anti-MPO antibodies.

Clinical Manifestations and Diagnosis

The typical organ involvement in MPA is vasculitis of the kidneys and lungs. Kidney involvement is nearly ubiquitous; as in GPA, the lesions are those of necrotizing glomerulonephritis. Crescent formation is common, and immune deposits are sparse or absent. Lung involvement occurs in more than half of cases, consisting of non-granulomatous alveolar infiltrates that may be fleeting or persistent and are histologically reflected as pulmonary capillaritis with neutrophilic infiltrates. Most ominous is diffuse alveolar hemorrhage, which can be fatal if not adequately managed. Upper airways remain uninvolved. Skin rashes (especially palpable purpura) are common.

Diagnosis requires the appropriate conjunction of symptoms and serologies. Most patients are positive for p-ANCA and

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CONT. anti-MPO antibodies. Biopsy of an affected organ reveals capillaritis, glomerulonephritis, and/or leukocytoclastic vasculitis in the absence of granulomas.

Management

Like GPA, MPA treatment requires high-dose glucocorticoids plus cyclophosphamide for 6 months, followed by maintenance therapy with methotrexate, azathioprine, or mycophenolate mofetil. As in GPA, rituximab for MPA has recently shown promise.

Eosinophilic Granulomatosis with Polyangiitis

Epidemiology and Pathophysiology

Eosinophilic granulomatosis with polyangiitis (EGPA) is the rarest ANCA-associated vasculitis. Strong association of EGPA with asthma and eosinophilia suggests an atopic trigger.

Clinical Manifestations and Diagnosis

Patients with EGPA report a preceding history of atopy, including allergic rhinitis, nasal polyps, or asthma. The symptomatology of EGPA depends upon localization of the vasculitis. Lung disease is common, manifested as infiltrates and capillaritis. Peripheral nerve disease is more common in EGPA than in other ANCA vasculitides, presenting as mono- or polyneuropathy or mononeuritis multiplex. Kidney disease is somewhat less common than in other ANCA diseases. Hypereosinophilia, in both the peripheral blood and involved tissues, is characteristic; a diagnosis of EGPA should be revisited in the absence of eosinophils. Tissue biopsy shows necrotizing vasculitis with eosinophilic infiltrates. Eosinophilic granulomas may be seen in the tissues as well as the vessels. IgE levels are frequently elevated. EGPA patients who are ANCA-positive typically display the p-ANCA/anti-MPO pattern. Because up to 40% of patients are ANCA-negative, a negative ANCA test should not eliminate EGPA as a diagnosis.

Management

One unique aspect of EGPA may be the sensitivity of eosinophils to glucocorticoids. In patients with mild or limited disease, glucocorticoid treatment alone may therefore be sufficient. In more severe disease, glucocorticoids plus cyclophosphamide is preferred, followed by maintenance therapy with a less toxic immunosuppressive agent. As in all ANCA diseases, the potential for permanent tissue damage mandates an early and aggressive approach if full return to function is to be anticipated.

KEY POINTS

- Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) typically affects the upper respiratory tract, lungs, and kidneys and is associated with c-ANCA and antiproteinase 3 (PR3) antibody positivity.

(Continued)

KEY POINTS *(continued)*

- Microscopic polyangiitis typically involves the kidneys and lungs, and patients classically express p-ANCA and antimyeloperoxidase (MPO) antibodies.
- Treatment of both granulomatosis with polyangiitis and microscopic polyangiitis consists of high-dose glucocorticoids plus cyclophosphamide for approximately 6 months, followed by maintenance therapy.
- Eosinophilic granulomatosis with polyangiitis is associated with atopy, hypereosinophilia, lung disease, and peripheral nerve disease; glucocorticoids may be sufficient for mild/limited disease, and more severe disease may be treated with glucocorticoids plus cyclophosphamide, followed by maintenance therapy.

Immune Complex-Mediated Vasculitis

Several vasculitides arise from the formation of immune complexes. If not cleared, such complexes deposit in small vessels, activate complement, and recruit neutrophils. Any organ may be affected, but skin and joint involvement is common. Dermal capillaritis characteristically allows erythrocyte extravasation (palpable purpura), worse in dependent areas. Influxed neutrophils undergo cell death and breakup (clasis) as well as release of pyknotic nuclei (nuclear dust), a process designated as leukocytoclastic vasculitis (**Figure 33**).

Cryoglobulinemic Vasculitis

Epidemiology and Pathophysiology

In cryoglobulinemic vasculitis, antibodies have the special characteristic of precipitating in vitro at temperatures below normal body temperature (37.0 °C [98.6 °F]). The immune complex formation that typically occurs in vivo in these diseases may not relate to this cryoglobulinemic property because body core temperature is sufficient to prevent cold-induced precipitation. However, severe cold exposure of the fingertips, ear helices, and tip of the nose may result in cold-related precipitation, vascular ischemia, and infarction.

Three types of cryoglobulins are recognized (**Table 35**). Type I is a monoclonal antibody, often resulting from hematologic malignancy. Type I cryoglobulins rarely form immune complexes in vivo but may cause hyperviscosity. Type II cryoglobulins consist of a polyclonal IgG antibody together with a monoclonal IgM with rheumatoid factor activity (that is, binds to other immunoglobulins, contributing to immune complex formation). Type II cryoglobulins precipitate ex vivo in the cold but also form immune complexes in vivo to generate vascular inflammation. Ninety percent of patients with type II cryoglobulinemia have chronic hepatitis C virus infection, which furnishes the antigen(s) for immune complex formation; the remaining 10% are idiopathic and designated as

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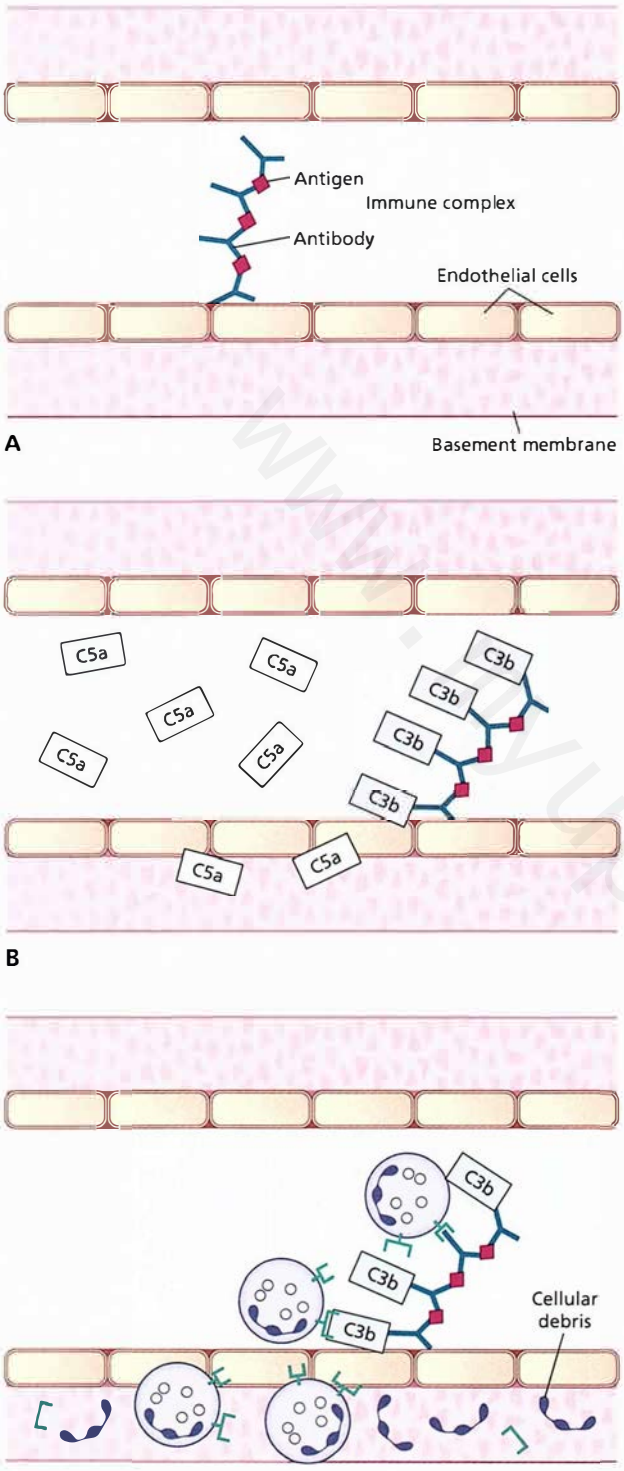

FIGURE 33. The process of classic immune complex-mediated small-vessel vasculitis. A, In the setting of antigen/antibody balance, immune complexes form that may become trapped in small vessels. B, The formation of immune complexes lead to complement activation by the classical pathway, particularly including the generation of C3b (an opsonin) and C5a (a chemoattractant). C, The presence of C5a attracts neutrophils, which engage C3b and antibody Fc tails to undergo further activation. Neutrophils also invade the vascular wall. Some neutrophils undergo cell death and breakdown (leukocytoclasis), resulting in the presence of cellular fragments within the vessel wall.

TABLE 35. Types of Cryoglobulins

Type	Composition	Common Underlying Conditions
I	Monoclonal IgM	Hematologic malignancy (e.g., Waldenstrom macroglobulinemia, multiple myeloma)
II	Polyclonal IgG + monoclonal IgM rheumatoid factor	Chronic hepatitis C infection; HIV infection; idiopathic (essential mixed)
III	Polyclonal IgG + polyclonal IgM rheumatoid factor	Autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis)

essential mixed cryoglobulinemia. Type III cryoglobulins are also mixed but consist of polyclonal IgG together with polyclonal IgM rheumatoid factor. Type III cryoglobulins typically occur secondary to other autoimmune diseases and resolve with appropriate disease treatment.

Clinical Manifestations and Diagnosis

As in all immune complex vasculitides, palpable purpura is the characteristic rash in type II cryoglobulinemia. Other organs characteristically involved include peripheral nerves and the kidneys (glomerulonephritis). Less commonly, gastrointestinal, central nervous system, and other organ involvement occurs.

Diagnosis depends upon recognition of palpable purpura in the setting of other relevant organ involvement. Positivity for hepatitis C suggests but does not prove a diagnosis of type II cryoglobulinemia. Characteristically, patients with cryoglobulinemic vasculitis manifest evidence of complement activation, with C4 disproportionately low relative to C3. Inflammatory markers are typically elevated. Absence of rheumatoid factor argues against type II or type III cryoglobulinemia. Cryoglobulins can be assessed directly in serum from blood that has been allowed to clot at 37.0 °C (98.6 °F). In patients with cryoglobulinemia, such serum, when incubated at 4.0 °C (39.2 °F), forms cryoprecipitates, the extent of which can be expressed as a volume-percent (cryocrit).

Management

Definitive cryoglobulinemia treatment requires clearance of the driving antigen. For patients with hepatitis C–related type II cryoglobulinemia, this means resolving the hepatitis C infection with antiviral therapy. However, if the vasculitic organ involvement is severe, reduction of cryoglobulins themselves is imperative. Classic treatment involves glucocorticoids, cyclophosphamide, and plasmapheresis. More recently, anti-B-cell therapy with rituximab has demonstrated efficacy at reducing cryoglobulinemia and may provide a less toxic alternative. H

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Henoch-Schönlein Purpura

Epidemiology and Pathophysiology

Henoch-Schönlein purpura (HSP) is the most common childhood vasculitis (incidence, 20/100,000) and tends to appear after upper respiratory infections. HSP is rarer among adults. The HSP antigen is unknown, but the immune complex antibodies are unique in belonging to the IgA subfamily.

Clinical Manifestations and Diagnosis

The characteristic symptoms of HSP are abdominal pain and palpable purpura. Purpuric lesions commonly occur on palms and soles. Gastrointestinal ischemia may be severe enough to cause intestinal bleeding. Arthritis is common, and other organ systems may be involved; patients with HSP may present with glomerulonephritis.

The diagnosis is based on the clinical picture in both children and adults. Laboratory studies are nonspecific but confirm systemic inflammation. Diagnosis is established by biopsy of the affected organ. Skin biopsy will show leukocytoclastic vasculitis and, on immunofluorescence, IgA and C3 complement deposition. Kidney biopsy will show IgA nephropathy. Serum IgA levels may be elevated.

Management

Pediatric HSP is typically self-limiting, and treatment usually requires only supportive care. When more severe organ involvement occurs, glucocorticoids may be considered but have limited benefit on the purpura and nephritis. Adults tend to experience a more severe course, are more likely to relapse, and are typically treated with glucocorticoids.

Hypersensitivity Vasculitis

Epidemiology and Pathophysiology

Hypersensitivity vasculitis represents a hypersensitivity response to a known or unknown antigen, such as a drug or infection. As in the other small-vessel vasculitides, hypersensitivity vasculitis typically results from immune complex formation and deposition. Complement is activated, and neutrophils accumulate in capillaries, arterioles, and postcapillary venules, often resulting in the classic pathologic appearance of a leukocytoclastic vasculitis. In contrast to HSP, IgA is usually not involved.

Clinical Manifestations and Diagnosis

As in all immune complex vasculitides, the characteristic rash of hypersensitivity vasculitis is palpable purpura (**Figure 34**). Other rashes, including vesicles, pustules, maculopapular lesions, and urticaria, may occur. Other organ systems are usually spared.

Management

Definitive hypersensitivity vasculitis management consists of removing the offending antigen, after which the rash should resolve within weeks. When the rash is severe, or if removal of the antigen is not readily accomplished, most clinicians consider prednisone to resolve the inflammatory component. Other agents that may help improve hypersensitivity vasculitis include colchicine, dapsone, and NSAIDs.



FIGURE 34. Palpable purpura is shown, the classic rash of small-vessel, immune complex-mediated vasculitides. The lesions are nonblanching and represent extravasations of blood from damaged vessels. Purpuric lesions are typically more prominent on the lower extremities, a consequence of the superimposed effect of gravity on oncotic pressure.

KEY POINTS

- Ninety percent of patients with type II cryoglobulinemia have chronic hepatitis C virus infection.
- Palpable purpura is the characteristic rash in type II cryoglobulinemia; other organs characteristically involved include peripheral nerves and the kidneys.
- Henoch-Schönlein purpura occurs mainly in children, and characteristic symptoms are abdominal pain and palpable purpura; this disease is typically self-limiting.
- Hypersensitivity vasculitis presents as palpable purpura and represents a hypersensitivity response to an antigen that typically resolves when the offending agent is removed.

Systemic Sclerosis

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis, with resultant thickening and hardening of the skin (scleroderma). Internal organ involvement is common and causes significant morbidity and mortality.

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Pathophysiology

Deposition of increased amounts of structurally normal collagen is the classic finding of SSc and the cause of most clinical manifestations. This fibrosing phenotype is accompanied by autoimmunity as well as small artery endothelial damage and dysfunction. Fibroblast activation and collagen deposition lead to tissue fibrosis in skin and other organs due to the complex interactions between the immune system, interstitium, and vasculature. The impact of each of these factors is variable and leads to heterogeneity in the clinical features.

The triggering and initial proliferating events of SSc remain undefined. No consistent environmental trigger has been identified. A role for heredity is supported by genetic loci associated with the disease, but these are shared with other autoimmune diseases and provide limited insight into the generation of the SSc phenotype.

Epidemiology

Annual incidence of SSc is 1 to 2/100,000 persons, and prevalence is 19 to 75/100,000. Peak age of onset occurs between 30 and 50 years, with a female predominance (3:1 ratio). SSc is more common (and perhaps more severe) in black persons.

Classification

SSc is the most characteristic of the scleroderma spectrum disorders, a group of diseases sharing the feature of skin hardening. The scleroderma spectrum disorders include SSc, localized scleroderma (in which fibrosis is histopathologically identical to SSc but limited to a single patch of the skin), and scleroderma-like conditions (which include other disorders associated with thickened, sclerotic skin). SSc is further characterized as two distinct subsets based on skin involvement: diffuse cutaneous systemic sclerosis (DcSSc) and limited cutaneous systemic sclerosis (LcSSc).

Table 36 describes the common manifestations and features of the scleroderma spectrum disorders.

KEY POINTS

- Diffuse cutaneous systemic sclerosis is characterized by extensive distal and proximal skin thickening (chest, abdomen, and arms proximal to wrists) and is commonly accompanied by internal organ fibrosis.
- Limited cutaneous systemic sclerosis is characterized by distal (face, neck, and hands), but not proximal, skin thickening; it is usually unaccompanied by internal organ fibrosis but is more likely to be associated with pulmonary arterial hypertension.

Diagnosis

SSc should be suspected in the presence of symmetric skin induration on the hands, arms, face, and/or torso. Isolated skin induration without any other features occurs in less than 10% of patients with SSc. Sclerodactyly (skin fibrosis of the fingers or toes) and characteristic extracutaneous features are often present and support the diagnosis. Skin induration plus one or more of the following extracutaneous features strongly suggests the diagnosis of SSc: Raynaud phenomenon, digital infarction, and/or pitting; heartburn, dysphagia, or diarrhea; hypertension and/or kidney disease; dyspnea on exertion, interstitial lung disease, or pulmonary arterial hypertension; or mucocutaneous telangiectasias. Skin thickening confined to a single area suggests localized scleroderma in its various forms; internal organ involvement is extremely rare in these limited conditions (see Table 36).

In patients with skin thickening and clinical features suggestive of SSc, autoantibody testing is done to further support the diagnosis. Antinuclear antibodies are often present (70% prevalence). Anticentromere antibodies are associated with LcSSc (15%-40% prevalence) and the CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome, whereas anti–Scl-70 antibodies are associated with DcSSc (15%-40% prevalence). Patients who have DcSSc without anti–Scl-70 antibodies may instead have antibodies to an alternative antigen, RNA polymerase III. Still other autoantibodies have been identified whose sensitivity for SSc is low (20%) but whose specificity is high (>95%) (**Table 37**).

A skin biopsy is usually not needed to confirm the diagnosis because the findings are classic and characteristic.

KEY POINT

- In patients with skin thickening and clinical features suggestive of systemic sclerosis, autoantibody testing (antinuclear, anti–Scl-70, anticentromere, and anti-RNA polymerase III) is done to further support the diagnosis.

Clinical Manifestations and Management

Treatments addressing the underlying mechanisms of SSc have yet to be developed. Instead, therapeutic options currently focus on managing individual organ manifestations.

Cutaneous Involvement

Skin thickening occurs in most patients with SSc. Skin involvement varies in both the extent of body surface involved and the severity of induration. In LcSSc, scleroderma is restricted to the hands and, to a lesser extent, the face and neck. Scleroderma involving the chest, abdomen, forearms, upper arms, and shoulders indicates DcSSc.

In early SSc, swelling, edema, and erythema of the hands and forearms may precede skin induration. Pruritus may be a significant symptom. Sclerodactyly may develop (**Figure 35**, on page 80), and vascular involvement (see Vascular Involvement)

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TABLE 36. Common Manifestations/Features of the Scleroderma Spectrum Disorders

Disorder	Manifestation/Feature	Comments
Systemic Sclerosis		
Diffuse cutaneous systemic sclerosis (DcSSc)	Distal and proximal skin thickening (chest, abdomen, arms proximal to wrists); commonly has visceral organ involvement	Skin involvement is extensive and is commonly accompanied by internal organ fibrosis and ILD
Limited cutaneous systemic sclerosis (LcSSc)	Distal (face, neck, hands), but not proximal, skin thickening; typically not accompanied by internal organ fibrosis	More likely to develop PAH and Raynaud phenomenon early in disease and display features of the CREST syndrome
Systemic sclerosis sine scleroderma	Fibrosing organ involvement without skin thickening	Difficult to diagnose; prognosis may be similar to LcSSc
Localized Scleroderma		
Morphea	Plaques generally on the trunk	Systemic manifestations or Raynaud phenomenon is extremely rare
Linear scleroderma	Streaks/lines of thickened skin	Same as above
Scleroderma-like Conditions[a]		
Eosinophilic fasciitis	Orange peel induration (peau d'orange) of proximal extremities with sparing of hands and face; peripheral eosinophilia; skin retraction over the superficial veins may be more apparent with elevation of an affected limb	Full-thickness skin biopsy demonstrates lymphocytes, plasma cells, and eosinophils infiltrating the deep fascia; glucocorticoids are the mainstay of treatment
Nephrogenic systemic fibrosis	Secondary to gadolinium in patients with kidney disease; brawny, wood-like induration of extremities, sparing the digits	Skeletal muscle fibrosis with contractures and/or cardiac muscle involvement can occur, with cardiomyopathy and increased mortality; changes in use and formulation of gadolinium have reduced incidence
Scleredema	Indurated plaques/patches on back, shoulder girdle, and neck	Typically seen in long-standing diabetes mellitus
Scleromyxedema	Waxy, yellow-red papules over thickened skin of face, upper trunk, neck, and arms; deposition of mucin with large numbers of stellate fibroblasts in the dermis	Associated with paraproteinemia (IgGλ) and may therefore occur in the setting of multiple myeloma or AL amyloidosis; more frequent in men
Chronic graft versus host disease	Lichen planus–like skin lesions or localized or generalized skin thickening	Occurs most commonly after hematopoietic stem cell transplantation; may occasionally be seen after blood transfusion in an immunocompromised host
Drug and toxin exposure	Can produce scleroderma-like tissue changes	Examples: bleomycin, docetaxel, pentazocine, L-tryptophan, organic solvents

CREST = calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension.

[a]Sclerderma-like skin changes may also occur as a manifestation of systemic endocrine, kidney, or infiltrative disorders.

TABLE 37. Autoantibodies and Their Associations in Systemic Sclerosis

Autoantibody	Clinical Associations	Comments
Antinuclear	DcSSc; LcSSc	Overall prevalence in SSc: 70%; not associated with specific manifestations
Anticentromere (kinetochore proteins)	LcSSc ± PAH	Overall prevalence in SSc about 30%; highly associated (>90%) with CREST variant of LcSSc
Anti–Scl-70 (DNA topoisomerase-1)	DcSSc; ILD	Overall prevalence in SSc: about 30%; highly associated with DcSSc
Anti-RNA polymerase III	DcSSc; kidney disease	Useful in DcSSc with negative Scl-70
Anti-U3-RNP (fibrillarin)	DcSSc; PAH; myositis	Associated with poor outcome; more common in black men
Anti-PM-Scl	Myositis	Associated with overlap syndrome and polymyositis
Anti-Ku	Myositis	Rare occurrence
Anti-Th/To	LcSSc; PAH	Rare occurrence

CREST= calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias; DcSSc = diffuse cutaneous systemic sclerosis; ILD = interstitial lung disease; LcSSc = limited cutaneous systemic sclerosis; PAH = pulmonary arterial hypertension; RNP = ribonucleoprotein; SSc= systemic sclerosis.

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FIGURE 35. Sclerodactyly in a patient with systemic sclerosis. Indurated/tight skin of the fingers with resorption at the tips, leading to loss of pulp.

can result in digital ulcers and pitting of the fingertips (**Figure 36**). Some patients develop telangiectasias and calcinosis cutis. Scleroderma of the face may lead to the reduction of skin wrinkles and limitation of the oral aperture. Late in the disease, induration improves and skin may become soft and thin, making the diagnosis difficult.

SSc pruritus is managed symptomatically with antihistamines and skin emollients. Limited data suggest that the early inflammatory phases of skin disease may respond to systemic glucocorticoids, weekly methotrexate, or other immunosuppressive therapies, and a therapeutic trial can be considered. However, glucocorticoids may potentiate the risk of renal crisis (see Kidney Involvement) and should be administered cautiously. The indurated, thickened phase of skin involvement responds poorly to therapy; no treatment has been shown to be consistently effective.

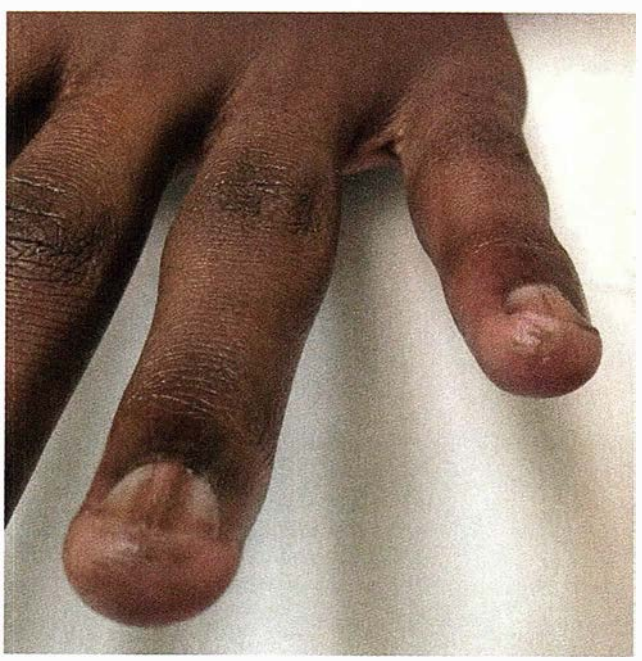

FIGURE 36. Digital pitting in a patient with systemic sclerosis. Digital pits and hyperkeratosis at the tips of the fourth and fifth fingers.

Musculoskeletal Involvement

In addition to hand swelling, patients with early SSc (especially DcSSc) often develop arthralgia, myalgia, and fatigue. Inflammatory arthritis with palpable tenderness and joint swelling is atypical; joint erosions should suggest an overlap with rheumatoid arthritis. Later in the disease, fibrosis of the periarticular structures leads to joint pain, immobility, and contractures, especially in the fingers and extremities. Fibrosis around tendons is sometimes associated with palpable and/or audible deep tendon friction rubs, which occur more commonly in DcSSc and may connote aggressive disease and internal organ involvement. Fibrosis also occurs around nerves, causing cranial and peripheral entrapment neuropathies and occasionally producing autonomic neuropathy. Fibrosis within muscle can lead to myopathy; myositis has also been reported.

Low-dose systemic glucocorticoids, methotrexate, and leflunomide may help treat inflammatory arthritis and myositis but have limited efficacy for other SSc musculoskeletal manifestations. Surgical release of entrapped nerves can relieve compressive symptoms. Surgical tendon release and/or reconstruction may occasionally be an option.

Vascular Involvement

Raynaud phenomenon (sequential white, blue, and red color changes in the digits precipitated by cold or stress) occurs in almost all patients with SSc. Raynaud phenomenon is initially transient and reversible; later, structural changes develop within small blood vessels, resulting in permanently impaired flow that produces acrocyanosis, digital pitting, and/or ulcerations. In contrast, primary Raynaud disease is commonly seen in young women, has a benign and usually self-limiting course, and does not cause vascular damage and digital ulcerations. It can be followed periodically in the absence of digital pits or nailfold capillary abnormalities.

In patients with LcSSc, Raynaud phenomenon may precede other disease manifestations by years or decades. In contrast, Raynaud phenomenon among DcSSc patients usually coincides with the appearance of skin and/or musculoskeletal manifestations. Office-based examination of the nailfold capillaries of patients with SSc using a dermatoscope or ophthalmoscope reveals both capillary destruction and dilated capillary loops, which can distinguish SSc from primary Raynaud as well as nonvascular causes of tissue fibrosis (**Figure 37**).

Avoidance of cold exposure, keeping core temperature warm to increase shunting of blood flow peripherally, and avoiding smoking reduce the risk of Raynaud episodes. Calcium channel blockers, antiplatelet agents, and topical nitrates are first-line pharmacotherapy and can reduce the number and severity of episodes. Refractory patients may be treated with phosphodiesterase-5 inhibitors (sildenafil or tadalafil). Endothelin-1 blockers can also be effective and may prevent

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FIGURE 37. A 40× magnification of the nailfold using wide-field microscopy revealing a capillary pattern characterized by dilatation in some areas and avascularity in others during the "active phase" of diffuse cutaneous systemic sclerosis.

recurrences of digital ulcerations. Regional sympathetic blockade or digital sympathectomy may be tried to reverse vasospasm and save an at-risk digit; localized injection of botulinum toxin A has also shown promise. Surgical debridement and amputations may be needed for severe ischemia and gangrene that does not respond to salvage therapy.

Gastrointestinal Involvement

More than 70% of patients with SSc have clinical gastrointestinal involvement. Upper involvement is common, with fibrosis causing pharyngeal dysfunction, esophageal hypomotility, and lower esophageal sphincter incompetence. Consequences include dysphagia, chronic gastroesophageal reflux, esophagitis, stricture, Barrett esophagus, and pulmonary microaspiration. Vascular abnormalities in the stomach cause angiodysplasias of the gastric antral mucosal lining (so-called watermelon stomach), resulting in recurrent bleeding and chronic anemia. Involvement of the intestines causes dysmotility, malabsorption, and blind loop formation. Patients may present with bloating, weight loss, alternating constipation and diarrhea, and pseudo-obstruction. Wide-mouthed diverticula may be seen on imaging studies of the colon but are rarely of clinical significance. Primary biliary cirrhosis may occur, especially in patients with LcSSc. Anal involvement can cause fecal incontinence.

H_2 blockers and proton pump inhibitors are effective therapies for esophagitis and gastritis. Dysmotility is managed with promotility agents such as metoclopramide; in refractory cases, octreotide can be tried. Malabsorption due to bacterial overgrowth is evaluated through glucose hydrogen breath testing and may be managed with rotating courses of antibiotics. Patients may also need nutritional support as well as enzyme and vitamin supplementation. Pseudo-obstruction is managed conservatively with bowel rest and proximal decompression as needed. Gastritis and vascular ectasia are evaluated with upper endoscopy; ectasias can be ablated with laser/photocoagulation.

Kidney Involvement

Kidney involvement is common in patients with SSc. Up to 50% of patients have mild proteinuria, elevation in the plasma creatinine concentration, and/or hypertension, but most do not progress to chronic kidney disease. Kidney involvement is more common and more severe in DcSSc. The most striking and life-threatening manifestation of kidney disease is scleroderma renal crisis (SRC). SRC occurs in 10% to 15% of patients, is more frequent in DcSSc, and tends to occur early in the disease course; if untreated, it carries a mortality rate approaching 90%. In SRC, involvement of afferent arterioles leads to glomerular ischemia and hyperreninemia. The typical presentation is acute kidney injury and severe hypertension, mild proteinuria, urinalysis with few cells or casts, microangiopathic hemolytic anemia, and thrombocytopenia. Some patients develop pulmonary edema and hypertensive encephalopathy. Occasionally, patients remain normotensive despite kidney dysfunction.

ACE inhibitors significantly improve kidney survival and decrease mortality among patients with SRC. The mechanism of action of ACE inhibitors is believed to be mitigation of the effect of interstitial fibrosis and vascular dysfunction in the glomerular arterial bed. Treatment with an ACE inhibitor should be initiated promptly in SSc patients with even mild hypertension or otherwise unexplained elevations in serum creatinine levels. The ACE inhibitor should be up-titrated until good control of blood pressure is achieved and continued even in the setting of kidney disease. Prophylactic use of ACE inhibitors in normotensive patients is controversial, with some studies suggesting worse overall outcomes. Angiotensin receptor blockers (ARBs) are an alternative for patients who cannot take ACE inhibitors, although ARBs are less effective for managing SRC.

Pulmonary Involvement

Pulmonary involvement is frequent (>70%) in patients with SSc and can be symptomatic and disabling. The two principal clinical manifestations are interstitial lung disease and pulmonary vascular disease. Other pulmonary manifestations include pleuritis, recurrent aspiration, organizing pneumonia, and hemorrhage from endobronchial telangiectasias. Patients with SSc also have an increased risk for developing lung cancer.

Interstitial Lung Disease

Interstitial lung disease (ILD) usually develops subacutely with progressive fibrosis. Patients with DcSSc and anti-Scl-70 antibodies are at higher risk for developing ILD. The most common symptom of ILD is slowly progressive dyspnea, at first on exertion, but later at rest. Other symptoms include nonproductive cough, decreased exercise tolerance, and chest pain. Auscultation reveals "Velcro"-like inspiratory crackles, most prominent at the lung bases. Some patients develop acute inflammatory response/alveolitis or early pulmonary fibrosis in the absence of respiratory symptoms or physical findings. Pulmonary function testing reveals decreased lung volumes and decreased DLCO. High-resolution noncontrast chest CT reveals ground glass and reticular linear opacities in patients

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with alveolitis or fibrosis, and honeycombing in the later stages. Lung biopsy is rarely needed but may be useful in patients with atypical presentations or concern about other diseases such as infection or cancer.

Patients with SSc who have evidence of alveolitis and/or rapidly progressive lung disease may be treated with immunosuppressive agents. Oral or intravenous cyclophosphamide provides modest benefit in the first year, but these benefits are lost by 24 months of follow-up. Azathioprine may have a role as maintenance therapy following a 6-month course of cyclophosphamide. High-dose glucocorticoids are frequently used in SSc patients with ILD, but there is no clear evidence of their benefit, and their use may convey an increased risk of SRC. H

Pulmonary Arterial Hypertension

Pulmonary vascular disease occurs in up to 40% of patients with SSc. Vascular disease leading to pulmonary arterial hypertension (PAH) may occur secondary to ILD (typically in DcSSC) or as an isolated process (typically in LcSSc). Patients are usually asymptomatic in early disease but later develop dyspnea on exertion and diminished exercise tolerance. Severe disease can lead to right-sided heart failure. Pulmonary artery thrombosis can also occur and is frequently fatal.

Pulmonary function tests and echocardiography are useful in the diagnosis and evaluation for PAH. Baseline and annual monitoring of PAH is recommended in all patients with SSc without advanced ILD. Pulmonary function tests demonstrate a reduced DLCO, and echocardiogram can estimate pulmonary artery systolic pressure in the presence of tricuspid regurgitation. Right heart catheterization (RHC) should be performed prior to initiation of treatment. RHC can accurately document the pressure, follow the readings, assess responsiveness to vasodilators, and guide choice of treatment.

All patients with PAH should be considered for oxygen supplementation. Anticoagulation should be considered after bleeding risk assessment. Vasodilating agents, including phosphodiesterase-5 inhibitors (sildenafil or vardenafil) and prostacyclin analogues (iloprost, epoprostenol, or treprostinil), have demonstrated efficacy in relieving symptoms of PAH associated with SSc. Endothelin receptor antagonists (bosentan and ambrisentan) have also shown efficacy in improving symptoms and delaying progression of PAH in SSc. Select patients may benefit from a vasodilator in combination with an endothelin receptor antagonist. Patients with PAH must be closely monitored using 6-minute walk tests and serial RHC studies.

Cardiac Involvement

Cardiac involvement in SSc may be due to cardiac fibrosis or coronary artery disease or secondarily due to systemic or pulmonary hypertension. Intrinsic cardiac fibrosis is uncommon and usually asymptomatic. Symptomatic cardiac involvement in SSc is rare (10%–20% prevalence) but has a poor prognosis, with 5-year mortality rates of 75%. Pericarditis and pericardial effusion occur but are rarely symptomatic. Coronary artery vasospasm and structural disease lead to contraction band necrosis (pathologic finding of ischemia followed by reperfusion due to vasospasm) and patchy myocardial fibrosis, promoting cardiomyopathy and heart failure. Conduction disturbances and arrhythmias are common and probably relate to fibrosis of the conduction system. Many deaths among patients with SSc are sudden and possibly a result of ventricular arrhythmia.

There is no specific treatment for cardiac fibrosis. Management of the complications and consequences of SSc cardiac disease should be carried out in collaboration with an experienced cardiologist. H

KEY POINTS

- In early systemic sclerosis, swelling, edema, and erythema of the hands and forearms may precede skin induration, and pruritus, sclerodactyly, and digital ulcers and pitting may develop.
- Upper gastrointestinal involvement is common in systemic sclerosis, with fibrosis causing pharyngeal dysfunction, esophageal hypomotility, and lower esophageal sphincter incompetence.
- Nailfold capillarioscopy can distinguish secondary Raynaud phenomenon associated with systemic sclerosis from primary Raynaud phenomenon.
- ACE inhibitors significantly improve kidney survival and decrease mortality among patients with scleroderma renal crisis.
- Baseline and annual monitoring of pulmonary arterial hypertension is recommended for all patients with systemic sclerosis without advanced interstitial lung disease.

Pregnancy and Systemic Sclerosis

Pregnancy in patients with SSc carries an increased risk of spontaneous miscarriage and abortion as well as increased rates of premature birth and low-birth-weight full-term infants. Pregnant patients with SSc may develop decompensated pulmonary arterial hypertension or scleroderma renal crisis, each carrying a high complication and/or mortality rate. It may be difficult to distinguish SSc kidney dysfunction from preeclampsia or eclampsia. Many medications useful in SSc are contraindicated in pregnancy. Management by an experienced physician is therefore imperative. See Principles of Therapeutics for more information on medications and pregnancy.

KEY POINT

- Pregnancy in patients with systemic sclerosis carries an increased risk of spontaneous miscarriage and abortion as well as increased rates of premature births and low-birth-weight full-term infants.

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Other Rheumatologic Diseases

Behçet Syndrome

Behçet syndrome is a form of vasculitis that affects small to large arterial vessels and can affect veins as well. All patients with this syndrome have recurrent painful oral ulcerations; patients may also demonstrate additional distinctive features, including hypopyon (**Figure 38**) and pathergy (**Figure 39**). Behçet syndrome is more common among individuals living in or with ancestry from East Asia to Turkey; prevalence is 6.6/100,000 in the United States, but 300/100,000 in Turkey. A genetic role in Behçet pathogenesis is underlined by the increased prevalence of HLA-B51 among affected individuals. Diagnostic criteria are listed in **Table 38**.

Other major manifestations include pulmonary artery, aorta, and/or femoral artery inflammation (3%-12% of patients). Aneurysms and stenosis can occur. A rare variant of Behçet is Hughes-Stovin syndrome, characterized by pulmonary artery aneurysms and systemic thrombophlebitis. Central nervous system involvement occurs in 3% to 25% and can include headaches, stroke, pyramidal signs, behavioral changes, or, rarely, dural sinus thrombosis. Gastrointestinal involvement may be hard to distinguish from inflammatory bowel disease, but ulceration typically involves the ileum rather than the rectal or perianal regions and does not lead to fistula formation.

Treatment is commensurate with disease severity. Low-dose prednisone or colchicine is used for oral/genital ulcers, and high-dose prednisone and immunomodulating agents such as azathioprine are used for more severe disease. Tumor necrosis factor (TNF)-α inhibitors, interferon alfa, and anti-interleukin (IL)-1β therapy have been used in recalcitrant or severe cases.

TABLE 38. The International Study Group Diagnostic Criteria for Behçet Syndrome

Recurrent painful oral ulceration (≥3 times in a 12-month period) is a mandatory feature for diagnosis. Ulcers can occur anywhere in the mouth or on the tongue and often resolve spontaneously within a few weeks.

At least two of the following are also required for diagnosis:

- Recurrent painful genital ulceration: These ulcers are found on the scrotum in men or the labia in women and may lead to scarring.
- Eye involvement: Panuveitis, isolated anterior uveitis or posterior uveitis, or retinal vasculitis can occur and be vision threatening. Hypopyon is a distinctive feature of the anterior uveitis of Behçet, in which a fluid collection of leukocytes is visible in the anterior chamber.
- Skin involvement: Erythema nodosum, pseudofolliculitis, or acneiform lesions can occur. Acneiform lesion on trunk or thighs should raise a concern for Behçet and may demonstrate small-vessel vasculitis on biopsy.
- Pathergy test: In some patients with Behçet, transient subcutaneous insertion of a sterile, large-bore needle under the skin results in the development of a pustule at the site 24-48 hours later. Positive pathergy tests occur more commonly in endemic areas and are rare in the United States.



FIGURE 38. The eye of this patient with Behçet syndrome shows hypopyon, a layered collection of pus in the anterior chamber, representing a form of anterior uveitis. In addition to Behçet, hypopyon may indicate the presence of other autoimmune diseases, sight-threatening infectious keratitis, or endophthalmitis.



FIGURE 39. Pathergy, a pustule-like lesion or papule that appears 48 hours after a sterile skin prick by a 20- to 21-gauge needle in Behçet syndrome.

KEY POINT

- Behçet syndrome is characterized by recurrent painful oral ulcers plus at least two of the following: recurrent genital ulcers, eye involvement, skin involvement, and pathergy.

Relapsing Polychondritis

Relapsing polychondritis (RP) is an inflammatory disease affecting cartilaginous tissues and is thought to be driven by an autoimmune response to type II collagen. **Table 39** presents the McAdams criteria for RP. Auricular involvement affects the helix but spares the earlobes (**Figure 40**). Nasal chondritis can result in collapse of the nasal bridge (saddle nose deformity), which can also be seen in trauma, granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), cocaine use, congenital syphilis, and leprosy. Airway stenosis from tracheal ring involvement and aortitis/large-vessel vasculitis may occur and be life-threatening. In 30% of patients, RP coexists with other inflammatory/autoimmune diseases.

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TABLE 39. McAdams Criteria for Diagnosis of Relapsing Polychondritis

Criteria[a]	Approximate Frequency
Recurrent bilateral auricular chondritis	90%
Nonerosive inflammatory polyarthritis	65%
Nasal chondritis	60%
Ocular inflammation (conjunctivitis, keratitis, scleritis/episcleritis, uveitis)	55%
Respiratory tract chondritis involving larynx or trachea	50%
Cochlear and/or vestibular dysfunction (neurosensory hearing loss, tinnitus, and/or vertigo)	10%

[a]Relapsing polychondritis is diagnosed when three of the six criteria are present.



FIGURE 40. Floppy ears in a patient with relapsing polychondritis. Chronic inflammation of the upper section of the ear eventually results in loss of cartilage and structural collapse. The ear lobe, which does not contain cartilage, is unaffected.

Patients who develop RP in their 60s or 70s should be evaluated for myelodysplastic syndrome.

RP is diagnosed by its typical clinical manifestations. Laboratory tests are nonspecific; acute phase reactants are elevated in 80%, and mild anemia is present in 44%. Anti–type II collagen antibodies are present in 33% but are not considered diagnostic. Patients with RP should undergo imaging (CT or MRI) to evaluate the large airways for inflammation/stenosis. Cartilage biopsy is usually unnecessary.

Auricular chondritis typically responds to low-dose prednisone. For more severe manifestations (for example, laryngotracheal chondritis or aortitis), high-dose prednisone is initiated. For persistent disease and/or glucocorticoid sparing, dapsone, methotrexate, azathioprine, cyclosporine, and cyclophosphamide have all been used. Biologic agents such as tocilizumab (an IL-6 receptor antagonist) are currently being assessed.

KEY POINT

- Relapsing polychondritis is characterized by chondritis of the ears, nose, and/or respiratory tract; nonerosive inflammatory polyarthritis; ocular inflammation; and cochlear and/or vestibular dysfunction.

Adult-Onset Still Disease

Adult-onset Still disease (AOSD) is a multisystem inflammatory disease characterized by high spiking fevers, a salmon-colored rash, arthritis, and high neutrophil counts (**Table 40**). The cause is uncertain, but cytokines (for example, IL-1β, IL-6, TNF-α, and IL-18) are significantly elevated, reflecting macrophage hyperactivation.

Atypical manifestations that may influence prognosis include myocarditis, disseminated intravascular coagulation, fulminant hepatitis, and the hemophagocytic syndrome, a life-threatening process characterized by fever, splenomegaly, cytopenias, elevated ferritin, and evidence of hemophagocytosis on bone marrow biopsy.

AOSD diagnosis is clinically based and requires exclusion of infection, malignancy, or other rheumatologic diseases. Erythrocyte sedimentation rate and C-reactive protein can be markedly elevated. Serum ferritin is elevated in 78% of patients, often to extremely high levels, and

TABLE 40. Yamaguchi Criteria for the Diagnosis of Adult-Onset Still Disease

Major Criteria[a]	Approximate Frequency
Daily spiking fever to 39.0 °C (102.2 °F)	99%
Arthralgia/arthritis >2 weeks	85%
Nonpruritic salmon-colored macular/maculopapular rash on trunk or extremities	85%
Leukocyte count >10,000/μL (10×10^9/L), >80% neutrophils	90%
Minor Criteria	**Approximate Frequency**
Sore throat	66%
Lymphadenopathy and/or splenomegaly	65%/50%
Elevated AST, ALT, or LDH	70%
Negative ANA and RF	N/A

ALT = alanine aminotransferase; ANA = antinuclear antibodies; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; RF = rheumatoid factor.

[a]Diagnosis requires five criteria with at least two major criteria.

Adapted with permission from Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's diesease. J Rheumatol. 1992 Mar;19(3):424-30. [PMID: 1578458]

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implies macrophage activation. Lymph node biopsy shows a reactive process on histology.

Therapy for AOSD includes high-dose NSAIDs and/or prednisone, with methotrexate as a standard second-line agent. Recently, treatment approaches employing anti-IL-1β (for example, anakinra) or anti-IL-6 (for example, tocilizumab) therapies have shown significant promise.

KEY POINTS

- Characteristics of adult-onset Still disease include daily spiking fever, arthritis, a salmon-colored rash, and extremely elevated serum ferritin.
- Diagnosis of adult-onset Still disease is clinically based and requires exclusion of infection, malignancy, or other rheumatologic diseases.

Autoinflammatory Diseases

The autoinflammatory diseases (also known as periodic fever syndromes) are rare monogenic diseases characterized by autoactivation of the innate immune system, including myeloid leukocyte activation and overproduction of inflammatory cytokines. Patients experience regular episodes of systemic inflammation in the absence of infection or autoimmunity. Autoinflammatory diseases may be inherited or acquired through mutation. It is anticipated that more syndromes will be described in the coming years.

The classic autoinflammatory disease is familial Mediterranean fever (FMF), associated with mutation of the *MEFV*$_1$ gene that codes for pyrin, a regulator of IL-1β production. More than 40 different mutations in *MEFV*$_1$ have been identified that result in FMF. Attacks last 1 to 3 days and are characterized by polyserositis, arthritis, erysipeloid rash around the ankles, and elevation of acute phase reactants. AA amyloidosis is a potential long-term consequence of FMF and other autoinflammatory diseases due to the production and deposition of serum amyloid A. FMF management includes chronic daily treatment with colchicine. Increasingly, management of autoinflammatory diseases is being directed at specific cytokines that are implicated as pathogenic.

Table 41 lists the features of currently recognized autoinflammatory diseases.

TABLE 41. Autoinflammatory Diseases

	FMF	TRAPS	HIDS	FCAS	MWS	NOMID
Inheritance	Autosomal recessive	Autosomal dominant	Autosomal recessive	Autosomal dominant	Autosomal dominant	Autosomal dominant
Age at Onset	65% <10 years of age; 90% <20 years of age	50% <10 years of age; up to 5th decade	Usually <5 years of age	<1 year of age	Childhood	Neonatal period
Ethnicity	Mediterranean	All	Northern European	European	European	All
Clinical Manifestations						
Attack Duration	12-72 h	Days to weeks	3-7 days	12-24 h	1-2 days	Progressive
Abdominal	Pain; serositis	Pain; serositis	Pain; vomiting	Nausea	Pain	-
Pleuritis	Common	Common	Rare	-	Rare	Rare
Arthritis	Monoarthritis of lower extremities	Large joints	Symmetric polyarthritis of large joints	Arthralgia	Arthralgia; oligoarthritis	Epiphyseal overgrowth; contractures
Rash	Erysipeloid on lower legs	Migratory with underlying myalgia	Diffuse maculopapular	Cold-induced; urticaria-like	Urticaria-like	Urticaria-like
Other Manifestations	High risk for amyloidosis	Conjunctivitis; periorbital edema	Cutaneous vasculitis; lymphadenopathy; elevated IgD	Conjunctivitis; headache; amyloidosis	Sensorineural deafness; conjunctivitis; amyloidosis	Sensorineural deafness; aseptic meningitis; mental retardation
Treatment	Colchicine	Glucocorticoids; TNF-α inhibitors	NSAIDs; glucocorticoids	IL-1β inhibition	IL-1β inhibition	IL-1β inhibition

FCAS = familial cold autoinflammatory syndrome; FMF = familial Mediterranean fever; HIDS = hyperimmunoglobulinemia D with periodic fever syndrome; IL = interleukin; MWS = Muckle-Wells syndrome; NOMID = neonatal-onset multisystem inflammatory disease; TNF = tumor necrosis factor; TRAPS = tumor necrosis factor receptor-associated periodic syndrome.

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KEY POINT

- Autoinflammatory diseases are characterized by episodes of systemic inflammation in the absence of infection or autoimmunity; these rare diseases may be inherited or acquired through mutation.

Sarcoidosis

Sarcoidosis is a multisystem disease characterized by noncaseating granulomas that form in tissues. Sarcoidosis most commonly affects the lungs and is therefore discussed in detail in MKSAP 17 Pulmonary and Critical Care Medicine. Although less common, the rheumatologic manifestations of sarcoidosis are important and discussed here.

Sarcoidosis can manifest as Löfgren syndrome, which is seen in younger adults and is characterized by acute arthritis, bilateral hilar lymphadenopathy, and erythema nodosum. When all three occur together, there is a 95% specificity for the diagnosis, and further diagnostic tests are unnecessary. The "arthritis" of Löfgren syndrome is actually a nondestructive periarthritis of the soft tissue, entheses, and tenosynovium. Symmetric ankle involvement is classic, but knees, wrists, and elbows can also be involved. Löfgren is more common among Europeans and is self-limited, with 90% of patients remitting within 12 months. Treatment is symptomatic and includes NSAIDs, colchicine, or low-dose glucocorticoids.

A more chronic form of true arthritis affects 1% to 4% of patients and occurs in more severe sarcoidosis. The arthritis is usually polyarticular, involving the shoulders, hands, wrists, knees, and ankles. An entire digit may be affected, leading to dactylitis. Black persons and those with sarcoid skin involvement are more likely to have chronic arthritis.

Granulomatous bone involvement occurs in 3% to 13% of patients, often those with more severe disease. The hands, feet, skull, ribs, sternum, nasal bones, pelvis, tibia, and femur may be affected. The radiographic pattern is lytic (focal areas of cyst formation), permeative (bone has a lacey appearance), or destructive.

Myopathy is a rare manifestation of systemic sarcoidosis. Acute myopathy can mimic polymyositis with proximal muscle weakness and muscle enzyme elevation. Chronic sarcoid myopathy affects older women, involves the proximal muscles, may have normal muscle enzymes, and occurs in the context of known disease. A nodular localized myopathy of sarcoidosis has also been described.

Granulomatous infiltration of the parotid glands may mimic Sjögren syndrome and produce sicca symptoms. The triad of sarcoid parotitis, uveitis, and fever is called uveoparotid fever or Heerfordt syndrome.

Sarcoid musculoskeletal involvement can be diagnosed via biopsy, and the extent and response to therapy can be gauged via gallium or PET scanning if needed. Treatment involves glucocorticoids or other immunosuppressants such as methotrexate, azathioprine, or mycophenolate mofetil as dictated by the disease burden. TNF-α inhibitors may be useful in more severe disease or where glucocorticoid use is problematic.

KEY POINTS

- Sarcoidosis can manifest as Löfgren syndrome, which is characterized by acute arthritis, bilateral hilar lymphadenopathy, and erythema nodosum; when all three occur together, there is a 95% specificity for the diagnosis, and further diagnostic tests are unnecessary. HVC
- A chronic form of polyarticular arthritis can be found in severe sarcoidosis, which may affect the shoulders, hands, wrists, knees, and ankles; an entire digit may also be involved, leading to dactylitis.

True Connective Tissue Diseases

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) defines a group of inherited genetic disorders of collagen-related (*COL*) genes or the procollagen lysyl hydroxylase (*PLOD*) gene, leading to defect(s) in the production, structure, or function of collagen. Most EDS variants are inherited as autosomal dominant mutations. EDS subcategories include the benign hypermobility type, the more severe kyphoscoliotic type, and the life-threatening vascular type in which large- to medium-sized vessels and organs such as the uterus or bowel can rupture.

EDS clinical characteristics include joint hypermobility, hyperextensible skin, atrophic scars, and velvety skin. Hypermobile joints may lead to joint dislocations or early osteoarthritis. Mitral, aortic, or tricuspid valve regurgitation may be present. Diagnosis is based on family history and clinical examination. Genetic consultation may be useful if the diagnosis is uncertain. Treatment is supportive. Patients with hypermobility should avoid activities that could lead to joint damage. Periodic echocardiography should assess cardiac status/aortic root size; invasive vascular procedures should be avoided for those with the vascular type of EDS.

EDS disorders require extensive counseling pertaining to issues of pregnancy both in terms of maternal complications of pregnancy and delivery as well as potential inherited disease in the child. Patients with vascular EDS should be evaluated promptly for any unexplained pain and should wear a medical alert identification bracelet.

Marfan Syndrome

Marfan syndrome (MFS) is an autosomal dominant condition characterized by a mutation in the gene for fibrillin 1 (*FBN1*). Fibrillin 1 is an important structural protein in tissues that contain elastic fibers, such as arteries, ligaments, and the structure that stabilizes the lens of the eye. Manifestations may relate to an overexpression of the

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cytokine transforming growth factor (TGF)-β. Clinical features include the following:

- Tall stature with short upper body to lower body ratio
- Arachnodactyly (long fingers; thumb and index finger overlap around the wrist)
- Anterior thoracic deformity: pectus excavatum or pectus carinatum
- Spinal curvature: scoliosis or kyphosis
- Hyperextensibility of skin
- Pes planus with a long narrow foot
- Myopia with dislocation of the lens (usually superiorly)
- Aortopathy of the ascending aorta: aortic regurgitation/dissection/aneurysm
- Mitral valve prolapse
- Pneumothorax from apical lung bullae
- Other: high arched palate, hernias, atrophic scarring over pectoral, deltoid, or lumbar areas

MFS diagnosis is made clinically, with genetic consultation if necessary. Testing for *FBN1* mutations is available. The 2012 revised Ghent criteria emphasize aortic root dilatation and lens dislocation for diagnosis but also include systemic features and *FBN1* mutations. Current guidelines recommend that echocardiography should be performed at the time of diagnosis to determine aortic root and ascending aortic diameters and 6 months later to determine their rate of enlargement. Annual imaging is recommended if stability of the aortic diameter is documented. If the maximal aortic diameter is 4.5 cm or greater, more frequent imaging should be considered.

For most patients with MFS, surgical repair of the dilated aortic root/ascending aorta is usually performed at a threshold of an external diameter of 5.0 cm. For women contemplating pregnancy, it is reasonable to prophylactically replace the aortic root and ascending aorta if the diameter is greater than 4.0 cm. β-Blockers are recommended to slow the aortopathy. Counseling regarding joint protection to prevent osteoarthritis is useful.

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) comprises four genetic syndromes characterized by autosomal dominant or recessive mutations in *COL* genes, leading to abnormalities in the structure of type I collagen. OI is associated with bone fractures, short stature, body deformity, hearing loss, and dental deformity. A characteristic feature of OI is blue sclerae (reflecting visibility of the underlying choroid) but is not specific to OI. Patients with pseudoxanthoma elasticum, ochronosis/alkaptonuria, Ehlers-Danlos syndrome, or Marfan syndrome may also have blue sclerae.

OI diagnosis is based on clinical findings and family history. Bisphosphonates may reduce fractures and improve skeletal growth, and orthopedic surgeons are often involved due to the fractures experienced by these patients.

KEY POINTS

- Clinical characteristics of Ehlers-Danlos syndrome include joint hypermobility, hyperextensible skin, atrophic scars, and velvety skin; diagnosis is based on family history and clinical examination.
- Marfan syndrome is associated with tall stature, arachnodactyly, anterior thoracic deformity, spinal curvature, and skin and ocular involvement; aortopathy and mitral valve prolapse are also common.
- Osteogenesis imperfecta is associated with bone fractures, short stature, body deformity, hearing loss, and dental deformity; blue sclerae is characteristic but nonspecific.

IgG4-Related Disease

IgG4-related disease is a recently recognized syndrome characterized by abundant IgG4-producing plasma cells seen on tissue biopsy; it unites an unlikely group of diseases under one banner (**Table 42**). Most of these conditions are characterized by infiltration of the affected tissue and the clinical consequences that infiltration entails. Almost any organ can be involved; lymph nodes are frequently affected. Most patients are men (60%-80%) older than age 50 years.

Diagnosis is made by tissue biopsy and the demonstration of a characteristic histology, which includes the following:

- Dense lymphoplasmacytic infiltrate
- CD4-positive T cells and plasma cells in germinal centers
- IgG4-staining plasma cells constituting more than 50% of the total plasma cells
- Storiform (spokes on a wheel–appearing) fibrosis
- Obliterative phlebitis
- Rare neutrophils and no granulomas

TABLE 42. Conditions Associated with IgG4-Related Disease

Condition	Organ Involved
Hypertrophic pachymeningitis	Dura mater
Lymphocytic hypophysitis	Pituitary gland
Idiopathic orbital inflammatory disease	Periocular mass
Mikulicz disease	Parotid glands
Dacryoadenitis	Lacrimal glands
Küttner tumor	Submandibular glands
Riedel thyroiditis	Thyroid
Inflammatory aortitis/vasculitis	Aorta/arteries
Autoimmune pancreatitis	Pancreas
Ormond disease (retroperitoneal fibrosis)	Periaortic mass
Tubulointerstitial nephropathy	Kidneys
Sclerosing cholangitis	Biliary tract

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Because serum IgG4 levels are elevated in only 70% of patients, a normal level does not rule out the disease. PET scan may identify involvement that is not clinically apparent and can document response to therapy. Initial treatment is prednisone, 0.5-0.6 mg/kg/d for 2 to 4 weeks, followed by a slow taper over months. Azathioprine, mycophenolate mofetil, and methotrexate have been used as glucocorticoid-sparing agents. Recently, rituximab has shown significant benefit in patients with IgG4-related disease and appears to selectively affect IgG4 production; it may replace prednisone as the treatment of choice in severe or refractory disease. Treatment response may be limited by the amount of fibrosis present prior to therapy initiation.

See MKSAP 17 Gastroenterology and Hepatology for information on IgG4-related pancreatitis.

KEY POINTS

- The conditions comprising IgG4-related disease are characterized by abundant IgG4-producing plasma cells seen on tissue biopsy, enlargement of the affected tissue, and the clinical consequences that enlargement entails.
- Serum IgG4 levels are elevated in only 70% of patients with IgG4-related disease; therefore, a normal level does not rule out the disease.

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 59-year-old man is evaluated for a 6-month history of gout. He was doing well on colchicine and allopurinol but developed hypersensitivity to allopurinol, which resolved with cessation of the agent. He then began to have more frequent gout flares; two flares occurred in the past month and were treated with prednisone. History is also significant for hypertension, chronic kidney disease, and dyslipidemia. Current medications are colchicine, lisinopril, metoprolol, and simvastatin.

On physical examination, temperature is 37.2 °C (98.9 °F), blood pressure is 142/86 mm Hg, pulse rate is 64/min, and respiration rate is 12/min. BMI is 30. The remainder of the examination is normal.

Laboratory studies reveal a serum creatinine level of 2.3 mg/dL (203.3 µmol/L), a serum urate level of 9.2 mg/dL (0.54 mmol/L), and normal liver chemistry studies; estimated glomerular filtration rate is 48 mL/min/1.73 m^2.

Which of the following is the most appropriate next step in management?

(A) Discontinue colchicine
(B) Start febuxostat
(C) Start pegloticase
(D) Start probenecid

Item 2

A 32-year-old woman undergoes a new patient evaluation. She was diagnosed with systemic lupus erythematosus 10 years ago; manifestations have included arthritis, pericarditis, leukopenia, and rash. She reports increasing difficulty using her hands due to joint deformities. Medications are hydroxychloroquine and prednisone.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 130/85 mm Hg, pulse rate is 80/min, and respiration rate is 16/min. BMI is 24. Examination of the hands reveals subluxation and ulnar deviation of the metacarpophalangeal joints on both hands, swan neck deformity of fingers on both hands, flexion and subluxation of the metacarpophalangeal joint of both thumbs, and hallux valgus of the first metatarsophalangeal joints bilaterally.

Hand radiographs demonstrate no deformities or evidence of erosions.

Which of the following is the most likely diagnosis?

(A) Hypermobility syndrome
(B) Jaccoud arthropathy
(C) Mixed connective tissue disease
(D) Rheumatoid arthritis

Item 3

A 30-year-old woman is evaluated for a 4-month history of increasing foot pain. She also has a 2-month history of increasing pain and swelling in her fingers and right wrist as well as morning stiffness for more than 1 hour. She has no other pertinent medical history and does not take any medications.

On physical examination, vital signs are normal. There are tenderness and swelling of the second and fifth proximal interphalangeal joints and the second and third metacarpophalangeal joints of the feet bilaterally, and tenderness with movement and swelling of the right wrist.

Radiographs of the hands and wrists are normal.

Which of the following combination of tests is most helpful in confirming the diagnosis?

(A) Anti-cyclic citrullinated peptide antibodies and antinuclear antibodies
(B) Anti-cyclic citrullinated peptide antibodies and C-reactive protein
(C) Anti-cyclic citrullinated peptide antibodies and rheumatoid factor
(D) Antinuclear antibodies and rheumatoid factor

Item 4

A 46-year-old woman is evaluated for a 3-month history of a rash during the summertime. She is otherwise well and takes no medications.

On physical examination, vital signs are normal. BMI is 23. Examination of the skin reveals eyelid swelling and a periorbital violaceous rash, erythema and poikiloderma of the anterior chest and upper back, and an erythematous papular rash on the hands; there is no malar eruption, skin thickening, or digital ulcers. Muscle strength and reflexes are normal.

The appearance of the hands is shown.



Laboratory studies:

Complete blood count	Normal
Chemistry panel	Normal
Aldolase	5.1 U/L (normal range, 1.0-8.0 U/L)
Creatine kinase	100 U/L
Antinuclear antibodies	Titer of 1:640
Anti-Jo-1 antibodies	Negative
Urinalysis	Normal

Electromyogram and chest radiograph are normal.

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Which of the following is the most likely diagnosis?

(A) Amyopathic dermatomyositis
(B) Polymorphous light eruption
(C) Rosacea
(D) Systemic lupus erythematosus

Item 5

A 62-year-old woman is evaluated for a 2-year history of progressively frequent and severe pain in the right knee. She has osteoarthritis with good control of her other joint symptoms with her current therapy that includes medication and a daily exercise regimen. She notes about 20 minutes of morning stiffness in the right knee with significant pain with use after rest; her activities are increasingly limited due to these symptoms. History is otherwise unremarkable. Medications are acetaminophen and celecoxib.

On physical examination, blood pressure is 135/82 mm Hg. BMI is 32. There are Heberden nodes of the second and fifth distal interphalangeal joints bilaterally and Bouchard nodes of the second and third proximal interphalangeal joints bilaterally. Bony hypertrophy of the knees is present. There is a positive bulge sign for effusion of the right knee with slight warmth but no erythema.

Standing radiographs of the knees show right (greater than left) medial joint-space narrowing, bilateral osteophytes, and bilateral peaking of the tibial spines.

Aspiration of the right knee is performed; synovial fluid analysis shows a leukocyte count of 250/μL (0.25×10^9/L) and no evidence of crystals.

Which of the following is the most appropriate next step in management?

(A) Administer intra-articular glucocorticoids
(B) Administer intra-articular hyaluronic acid
(C) Refer for arthroscopic lavage
(D) Substitute indomethacin for celecoxib

Item 6

A 72-year-old man is evaluated in the emergency department for acute onset of pain and swelling of the left knee. He was diagnosed with community-acquired pneumonia 4 days ago, and a 7-day course of clarithromycin was started at that time. He reports marked improvement of his respiratory symptoms. History is also significant for gout, with attacks occurring approximately once a year; hypertension; diet-controlled diabetes mellitus; and chronic kidney disease. Other medications are nifedipine and hydrochlorothiazide.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 117/86 mm Hg, pulse rate is 76/min, and respiration rate is 14/min. BMI is 32. Mildly decreased breath sounds in the right lung midfield are noted. The left knee is swollen, red, warm, tender, and fluctuant with limited range of motion.

Laboratory studies are significant for a leukocyte count of 7200/μL (7.2×10^9/L) and a serum creatinine level of 1.7 mg/dL (150.3 μmol/L).

A radiograph of the left knee is normal.

Aspiration of the left knee is performed; synovial fluid analysis reveals a leukocyte count of 20,000/μL (20×10^9/L), extracellular and intracellular urate crystals, and a negative Gram stain.

Which of the following is the most appropriate treatment?

(A) Acetaminophen
(B) Colchicine
(C) Indomethacin
(D) Intra-articular glucocorticoids

Item 7

A 65-year-old man is evaluated for severe abdominal pain, joint pain, and a rash. He states that he had an upper respiratory infection about 10 days ago. Three days ago he noted a rash on his lower extremities. One day later, he experienced pain in his knees and ankles, along with abdominal pain that worsened over the past two days. He reports no visual symptoms, numbness, weakness, or other symptoms.

On physical examination, the patient appears uncomfortable. The chest and cardiac examinations are unremarkable. Decreased bowel sounds and diffuse abdominal tenderness without rebound are noted. The knees and ankles are tender and mildly swollen. Palpable purpuric lesions are present on the lower extremities, including the soles of the feet. The remainder of the physical examination reveals no abnormalities.

Laboratory studies show a normal complete blood count, an erythrocyte sedimentation rate of 88 mm/h, a serum creatinine level of 1.7 mg/dL (150.3 μmol/L), and a urinalysis showing 3+ protein, 20-30 erythrocytes/hpf, 20-30 leukocytes/hpf, and mixed granular and cellular casts. A stool test is positive for occult blood.

An abdominal ultrasound reveals thickening and edema of the ileum. A biopsy of an affected skin lesion demonstrates the presence of small-vessel, leukocytoclastic vasculitis accompanied by deposition of IgA.

Which of the following is the most appropriate therapy at this time?

(A) Cyclophosphamide
(B) Dapsone
(C) Ibuprofen
(D) Prednisone

Item 8

A 28-year-old woman is evaluated for a 6-month history of joint pain and swelling. She was diagnosed with rheumatoid arthritis 5 years ago; current medications are etanercept, sulfasalazine, and etodolac. She was initially treated with methotrexate, which was stopped due to gastrointestinal intolerance, and she refuses to retry it.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 126/74 mm Hg, pulse rate is 68/min, and respiration rate is 14/min. BMI is 24. Two proximal interphalangeal (PIP) joints of the left

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hand and one metacarpophalangeal (MCP) joint bilaterally are swollen and tender. Examination of the elbows, wrists, knees, and feet is normal. The remainder of the examination, including cardiopulmonary examination, is normal.

Laboratory studies, including complete blood count, chemistry panel, and liver chemistries, are normal; erythrocyte sedimentation rate is 35 mm/h, and C-reactive protein level is 1.1 mg/dL (11 mg/L).

Which of the following is the most appropriate next step in the management of this patient's disease activity?

(A) Add abatacept
(B) Add anakinra
(C) Add leflunomide
(D) Add rituximab

Item 9

A 42-year-old woman is evaluated for a 4-year history of diffuse muscle and joint pain, most notably of her shoulders, low back, hips, and knees. The pain is present in the morning and throughout the day. She wakes unrefreshed and reports problems with her memory. She also describes diarrhea alternating with constipation with no blood or mucus in the stool. She reports no weight loss. She quit working 2 years ago due to her symptoms, which were made worse by her work as a baker. She has been to multiple medical providers who have not established a diagnosis despite numerous tests.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 134/88 mm Hg, pulse rate is 92/min, and respiration rate is 16/min. BMI is 36. Muscles are generally tender to light palpation but without weakness on muscle strength testing. The remainder of the examination is normal.

Laboratory studies, including complete blood count, chemistry panel, erythrocyte sedimentation rate, serum creatine kinase, and thyroid-stimulating hormone, are normal.

Which of the following is the most likely diagnosis?

(A) Adrenal insufficiency
(B) Fibromyalgia
(C) Hypothyroidism
(D) Polymyositis

Item 10

A 28-year-old woman seeks preconception counseling. She has a 4-year history of systemic lupus erythematosus (SLE) with manifestations of photosensitive rash, arthritis, and pericarditis; she has been treated with hydroxychloroquine and low-dose prednisone with good control of her symptoms for 18 months. She has never been pregnant. She also takes vitamin D and calcium.

The physical examination and vital signs are normal.

Laboratory studies indicate that the patient's SLE is quiescent. A recent urinalysis is normal, and a previously checked antiphospholipid panel and lupus anticoagulant were negative.

SLE antinuclear antibody profile:

Antinuclear antibodies	Positive (titer: 1:320), speckled pattern
Anti-Ro/SSA antibodies	Positive
Anti-double-stranded DNA antibodies	Negative
Anti-U1-ribonucleoprotein antibodies	Negative
Anti-Smith antibodies	Negative

The increased risk of preeclampsia and preterm delivery in SLE as well as avoidance of NSAIDs prior to conception and in the later stages of pregnancy is discussed.

Which of the following also needs to be discussed with this patient based on her antibody profile?

(A) Need to discontinue hydroxychloroquine
(B) Risk of congenital heart block in her child
(C) Risk of developing lupus nephritis
(D) Risk of developing subacute cutaneous lupus

Item 11

A 50-year-old man is evaluated for an 8-year history of joint pain, particularly in the hands, and progressively worsening fatigue. Medical history is otherwise unremarkable. He takes ibuprofen as needed.

On physical examination, vital signs are normal. BMI is 32. There are swelling and tenderness of the second and third metacarpophalangeal (MCP) joints bilaterally, and tenderness but no swelling of the fourth and fifth MCP joints bilaterally. There is bony hypertrophy of the first MCP joints and knees bilaterally. The proximal interphalangeal joints and wrists are normal.

Laboratory studies are notable for an alanine aminotransferase level of 53 U/L and an aspartate aminotransferase level of 55 U/L; rheumatoid factor is negative.

A radiograph of the hand is shown (see top of next page).

Which of the following is the most appropriate diagnostic test to perform next?

(A) Anti-cyclic citrullinated peptide antibody assay
(B) Hepatitis C antibody assay
(C) Serum α-fetoprotein measurement
(D) Transferrin saturation measurement

Item 12

A 25-year-old man is evaluated for a 3-year history of low back and bilateral buttock pain that has gradually increased over the past year. The pain is worse in the morning and after inactivity; he feels better after stretching his back. He has 90 minutes of morning stiffness in his back. Ibuprofen provides moderate relief of symptoms. He reports no other arthritic symptoms, rash, or gastrointestinal symptoms. Family history is notable for his paternal uncle with long-standing back problems.

On physical examination, vital signs are normal. There is painful and diminished forward flexion and extension of the lumbar spine. Tenderness to palpation over both buttocks is noted.

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ITEM 11

Laboratory studies reveal an erythrocyte sedimentation rate of 35 mm/h; HLA-B27 testing is negative.

Plain radiographs of the lumbar spine and sacroiliac joints are normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT of the sacroiliac joints
(B) MRI of the sacroiliac joints
(C) Technetium bone scan
(D) Ultrasonography of the sacroiliac joints

Item 13

A 52-year-old woman is evaluated for an 8-week history of fatigue and shortness of breath. She has gastroesophageal reflux disease, hypertension, and a 3-year history of limited cutaneous systemic sclerosis. Medications are omeprazole, nifedipine, lisinopril, and aspirin.

On physical examination, temperature is 36.4 °C (97.6 °F), blood pressure is 126/72 mm Hg, pulse rate is 114/min, and respiration rate is 20/min. BMI is 24. Oxygen saturation is 88% on ambient air. A prominent single S_2 is heard. The chest is clear on auscultation. Sclerodactyly and multiple healed digital pits are noted. There is no rash.

Chest radiograph is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bronchoscopy with bronchoalveolar lavage
(B) Doppler echocardiography
(C) N-terminal proBNP (B-type natriuretic peptide) measurement
(D) Right heart catheterization

Item 14

A 34-year-old woman is evaluated during a follow-up visit for polymyositis. She was diagnosed 1 year ago and has responded well to therapy. She reports no weakness, chest pain, or shortness of breath on exertion. Current medications are prednisone and azathioprine.

On physical examination, temperature is normal, blood pressure is 106/72 mm Hg, pulse rate is 84/min, and respiration rate is 26/min. BMI is 23. Oxygen saturation is 98% on ambient air. Cardiac and pulmonary examinations are normal. Strength is normal in proximal and distal muscles. Slight hyperkeratosis and cracking of the palmar surface of the hands are present. There are no other rashes, skin thickening, or digital ulcers.

Laboratory studies are notable for a serum creatine kinase level of 100 U/L, an antinuclear antibody titer of 1:1280, and anti-Jo-1 antibody positivity.

Electrocardiogram is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) 6-Minute walk test
(B) Cardiac MRI
(C) Chest radiography
(D) Exercise stress testing
(E) No additional testing

Item 15

A 52-year-old woman is evaluated during a follow-up visit for a 6-year history of rheumatoid arthritis. She has not responded to combination therapy with methotrexate and etanercept, abatacept, or rituximab. Current medications are methotrexate and tofacitinib, which was initiated 1 month ago.

On physical examination, vital signs are normal. Examination of the joints shows mild swelling and tenderness of the proximal interphalangeal and metacarpophalangeal joints and wrists bilaterally.

Which of the following laboratory studies should be monitored in this patient?

(A) Alkaline phosphatase
(B) Bilirubin
(C) Glucose
(D) Lipid profile

Item 16

A 56-year-old man is evaluated during a follow-up visit. He was diagnosed with gout 4 months ago based on recurrent episodes of podagra and a serum urate level of 7.2 mg/dL (0.42 mmol/L). Colchicine and allopurinol were initiated at

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that time and have been maintained at their initial doses. History is also significant for chronic kidney disease and hypertension, for which he takes losartan.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 130/85 mm Hg, pulse rate is 75/min, and respiration rate is 15/min. BMI is 27. There is no swelling of the joints. The remainder of the examination is unremarkable.

Current laboratory studies reveal a serum urate level of 6.4 mg/dL (0.38 mmol/L) and a serum creatinine level of 2.1 mg/dL (185.6 μmol/L).

Which of the following is the most appropriate management?

(A) Discontinue colchicine
(B) Discontinue losartan
(C) Increase allopurinol
(D) No change in therapy

Item 17

An 82-year-old woman is evaluated for a 2-week history of left-sided headaches with pain on chewing, accompanied by achiness in the shoulders and hips. She has no other pertinent personal or family history. She takes no medications.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 132/86 mm Hg, pulse rate is 88/min, and respiration rate is 18/min. BMI is 25. Eye examination is normal. There are tenderness and swelling over the left temporal area. Moderate to severe pain on range of motion of the shoulders and hips is noted. There is no pain over the temporomandibular joints on palpation.

Laboratory studies, including basic metabolic panel, complete blood count, and liver chemistries, are normal; erythrocyte sedimentation rate is 85 mm/h.

Which of the following is the most appropriate immediate next step in management?

(A) Initiate prednisone, 15 mg/d
(B) Initiate prednisone, 60 mg/d
(C) Obtain MRI of the head
(D) Obtain temporal artery biopsy

Item 18

A 25-year-old woman is evaluated for a 2-month history of increasing joint pain and swelling. She was diagnosed with rheumatoid arthritis 1 year ago and initially treated with methotrexate with good response but recently has had more pain and swelling. With an increase of the methotrexate dosage and the addition of sulfasalazine and hydroxychloroquine, there was improvement but incomplete control of the disease. She also takes naproxen daily.

On physical examination, vital signs are normal. BMI is 23. Two metacarpophalangeal joints of both hands are tender and swollen. There is palpable warmth and tenderness of both wrists. The remainder of the examination is normal.

Laboratory studies, including complete blood count, chemistry panel, and liver chemistries, are normal; erythrocyte sedimentation rate is 45 mm/h, C-reactive protein level is 1.8 mg/dL (18 mg/L), and rheumatoid factor is 112 U/mL (112 kU/L). Hepatitis B and C serologies are negative.

The decision is made to start treatment with adalimumab.

Which of the following is the most appropriate screening test to perform before initiating adalimumab?

(A) Chest radiography
(B) Immunoglobulin level measurement
(C) Interferon-γ release assay
(D) Radiography of hands and feet

Item 19

A 30-year-old man is evaluated for a 1-year history of low back pain. The pain frequently spreads to the buttocks but does not radiate to the legs. The pain is worse in the morning and is associated with stiffness but improves 2 hours later after he starts working. Symptoms are worse at the end of the day and during the night. He takes ibuprofen with good relief of the pain. He is otherwise healthy and reports no other joint pain, rash, diarrhea, or dysuria.

On physical examination, vital signs are normal. Eye examination is normal. There is mild pain with normal range of motion in all directions of the lumbar spine. Tenderness over the buttocks is noted. There is no joint swelling or tenderness in the upper or lower extremities. There is no rash or nail pitting.

Laboratory studies are significant for an erythrocyte sedimentation rate of 40 mm/h, and HLA-B27 testing is positive.

Plain radiographs of the lumbar spine and sacroiliac joints are normal.

Which of the following is the most likely diagnosis?

(A) Ankylosing spondylitis
(B) Lumbar degenerative disk disease
(C) Psoriatic arthritis
(D) Reactive arthritis

Item 20

A 52-year-old woman is evaluated for a 6-year history of Sjögren syndrome. During the past 3 months, she has had low-grade fevers up to 37.5 °C (99.5 °F), weight loss of 6.8 kg (15 lb), and increased fatigue and sicca symptoms. She recently noted a rash on her legs. She reports no current joint pain. Medications are hydroxychloroquine and acetaminophen as needed.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 135/85 mm Hg, and pulse rate is 82/min. BMI is 28. The oral mucosa is dry. Bilateral parotid fullness is present. There is bilateral cervical adenopathy. The tip of the spleen is palpable. There are a few scattered palpable purpura on the lower legs. The remainder of the physical examination is unremarkable.

Laboratory studies show a normal complete blood count except for a hemoglobin level of 11 g/dL (110 g/L); serum C3 and C4 levels are low, and serum and urine protein electrophoresis reveals M-component.

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Chest radiograph and echocardiogram are normal. CT scan of the abdomen shows numerous enlarged retroperitoneal lymph nodes and splenomegaly.

Which of the following is the most appropriate next step in the management of this patient?

(A) Obtain a lymph node biopsy
(B) Obtain a skin biopsy
(C) Order heterophile antibody testing
(D) Start prednisone
(E) Start prednisone and cyclophosphamide

Item 21

A 30-year-old man is evaluated for a 6-month history of pain behind his right heel. The pain is worse after immobility, and he has morning stiffness in the foot lasting 1 hour. He has tried acetaminophen without much relief. History is also significant for a 3-year history of intermittent left eye uveitis treated with a prednisolone ophthalmic solution. He has no other symptoms.

On physical examination, vital signs are normal. There is no tenderness of the lumbar spine or sacroiliac joints; full range of motion of the lumbar spine is noted. Mild swelling and tenderness at the insertion of the Achilles tendon are noted. The remainder of the examination is normal.

Radiographs of the sacroiliac joints are normal. Radiographs of the right heel show soft-tissue swelling and an erosion at the insertion of the Achilles tendon.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Anti-cyclic citrullinated peptide antibody assay
(B) Antineutrophil cytoplasmic antibody assay
(C) Antinuclear antibody assay
(D) HLA-B27 testing

Item 22

A 22-year-old woman is evaluated for a 2-year history of recurrent abdominal pain often accompanied by fever; episodes occur every 3 to 4 months and last 1 to 3 days and resolve completely. She went to the emergency department during an episode 6 weeks ago. She was noted to be mildly febrile, and laboratory studies showed an erythrocyte sedimentation rate of 84 mm/h and a leukocyte count of 16,000/μL (16×10^9/L) with neutrophilia. She was diagnosed with viral gastroenteritis and recovered completely with supportive treatment. She has been treated on several occasions for cellulitis that occurs on her foot or lower extremity, but the reason for repeated infection or a responsible organism has not been identified. On two occasions, she had pain and swelling in the knee that lasted several weeks and was not associated with the abdominal pain. She has tried naproxen without relief. She currently feels well and has no complaints.

On physical examination today, temperature is 36.6 °C (97.9 °F), blood pressure is 120/74 mm Hg, pulse rate is 74/min, and respiration rate is 14/min. BMI is 23. The cardiopulmonary and abdominal examinations are normal. There is no joint swelling.

Current laboratory studies, including complete blood count, chemistry panel, and erythrocyte sedimentation rate, are normal.

Which of the following is the most appropriate treatment?

(A) Anakinra
(B) Colchicine
(C) Indomethacin
(D) Prednisone

Item 23

A 75-year-old woman is evaluated for progressive left knee pain. She has a 20-year history of bilateral knee osteoarthritis. There is no recent history of injury. She was recently discharged from the hospital for gastrointestinal bleeding related to her use of ibuprofen. She experienced only transient relief from previous glucocorticoid and hyaluronic acid injections. She is enrolled in physical therapy and exercises to increase her quadriceps strength. History is also significant for hypertension, coronary artery disease, hypercholesterolemia, and osteoporosis. Other medications are omeprazole, aspirin, lisinopril, propranolol, rosuvastatin, and alendronate.

On physical examination, vital signs are normal. BMI is 24. Mild weakness on muscle group testing and atrophy are noted in the quadriceps. There is marked bony hypertrophy of the left knee (greater than the right) without warmth, erythema, or effusion.

Which of the following is the most appropriate management for this patient?

(A) Celecoxib
(B) Duloxetine
(C) Fentanyl
(D) Prednisone

Item 24

A 45-year-old woman is evaluated in the emergency department for progressive shortness of breath and fatigue for the past 6 weeks. She also has a 5-year history of diffuse cutaneous systemic sclerosis. Medications are nifedipine, lisinopril, omeprazole, and aspirin.

On physical examination, the patient is alert but short of breath. Temperature is 37.2 °C (99.0 °F), blood pressure is 126/92 mm Hg, pulse rate is 124/min, and respiration rate is 26/min. BMI is 25. Oxygen saturation is 98% on 2 L of oxygen. Cardiac examination is normal. Velcro-like crackles are heard throughout the chest. Diffuse skin thickening of the face, anterior chest, arms stopping at the elbows, and legs is present; sclerodactyly of the fingers is also noted. There is no rash. Pedal edema is present.

Chest radiograph shows bilateral reticulonodular infiltrates and ground glass opacities with normal cardiac silhouette. High-resolution CT scan is consistent with active nonspecific interstitial pneumonitis. An open lung biopsy confirms the diagnosis of nonspecific interstitial pneumonitis.

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Which of the following is the most appropriate treatment?

CONT.
(A) Cyclophosphamide
(B) D-penicillamine
(C) Infliximab
(D) Methotrexate

Item 25

A 72-year-old man is evaluated in the emergency department for acute swelling, severe pain, and warmth of the right knee that woke him from sleep. He does not recall any inciting injury to the knee. Three months ago, he had an acutely swollen great toe that improved within 3 days, for which he did not seek treatment. History is also significant for hypertension and diabetes mellitus. Medications are hydrochlorothiazide and metformin.

On physical examination, temperature is 37.8 °C (100.1 °F), blood pressure is 130/75 mm Hg, pulse rate is 90/min, and respiration rate is 12/min. BMI is 33. The right knee is warm and swollen without overlying erythema; tenderness to palpation and decreased range of motion due to pain are noted. There is no skin breakdown or abrasions over the right knee. Examination of the other joints is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Obtain a knee MRI
(B) Obtain a serum urate level
(C) Perform joint aspiration
(D) Start empiric colchicine

Item 26

A 40-year-old woman is evaluated for a 6-month history of pain and swelling in her left thumb, left fifth finger, and left foot. She also has morning stiffness lasting 2 to 3 hours. She has a 4-year history of lumbar and thoracic back pain that is worse with bending and lifting and is better with rest. Naproxen is only mildly helpful for the pain.

On physical examination, vital signs are normal. Patches of erythema and scaling behind the right ear and on the scalp at the occiput are noted. Fusiform swelling of the left thumb and left fifth finger is present. Tenderness and swelling at the left third metatarsophalangeal joint are noted. There is mild lumbar tenderness, and full range of motion of the lumbar spine and cervical spine is noted. No other joint swelling or tenderness is present.

Nail findings are shown (see top of next column).

Laboratory studies, including complete blood count with differential, comprehensive metabolic panel, rheumatoid factor, and urinalysis, are normal; HLA-B27 testing is positive.

Which of the following is the most likely diagnosis?

(A) Ankylosing spondylitis
(B) Inflammatory bowel disease–associated arthritis
(C) Psoriatic arthritis
(D) Reactive arthritis



ITEM 26

Item 27

A 42-year-old man is evaluated in the hospital for a 2-week history of progressive shortness of breath, with hemoptysis developing in the past 48 hours. During the past week he has also noted weakness of the left foot, numbness in the right hand, and the onset of a rash. He has a 7-year history of asthma. His only medication is an as-needed albuterol metered-dose inhaler.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 142/87 mm Hg, pulse rate is 72/min, and respiration rate is 26/min. Diffuse crackles are heard in the lung fields. Diminished sensation in the right hand and weakness on dorsiflexion in the left foot are noted. There is palpable purpura on the arms and legs. The remainder of the physical examination is normal.

Laboratory studies:

Erythrocyte sedimentation rate	98 mm/h
Leukocyte count	16,000/μL (16×10^9/L), 22% eosinophils
Creatinine	0.8 mg/dL (70.7 μmol/L)
IgE	Elevated
ANCA	Negative
Antimyeloperoxidase antibodies	Negative
Antiproteinase 3 antibodies	Negative
Urinalysis	Normal

Chest radiograph shows diffuse pulmonary infiltrates.

Which of the following is the most likely diagnosis?

(A) Cryoglobulinemia
(B) Eosinophilic granulomatosis with polyangiitis
(C) Granulomatosis with polyangiitis
(D) Microscopic polyangiitis

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Item 28

A 42-year-old woman is evaluated for a 3-month history of symmetric proximal muscle weakness. She takes no medications.

On physical examination, vital signs are normal. Symmetric weakness of the arm and thigh muscles is noted. There are no skin findings.

Laboratory studies are significant for a serum creatine kinase level of 2000 U/L and a normal thyroid-stimulating hormone level.

Electromyogram shows increased insertional activity, spontaneous fibrillations, and polyphasic motor unit potentials in the proximal muscles. MRI of the thighs shows inflammatory changes in the quadriceps.

A muscle biopsy is recommended, but the patient refuses.

Which of the following is the most appropriate treatment at this time?

(A) Adalimumab
(B) Cyclosporine
(C) Leflunomide
(D) Prednisone

Item 29

A 71-year-old man is evaluated for long-standing stiffness, decreased range of motion, and pain of the neck, mid back, and low back. He has no history of falls or injuries. The stiffness and pain do not improve with activity and are not noticeably worse in bed or with inactivity. Acetaminophen provides minimal relief. He has no other medical problems.

On physical examination, vital signs and BMI are normal. Skin examination is normal. Bony hypertrophy of the second through fifth distal interphalangeal joints and the second and fifth proximal interphalangeal joints is present. Marked reduction in thoracic lateral bending and reduction of spinal flexion and extension are noted.

Plain radiographs of the thoracic spine show flowing osteophytes involving the anterolateral aspect of the thoracic spine at five contiguous vertebrae; there is normal disk height, the apophyseal joints are without osteophytes or bony sclerosis, and the sacroiliac joints are without erosions.

Which of the following is the most likely diagnosis?

(A) Ankylosing spondylitis
(B) Degenerative disk disease
(C) Diffuse idiopathic skeletal hyperostosis
(D) Psoriatic arthritis

Item 30

A 46-year-old woman is evaluated for a 1-week history of symmetric polyarthritis of the hands, wrists, and knees, accompanied by a rash. She is a home health aide. She has no other pertinent history and takes no medications.

On physical examination, temperature is 37.7 °C (99.8 °F), blood pressure is 118/72 mm Hg, pulse rate is 78/min, and respiration rate is 13/min. BMI is 22. There are symmetric tenderness, warmth, erythema, and swelling of the wrists, proximal interphalangeal and metacarpophalangeal joints, and knees bilaterally. Bilateral knee effusions are noted. There is mild right upper quadrant pain. A maculopapular rash over the trunk and legs is present.

Laboratory studies:

Erythrocyte sedimentation rate	63 mm/h
Alanine aminotransferase	1050 U/L
Aspartate aminotransferase	800 U/L
Creatinine	Normal

Which of the following is the most likely diagnosis?

(A) Autoimmune hepatitis
(B) Hemochromatosis
(C) Hepatitis B virus–associated arthritis
(D) Primary biliary cirrhosis

Item 31

A 65-year-old woman is seen at the request of her ophthalmologist. Two days ago, she was diagnosed with scleritis and began using an ophthalmic prednisolone solution. She notes progressive fatigue and intermittent episodes of sinus congestion during the past 5 weeks. She has a 10-year history of joint pain in her hands and low back pain that has not recently changed. History is also significant for hypertension diagnosed 3 months ago, for which she takes hydrochlorothiazide. She reports no dyspnea, cough, rash, diarrhea, or abdominal pain.

On physical examination, vital signs are normal. The ears are normal. Right eye scleral injection is present. There is mild redness and crusting of the nasal mucosa. There are no oral ulcerations. There is bony enlargement with tenderness over the distal interphalangeal joints bilaterally and squaring with tenderness over the first carpometacarpal joints bilaterally. Mild lumbar and paraspinal muscle tenderness is present; full range of motion of the lumbar spine is noted. There is no sacroiliac joint tenderness. The remainder of the physical examination is normal.

Laboratory studies:

Comprehensive metabolic panel	Normal
Erythrocyte sedimentation rate	55 mm/h
Hemoglobin	11 g/dL (110 g/L)
Leukocyte count	5000/μL (5.0×10^9/L)
Platelet count	550,000/μL (550×10^9/L)
Urinalysis	2+ protein; trace blood; no leukocytes; 1 erythrocyte cast

Chest radiograph is normal.

Which of the following is the most likely diagnosis?

(A) Ankylosing spondylitis
(B) Behçet syndrome
(C) Granulomatosis with polyangiitis
(D) Sarcoidosis

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Item 32

An 80-year-old man is evaluated for severe right knee pain that began yesterday. He has a 10-year history of gout that has affected his great toes and knees; his last attack was 2 years ago in the right great toe. Medications are allopurinol and ibuprofen as needed.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 150/85 mm Hg, pulse rate is 80/min, and respiration rate is 16/min. BMI is 31. The right knee is warm, swollen, slightly erythematous, and tender; range of motion is limited to 90 degrees of flexion and associated with pain. There is no inflammation in the remainder of the joints.

Aspiration of the right knee yields 30 mL of cloudy yellow fluid. Synovial fluid leukocyte count is 55,000/μL (55×10^9/L), with 95% polymorphonuclear cells. Extracellular negatively birefringent needle-shaped crystals are seen under polarized light. Synovial fluid Gram stain is negative. Synovial fluid cultures are pending.

Which of the following is the most appropriate treatment?

(A) Add probenecid
(B) Increase allopurinol
(C) Perform an intra-articular glucocorticoid injection
(D) Start antibiotics
(E) Start prednisone

Item 33

A 25-year-old woman is evaluated during a follow-up visit for an 18-month history of ankylosing spondylitis. She has minimal lower back pain with morning stiffness lasting 20 minutes. She is able to pursue her activities of daily living without any restrictions. She has been taking etanercept for 1 year with good results.

On physical examination, vital signs are normal. Full range of motion of the thoracic and cervical spine without tenderness is noted. There is no lumbar or sacroiliac tenderness. The Schober test increases by 5 cm (same as at the time of diagnosis).

Laboratory studies are notable for a normal erythrocyte sedimentation rate and a normal C-reactive protein level.

At the time of diagnosis, radiographs showed normal thoracic and lumbar spine and sacroiliac joints, and an MRI showed edema of the sacroiliac joints and in the lumbar and thoracic spine.

Which of the following should be performed next?

(A) Bone scan
(B) CT of the sacroiliac joints
(C) MRI of the sacroiliac joints
(D) Plain radiography of the sacroiliac joints
(E) No new imaging

Item 34

A 35-year-old man is evaluated for a 2-month history of abrupt left knee swelling. He notes prominent stiffness of both joints but no significant pain. He previously felt well. He lives in Vermont and goes hiking during the summer. He has not had any episodes of diarrhea or abdominal pain and reports no trauma to the knee, fever, rash, or known insect bites. He does not have a history of sexually transmitted infections. He has no history of injection drug use and does not take any medications.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 115/70 mm Hg, pulse rate is 82/min, and respiration rate is 12/min. BMI is 20. There is a large effusion over the left knee with warmth and mild tenderness but no overlying erythema; range of motion is limited by swelling, but stability is intact. There is no heart murmur. Lung and abdominal examinations are normal. There are no skin lesions.

Laboratory studies reveal an erythrocyte sedimentation rate of 12 mm/h and a leukocyte count of 6000/μL (6.0×10^9/L).

Radiograph of the left knee shows a large effusion but is otherwise unremarkable.

Which of the following is most likely to provide the diagnosis?

(A) Blood cultures
(B) Lyme serologic testing
(C) MRI of the knee
(D) Synovial fluid cultures

Item 35

A 21-year-old woman is evaluated for a 3-week history of painful nodules and a rash in the lower extremities, along with pain and swelling of the wrists, knees, and ankles. She reports a low-grade fever and a 2.7-kg (6.0-lb) weight loss since the onset of symptoms. She has taken naproxen with some relief. History is significant for gastroesophageal reflux disease and acne. Medications are over-the-counter famotidine as needed and minocycline.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 110/60 mm Hg, pulse rate is 92/min, and respiration rate is 16/min. BMI is 24. Mild swelling of the wrists, knees, and ankles is noted. There are scattered 1- to 2-cm painful erythematous nodules as well as livedo reticularis in the lower extremities beginning at the thighs. The remainder of the examination is normal.

Laboratory studies:

Antinuclear antibodies	Positive (titer: 1:320)
Anti–double-stranded DNA antibodies	Negative
Anti-Smith antibodies	Negative
Anti-U1-ribonucleoprotein antibodies	Negative
Anti-Ro/SSA antibodies	Negative
Anti-La/SSB antibodies	Negative
Antihistone antibodies	Negative
ANCA	Positive (titer: 1:320) in a perinuclear pattern; negative for myeloperoxidase
Urinalysis	Normal

Chest radiograph is normal.

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Which of the following is the most appropriate next step in management?

(A) Start azathioprine
(B) Start high-dose prednisone
(C) Discontinue famotidine
(D) Discontinue minocycline

Item 36

A 61-year-old man is evaluated for a 10-month history of generalized weakness. He reports no pain or myalgia. History is significant for hypercholesterolemia treated with a stable dose of simvastatin for the past 3 years.

On physical examination, temperature is normal, blood pressure is 138/74 mm Hg, pulse rate is 70/min, and respiration rate is 16/min. BMI is 27. There is symmetric weakness of the arm and thigh muscles with slightly reduced grip and power of the finger flexors. No muscle tenderness is noted. There is no rash, skin thickening, or digital ulcers. Reflexes and the remainder of the physical examination are normal.

Laboratory studies are notable for a normal complete blood count, an erythrocyte sedimentation rate of 23 mm/h, and a serum creatine kinase level of 365 U/L.

Chest radiograph is normal. Electromyogram and nerve conduction studies show myopathic changes in the proximal and distal muscles of the extremities as well as some neurogenic changes.

Which of the following is the most likely diagnosis?

(A) Amyotrophic lateral sclerosis
(B) Inclusion body myositis
(C) Myasthenia gravis
(D) Statin-induced myopathy

Item 37

A 72-year-old man is evaluated for a 1-year history of progressive worsening of bilateral knee pain and stiffness. He has had no locking, popping, or giving way in either knee. He has pain in both knees at rest and at night, which awakens him from sleep. He has no history of injury. Acetaminophen and over-the-counter ibuprofen improve his pain temporarily.

On physical examination, vital signs are normal. BMI is 35. Bilateral bony hypertrophy and valgus deformity of the knees are noted. There is no warmth, erythema, swelling, or effusion. Anterior drawer sign is negative, and there is no compromise in stability.

Which of the following studies of the knees is the most appropriate diagnostic test to perform next?

(A) Bone scintigraphy
(B) MRI
(C) Standing plain radiography
(D) Ultrasonography

Item 38

A 60-year-old woman is evaluated during a follow-up visit for Sjögren syndrome. She reports persistent eye discomfort described as a sandy or gritty sensation. She has had recurrent corneal abrasions and erosions. She has been using artificial tears with minimal improvement. She saw her ophthalmologist who inserted punctal plugs, but they caused excessive tearing and were removed. She otherwise feels well and reports no fever, chills, weight loss, rash, joint pain, chest pain, or dyspnea.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 135/80 mm Hg, pulse rate is 75/min, and respiration rate is 18/min. The oral mucosa is dry. Moderately injected sclerae are noted. There is no cervical or supraclavicular adenopathy and no parotid gland swelling. Lung, heart, musculoskeletal, and skin examinations are normal.

Which of the following is the most appropriate treatment?

(A) Certolizumab pegol
(B) Cyclosporine drops
(C) Hydroxychloroquine
(D) Olopatadine drops
(E) Prednisone

Item 39

A 25-year-old man undergoes a new patient evaluation. He has Marfan syndrome. His clinical course has been unremarkable. History is significant for inguinal hernia repair; family history is notable for his father who has Marfan syndrome. The patient takes no medications.

On physical examination, temperature is 37.4 °C (99.3 °F), blood pressure is 134/89 mm Hg, pulse rate is 80/min, and respiration rate is 14/min. BMI is 22. Tall stature and pectus excavatum are noted. Oral examination demonstrates a high arched palate. Arachnodactyly is noted. Scoliosis is present on forward bending. Examination of the feet reveals bilateral pes planus without obvious osteoarthritic mid-foot changes.

Which of the following is the most appropriate periodic imaging test for this patient?

(A) Abdominal ultrasonography
(B) Chest radiography
(C) Echocardiography
(D) Spine radiography

Item 40

A 32-year-old woman is evaluated for a new rash on her legs. She was diagnosed with pyelonephritis 4 days ago and was started on a 7-day regimen of trimethoprim-sulfamethoxazole based on urine culture and sensitivity data; her urinary symptoms have improved. Medical history includes Hashimoto thyroiditis treated with levothyroxine; her dose was increased 4 weeks ago based on thyroid function studies. Medical history is otherwise unremarkable.

On physical examination, temperature is normal, blood pressure is 124/82 mm Hg, pulse rate is 66/min, and respiration rate is 13/min. BMI is 21. Cardiopulmonary examination is unremarkable. The abdomen is soft and nontender. Musculoskeletal examination shows no evidence of joint swelling, warmth, or tenderness. The remainder of the examination is normal.

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The appearance of the legs is shown.



Which of the following is the most appropriate next step in management?

(A) Discontinue trimethoprim-sulfamethoxazole
(B) Initiate prednisone
(C) Measure antihistone antibodies
(D) Obtain skin biopsy

Item 41

A 30-year-old woman is evaluated during a follow-up visit for systemic lupus erythematosus. She was diagnosed 3 months ago after presenting with pericarditis and arthritis. She was initially treated with prednisone, 40 mg/d, with improvement of her presenting symptoms. The prednisone has been tapered over 3 months to her current dose of 10 mg/d with no recurrence. She also takes vitamin D and a calcium supplement.

On physical examination, vital signs are normal. BMI is 25. Cardiac examination is normal. There is no evidence of arthritis. The remainder of the examination is normal.

Which of the following is the most appropriate next step in treating this patient?

(A) Add azathioprine
(B) Add hydroxychloroquine
(C) Add mycophenolate mofetil
(D) Add a scheduled NSAID

Item 42

A 65-year-old man is evaluated during a follow-up visit for gout. He initially presented 6 months ago with acute pain and swelling of the right great toe and a serum urate level of 7.2 mg/dL (0.42 mmol/L); symptoms resolved with naproxen. He then presented last week with recurrent symptoms of great toe pain, redness, and swelling that began during sleep. Colchicine was initiated, and symptoms resolved. History is also significant for hypertension, coronary artery disease, hyperlipidemia, and urolithiasis. Current medications are colchicine, metoprolol, simvastatin, and low-dose aspirin.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 138/80 mm Hg, pulse rate is 60/min, and respiration rate is 15/min. BMI is 30. Examination of the joints reveals no swelling.

Laboratory studies reveal a serum urate level of 7.6 mg/dL (0.45 mmol/L) and normal kidney and liver chemistries.

Which of the following is the most appropriate treatment for this patient?

(A) Discontinue aspirin
(B) Discontinue colchicine
(C) Start allopurinol
(D) Start probenecid

Item 43

A 50-year-old woman is evaluated for slowly worsening joint pain in her fingers for the past 5 years. She notes swelling, morning stiffness lasting 10 minutes, and pain that is worse after housework or typing. She has no other joint pain and otherwise feels well. She reports no fevers, weight loss, rashes, alopecia, oral ulcers, dyspnea, chest pain, or abdominal pain. The patient takes no medications.

On physical examination, vital signs are normal. There is squaring, crepitus, and tenderness of the first carpometacarpal joints. Bony enlargement and tenderness over all distal interphalangeal (DIP) joints are present. Limited range of motion of the thumbs and DIP joints is noted. There is no joint warmth, redness, or effusions. The remainder of the joint examination is normal.

Which of the following is the most appropriate next step in management?

(A) Anti-double-stranded DNA antibody testing
(B) Antinuclear antibody testing
(C) Radiography of the hands
(D) Rheumatoid factor testing
(E) No further testing

Item 44

A 74-year-old man is evaluated for a 2-month history of progressively worsening bilateral shoulder and hip pain. He currently has difficulty rising from a chair and reaching overhead because of the pain. He also reports fatigue, malaise, and 4.5-kg (10-lb) weight loss during this period. He reports no other symptoms. He takes acetaminophen as needed for pain with little or no relief.

On physical examination, the patient appears depressed. Temperature is 37.9 °C (100.2 °F), blood pressure is 126/66 mm Hg, pulse rate is 72/min, and respiration rate is 18/min. BMI is 26. There is markedly limited range of motion of the shoulders and hips due to pain; strength cannot be

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adequately assessed. The remainder of the physical examination is normal.

Laboratory studies, including basic metabolic panel, complete blood count, liver chemistries, and thyroid-stimulating hormone level, are normal. Erythrocyte sedimentation rate is 68 mm/h.

Which of the following is the most appropriate treatment?

(A) Aspirin, 81 mg/d
(B) Aspirin, 650 mg three times daily
(C) Duloxetine, 60 mg/d
(D) Prednisone, 15 mg/d
(E) Prednisone, 60 mg/d

Item 45

A 45-year-old man is evaluated for a 2-week history of progressive pain and swelling of the third and fourth toes of the right foot. He has a rash on the soles of his feet that appeared 4 weeks ago. He reports no fever, back pain, chest pain, dyspnea, dysuria, diarrhea, ocular problems, oral ulcers, Raynaud phenomenon, psoriasis, or photosensitivity. He is sexually active. He takes no medications.

On physical examination, vital signs are normal. There is no nail pitting. Dactylitis and diffuse swelling of the right third and fourth toes are noted. The soles of the feet have yellow-brown vesicles and hyperkeratotic nodules with overlying keratotic crust. The remainder of the examination is normal.

Laboratory studies reveal an erythrocyte sedimentation rate of 35 mm/h; complete blood count with differential and urinalysis are normal.

Radiographs of the toes reveal diffuse soft-tissue swelling of the right third and fourth toes but are otherwise normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Anti-cyclic citrullinated peptide antibody assay
(B) Antinuclear antibody assay
(C) DNA amplification urine test for *Chlamydia trachomatis*
(D) HLA-B27 testing

Item 46

A 52-year-old man is evaluated during a follow-up visit for a 2-year history of progressively symptomatic rheumatoid arthritis. He reports increased difficulty with his job due to persistent pain and swelling in the first proximal interphalangeal joints, second and third metacarpophalangeal joints, and bilateral wrists. He also has increased difficulty climbing stairs due to persistent pain and swelling in the right knee. Medications are methotrexate, 25 mg weekly; prednisone, 10 mg/d; naproxen; and folic acid.

On physical examination, vital signs are normal. There is 1+ tenderness to palpation and 1+ swelling of the affected joints.

Plain radiographs of the hands and wrists show periarticular osteopenia, multiple erosions, and carpal joint-space narrowing. Plain radiographs of the knees show medial and lateral joint-space narrowing.

Which of the following is the most appropriate next step in management?

(A) Add etanercept
(B) Add rituximab
(C) Increase methotrexate
(D) Increase prednisone

Item 47

A 39-year-old man is evaluated for a lower extremity rash of 3 weeks' duration. He has no recent history of a cold, flu, or other infection. He takes no medications.

On physical examination, temperature is 37.3 °C (99.2 °F), blood pressure is 136/86 mm Hg, pulse rate is 66/min, and respiration rate is 12/min. BMI is 24. Small vascular infarctions are observed on the ears and fingertips. There are scattered palpable purpuric lesions on the bilateral lower extremities, which are less prominent on the soles. Strength is reduced in the right wrist.

Laboratory studies:

Erythrocyte sedimentation rate	66 mm/h
C3	Normal
C4	Decreased
Creatinine	2.1 mg/dL (185.6 µmol/L)
Rheumatoid factor	Positive
Hepatitis C antibodies	Positive, genotype 2
Serum protein electrophoresis	Monoclonal spike in IgG band
Urinalysis	Positive for erythrocytes, leukocytes, erythrocyte casts

Which of the following is most likely to establish the diagnosis?

(A) Anti-cyclic citrullinated peptide antibody levels
(B) Anti-glomerular basement membrane antibody levels
(C) Antinuclear antibody levels
(D) p-ANCA levels
(E) Serum cryoglobulin levels

Item 48

A 71-year-old woman is evaluated during an office visit. Four months ago, she fell on an outstretched hand. During the next several weeks, she noted gradual pain, stiffness, and swelling of her right shoulder; the pain occurs with movement and at night. History is significant for knee osteoarthritis, gout, and hypertension. Medications are acetaminophen, colchicine, allopurinol, and lisinopril.

On physical examination, vital signs are normal. BMI is 25. The right shoulder has a large effusion without warmth or overlying erythema; range of motion is limited by pain and swelling, and prominent crepitus is palpable with motion.

Erythrocyte sedimentation rate, leukocyte count, C-reactive protein level, and serum urate level are within normal limits.

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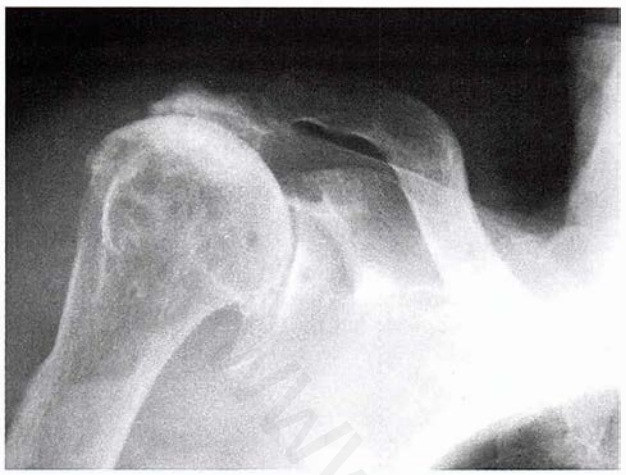
A radiograph of the shoulder is shown.



Aspiration of the right shoulder shows blood-tinged synovial fluid with a leukocyte count of 8300/μL (8.3×10^9/L); Gram stain is negative, and there are no crystals.

Which of the following is the most likely diagnosis?

(A) Acute calcium pyrophosphate crystal arthritis
(B) Acute gouty arthritis
(C) Basic calcium phosphate deposition
(D) Infectious arthritis

Item 49

A 23-year-old woman is evaluated for a 1-week history of fevers, malaise, aches of her elbows and left knee, and pain of her wrists, hands, and ankles that is worse with movement. She has noticed transient skin lesions resembling pustules. She reports no urinary symptoms or vaginal discharge. She has no history of illicit drug use; she drinks alcohol socially and is sexually active. She has not traveled recently. Her only medication is an oral contraceptive.

On physical examination, the patient appears uncomfortable. Temperature is 38.3 °C (100.9 °F), blood pressure is 115/75 mm Hg, pulse rate is 95/min, and respiration rate is 12/min. BMI is 23. Ulnar deviation of the wrists while holding the thumbs down elicits pain over the radial side of the wrists (positive Finkelstein test). There is generalized swelling of several fingers with tenderness to palpation diffusely. The left knee is warm, with a small effusion and pain with range of motion. The ankles have tenderness to palpation over the posterior aspects, with erythema along the Achilles tendons and pain with range of motion bilaterally. There are a few scattered vesiculopustular lesions over the palmar aspect of the hands and upper extremities.

Laboratory studies reveal a leukocyte count of 13,500/μL (13.5×10^9/L) and normal kidney and liver chemistries.

Which of the following is most likely to provide the diagnosis?

(A) Cervical culture
(B) Hepatitis B serologies
(C) Rapid streptococcal antigen testing
(D) Synovial fluid analysis

Item 50

A 26-year-old woman seeks preconception counseling. She has a 3-year history of rheumatoid arthritis. Medications are methotrexate, hydroxychloroquine, low-dose prednisone, and folic acid. Currently her disease is under excellent control.

On physical examination, vital signs are normal. There is no warmth, erythema, swelling, or tenderness of the joints.

Which of the following is the most appropriate next step in management?

(A) Discontinue hydroxychloroquine
(B) Discontinue methotrexate
(C) Discontinue prednisone
(D) Discontinue prednisone, methotrexate, and hydroxychloroquine

Item 51

A 52-year-old man is evaluated for a 4-month history of slowly progressive unilateral proptosis. He reports enlargement of the glands under his jaw on both sides. He generally feels well and has no other medical problems. He takes no medications.

On physical examination, vital signs are normal. Marked proptosis of the left eye is noted; there is no inflammation of the sclerae or conjunctivae. There is bilateral enlargement of the lacrimal, parotid, and submandibular glands. There is an enlarged lymph node at the angle of the jaw on the right. The remainder of the examination is normal.

Laboratory studies include a normal complete blood count with differential, chemistry panel, liver chemistries, antinuclear antibody panel, and urinalysis.

MRI of the head and orbits demonstrates a homogeneous enhancing mass behind the left eye and enlargement of the parotid and submandibular glands. Biopsy of the ocular mass demonstrates a lymphoplasmacytic infiltrate with storiform fibrosis and obliterative phlebitis, rare neutrophils, and no granulomas; a monoclonal population of cells is not identified.

Which of the following is the most likely diagnosis?

(A) Hodgkin lymphoma
(B) IgG4-related disease
(C) Sarcoidosis
(D) Sjögren syndrome

Item 52

A 58-year-old woman is evaluated for a 2-year history of hand pain and increasing difficulty using her hands. She reports worsening grip strength as well as increasing pain in the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints. She has intermittent erythema

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and swelling in some of these joints (such as the fifth DIP joint and the right second PIP and left third PIP joints) sometimes lasting for weeks at a time. She takes naproxen twice daily.

On physical examination, vital signs are normal. BMI is 29. Bony hypertrophy and malalignment of the DIP joints are noted; there is mild erythema over the right fifth DIP joint. There are bony hypertrophy of the PIP joints and swelling and tenderness of the right second PIP joint and the left third PIP joint. There is bony hypertrophy of the first carpometacarpal (CMC) joint bilaterally.

Laboratory studies, including a complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum creatinine, rheumatoid factor, anti-cyclic citrullinated antibodies, and urinalysis, are normal.

Plain hand radiographs show central erosions and collapse of the subchondral bone in the right second PIP joint and the left third PIP joint; osteophytes at the second, third, and fifth DIP joints bilaterally; and joint-space narrowing at the first CMC joint bilaterally. There is no periarticular osteopenia or marginal erosions.

Which of the following is the most likely diagnosis?

(A) Erosive osteoarthritis
(B) Reactive arthritis
(C) Rheumatoid arthritis
(D) Tophaceous gout

Item 53

A 44-year-old man is evaluated for a 2-month history of color change in the hands when exposed to the cold, finger skin tightness with palpable nodules, fatigue, and pruritus. He has no other medical problems and takes no medications or nutritional supplements.

On physical examination, vital signs are normal. BMI is 23. Skin thickening of the face and fingers is noted. There are a few firm, gritty nodules on the palmar aspect of the digits. There is no rash or digital pits.

The appearance of the hands is shown.



Which of the following is the most likely diagnosis?

(A) Eosinophilia myalgia syndrome
(B) Limited cutaneous systemic sclerosis
(C) Morphea
(D) Primary biliary cirrhosis

Item 54

A 42-year-old woman is evaluated for a 6-month history of pain and swelling of several small hand joints, an elbow, and an ankle. She gets modest relief with naproxen. She has no other medical problems and takes no additional medications.

On physical examination, vital signs are normal. There are tenderness to palpation and swelling of the second and third proximal interphalangeal joints bilaterally, second and fifth metacarpophalangeal joints bilaterally, left wrist, right elbow, and right ankle. The remainder of the physical examination is normal.

Laboratory studies are significant for a rheumatoid factor of 85 U/mL (85 kU/L) and positive anti-cyclic citrullinated peptide antibodies.

Radiographs of the hands and wrists show periarticular osteopenia at the metacarpophalangeal joints and a marginal erosion at the right second metacarpal head.

Which of the following is the most appropriate initial treatment?

(A) Hydroxychloroquine
(B) Methotrexate
(C) Rituximab
(D) Tofacitinib

Item 55

A 40-year-old woman is evaluated for a 7-year history of color changes associated with pain that occurs in her fingers. Her second and third fingertips turn white in the cold, then become blue, and eventually become dark red and painful. These symptoms last approximately 15 minutes before resolving. She also reports a 3-month history of pain and swelling in the second and third metacarpophalangeal joints. History is also significant for dry eyes and dry mouth of 5 years' duration as well as recent onset of diffusely puffy hands and increasing fatigue. She reports no gastrointestinal symptoms, including gastroesophageal reflux disease. She takes no medications.

On physical examination, vital signs are normal. No rash or oral ulcers are noted. Slightly cool, diffusely edematous fingers are noted. Scattered palmar telangiectasias are present. There is swelling and tenderness of the second and fourth metacarpophalangeal joints.

Laboratory studies:

C3	Normal
C4	Normal
Creatine kinase	596 U/L
Creatinine	Normal
Antinuclear antibodies	Positive (titer: 1:320)
Anti-double-stranded DNA antibodies	Negative
Anti-Ro/SSA antibodies	Negative
Anti-La/SSB antibodies	Negative
Anti-Scl-70 antibodies	Negative
Anti-Smith antibodies	Negative
Anti-U1-ribonucleoprotein antibodies	Positive
Urinalysis	Negative

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Which of the following is the most likely diagnosis?

(A) Mixed connective tissue disease
(B) Polymyositis
(C) Systemic lupus erythematosus
(D) Systemic sclerosis
(E) Undifferentiated connective tissue disease

Item 56

A 28-year-old woman is evaluated in the emergency department for a 1-day history of progressive shortness of breath, cough, and hemoptysis. She reports a fever but no chills. She has a 2-year history of systemic lupus erythematosus. Medications are mycophenolate mofetil, hydroxychloroquine, prednisone, naproxen as needed, vitamin D, and calcium.

On physical examination, temperature is 38.9 °C (102.0 °F), blood pressure is 100/60 mm Hg, pulse rate is 110/min, and respiration rate is 24/min. Oxygen saturation is 88% on ambient air. BMI is 29. Diffuse hair thinning is noted. A malar rash is present. There is symmetric swelling of metacarpophalangeal and proximal interphalangeal joints as well as both wrists and knees. There are no cardiac rubs or murmurs. Diffuse crackles are heard on lung auscultation.

Laboratory studies:

Hematocrit	22% (30% in office 1 week ago)
Leukocyte count	3200/μL (3.2×10^9/L)
Platelet count	90,000/μL (90×10^9/L)
Creatinine	1.3 mg/dL (115 μmol/L)
Urinalysis	3+ blood; 2+ protein; erythrocyte casts

Chest radiograph reveals diffuse bilateral pulmonary infiltrates with sparing of the apices.

Which of the following is most likely to establish a diagnosis?

(A) Bronchoalveolar lavage and biopsy
(B) Chest CT
(C) MRI of the chest
(D) Pulmonary angiography

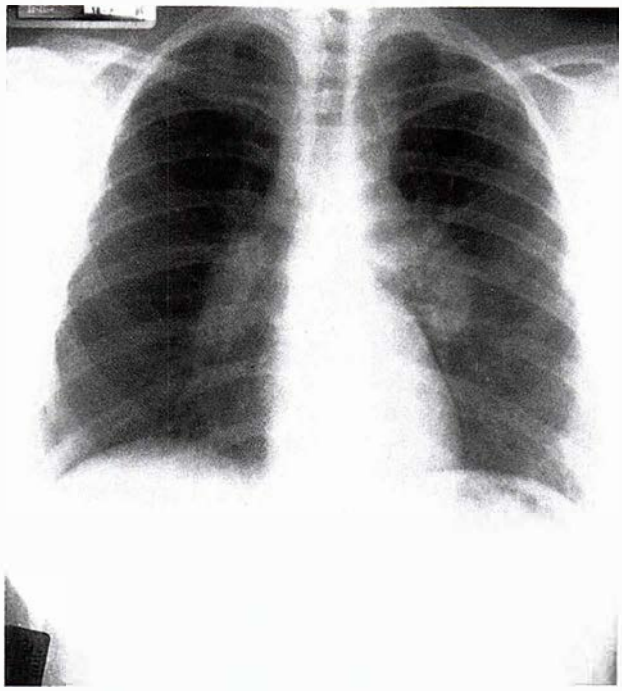
Item 57

A 24-year-old woman is evaluated for a 1-week history of tender nodules over the legs about 2 to 3 cm in size along with pain and stiffness in the ankles. She also notes a nonproductive cough of 3 days' duration. Her only medication is an oral contraceptive.

On physical examination, temperature is 38.4 °C (101.1 °F), blood pressure is 110/65 mm Hg, pulse rate is 85/min, and respiration rate is 18/min. BMI is 24. There are four 3-cm erythematous tender nodules on the left anterior lower leg and three on the right. Swelling of both ankles with tenderness at the right Achilles tendon insertion into the calcaneus is noted; no other joints are swollen. Cardiopulmonary examination is normal.

Laboratory studies reveal an erythrocyte sedimentation rate of 38 mm/h and a hematocrit of 35%; leukocyte and platelet counts are normal.

A chest radiograph is shown.



Which of the following is the most appropriate treatment?

(A) Adalimumab
(B) High-dose prednisone
(C) Methotrexate
(D) Naproxen

Item 58

A 35-year-old man is evaluated for a 4-week history of persistent pain and swelling in the left knee and right ankle. Symptoms are worse in the morning and associated with stiffness lasting 1 hour. Ibuprofen is beneficial. Seven weeks ago he had diarrhea that lasted one week and resolved without treatment. One week ago he was diagnosed with anterior uveitis, which is resolving with a prednisolone ophthalmic solution. He reports no current gastrointestinal or genitourinary symptoms, rash, or cardiorespiratory symptoms.

On physical examination, vital signs are normal. Slightly injected sclera of the right eye is noted. There are swelling, warmth, and tenderness of the right knee joint. Tenderness and swelling at the right Achilles tendon insertion to the calcaneus are noted. There is no rash or nail pitting. The remainder of the physical examination is normal.

Laboratory studies done at the time of the visit:

Complete blood count with differential	Normal
Erythrocyte sedimentation rate	30 mm/h
Stool cultures	Negative
Urinalysis	Normal
DNA amplification urine test for *Chlamydia trachomatis*	Negative

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Aspiration of the left knee is performed; synovial fluid analysis reveals a leukocyte count of 15,000/μL (15×10^9/L) with 70% monocytes and no crystals. Gram stain is negative, and cultures are pending.

Radiographs of the knee and ankle are normal.

Which of the following is the most likely diagnosis?

(A) Infectious arthritis
(B) Psoriatic arthritis
(C) Reactive arthritis
(D) Rheumatoid arthritis

Item 59

A 68-year-old man is evaluated during a follow-up visit for long-standing tophaceous gout that caused almost monthly gout flares. Five months ago, colchicine and allopurinol were initiated. He reached his serum urate goal (<6.0 mg/dL [0.35 mmol/L]) within 3 months of starting therapy, and he has not had a gout flare since reaching this target. He has not developed any new tophi; his original tophi on his hands and elbows have begun to shrink in size. History is also significant for hypertension, for which he takes losartan.

On physical examination, temperature is 37.2 °C (98.9 °F), blood pressure is 133/79 mm Hg, pulse rate is 79/min, and respiration rate is 12/min. BMI is 28. A moderate-sized tophus is visible on the right elbow as well as two small tophi on different distal interphalangeal joints. There is no swelling or tenderness to palpation of any joints.

Current laboratory studies reveal a serum urate level of 5.4 mg/dL (0.32 mmol/L) and normal kidney and liver chemistries.

Which of the following is the most appropriate next step in management?

(A) Add probenecid
(B) Change allopurinol to febuxostat
(C) Continue colchicine and allopurinol
(D) Discontinue colchicine

Item 60

A 27-year-old man is evaluated for a 2-year history of ankylosing spondylitis. Symptoms were initially responsive to physical therapy and naproxen; however, for the past 6 months he has experienced increasing back and buttock pain and stiffness, with difficulty bending downward. One month ago naproxen was discontinued, and indomethacin was initiated but with no improvement.

On physical examination, vital signs are normal. BMI is 25. Tenderness to palpation over the sacroiliac joints and lower lumbar spine is noted. There is limited range of motion of the lumbar spine manifested by an increase of 1 cm of change on forward flexion.

Laboratory studies reveal an erythrocyte sedimentation rate of 40 mm/h.

In addition to continuing physical therapy, which of the following is the most appropriate treatment?

(A) Adalimumab
(B) Methotrexate
(C) Rituximab
(D) Sulfasalazine

Item 61

A 28-year-old woman is evaluated for a 2-week history of left hip pain that occurs at night and with walking. She has a 1-year history of systemic lupus erythematosus with class IV nephritis. Treatment has included prednisone as high as 60 mg/d and cyclophosphamide. Current medications are mycophenolate mofetil, hydroxychloroquine, prednisone, furosemide, lisinopril, calcium, and vitamin D.

On physical examination, vital signs are normal. BMI is 26. She has a cushingoid appearance. There is pain on internal rotation of the left hip. There is no pain on hip adduction or with pressure over the lateral hip. The remainder of the examination is normal.

Laboratory studies reveal an erythrocyte sedimentation rate of 18 mm/h, normal complement (C3 and C4) levels, and stable anti-double-stranded DNA antibodies.

Anterior-posterior pelvis and lateral left hip radiographs are normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT of the left hip
(B) MRI of the left hip
(C) Repeat plain radiography in 1 month
(D) Ultrasonography of the left hip

Item 62

A 58-year-old woman is evaluated in the hospital for a 3-month history of fatigue and a 4.5-kg (10-lb) weight loss. She also has dermatomyositis that was diagnosed 1 year ago, at which time she underwent detailed evaluation for myopathy and age-appropriate malignancy screening. She has also noticed worsening muscle weakness and rash in the past 2 weeks.

On physical examination, temperature is normal, blood pressure is 118/94 mm Hg, pulse rate is 90/min, and respiration rate is 16/min. BMI is 27. Cardiac and pulmonary examinations are normal. Abdominal examination reveals ascites without organomegaly. There is symmetric weakness of the arm and thigh muscles. A violaceous rash is present on the extensor surface of the metacarpophalangeal joints. A few areas of palpable purpura on the lower extremities are noted.

Laboratory studies:

Complete blood count	Normal
Chemistry panel	Normal
Aldolase	31 U/L (normal range, 1.0–8.0 U/L)
Aspartate aminotransferase	98 U/L
Creatine kinase	1400 U/L
Antinuclear antibodies	Titer of 1:640
Urinalysis	Normal

Which of the following is the most appropriate diagnostic test to perform next?

(A) Chest CT with contrast
(B) Liver biopsy

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(C) PET scan
(D) Thigh muscle MRI
(E) Transvaginal pelvic ultrasonography

Item 63

A 52-year-old man is evaluated in the hospital for fever, malaise, arthralgia, left foot drop, abdominal pain that is worse after eating, and a 4.5-kg (10-lb) weight loss, all of which gradually developed over the past 2 months.

On physical examination, temperature is 38.4 °C (101.1 °F), blood pressure is 154/92 mm Hg, pulse rate is 76/min, and respiration rate is 18/min. BMI is 29. There is no temporal or sinus tenderness. The nasal passages and oropharynx are normal. The chest is clear. An abdominal bruit is heard on the right, inferior to the costal margin. The abdomen is otherwise normal. The testicles are tender to palpation. The joints are tender to palpation without synovitis. Weakness of the left foot to dorsiflexion is noted.

The appearance of the trunk and thighs is shown.



Laboratory studies:

Erythrocyte sedimentation rate	72 mm/h
Complements (C3 and C4)	Normal
Creatinine	2.2 mg/dL (194.5 µmol/L)
IgA	Normal
Hepatitis B surface antigen	Positive
Hepatitis B surface antibodies	Negative
Hepatitis C antibodies	Negative
ANCA	Negative
Urinalysis	Negative

Chest radiograph is unremarkable. Abdominal angiogram shows aneurysms and stenoses of the mesenteric and renal arteries.

Which of the following is the most likely diagnosis?

(A) Goodpasture syndrome
(B) Granulomatosis with polyangiitis
(C) Henoch-Schönlein purpura
(D) Polyarteritis nodosa

Item 64

A 34-year-old man is evaluated for progressive left knee pain. The pain causes difficulty with his work as a mail carrier, particularly when walking. His occupation does not require repetitive bending. He played football in college and experienced left knee trauma during sports participation; he underwent left meniscectomy and stopped playing sports. His mother has osteoarthritis of the hands that developed at age 65 years.

On physical examination, vital signs are normal. BMI is 27. Bone hypertrophy of the left knee is noted. There is crepitus but no warmth, erythema, swelling, or effusion of the knees.

Plain radiographs (anteroposterior views) show medial joint-space narrowing of both knees but greater on the left as well as osteophytes and bony sclerosis of the tibial plateau of the left knee; there is no periarticular osteopenia or erosive or destructive changes.

Which of the following is the most likely cause of this patient's left knee osteoarthritis?

(A) BMI
(B) Family history
(C) Meniscectomy
(D) Occupation

Item 65

H

A 62-year-old woman is evaluated in the emergency department for right knee pain. Three days ago she developed increasing pain, swelling, warmth, and erythema of the right knee as well as fevers and chills. She underwent total knee replacement of her right knee 2 months ago.

On physical examination, temperature is 38.4 °C (101.2 °F), blood pressure is 110/75 mm Hg, pulse rate is 98/min, and respiration rate is 12/min. BMI is 23. The right knee has a well-healed surgical scar, but there are significant knee joint swelling, warmth, tenderness to palpation, mild overlying erythema, and decreased range of motion. The remainder of the examination is normal.

Laboratory studies reveal a leukocyte count of 15,500/µL (15.5×10^9/L) with 89% neutrophils, a C-reactive protein level of 6.8 mg/dL (68 mg/L), and an erythrocyte sedimentation rate of 45 mm/h.

Radiograph of the right knee shows only an effusion.

Which of the following is the most appropriate next step in management?

(A) Begin vancomycin and cefepime
(B) Obtain blood and synovial fluid cultures
(C) Obtain a bone scan
(D) Obtain a CT of the knee

Item 66

A 76-year-old man seeks advice regarding dietary modifications to help prevent gout flares. He recently experienced his first episode of podagra. At his initial visit, serum urate level was 7.2 mg/dL (0.42 mmol/L). History is also significant for hypertension, for which he takes losartan.

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On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 135/80 mm Hg, pulse rate is 80/min, and respiration rate is 15/min. BMI is 27. The remainder of the examination is unremarkable.

In addition to meat restriction, increased intake of which of the following may help to decrease this patient's risk of gout flares?

(A) Leafy green vegetables
(B) Low-fat dairy products
(C) Red wine
(D) Shellfish

Item 67

A 29-year-old woman is evaluated for increasing fatigue and diffuse pain of 6 months' duration. The pain becomes more severe for several days if she "overdoes it." She reports chronically poor sleep and has difficulty concentrating at work. History is also significant for hypothyroidism, for which she takes levothyroxine. She takes ibuprofen as needed for the pain, which provides minimal benefit.

On physical examination, vital signs are normal. BMI is 25. Tenderness to palpation of multiple muscle groups is noted. Muscle strength is normal. There is no joint swelling or rash. The remainder of the examination is normal.

Laboratory studies, including complete blood count, chemistry panel, erythrocyte sedimentation rate, and thyroid-stimulating hormone, are normal.

Which of the following is the most appropriate next step in management?

(A) Begin scheduled ibuprofen
(B) Increase levothyroxine
(C) Obtain an antinuclear antibody panel
(D) Start an aerobic exercise program

Item 68

A 75-year-old man is evaluated for gradual progression of right knee pain. He has a 10-year history of right knee osteoarthritis, which was previously controlled with acetaminophen. He recently discontinued the acetaminophen because of continued pain and began over-the-counter oral naproxen, with good results. He can walk again without pain or difficulty. He has no other medical problems and takes no other medications.

On physical examination, blood pressure is 124/82 mm Hg. The right knee demonstrates evidence of bony enlargement and crepitus on flexion and extension; no warmth, tenderness, or effusion is noted.

Which of the following is the most appropriate next step in management?

(A) Continue oral naproxen
(B) Discontinue oral naproxen; begin celecoxib
(C) Discontinue oral naproxen; begin a topical NSAID
(D) Refer for knee joint replacement

Item 69

A 52-year-old man is evaluated for a 6-month history of increasingly swollen and painful joints of the fingers of both hands, both wrists, and the left ankle associated with 90 minutes of morning stiffness. He has tried over-the-counter ibuprofen and naproxen without sustained benefit. He has no other symptoms.

On physical examination, vital signs are normal. There are swelling and tenderness of the second, third, and fifth proximal interphalangeal joints; first, second, and third metacarpophalangeal joints; both wrists; and left ankle. Decreased range of motion of the right wrist is noted. The remainder of the physical examination is normal.

Laboratory studies reveal an erythrocyte sedimentation rate of 45 mm/h and a C-reactive protein level of 5.2 mg/dL (52 mg/L); rheumatoid factor and anti-cyclic citrullinated peptide antibody tests are negative.

Hand radiographs show an erosion of the second right metacarpal head with mild symmetric joint-space narrowing and mild periarticular osteopenia of the metacarpophalangeal joints; there is no bony sclerosis or osteophytes.

Which of the following is the most likely diagnosis?

(A) Osteoarthritis
(B) Rheumatoid arthritis
(C) Sarcoidosis
(D) Systemic lupus erythematosus

Item 70

A 41-year-old man is evaluated for a 1-month history of daily fever as high as 39.0 °C (102.2 °F), a 4.5-kg (10.0-lb) weight loss, myalgia, and swollen lymph nodes. He reports joint pain and stiffness in the shoulders, hands, wrists, and knees. He has also noted a pink rash over the trunk and extremities associated with the fever.

On physical examination, temperature is 38.4 °C (101.1 °F), blood pressure is 128/78 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. BMI is 28. Multiple enlarged lymph nodes in the anterior cervical chain are present. Splenomegaly is noted. There is an erythematous maculopapular rash on the trunk and extremities. Swelling of the wrists and knees is present. The remainder of the examination is normal.

Laboratory studies:

Erythrocyte sedimentation rate	100 mm/h
Hematocrit	31%
Leukocyte count	30,000/μL (30×10^9/L), with 80% neutrophils; no blasts
Platelet count	350,000/μL (350×10^9/L)
Alanine aminotransferase	68 U/L
Aspartate aminotransferase	75 U/L
C-reactive protein	30 mg/dL (300 mg/L)
Creatinine	0.9 mg/dL (79.6 μmol/L)
Ferritin	20,000 ng/mL (20,000 μg/L)
Urinalysis	Normal

Chest radiograph is normal.

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Which of the following is the most likely diagnosis?

(A) Acute myeloid leukemia
(B) Adult-onset Still disease
(C) Granulomatosis with polyangiitis
(D) Systemic lupus erythematosus

Item 71

A 29-year-old man is evaluated for pain and photophobia in the left eye that began 3 days ago. He reports a 6-month history of recurrent painful oral and genital ulcers that last 1 to 2 weeks and then resolve, as well as waxing and waning knee, ankle, and wrist pain during this time. Medical history had been unremarkable until the onset of these symptoms, and he takes no medications.

On physical examination, temperature is 38.2 °C (100.7 °F), blood pressure is 134/82 mm Hg, pulse rate is 90/min, and respiration rate is 14/min. BMI is 22. The left eye is diffusely erythematous, and a small amount of white fluid on the bottom of the anterior chamber is noted. There is an ulcer on the right side of the tongue.

The genital ulcers are shown.



Laboratory studies show an erythrocyte sedimentation rate of 76 mm/h as well as a normal complete blood count and metabolic profile.

The patient is urgently referred to an ophthalmologist.

Which of the following is the most likely diagnosis?

(A) Behçet syndrome
(B) Cytomegalovirus infection
(C) Herpes simplex virus type 1 infection
(D) Reactive arthritis

Item 72

A 66-year-old man is evaluated for a 2-month history of right knee pain. The pain is worse with walking and is accompanied by approximately 5 minutes of morning stiffness. Medical history is significant for chronic kidney disease, hypertension, and mild gastroesophageal reflux disease. Medications are lisinopril, hydrochlorothiazide, and ranitidine as needed for heartburn.

On physical examination, vital signs are normal. BMI is 29. Medial joint line tenderness and mild crepitus are noted in the right knee. There is no redness, warmth, or instability of the affected joint; minimal swelling is noted.

Laboratory studies reveal a serum creatinine level of 1.6 mg/dL (141.4 µmol/L).

Radiographs of the right knee show mild medial joint-space narrowing, subchondral sclerosis of the same region, and small osteophytes at the medial femoral and tibial joint margins.

In addition to an exercise program, which of the following is the most appropriate initial treatment?

(A) Acetaminophen
(B) Celecoxib
(C) Colchicine
(D) Ibuprofen

Item 73

A 24-year-old woman is evaluated for a 6-month history of color change in her hands and feet, which is worse during stress. She is a nonsmoker. Family history is negative.

On physical examination, temperature is normal, blood pressure is 116/72 mm Hg, pulse rate is 64/min, and respiration rate is 12/min. BMI is 22. There is mild reversible discoloration of the fingertips upon exposure to cold. Cool tips of the fingers without digital pits are noted. Cardiopulmonary examination is normal. Muscle strength and reflexes are normal. There is no rash. The remainder of the examination is normal.

Laboratory studies, including complete blood count and chemistry panel, are normal. Nailfold capillary examination is normal.

Which of the following is the most appropriate next step in management?

(A) Measure antinuclear and anti-U1-ribonucleoprotein antibodies
(B) Measure antiphospholipid antibody panel and cryoglobulins
(C) Obtain digital arteriography
(D) Clinical observation

Item 74

A 64-year-old man is evaluated in the emergency department for progressively deteriorating mental status. His wife states that he has been experiencing episodic headaches during the past several months, and his mental status has changed progressively over the past several days. History is significant for atherosclerosis, hypertension, and coronary artery disease. He has a 40-pack-year history of smoking. Medications are atorvastatin, lisinopril, and low-dose aspirin.

On physical examination, the patient is alert and oriented to self but not to place or year. Vital signs are normal. BMI is 26. On the Mini-Mental State Examination, he is unable to do serial sevens, is able to recall only one object out of three, and cannot draw a geometric figure that is shown to him. The remainder of the examination, including the neurologic assessment, is within normal limits.

Laboratory studies, including complete blood count, basic metabolic panel, liver chemistries, and urinalysis, are normal; erythrocyte sedimentation rate is 22 mm/h.

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Lumbar puncture is performed; cerebrospinal fluid analysis reveals a leukocyte count of 15/μL (15×10^6/L), 90% lymphocytes, and a protein level of 45 mg/dL (450 mg/L).

Chest radiograph is unremarkable. A brain MRI shows scattered lesions, mainly in the white matter, and an MR angiogram shows possible narrowing of the intracerebral arteries.

Which of the following is the most appropriate next step in management?

(A) Initiate azathioprine
(B) Initiate cyclophosphamide and glucocorticoids
(C) Obtain functional MRI
(D) Obtain intracerebral angiography and brain biopsy

Item 75

A 45-year-old woman is evaluated for a 2-week history of nausea, right upper quadrant abdominal pain and fullness, and malaise. She has rheumatoid arthritis that was diagnosed 2 years ago. Initial treatment with methotrexate lost its efficacy after 6 months, and she was switched to leflunomide. She had partial response to leflunomide and was started on etanercept in combination. Other medications are sulfasalazine and naproxen. In the past 6 months, she has had no active swollen or tender joints.

On physical examination, vital signs are normal. BMI is 28. Icterus is noted. The liver is palpable with slight tenderness. Murphy sign is negative. The remainder of the examination is normal.

Laboratory studies:

Hemoglobin	11.1 g/dL (111 g/L)
Leukocyte count	12,500/μL (12.5×10^9/L)
Alkaline phosphatase	162 U/L
Alanine aminotransferase	73 U/L
Aspartate aminotransferase	81 U/L
Total bilirubin	2.6 mg/dL (44.5 μmol/L)
Hepatitis B serologies	Negative
Hepatitis C serologies	Negative

Abdominal ultrasound shows multiple gallstones, no thickening of the gallbladder, and normal extrahepatic bile ducts.

Which of the following is the most appropriate next step in management?

(A) Discontinue etanercept
(B) Discontinue leflunomide
(C) Schedule a cholecystectomy
(D) Schedule a liver biopsy

Item 76

A 55-year-old man is evaluated during a follow-up visit for gout. Two years ago, he had been treated with allopurinol and developed a hypersensitivity reaction. Over the past several months, he has had recurrent attacks of acute, episodic swelling of the first metatarsophalangeal joints with increasing involvement of other joints, including the ankles and knees. Laboratory studies showed significant hyperuricemia. History is also significant for Crohn disease, hypertension, chronic kidney disease (estimated glomerular filtration rate of 55 mL/min/1.73 m^2), and nonalcoholic fatty liver disease. Current medications are diltiazem and azathioprine, which he has been taking for the past 9 months.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 125/70 mm Hg, pulse rate is 80/min, and respiration rate is 12/min. BMI is 28. The examination is unremarkable, including no joint abnormalities.

Which of the following is a contraindication to the use of febuxostat in this patient?

(A) Azathioprine
(B) Diltiazem
(C) Mild to moderate chronic kidney disease
(D) Nonalcoholic fatty liver disease

Item 77

A 28-year-old woman is evaluated in the emergency department for a 3-week history of progressively worsening pain in the left arm. The pain worsens with use of the arm. She also notes fatigue, malaise, and the inability to walk long distances due to discomfort in her legs. She reports no cough, nausea, vomiting, or burning on urination. She takes no medications.

On physical examination, temperature is 38.1 °C (100.5 °F), blood pressure is 166/95 mm Hg in the right arm and 115/56 mm Hg in the left arm, pulse rate is 72/min, and respiration rate is 14/min. BMI is 27. Pallor of the fingertips and delayed capillary refill of the nail beds are noted in the left hand. A diminished radial pulse of the left arm and decreased dorsalis pedis pulses bilaterally are noted. A bruit is heard over the mid abdomen. There is no rash.

Laboratory studies:

Erythrocyte sedimentation rate	115 mm/h
Creatinine	1.3 mg/dL (115 μmol/L)
Partial thromboplastin time	Normal
Prothrombin time	Normal
D-dimer	Negative
Urinalysis	Normal

Which of the following is the most appropriate diagnostic test to perform next?

(A) Antimyeloperoxidase antibody assay
(B) Antiphospholipid antibody assay
(C) Aortic arteriography
(D) Temporal artery biopsy

Item 78

A 28-year-old woman seeks preconception counseling. She has a 5-year history of systemic lupus erythematosus, which initially presented with nephritis, rash, and arthritis. Her disease has been well controlled for 1 year with hydroxychloroquine, mycophenolate mofetil, and prednisone, 5 mg/d.

On physical examination, vital signs are normal. BMI is 28. There is a discoid rash on the ear pinna, unchanged since the last examination. No other rashes or ulcers are noted.

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The remainder of the examination, including cardiopulmonary examination, is normal.

Laboratory studies, including complete blood count, chemistry panel, liver chemistries, complement levels, and urinalysis, are normal.

Which of the following is the most appropriate next step in management?

(A) Discontinue hydroxychloroquine
(B) Discontinue mycophenolate mofetil
(C) Discontinue prednisone
(D) Continue current regimen
(E) Stop all medications

Item 79

A 42-year-old woman is evaluated for a 4-month history of progressive right hip pain. Plain radiographs obtained 2 months ago showed early osteoarthritis. Her symptoms have steadily worsened and are now limiting mobility. She reports no recent trauma or injuries, fevers, or pain of other joints. She is originally from India. She has lived in the United States for 15 years but visits her family abroad occasionally. She reports no injection drug use and is not sexually active. She was found to be positive for latent tuberculosis infection several years ago and underwent standard treatment at that time. History is significant for rheumatoid arthritis, for which she takes methotrexate and folic acid; she also started etanercept 3 months ago.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 135/80 mm Hg, pulse rate is 75/min, and respiration rate is 12/min. BMI is 23. Range of motion of the right hip is limited by pain without overlying erythema or warmth. There are no visible joint or skin abnormalities. There are no heart murmurs, and the lungs are clear.

Laboratory studies reveal an erythrocyte sedimentation rate of 40 mm/h; complete blood count and kidney and liver chemistries are normal.

Radiograph of the right hip reveals an effusion and new erosive changes.

Arthrocentesis of the right hip is performed.

Which of the following is the most likely cause of this patient's hip pain?

(A) Gout
(B) *Mycobacterium tuberculosis* infection
(C) *Neisseria gonorrhea* infection
(D) Rheumatoid arthritis

Item 80

A 35-year-old woman is evaluated for weakness in the right foot and left wrist with paresthesia in the right leg, right foot, left forearm, and left hand. She also reports facial erythema and joint stiffness. She has a 6-year history of systemic lupus erythematosus (SLE). Medications are hydroxychloroquine, prednisone, vitamin D, and calcium.

On physical examination, vital signs are normal. There is a new malar rash. Swelling of the second through fourth metacarpophalangeal joints of the hands is present. There is dorsiflexion weakness of the right ankle and a left wrist drop. Reflexes are normal. The remainder of the examination is normal.

Laboratory studies indicate that her SLE appears to be active with an elevation of erythrocyte sedimentation rate compared with baseline, leukopenia, and anemia typical of her previous SLE flares.

Which of the following is the most appropriate next step in management?

(A) Discontinue hydroxychloroquine
(B) Obtain electromyography/nerve conduction studies
(C) Obtain MRI of the cervical spine
(D) Obtain skin biopsy for small-fiber neuropathy

Item 81

A 40-year-old man has a 15-year history of well-controlled chronic plaque psoriasis and psoriatic arthritis and is now evaluated for a severe flare of both the skin and joint disease. One month ago, he developed severe pain and swelling of the hands, elbows, knees, ankles, and toes; symptoms have been unresponsive to ibuprofen. He also developed sudden worsening of psoriasis over the trunk and extremities. He notes increased fatigue and intermittent lymphadenopathy in the neck for the past 3 months. He has no other symptoms. His only medication is sulfasalazine.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 130/85 mm Hg, and pulse rate is 80/min. Swelling and tenderness of the bilateral elbows, wrists, proximal interphalangeal joints, knees, ankles, and metatarsophalangeal joints are noted. Oropharyngeal candidiasis is present. Cervical lymphadenopathy is noted bilaterally. Except for the skin, the remainder of the physical examination is normal.

The appearance of the skin is shown.



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Which of the following is the most appropriate diagnostic test to perform next?

(A) Heterophile antibody testing
(B) HIV antibody testing
(C) HLA-B27 testing
(D) Lyme antibody testing
(E) Rapid streptococcal testing

Item 82

A 28-year-old woman is evaluated for a 1-week history of pain and morning stiffness in her hands. Three weeks ago, she had muscle aches, malaise, fevers, and coryza, all of which have resolved. She is an elementary school teacher; prior to her initial illness, several children in her class had similar symptoms accompanied by an erythematous rash on the cheeks. She does not have other pertinent personal or family history, and she takes no medications.

On physical examination, temperature is 37.3 °C (99.2 °F), blood pressure is 120/78 mm Hg, pulse rate is 66/min, and respiration rate is 13/min. BMI is 22. Symmetric wrist, metacarpophalangeal, and proximal interphalangeal joint tenderness and pain with motion are noted without significant joint swelling. The remainder of the examination is normal.

Laboratory studies are significant for an erythrocyte sedimentation rate of 38 mm/h.

Which of the following is the most appropriate initial treatment?

(A) Azithromycin
(B) Ibuprofen
(C) Interferon alfa
(D) Prednisone

Item 83

A 52-year-old man is evaluated in the hospital for several episodes of hemoptysis that developed over the past day. He reports feeling well until about 3 weeks ago when he developed myalgia, arthralgia, occasional epistaxis, and diminished hearing. One week ago he developed a rash and weakness in his right hand. History is otherwise unremarkable, and he takes no medications.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 152/100 mm Hg, pulse rate is 72/min, and respiration rate is 24/min. Conjunctivitis is present in both eyes. Decreased hearing in both ears is noted. Bilateral maxillary sinus tenderness is present. Chest examination reveals diffuse rhonchi. The right hand has decreased grip strength. Palpable purpura of the bilateral lower extremities is present.

Laboratory studies:

Erythrocyte sedimentation rate	84 mm/h
Leukocyte count	12,300/μL (12.3 × 10^9/L), eosinophils <2%
Complements (C3, C4)	Normal
Creatinine	2.1 mg/dL (185.6 μmol/L)
Urinalysis	3+ protein; 50 erythrocytes/hpf; 20 leukocytes/hpf; several mixed cellular casts

Sinus radiograph shows bony erosion of the septum and turbinates. Chest radiograph shows diffuse infiltrates.

Which of the following is most likely to establish the diagnosis?

(A) Anti-double-stranded DNA antibody levels
(B) Antimyeloperoxidase antibody levels
(C) Antiproteinase 3 antibody levels
(D) Serum cryoglobulin levels

Item 84

A 31-year-old woman is evaluated during a follow-up visit for systemic lupus erythematosus. She was diagnosed 6 months ago after presenting with a malar rash, pericarditis, and arthritis. She was initially treated with prednisone, 40 mg/d, and hydroxychloroquine with good control of symptoms. The prednisone was subsequently tapered to the current dose of 5 mg/d.

On physical examination, temperature is normal, blood pressure is 130/92 mm Hg, pulse rate is 90/min, and respiration rate is 16/min. BMI is 27. There is edema of the lower extremities to just above the ankles. There are no cardiac or pleural rubs. No rash is present.

Laboratory studies:

	One month ago	Today
C3	Normal	Decreased
C4	Normal	Decreased
Creatinine	0.7 mg/dL (61.9 μmol/L)	1.3 mg/dL (115 μmol/L)
Anti-double-stranded DNA antibodies	225 U/mL	721 U/mL
Urinalysis	Trace erythrocytes; trace protein	1+ erythrocytes; 2+ protein; 1 erythrocyte cast; no bacteria
Spot urine protein-creatinine ratio	300 mg/g	1200 mg/g

In addition to an increase in prednisone, which of the following is the most appropriate next step in management?

(A) Add methotrexate
(B) Repeat laboratory testing in 1 month
(C) Schedule kidney biopsy
(D) Schedule renal artery Doppler examination

Item 85

A 55-year-old man is diagnosed with hypertension. Other than a single episode of podagra 6 months ago, his medical history is unremarkable. He takes no medications. Family history is notable for his father and brother who have gout and hypertension.

On physical examination, temperature is 36.6 °C (97.9 °F), blood pressure is 152/100 mm Hg, pulse rate is 82/min, and respiration rate is 14/min. BMI is 24. The remainder of the physical examination is unremarkable.

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Laboratory studies are significant for normal blood urea nitrogen, serum creatinine, and electrolyte levels; the serum urate level is 7.9 mg/dL (0.47 mmol/L).

Which of the following antihypertensive drugs is the most appropriate for this patient?

(A) Hydrochlorothiazide
(B) Lisinopril
(C) Losartan
(D) Metoprolol

Item 86

A 71-year-old man is evaluated for severe tophaceous gout. Colchicine has been effective in reducing flares to approximately two in the past year. On initial evaluation 1 year ago, serum urate level was 10.2 mg/dL (0.60 mmol/L). Allopurinol was initiated but subsequently discontinued because of gastrointestinal intolerance. He was switched to febuxostat, which was increased to maximum dose without success in reaching the serum urate goal of less than 6.0 mg/dL (0.35 mmol/L). He recently had a gout flare of his right great toe, which has nearly resolved.

On physical examination, temperature is 36.6 °C (97.9 °F), blood pressure is 140/80 mm Hg, pulse rate is 89/min, and respiration rate is 15/min. BMI is 32. Bulky tophi are present over bilateral elbows, hands, and feet with drainage of pasty material from a large tophus over the second metacarpophalangeal joint of the left hand. There are mild swelling and tenderness to palpation over the right first metatarsophalangeal joint.

Laboratory studies reveal a serum urate level of 10.9 mg/dL (0.64 mmol/L), an estimated glomerular filtration rate of 42 mL/min/1.73 m^2, and a normal glucose-6-phosphate dehydrogenase level.

Which of the following is the most appropriate next step in management?

(A) Add pegloticase
(B) Start prednisone
(C) Switch colchicine to anakinra
(D) Switch febuxostat to pegloticase

Item 87

A 25-year-old woman is evaluated during a follow-up visit for systemic lupus erythematosus. She was feeling well until 2 weeks ago when she developed increased fatigue and diffuse arthralgia. Medications are hydroxychloroquine and ibuprofen as needed.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 140/80 mm Hg, pulse rate is 80/min, and respiration rate is 16/min. There is diffuse alopecia of the scalp. Malar erythema is noted. Heart sounds are normal, and the chest is clear. Examination of the abdomen is normal. Tenderness with minimal swelling of the proximal interphalangeal joints is present bilaterally. Small effusions on both knees with pain on range of motion are noted.

Laboratory studies:

Leukocyte count	3000/μL (3.0×10^9/L), with 900 lymphocytes
Creatinine	Normal
Electrolytes	Normal
Urinalysis	2+ protein; trace blood

Which of the following tests should be obtained next?

(A) Anti–double-stranded DNA antibodies
(B) Antinuclear antibodies
(C) Anti-Ro/SSA and anti-La/SSB antibodies
(D) Anti-Smith antibodies
(E) Anti-U1-ribonucleoprotein antibodies

Item 88

A 31-year-old woman is evaluated in the hospital for headache, blurred vision, and nausea occurring for the past 12 hours. She has a 2-year history of diffuse cutaneous systemic sclerosis with recent worsening of Raynaud phenomenon that is treated with nifedipine.

On physical examination, the patient is alert but is somnolent and has altered sensorium. Temperature is normal, blood pressure is 150/92 mm Hg, pulse rate is 104/min, and respiration rate is 16/min. BMI is 22. Oxygen saturation is 95% on ambient air. Cardiopulmonary examination is normal. Examination of the skin reveals diffuse skin thickening of the face, anterior chest, and distal extremities; sclerodactyly; and multiple healed digital pits. Neurologic examination is nonfocal.

Laboratory studies:

Complete blood count	Normal
Albumin	3.0 g/dL (30 g/L)
Bicarbonate	32 mEq/L (32 mmol/L)
Creatinine	4.2 mg/dL (371.3 μmol/L); baseline, 0.8 mg/dL (70.7 μmol/L)
Urinalysis	2+ protein; 3 erythrocytes/hpf; 5 leukocytes/hpf; few granular casts
Urine protein-creatinine ratio	1200 mg/g

Chest radiograph is normal. Noncontrast CT of the head is normal. MRI of the brain shows bilateral parietal lobe white matter prominence.

Which of the following is the most appropriate treatment?

(A) Captopril
(B) Cyclophosphamide
(C) Methylprednisolone
(D) Sildenafil

Item 89

A 55-year-old woman is evaluated for a 3-year history of gradual left knee pain. She reports increased difficulty with stair climbing and an increase in pain over the past 6 months. She has no history of injury. She was prescribed acetaminophen, 1000 mg three times daily, and an exercise

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program 3 months ago but continues to have activity-limiting symptoms. Family history is notable for her mother who had a total knee replacement at the age of 65 years.

On physical examination, vital signs are normal. BMI is 31. There is bony hypertrophy of the left knee and the first metacarpophalangeal joints without warmth, erythema, swelling, or effusion.

Laboratory studies, including an erythrocyte sedimentation rate and serum creatinine, are normal.

Knee radiographs (including standing views) show medial joint-space narrowing and small osteophytes of the left knee; there is no periarticular osteopenia or marginal erosions.

Which of the following is the most appropriate next treatment?

(A) Capsaicin
(B) Diclofenac
(C) Duloxetine
(D) Hyaluronic acid
(E) Hydrocodone

Item 90

A 56-year-old man is evaluated for painless intermittent bloody urine of 6 weeks' duration. History is significant for granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) diagnosed 10 years ago, which is now in remission; he was treated with prednisone for 3 years and oral cyclophosphamide for 1 year. He also has hypertension and hyperlipidemia. Current medications are metoprolol and atorvastatin.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 146/94 mm Hg, pulse rate is 68/min, and respiration rate is 14/min. BMI is 28. There are no rashes or ulcers. Genitalia are normal. The remainder of the examination, including cardiopulmonary examination, is normal.

Laboratory studies:

Chemistry panel and kidney function tests	Normal
Hemoglobin	12.1 g/dL (121 g/L)
Erythrocyte sedimentation rate	35 mm/h
p-ANCA	Negative
Antimyeloperoxidase antibodies	Negative
Antiproteinase 3 antibodies	Negative
Urinalysis	Trace protein; 10-20 erythrocytes/hpf; 0-2 leukocytes/hpf; no casts
Urine cultures	Negative

A chest radiograph is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT of the abdomen and pelvis with contrast
(B) Cystoscopy
(C) Kidney and bladder ultrasonography
(D) Urine eosinophil measurement
(E) Urine protein-creatinine ratio

Item 91

H

A 35-year-old woman is evaluated in the hospital for a 6-month history of worsening fatigue and a 3-week history of progressive shortness of breath. Over the past 2 weeks she has developed orthopnea and leg edema. Medical history is significant for diffuse cutaneous systemic sclerosis and gastroesophageal reflux disease. Her only medication is omeprazole.

On physical examination, the patient is alert but in respiratory distress. Temperature is 37.2 °C (99.0 °F), blood pressure is 106/74 mm Hg, pulse rate is 108/min, and respiration rate is 24/min. BMI is 31. Oxygen saturation is 92% on ambient air. An S_3 and elevated jugular venous pressure are noted. Crackles are noted at the lung bases. Diffuse skin thickening of the face, anterior chest, arms stopping at the elbows, and legs is noted; there is sclerodactyly of the hands. There is lower extremity edema to the knees.

Laboratory studies are normal except for a serum creatinine level of 2.2 mg/dL (194.5 µmol/L).

Chest radiograph shows bilateral pleural effusions and diffuse alveolar infiltrates. Echocardiogram shows generalized myocardial hypokinesis and a left ventricular ejection fraction of 20%. Electrocardiogram shows nonspecific T-wave changes.

Which of the following is the most likely cause of this patient's clinical presentation?

(A) Cardiomyopathy
(B) Constrictive pericarditis
(C) Pulmonary arterial hypertension
(D) Scleroderma renal crisis

Item 92

A 32-year-old woman is evaluated for a 2-month history of weight loss, abdominal cramping, and loose stools. Her stools are malodorous, but she has not noted any blood associated with her bowel movements. Although her appetite is good, she has lost 3.2 kg (7.0 lb). She has an 8-year history of diffuse cutaneous systemic sclerosis.

On physical examination, temperature is normal, blood pressure is 146/92 mm Hg, pulse rate is 94/min, and respiration rate is 16/min. BMI is 19. Cardiopulmonary examination is normal. The abdomen is soft and nontender with normal bowel sounds. Diffuse skin thickening of the face, anterior chest, and distal extremities is noted as well as sclerodactyly and multiple healed digital pits. There is no rash. Muscle strength and reflexes are normal.

Laboratory studies:

Hematocrit	30%
Albumin	2.6 g/dL (26 g/L)
Alanine aminotransferase	Normal
Aspartate aminotransferase	Normal
Total bilirubin	Normal
Lipase	Normal
Urinalysis	Normal

Which of the following is the most appropriate diagnostic test to perform next?

(A) Colonoscopy
(B) CT of the abdomen and pelvis with contrast

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(C) Endoscopic retrograde cholangiopancreatography
(D) Glucose hydrogen breath test

Item 93

A 65-year-old woman is evaluated for bilateral hand and wrist pain that worsens with activity. She reports no swelling or redness but has morning stiffness lasting less than 30 minutes. History is also significant for hypertension and diabetes mellitus. There is no personal or family history of psoriasis. Medications are hydrochlorothiazide and metformin.

On physical examination, vital signs are normal. BMI is 29. The right wrist has a mild effusion and slightly reduced range of motion. There is mild pain with range of motion of both wrists. The hands have bony hypertrophy of the proximal and distal interphalangeal joints, with mild tenderness to palpation but no swelling. Bilateral crepitus of the knees is noted. There are no rashes or nail changes.

Laboratory studies reveal a negative rheumatoid factor, and erythrocyte sedimentation rate, C-reactive protein, and serum urate levels are within normal limits.

A radiograph of the wrist is shown.



Aspiration of the wrist is performed, and results are pending.

Which of the following is the most likely diagnosis?

(A) Chronic gouty arthropathy
(B) Osteoarthritis with calcium pyrophosphate deposition
(C) Psoriatic arthritis
(D) Rheumatoid arthritis

Item 94

A 74-year-old woman is evaluated during a follow-up visit for polymyalgia rheumatica diagnosed 8 weeks ago after developing shoulder and hip girdle pain and morning stiffness. Symptoms resolved on prednisone, 15 mg/d. She feels well and reports no headache, jaw claudication, visual changes, or recurrence of myalgia or stiffness. History is significant for type 2 diabetes mellitus and hypertension. Medications are metformin, lisinopril, and prednisone, which has been tapered to 10 mg/d.

On physical examination, temperature is normal, blood pressure is 140/80 mm Hg, pulse rate is 70/min, and respiration rate is 14/min. BMI is 31. There is no temporal tenderness or induration. No carotid or subclavian bruits are present. Good range of motion without pain in the shoulders and hips is noted. Proximal strength is normal.

Laboratory studies:

	Initial	Current
Erythrocyte sedimentation rate	90 mm/h	42 mm/h
Hemoglobin	11.5 g/dL (115 g/L)	12 g/dL (120 g/L)

Which of the following is the most appropriate management at this time?

(A) Increase prednisone
(B) Increase prednisone and add methotrexate
(C) Schedule temporal artery biopsy
(D) Continue current treatment

Item 95

H

A 47-year-old woman is evaluated in the emergency department for sharp mid-chest pain that developed abruptly. The pain is exacerbated by lying down, deep inspiration, or coughing but improves when she sits up.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 140/88 mm Hg, pulse rate is 100/min, and respiration rate is 22/min. A friction rub at the left sternal border is heard. The lungs are clear. There are swelling and tenderness of the second and third proximal interphalangeal and metacarpophalangeal joints.

Electrocardiogram shows diffuse ST-segment elevations in all leads except aVR and V_1 and PR-segment depression in leads V_2 to V_6.

Which of the following is the most likely cause of this patient's pericarditis?

(A) Ankylosing spondylitis
(B) Polymyalgia rheumatica
(C) Psoriatic arthritis
(D) Rheumatoid arthritis

Item 96

H

An 80-year-old woman was hospitalized 2 days ago for upper gastrointestinal bleeding due to peptic ulcer disease. She was placed on omeprazole and given intravenous normal saline for hydration. Today she has developed right knee pain and swelling. History is also significant for osteoarthritis of the hands and knees. Her only medication prior to admission was ibuprofen as needed.

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H CONT.

On physical examination, temperature is 37.8 °C (100.0 °F); the remainder of the vital signs is normal. Hand findings are consistent with osteoarthritis. The right knee is warm with a large effusion, is tender to palpation, and has limited flexion to 90 degrees.

Aspiration of the right knee is performed; the synovial fluid is yellow and cloudy, and the leukocyte count is 15,000/μL (15×10^9/L).

Which of the following synovial fluid tests will be most helpful in establishing a diagnosis?

(A) Antinuclear antibody measurement
(B) Glucose measurement
(C) Gram stain, culture, and crystal analysis
(D) Protein measurement

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Answers and Critiques

Item 1 Answer: B

Educational Objective: Treat hyperuricemia with febuxostat in a patient with an adverse reaction to allopurinol.

Febuxostat is indicated for this patient with frequent gout attacks. He had been taking allopurinol, a first-line agent for serum urate reduction in patients with gout. Urate-lowering therapy is indicated for patients with gout who experience repeated attacks (≥2 per year), have one attack in the setting of chronic kidney disease (CKD) of stage 2 or worse, have tophaceous deposits found on examination or imaging, or have a history of urolithiasis. This patient developed an adverse reaction to allopurinol but still needs urate-lowing therapy. Febuxostat is a newer non-purine, non-competitive xanthine oxidase inhibitor, which is a viable alternative to allopurinol. It can be used in patients with mild to moderate CKD and is safe to try after an adverse reaction or failure of allopurinol.

Anti-inflammatory prophylaxis to prevent gout attacks is recommended when urate-lowering therapy is initiated because of the paradoxical increased risk of acute gout attacks when serum urate levels are rapidly decreased by medication. Prophylaxis should be continued in the presence of any active disease (tophi or flares). Colchicine is a first-line option for gout prophylaxis and should not be discontinued in this patient who requires flare prophylaxis during urate-lowering therapy.

Pegloticase is an intravenous synthetic uricase replacement approved for treatment-failure gout. Pegloticase is immunogenic, and the development of antibodies eventually occurs in most patients taking the drug, which leads to reduced effectiveness and increases the risk of hypersensitivity reactions.

The uricosuric drugs probenecid and sulfinpyrazone promote kidney clearance of uric acid by inhibiting urate-anion exchangers in the proximal tubule responsible for urate reabsorption. These agents are relatively contraindicated in patients with impaired kidney function or those at risk for kidney stones.

KEY POINT

- In patients with gout who require urate-lowering therapy, febuxostat is a viable alternative for those who have an adverse reaction to allopurinol.

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Item 2 Answer: B

Educational Objective: Diagnose Jaccoud arthropathy in a patient with systemic lupus erythematosus.

The most likely diagnosis is Jaccoud arthropathy, which is most commonly caused by systemic lupus erythematosus (SLE). SLE arthritis is nonerosive, but persistent periarticular inflammation that affects the structural integrity of the joint capsule/supporting joint ligaments can result in Jaccoud arthropathy, or reversible hand deformities, which is characterized by reducible subluxation of the digits, swan neck deformities, and ulnar deviation of the fingers due to attenuation of the joint-supporting structures. It is reported to occur in 5% of patients with SLE and can be confused with rheumatoid arthritis. Jaccoud arthropathy can be seen in other inflammatory illnesses, including scleroderma, mixed connective tissue disease, and Sjögren syndrome, and was first described in patients with recurrent episodes of rheumatic fever. This patient with SLE demonstrates the classic features of Jaccoud arthropathy, including subluxation, ulnar deviation, and swan neck deformities, with radiographs that do not show evidence of erosions.

Joint hypermobility refers to the ability to painlessly move a joint beyond normal range of movement. Hypermobility syndrome describes a disorder characterized by musculoskeletal pain and generalized joint hypermobility occurring in otherwise healthy individuals. Patients with joint hypermobility can rarely have swan neck deformities but do not generally have deformities of the severity seen in this patient. In addition, the presence of another disease that can cause joint hypermobility (SLE in this patient) excludes hypermobility syndrome.

Mixed connective tissue disease (MCTD) is characterized by features of systemic sclerosis, polymyositis, and SLE and is by definition associated with high titers of anti-U1-ribonucleoprotein antibodies. This patient does not have any of the characteristic symptoms of MCTD, including Raynaud phenomenon, hand edema, puffy fingers, and/or prominent synovitis.

Rheumatoid arthritis generally causes nonreducible hand deformities; furthermore, severe hand changes associated with rheumatoid arthritis typically show erosions on radiograph and periarticular osteopenia, which are not present in this patient.

KEY POINT

- Jaccoud arthropathy is a nonerosive arthritis most commonly caused by systemic lupus erythematosus and is characterized by reducible subluxation of the digits, swan neck deformities, and ulnar deviation of the fingers due to attenuation of the joint-supporting structures.

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Item 3 Answer: C

Educational Objective: Diagnose rheumatoid arthritis with appropriate laboratory testing.

This patient most likely has rheumatoid arthritis (RA), and testing for both anti-cyclic citrullinated peptide (CCP) antibodies and rheumatoid factor will be most helpful in confirming the diagnosis. RA is an autoimmune disorder that typically presents as a symmetric inflammatory polyarthritis affecting the proximal interphalangeal and metacarpophalangeal joints of the fingers, the wrists, and the analogous joints of the feet. Prolonged morning stiffness is common. Anti-CCP antibody testing has the greatest specificity (95%) for the diagnosis of RA. Although no single laboratory test will diagnose RA, the combination of a compatible clinical presentation and a positive rheumatoid factor and positive anti-CCP antibodies is more specific for the diagnosis than any other combination of tests. Approximately 75% of patients with RA are rheumatoid factor positive, but specificity is only around 80%. Rheumatoid factor positivity frequently occurs in other autoimmune disorders and chronic infections, most notably chronic active hepatitis C virus infection.

Testing for antinuclear antibodies (ANA) is usually performed in patients with suspected systemic lupus erythematosus (SLE). A new onset of polyarticular inflammatory arthritis as seen in this patient can be indicative of SLE; however, she has no other signs or symptoms suggestive of SLE such as alopecia, aphthous ulcers, malar rash, pericardial and pleural serositis, or cytopenias. Furthermore, an ANA test may be positive in 40% of patients with RA and would not distinguish between RA and SLE with as much specificity as the combination of anti-CCP antibodies and rheumatoid factor.

Although an elevated C-reactive protein may provide laboratory evidence of inflammation that can complement the physical examination findings of inflammatory synovitis, this inflammatory marker lacks diagnostic specificity and does not distinguish RA from other forms of inflammatory arthritis.

KEY POINT

- The combination of anti-cyclic citrullinated peptide antibodies and rheumatoid factor has the greatest specificity for the diagnosis of rheumatoid arthritis.

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Item 4 Answer: A

Educational Objective: Diagnose amyopathic dermatomyositis.

The most likely diagnosis is amyopathic dermatomyositis. This patient has a clinical presentation of heliotrope eruption in the form of a violaceous periorbital rash, Gottron papules over the extensor surface of small joints of the hands, and photodistributed violaceous poikiloderma (V sign and Shawl sign) without muscle weakness. These are findings of skin involvement seen in dermatomyositis without any clinical, serum, or electromyogram (EMG) findings of muscle involvement or myositis, suggesting the diagnosis of amyopathic dermatomyositis. Amyopathic dermatomyositis is seen in about 20% to 25% of patients with dermatomyositis, but some of these patients have evidence of myositis on one of the evaluation studies (muscle enzymes, EMG, or muscle biopsy) in the absence of muscle weakness. To qualify for the diagnosis of amyopathic dermatomyositis, the patient should have the characteristic rash but no clinical, laboratory, or muscle evaluation findings of myositis. Amyopathic dermatomyositis may be triggered by sunlight exposure and also is associated with an underlying malignancy. Treatment is usually with glucocorticoids and immunosuppressive agents.

Polymorphous light eruption (PMLE) is another dermatologic condition in which patients develop skin lesions after exposure to sunlight; these lesions last several days and resolve spontaneously in the absence of reexposure. A variety of skin lesions may be seen in PMLE, including urticarial wheals, papules, plaques, and vesicles. PMLE usually develops early in the spring, with the first few exposures to sunlight, and can be triggered by intense exposures. These lesions occur in photodistributed areas but lack characteristic heliotrope or Gottron eruptions. A diagnosis of PMLE is unlikely in this patient.

Rosacea is a chronic, inflammatory condition that causes an acneiform eruption and flushing on the mid-face. There are two types, vascular and papular pustular (inflammatory) rosacea. Vascular rosacea presents as persistent flushing, especially of the central face, with prominent telangiectasias. Pustules and papules are seen in the inflammatory variant, but in contrast to acne, rosacea pustules are not follicular based. The patient's findings are not consistent with rosacea.

Although this patient has positive antinuclear antibodies, she lacks the associated findings of systemic lupus erythematosus (SLE), including malar/discoid rash, arthritis, organ involvement, and kidney disease. SLE can cause a rash on the hands similar to Gottron papules, but it more typically involves skin located between the joints.

KEY POINT

- Amyopathic dermatomyositis refers to dermatomyositis with cutaneous involvement in the absence of clinical, laboratory, electromyogram, or biopsy evidence of myositis.

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Item 5 Answer: A

Educational Objective: Treat inadequately controlled osteoarthritis with intra-articular glucocorticoids.

Intra-articular glucocorticoids are appropriate for this patient. She has osteoarthritis in multiple joints based on her history, physical examination, and plain radiographs. Although her overall osteoarthritis symptoms appear to be well controlled, the right knee is clearly more affected than any other joint. Therefore, therapy targeted toward this joint is indicated, and intra-articular glucocorticoids are the most appropriate choice for this patient to address her localized symptoms. Meta-analyses of clinical trials evaluating the use of glucocorticoid injection in osteoarthritis suggest that the technique may be particularly helpful. Individual studies have shown that the presence of an effusion, withdrawal of fluid from the knee, severity of disease, absence of synovitis, injection delivery under ultrasound guidance, and greater symptoms at baseline may all improve the likelihood of response.

Hyaluronic acid injections have shown only a minimal degree of benefit in the treatment of knee osteoarthritis. They generally require a series of three weekly injections and are more invasive, considerably more expensive, and less predictably efficacious than glucocorticoid injections.

Arthroscopic lavage for knee osteoarthritis is a technique in which fluid is instilled and aspirated from the joint through an arthroscope with the intention of removing the debris often present in these joints. Although observational studies originally suggested that the technique might be of benefit, more recent studies and meta-analyses have suggested otherwise. No differences in pain measured by visual analogue scale or function measured by the Western Ontario McMaster University Index have been identified in controlled trials using sham procedures.

The patient's symptoms are reasonably well controlled on her current NSAID. Therefore, there is no clear benefit to switching to another medication within this class.

KEY POINT

- Targeted therapy with an intra-articular glucocorticoid injection is appropriate in patients with osteoarthritis who have one symptomatic joint.

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Item 6 Answer: D

Educational Objective: Treat an acute monoarticular gouty attack with intra-articular glucocorticoids.

Intra-articular glucocorticoid therapy is appropriate for this patient. Intra-articular glucocorticoid injections are a good treatment strategy when only one or two joints are affected, the presence of joint infection has been ruled out, and oral therapies have potential adverse events. This patient has a history of gout and currently presents with evidence of an acute gouty attack in the knee. Given the synovial fluid leukocyte count (<50,000/μL [50×10^9/L]), the documented presence of intracellular crystals, and the negative synovial fluid Gram stain, the probability of a joint infection is very low. The onset of gout in this patient was preceded by community-acquired pneumonia, which may have promoted the gout attack by causing fever and dehydration. Treatment for acute gout should focus on anti-inflammatory therapy, typically using colchicine, an NSAID, or a glucocorticoid. Although all three would effectively treat this patient's gout, the best choice would be an intra-articular glucocorticoid because of potential adverse effects of the other anti-inflammatories. Although both systemic and local glucocorticoid therapy are effective in treating acute gout, intra-articular glucocorticoids are preferred in this patient to avoid systemic immunosuppressive effects in the setting of resolving pneumonia and the possible adverse impact of systemic glucocorticoids in a patient with diabetes mellitus.

Acetaminophen is analgesic but not anti-inflammatory and does not promote the resolution of a gouty attack.

Colchicine effectively treats acute gout, especially in the early phases of an attack. However, colchicine is metabolized by the hepatic CYP3A4 enzyme, which clarithromycin strongly inhibits; coadministration raises the risk of colchicine toxicity and even death, and colchicine should be avoided while this patient is taking clarithromycin.

The presence of significant kidney disease makes the use of an NSAID such as indomethacin undesirable because cyclooxygenase inhibition adversely affects the kidneys.

KEY POINT

- Intra-articular glucocorticoid injections are a good treatment strategy when only one or two joints are affected, the presence of joint infection has been ruled out, and oral therapies have potential adverse events.

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Item 7 Answer: D

Educational Objective: Treat an adult with severe Henoch-Schönlein purpura using prednisone.

Prednisone is appropriate for this patient. His findings demonstrate the presence of a small-vessel vasculitis affecting

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the skin, joints, kidneys, and gastrointestinal tract. Deposition of IgA in the skin confirms the diagnosis of adult-onset Henoch-Schönlein purpura (HSP). In children, HSP is generally a benign, self-limited condition, and treatment is most commonly supportive pending spontaneous remission. HSP in adults is less common and typically is more severe. Although adult HSP also tends to run a self-limited course, adults with HSP are more likely to experience severe disease and to accumulate irreversible organ damage before the acute disease resolves. In this case, the involvement of multiple organ systems, including the gastrointestinal tract, probably warrants prednisone treatment based upon expert consensus recommendation.

Cyclophosphamide is an alkylating agent and potent immunosuppressant. It is commonly used for treatment of severe autoimmune disease such as systemic lupus erythematosus and ANCA-associated vasculitis. Its use in adult-onset HSP is less well established; although it is sometimes used in conjunction with prednisone for severe HSP nephritis, it would not be a first-choice therapy in the absence of prednisone use.

Dapsone is an antibiotic that has antileukocyte activity and is occasionally used to treat the leukocytoclastic vasculitides, including HSP. However, given the severity of this patient's condition, dapsone is less likely to be effective, and prednisone use is warranted.

Like all NSAIDs, ibuprofen may help alleviate joint pain and swelling and may have some modest effect on reducing the inflammation of small-vessel vasculitis. However, ibuprofen is unlikely to be adequately effective in a serious case such as this. Moreover, the nephrotoxic and antiplatelet effects of an NSAID would be undesirable in this patient who already has acute kidney injury and intestinal bleeding.

KEY POINT

- Treatment with prednisone should be considered for patients who have severe Henoch-Schönlein purpura with involvement of multiple organ systems.

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Item 8 Answer: C

Educational Objective: Avoid combining biologic agents when treating rheumatologic disease.

Addition of the nonbiologic disease-modifying antirheumatic drug (DMARD) leflunomide is indicated for this patient. She has chronic moderate to severe rheumatoid arthritis with one or more poor prognostic markers, which may include young age, involvement of more than three joints, seropositivity, elevated inflammatory markers, and radiographic changes. She has continued to have active disease despite treatment with sulfasalazine and the biologic agent etanercept as suggested by continued synovitis of four joints and elevated inflammatory markers. A "treat to target" approach has been found to improve the outcomes in patients such as in this case, and additional therapy is needed to achieve a low disease activity or remission. A combination of a biologic agent (preferably a tumor factor necrosis α inhibitor) and a nonbiologic DMARD is thought to be the best option to achieve this goal. Because of her side-effect history with methotrexate, the addition of the alternative nonbiologic DMARD leflunomide at this point would be the next best strategy.

Biologic agents are frequently used in combination with a nonbiologic DMARD. However, concurrent use of two or more biologic agents is not recommended because infection rates are significantly increased with minimal, if any, added efficacy. Therefore, the addition of abatacept, anakinra, or rituximab is inappropriate.

KEY POINT

- Concurrent use of two or more biologic agents is not recommended because infection rates are significantly increased with minimal, if any, added efficacy.

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Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012 May;64(5):625-39. [PMID: 22473917]

Item 9 Answer: B

Educational Objective: Diagnose fibromyalgia.

The most likely diagnosis is fibromyalgia, which is characterized by chronic widespread pain, tenderness of skin and muscles to pressure (allodynia), fatigue, sleep disturbance, and exercise intolerance. Previous lack of response to multiple medications, including NSAIDs, also provides a diagnostic clue. Examination is generally unremarkable except for allodynia. An association with other pain syndromes, including irritable bowel syndrome, irritable bladder, pelvic pain, vulvodynia, headache, and temporomandibular jaw pain, is not uncommon. This patient fulfills the 2010 American College of Rheumatology diagnostic criteria for fibromyalgia (widespread pain, wakes unrefreshed, significant fatigue, and cognitive difficulties), with symptoms present for more than 3 months.

The clinical manifestations of adrenal insufficiency are often insidious, with fatigue and malaise being the dominant symptoms; a high degree of clinical suspicion may be needed to pursue the diagnosis in the presence of subtle systemic symptoms. The patient's 4-year history of symptoms and a normal chemistry panel makes adrenal insufficiency unlikely.

The numerous and largely nonspecific clinical manifestations of hypothyroidism include fatigue, reduced endurance, weight gain, cold intolerance, constipation, impaired concentration and short-term memory, dry skin, edema, mood changes, depression, psychomotor retardation, muscle cramps, myalgia, menorrhagia, and reduced fertility. Some patients with mild hypothyroidism will exhibit few

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or none of these symptoms. A normal thyroid-stimulating hormone level makes hypothyroidism very unlikely.

The classic findings of polymyositis are symmetric proximal muscle weakness with little or no pain and elevation in muscle-associated enzymes. This patient has pain, a normal serum creatine kinase level, and no true weakness on examination, making polymyositis an unlikely diagnosis.

KEY POINT

- Current criteria for the diagnosis of fibromyalgia include chronic widespread pain, fatigue, waking unrefreshed, and cognitive symptoms, with symptoms present for more than 3 months.

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Item 10 Answer: B

Educational Objective: Provide preconception counseling to a patient with systemic lupus erythematosus who has positive anti-Ro/SSA antibodies.

Preconception counseling regarding congenital heart block in her child is appropriate for this patient with systemic lupus erythematosus (SLE) who is positive for anti-Ro/SSA antibodies. Patients with SLE experience miscarriage, stillbirth, preeclampsia and premature delivery two to five times more often than patients without the disease. This patient has mild SLE, and her disease has been quiescent for 18 months; therefore, this is an appropriate time to attempt pregnancy. Expert opinion recommends conception when SLE has been quiescent for at least 6 months. A major risk to her child would be congenital heart block, which affects approximately 2% of pregnancies in which the mother is positive for anti-Ro/SSA or anti-La/SSB antibodies. Some of these newborns require pacing from birth if there is complete heart block at delivery. Pregnancies in mothers who are positive for anti-Ro/SSA or anti-La/SSB antibodies should be monitored closely and should include input from high-risk obstetrics and neonatology because these antibodies can pass the placenta and affect the developing cardiac conduction system. If the mother has had a previously affected child, subsequent pregnancies carry a 12% risk of congenital heart block. Positivity for anti-Ro/SSA or anti-La/SSB antibodies also confers a risk for neonatal lupus erythematosus, which is characterized by rash as well as hematologic and hepatic abnormalities that generally resolve when the antibody dissipates. The use of phototherapy for neonatal hyperbilirubinemia may cause the rash to develop because the antibody is associated with photosensitivity.

Hydroxychloroquine is thought to be safe in pregnancy and has been shown to reduce the risk of congenital heart block in newborns whose mothers are positive for anti-Ro/SSA or anti-La/SSB antibodies. It should therefore not be discontinued in this patient.

This patient is not at an increased risk of lupus nephritis because it has not been a feature of her disease to date, and she is negative for anti-double-stranded DNA antibodies.

Although anti-Ro/SSA antibodies increase the risk of developing subacute cutaneous lupus, pregnancy does not increase this risk further and does not need to be part of preconception counseling. Because a photosensitive rash has been one of the features of this patient's illness, she is aware of the hazard of sun exposure.

KEY POINT

- Neonatal congenital heart block affects approximately 2% of pregnancies in which the mother is positive for anti-Ro/SSA or anti-La/SSB antibodies.

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Lateef A, Petri M. Management of pregnancy in systemic lupus erythematosus. Nat Rev Rheumatol. 2012 Dec;8(12):710-8. [PMID: 22907290]

Item 11 Answer: D

Educational Objective: Diagnose hemochromatosis as a cause of secondary osteoarthritis.

Measurement of transferrin saturation is the most appropriate diagnostic test to perform next in this patient. He has signs and symptoms suggestive of hemochromatosis, an autosomal recessive disorder characterized by increased absorption of iron from the gut. Approximately 40% to 60% of patients with hemochromatosis develop arthropathy that is osteoarthritis-like, but characteristically involves the second and third metacarpophalangeal (MCP) or wrist joints. Transferrin saturation and serum ferritin levels are usually elevated in patients with arthropathy due to hemochromatosis. Although a variety of more specific diagnostic maneuvers may be undertaken, including liver biopsy and genetic testing for homozygosity for the C282Y mutation of the *HFE* gene, the most appropriate and cost-effective next step is measurement of transferrin saturation. A consensus does not exist for transferrin saturation cut-off levels for diagnosis of hemochromatosis, with some guidelines recommending a value of greater than 60% in men or greater than 50% in women, and others suggesting a level of greater than 55% for all patients. Measurement of ferritin levels is indicated in patients with an elevated transferrin saturation; a markedly elevated level further supports the diagnosis and predicts the development of symptoms. The presence of clinical MCP involvement with radiographic evidence of hook-shaped osteophytes is most characteristic of hemochromatosis.

Anti-cyclic citrullinated peptide antibodies are never associated with hemochromatosis, and rheumatoid factor is generally negative in patients with hemochromatosis as seen in this patient. These autoantibodies have specificity for rheumatoid arthritis.

Arthritis may occur in up to 20% of patients with hepatitis C virus infection and may mimic rheumatoid arthritis clinically and radiographically. However, the characteristic findings of hemochromatosis on this patient's radiographs

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and the lack of more typical findings of erosions or bony decalcification adjacent to the involved joints make a diagnosis of hepatitis C–associated arthritis less likely.

Serum α-fetoprotein is elevated in liver disease such as acute or chronic viral hepatitis infection as well as in hepatocellular and numerous other cancers. It would have little diagnostic specificity in this clinical setting.

KEY POINT

- Secondary osteoarthritis may occur in the setting of hemochromatosis, which is associated with an arthropathy that is osteoarthritis-like, but characteristically involves the metacarpophalangeal and wrist joints.

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Item 12 Answer: B

Educational Objective: Diagnose spondyloarthritis using MRI.

MRI of the sacroiliac joints and/or spine is the most appropriate diagnostic test to perform next in this patient with suspected spondyloarthritis, considered in patients with chronic inflammatory back pain beginning before the age of 45 years. It is important to establish the diagnosis of spondyloarthritis even if it will not change immediate management because it requires life-long monitoring for the development of cardiovascular and other major organ damage. A positive HLA-B27 can be supportive of this diagnosis, but a negative result does not rule it out. Conventional radiographs can demonstrate sacroiliitis (erosive changes and sclerosis) but may be normal in early disease. If there is high suspicion for axial inflammation and conventional radiographs are normal, MRI of the sacroiliac joints and/or spine should be considered to further evaluate for inflammation. MRI is the most sensitive imaging technique for detecting early inflammation in the spine and sacroiliac joints. Although his radiographs and HLA-B27 testing were negative, this 25-year-old patient has probable inflammatory back (morning stiffness lasting 90 minutes) and sacroiliac pain, making spondyloarthritis, specifically ankylosing spondylitis, a likely diagnosis. Advanced imaging is often needed to show sacroiliac joint abnormalities.

CT of the sacroiliac joints can provide evidence of erosive changes in the bone but has limited ability to detect soft-tissue inflammation of the spine and may be normal until bony changes are present.

When injected intravenously, technetium-99m binds to hydroxyapatite crystals. Increased uptake reflects increased bone turnover related to infection, cancer, trauma, and arthritis. Because of these characteristics, a positive scan is a sensitive but nonspecific indicator of bone, joint, and periarticular disorders and may be most useful when other first-line imaging modalities are negative but the suspicion of disease remains high.

Ultrasonography is relatively inexpensive, poses no radiation hazard, can scan across three-dimensional structures, and may be used concurrently with physical examination to evaluate moving structures (for example, tendon evaluation). Musculoskeletal ultrasonography can be helpful in detecting evidence of peripheral enthesitis and arthritis but has not demonstrated usefulness in detecting axial involvement such as sacroiliitis.

KEY POINT

- MRI is the most sensitive imaging technique for detecting early inflammation in the spine and sacroiliac joints in patients with suspected spondyloarthritis.

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Item 13 Answer: B

Educational Objective: Diagnose pulmonary arterial hypertension in a patient with limited cutaneous systemic sclerosis.

Doppler echocardiography is the most appropriate test to perform next in this patient with a 3-year history of limited cutaneous systemic sclerosis (LcSSc) who now presents with shortness of breath and fatigue, a prominent single S_2, and a normal pulmonary examination and chest radiograph. LcSSc is characterized by isolated distal skin thickening (face, neck, and hands distal to wrists), is typically not accompanied by internal organ fibrosis, and is more likely to be associated with pulmonary arterial hypertension (PAH). The initial screening test for those with systemic sclerosis who have suspected PAH is echocardiography, which can rapidly and noninvasively estimate elevated pulmonary pressure as well as rule out some etiologies in the differential diagnosis such as intracardiac shunts, valvular heart disease, or heart failure. A moderate to high tricuspid gradient correlates well with PAH confirmed with gold standard right heart catheterization, which is 97% specific but may not be sensitive.

Bronchoscopy with lavage is often used in immunocompromised patients with rapidly deteriorating lung function to assess for infection and/or pulmonary hemorrhage. This test is not indicated in a patient with findings suggestive of PAH.

B-type natriuretic peptide (BNP) or N-terminal proBNP levels should be assessed in patients suspected of having heart failure. Preliminary data suggest that N-terminal proBNP may be helpful in the assessment of PAH and may provide prognostic information. BNP and N-terminal proBNP measurement cannot be recommended at this time until further studies validate their usefulness in patients with PAH.

In patients with echocardiographic findings suggesting PAH, an array of studies (such as imaging of the chest to

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assess parenchymal lung disease; V/Q scanning to assess potential chronic thromboembolic disease; pulmonary function testing with DLCO; serologic studies for connective tissue disease, liver disease, and HIV; and sleep studies) are helpful in selected patients. All patients suspected of having PAH should be considered for right heart/pulmonary artery catheterization to confirm the diagnosis suggested by clinical presentation, echocardiography, and pulmonary function tests and to accurately measure the arterial pressure. It is also very useful in evaluating responsiveness to therapeutic medications and helps guide therapy. However, right heart catheterization follows these preliminary diagnostic tests and would not be done next.

KEY POINT

- Echocardiography can rapidly and noninvasively estimate elevated pulmonary pressure as well as rule out some etiologies in the differential diagnosis of pulmonary arterial hypertension.

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Item 14 Answer: C

Educational Objective: Recognize the risk of interstitial lung disease in patients with polymyositis.

Chest radiography is the most appropriate diagnostic test to perform next in this patient with polymyositis who has positive anti-Jo-1 antibodies and features of the antisynthetase syndrome. Pulmonary manifestations of dermatomyositis and polymyositis are common and may result from interstitial lung disease (ILD), hypoventilation (weakness of respiratory muscles), aspiration pneumonia, and, rarely, pulmonary arterial hypertension (PAH). Clinical manifestations of ILD range from being asymptomatic to severe progressive cough and dyspnea. ILD is strongly associated with the presence of positive autoantibodies to transfer RNA synthetases, including anti-Jo-1 antibodies. In clinical practice, chest radiography, high-resolution chest CT, and pulmonary function testing are used to evaluate for the presence of this manifestation, and periodic follow-up in an asymptomatic patient is appropriate. Various patterns of ILD occur, ranging from nonspecific interstitial pneumonitis (most common) to usual interstitial pneumonia or bronchiolitis obliterans organizing pneumonia. The pattern of involvement determines glucocorticoid responsiveness and, ultimately, prognosis.

6-Minute walk testing is an important test used in the evaluation and follow-up of patients with an established diagnosis of PAH, but there is no evidence that this patient has PAH.

Myocarditis has a highly variable presentation, including fatigue, chest pain, heart failure, cardiogenic shock, arrhythmias, and sudden death. This patient has no cardiovascular symptoms suggesting myocarditis, and a cardiac MRI is not necessary in a patient with a low suspicion for this condition.

Coronary artery disease most classically presents with exertional substernal chest pain relieved with rest or nitroglycerin. Variant presentation may include dyspnea on exertion and exertional fatigue. Exercise stress testing would be indicated if there was a high level of suspicion for coronary artery disease, which is not the case here.

No additional testing is incorrect because ILD may be asymptomatic in some patients and can be missed without additional testing.

KEY POINT

- Interstitial lung disease is strongly associated with polymyositis and the presence of positive autoantibodies to transfer RNA synthetases, including anti-Jo-1 antibodies.

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Item 15 Answer: D

Educational Objective: Identify the association of tofacitinib with a risk of causing an abnormal lipid profile.

The lipid profile should be monitored in this patient with rheumatoid arthritis who began taking tofacitinib 1 month ago. Elevation of all components of the lipid panel, including cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol, has been found to occur as rapidly as 1 month after initiation of therapy with the biologic agent tofacitinib. Generally, these elevations remain stable over time. In the first 3 months of clinical trials evaluating the efficacy of tofacitinib, mean LDL cholesterol increased by 15%, and mean HDL cholesterol increased by 10%. In a subsequent clinical trial, statin therapy resulted in a return to pretreatment levels of LDL cholesterol. It is unknown to what extent these lipid abnormalities may impact the long-term risk of cardiovascular disease in patients treated with tofacitinib. Tofacitinib may initially raise then lower leukocyte counts. Furthermore, lymphopenia, neutropenia, and anemia may be seen with long-term use.

Elevated aminotransaminase levels may be seen with exposure to tofacitinib. However, abnormalities of bilirubin, glucose, and alkaline phosphatase would not be expected to result from exposure to 1 month of therapy with tofacitinib.

KEY POINT

- The biologic agent tofacitinib is associated with a risk of causing an abnormal lipid profile.

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Item 16 Answer: C

Educational Objective: Prevent gout by titrating allopurinol to achieve a target serum urate level.

The allopurinol dose should be increased for this patient with gout who has not yet reached the serum urate target goal of less than 6.0 mg/dL (0.35 mmol/L). Allopurinol is considered a first-line agent for serum urate reduction in patients with gout. Historically, concern has been expressed regarding allopurinol dosing and the risk of hypersensitivity reaction; however, it appears that gradual dose escalation with monitoring for side effects is a safe approach, even in patients with chronic kidney disease. Recent American College of Rheumatology recommendations advocate for a starting dose of 100 mg/d (or 50 mg/d in those with stage 4 or 5 chronic kidney disease) with titration upward every 2 to 5 weeks, aiming for a target serum urate level of less than 6.0 mg/dL (0.35 mmol/L). Despite the patient's kidney dysfunction, it is safe to up titrate the allopurinol gradually over several months to reach the target goal. If intolerance to allopurinol emerges, alternative urate-lowering therapy (such as the xanthine oxidase inhibitor febuxostat) should be pursued.

Gout flare prophylaxis such as colchicine should be maintained during urate-lowering therapy because patients are paradoxically at increased risk of gout flares during this time.

This patient is taking losartan to treat hypertension. This agent should not be discontinued because it has uricosuric effects and thus may be helping with efforts to lower his serum urate level.

This patient is not yet at the target serum urate goal; therefore, continuation of the same therapy is not appropriate.

KEY POINT

- Gradual dose escalation of allopurinol, with monitoring for side effects, is a safe approach for patients (even those with chronic kidney disease) with gout who have not reached a target serum urate level of less than 6.0 mg/dL (0.35 mmol/L).

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Item 17 Answer: B

Educational Objective: Treat giant cell arteritis with high-dose prednisone.

Treatment with prednisone, 60 mg/d (or 1 mg/kg/d), is indicated immediately for this patient. She has temporal artery pain and tenderness, along with jaw claudication in the setting of low-grade fever and a very high erythrocyte sedimentation rate. Given her age, these findings are most consistent with giant cell arteritis (GCA). The presence of shoulder and hip symptoms is consistent with polymyalgia rheumatica (PMR), which commonly co-occurs in patients with GCA (approximately 50% of cases). Despite a lack of visual symptoms to date, the patient is at risk of acute and potentially catastrophic visual loss. Immediate treatment is therefore warranted, the standard regimen being prednisone at a dose of 60 mg/d. (In the setting of severe visual loss, high-dose pulse glucocorticoids might be considered.) The addition of low-dose aspirin has been shown in limited studies to further reduce the risk of visual loss in patients with GCA already receiving prednisone and is favored by some experts.

Low-dose prednisone in the range of 10 to 20 mg/d is generally adequate treatment for isolated PMR but has not been shown to adequately treat GCA or to prevent visual complications.

MRI of the head permits the visualization of structures that could potentially be associated with headache and/or visual symptoms, including tumors, hydrocephalus, and/or large aneurysms. However, the presence of jaw claudication, as well as the presence of PMR symptoms, is not consistent with an intracranial lesion.

A temporal artery biopsy should be obtained as rapidly as possible to confirm the GCA diagnosis and to help direct long-term management; however, the histopathology of the disease will still be readable up to 1 to 2 weeks after initiation of treatment, and treatment should not be deferred pending biopsy.

KEY POINT

- Immediate treatment with prednisone, 60 mg/d (or 1 mg/kg/d), is indicated for patients with suspected giant cell arteritis to prevent visual complications.

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Item 18 Answer: C

Educational Objective: Screen for tuberculosis prior to starting biologic therapy.

Screening for tuberculosis using an interferon-γ assay is indicated for this patient before initiation of a tumor necrosis factor (TNF)-α inhibitor. This patient with rheumatoid arthritis has active disease despite treatment with triple therapy using nonbiologic disease-modifying antirheumatic drugs. In addition, she has poor prognostic markers, including positive rheumatoid serology and high inflammatory markers. Appropriate therapy with a biologic agent is being planned. TNF-α inhibitors are the mainstay of initial biologic therapy for rheumatoid arthritis. Reactivation of tuberculosis is a significant risk for most biologic agents, and particularly with TNF-α inhibitors because they inhibit formation of granuloma. Prior to starting any biologic agent, appropriate testing for latent tuberculosis is needed by obtaining either a tuberculosis skin test or an interferon-γ release assay (IGRA). Either of these two tests can be used to screen for

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latent tuberculosis. IGRA is more costly but may be more sensitive in patients on immunosuppressive therapy.

Chest radiography will be needed if the patient is symptomatic with pulmonary symptoms or has positive testing for latent tuberculosis infection but is currently not necessary.

Common variable immunodeficiency (CVID) occurs in both adults and children. Serum IgG levels are markedly reduced, and serum IgA and/or IgM levels are frequently low. Patients with CVID frequently develop chronic lung diseases, autoimmune disorders such as rheumatoid arthritis, malabsorption, recurrent infections, and lymphoma. Recurrent sinopulmonary infections, ear infections, and conjunctivitis are common. Measuring immunoglobulin levels in this patient without evidence of recurrent infection is not indicated.

Radiographs of the hands and feet can confirm the presence of erosions in active rheumatoid disease but are not needed in this patient prior to starting a biologic because disease activity has already been established by physical examination and laboratory testing.

KEY POINT

- Screening for tuberculosis is indicated before initiation of any biologic agent.

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Item 19 Answer: A

Educational Objective: Diagnose ankylosing spondylitis.

The most likely diagnosis is ankylosing spondylitis, which is characterized by inflammatory back pain that manifests as pain and stiffness in the spine that is worse after immobility and better with use. Symptoms are prominent in the morning (>1 hour), and patients can be symptomatic during the night. Buttock pain is common and correlates with sacroiliitis, which is typically bilateral. This patient has symptoms/signs consistent with ankylosing spondylitis, including more than 3 months of inflammatory back pain of primarily axial involvement, age of onset younger than 45 years, a positive HLA-B27, and a good response to an NSAID. The lack of sacroiliitis or other inflammatory changes on his radiographs does not rule out this diagnosis; these changes may not be evident early in the disease course and may not be seen on plain radiographs if there are no bone erosions. He fulfills the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial spondyloarthritis because he has a positive HLA-B27 plus at least two other features of spondyloarthritis, including inflammatory back pain and a good response to NSAIDs. The ASAS classification criteria use a nomenclature that defines spondyloarthritis as axial or peripheral, and ankylosing spondylitis would be the prototype disease in the spectrum of axial spondyloarthritis. These criteria allow patients who have not yet developed radiographic sacroiliitis to be classified as having "non-radiographic" axial spondyloarthritis.

Distinguishing between inflammatory and noninflammatory joint pain is critical in evaluating patients with musculoskeletal conditions. Inflammation may be the only symptom that distinguishes ankylosing spondylitis from lumbar degenerative disk disease. Subjective manifestations of joint inflammation include morning stiffness for more than 1 hour. Lumbar degenerative disk disease is not likely in this patient because his radiographs are normal and he has inflammatory back pain.

Characteristic features of psoriatic arthritis include enthesitis, dactylitis, tenosynovitis, arthritis of the distal interphalangeal joints, asymmetric oligoarthritis, and spondylitis. The HLA-B27 antigen may be positive in patients with axial involvement. Psoriatic arthritis involving only the axial skeleton is possible in this patient but less likely because he has no evidence of psoriasis.

Reactive arthritis (formerly known as Reiter syndrome) is a postinfectious arthritis that occurs in both men and women. Infections may include urethritis or diarrhea, although patients may be asymptomatic. Arthritis, usually oligoarticular, develops several days to weeks after the infection. The HLA-B27 antigen may be positive in these patients. Reactive arthritis is also less likely as this patient has no history of a gastrointestinal or genitourinary infection preceding the onset of arthritis.

KEY POINT

- Ankylosing spondylitis is characterized by inflammatory back pain that manifests as pain and stiffness in the spine that is worse after immobility and better with use.

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Item 20 Answer: A

Educational Objective: Recognize lymphoma in a patient with Sjögren syndrome.

The most appropriate next step in the management of this patient is to obtain a lymph node biopsy. This patient has Sjögren syndrome, an immune-mediated disease manifesting primarily as inflammation of exocrine glands, including the major and minor salivary glands, lacrimal glands, and, less commonly, other exocrine glands such as the pancreas. Patients with Sjögren syndrome are at significant risk of developing lymphoma, the most common being diffuse B-cell and mucosa-associated lymphoid tissue (MALT) lymphomas; this risk is up to 44-fold higher than in the general population. It is thought that chronic B-cell activation may lead to the development of a clone of malignant B cells. Hypocomplementemia, splenomegaly, lymphadenopathy, gammopathy,

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skin vasculitis, and cryoglobulinemia predict the development of, and accompany, lymphoma. With this patient's clinical history and findings, lymphoma must be in the differential and should be evaluated with a lymph node biopsy.

Biopsy of the rash will demonstrate leukocytoclastic vasculitis, which frequently accompanies lymphoma, but will not be able to diagnose the underlying lymphoma.

Heterophile antibody testing is not indicated because the complete blood count results do not demonstrate lymphocytosis, and the patient's symptoms and findings are much more concerning for lymphoma.

Prednisone and cyclophosphamide therapy may be helpful for some of this patient's symptoms, including vasculitis, but are premature at this time until lymphoma has been either identified or excluded. If there is no lymphoma and Sjögren syndrome is believed to be active and causing vasculitis, then these therapies could be considered.

KEY POINT

- Patients with Sjögren syndrome have up to a 44-fold higher risk of developing lymphoma, the most common being diffuse B-cell and mucosa-associated lymphoid tissue (MALT) lymphomas.

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Item 21 Answer: D

Educational Objective: Utilize HLA-B27 testing to aid in the diagnosis of spondyloarthritis.

The most appropriate diagnostic test to perform next is HLA-B27 testing. The patient has uveitis and enthesitis at the Achilles tendon, which are suggestive of peripheral spondyloarthritis. The Assessment of SpondyloArthritis international Society classification criteria for peripheral and axial spondyloarthritis are primarily used for research purposes, although they include many of the common symptoms, signs, and tests that are useful in diagnosing these disorders. Classification criteria include several other manifestations, including psoriasis, inflammatory bowel disease, preceding infection, and sacroiliitis, which are absent in this patient. HLA-B27 is included in the criteria and, in the absence of other sufficient manifestations, can be helpful in supporting the diagnosis of peripheral or axial spondyloarthritis. HLA-B27 testing has limitations because of its approximately 5% prevalence in the general population, which can lead to false positives in diagnosis. Therefore, HLA-B27 is not a useful test in a patient in whom clinical suspicion for spondyloarthritis is low (for example, a 65-year-old patient with noninflammatory or mechanical back pain). Furthermore, it does not add anything in the setting of a high suspicion for spondyloarthritis when there are sufficient other findings to establish a diagnosis (for example, a 35-year-old man with a 12-month history of anterior uveitis, chronic inflammatory back pain, and radiographic evidence of sacroiliitis).

Testing for anti-cyclic citrullinated peptide antibodies can be useful in patients with suspected rheumatoid arthritis, which is characterized by an inflammatory polyarthritis of small joints. Rheumatoid arthritis is unlikely in this patient because he only has enthesitis, an uncommon presentation of rheumatoid arthritis.

The ANCA-associated vasculitides include granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome). Granulomatosis with polyangiitis is a systemic necrotizing vasculitis that predominantly affects the upper and lower respiratory tract and kidneys. More than 70% of patients have upper airway manifestations such as sinusitis or nasal, inner ear, or laryngotracheal inflammation. Microscopic polyangiitis is a necrotizing vasculitis that predominantly affects the lungs and kidneys. Eosinophilic granulomatosis with polyangiitis is an eosinophil-rich necrotizing vasculitis predominantly affecting the respiratory tract and other major organs. This patient does not have clinical evidence of ANCA-associated vasculitis; therefore, testing for ANCA is not indicated.

Antinuclear antibody testing is useful for patients with suspected systemic lupus erythematosus (SLE); however, SLE does not usually cause enthesitis or uveitis as seen in this patient.

KEY POINT

- HLA-B27 testing can be helpful in supporting the diagnosis of spondyloarthritis in the absence of other sufficient manifestations.

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Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011 Jan;70(1):25-31. [PMID: 21109520]

Item 22 Answer: B

Educational Objective: Treat a patient who has familial Mediterranean fever with colchicine.

Colchicine is appropriate for this patient who has familial Mediterranean fever (FMF), an autosomal recessive disease characterized by episodes of fever, polyserositis, arthritis, erysipeloid rash around the ankles, and elevated acute phase reactants. Attacks last 1 to 3 days and are self-limited but can be dramatic. FMF is associated with mutation of the *MEFV* gene; testing for *MEFV* mutations is available and should be considered as an aid to diagnosis, although not all mutations have been identified. AA amyloidosis is a potential long-term consequence of FMF due to the production and accumulation of serum amyloid A. Colchicine affects the function of various inflammatory cells that are thought to play a role in the cytokine overproduction seen in FMF. A response to colchicine is

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useful in the clinical diagnosis of FMF because it can prevent attacks as well as AA amyloidosis. Treatment with colchicine is therefore indicated for this patient who most likely has FMF, as manifested by her history of febrile attacks of abdominal serositis, erysipelas-like skin lesions that mimic cellulitis, and inflammatory arthritis occurring independently of the febrile episodes.

FMF genetic mutations affect the function of pyrin that results in overactivation of the inflammasome. The inflammasome is an important constituent of the innate immune system that is responsible for production of interleukin (IL)-1; dysregulation of the inflammasome, as in FMF, results in overproduction of IL-1. The IL-1 inhibitor anakinra can be used in patients with FMF who are unresponsive to colchicine; however, this agent is not first-line therapy.

NSAIDs and prednisone have not been shown to have a significant impact on the disease progression or symptoms associated with FMF.

KEY POINT

- Familial Mediterranean fever is characterized by episodes of fever, polyserositis, arthritis, erysipeloid rash around the ankles, and elevated acute phase reactants; a response to colchicine is useful in the clinical diagnosis.

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Ben-Chetrit E, Touitou I. Familial Mediterranean fever in the world. Arthritis Rheum. 2009 Oct 15;61(10):1447-53. [PMID: 19790133]

Item 23 Answer: B

Educational Objective: Treat osteoarthritis with duloxetine.

The serotonin-norepinephrine reuptake inhibitor duloxetine is appropriate for this patient with osteoarthritis. The pharmacologic management of osteoarthritis pain can be difficult because therapy for symptom relief does not halt or reverse the disease process. Furthermore, all potential agents have side effects, some severe, and elderly patients can be at particularly high risk for developing them. The optimal choice of therapy relies on the risks and benefits of each agent in the context of the patient's comorbidities. This patient has already tried an NSAID (ibuprofen) as well as glucocorticoid and hyaluronic injections without symptomatic relief and has recently experienced an episode of gastrointestinal bleeding. Duloxetine is a reasonable choice given the patient's comorbidities and recent history of gastrointestinal bleeding. Compared with placebo, duloxetine significantly reduces pain and improves physical functioning in patients with knee osteoarthritis. In short-term studies, duloxetine was not associated with an increase in the adverse event rate compared with placebo. Unlike NSAIDs, duloxetine does not increase the risk for a recurrence of peptic ulcer disease. There are no medication interactions that contraindicate its use in this patient.

In an elderly patient who has had a recent bleeding peptic ulcer, the use of any NSAID, including the cyclooxygenase-2 inhibitor celecoxib, is inadvisable because the risk of recurrence with repeated exposure is high.

Narcotic use in the elderly, although not associated with ulcer risk or gastrointestinal bleeding, should also be approached cautiously. Short-acting narcotics should be tried first, and long-acting agents such as fentanyl may be used when other agents have failed. However, in this elderly patient at risk for falling due to her recent hospitalization, debilitation, quadriceps weakness, and a history of osteoporosis, fentanyl is not the optimal choice.

Although intra-articular glucocorticoids can be of benefit in the management of individual joints in osteoarthritis, there is no evidence that oral glucocorticoids would be of benefit. Furthermore, the likelihood of adverse effects with extended use is high in this patient.

KEY POINT

- Compared with placebo, duloxetine significantly reduces pain and improves physical functioning in patients with knee osteoarthritis.

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Item 24 Answer: A

Educational Objective: Treat a patient who has interstitial lung disease associated with diffuse cutaneous systemic sclerosis.

Cyclophosphamide is appropriate for this patient who has interstitial lung disease (ILD) associated with diffuse cutaneous systemic sclerosis (DcSSc). This patient with DcSSc presents with dyspnea, decreased exercise tolerance, and characteristic Velcro-like crackles. These clinical findings are strongly suggestive of ILD and are supported by the imaging studies and confirmed by open lung biopsy. Patients with systemic sclerosis who have active inflammatory lung disease may be treated with immunosuppressive agents. Cyclophosphamide is the only treatment shown to have some benefit in patients with ILD associated with DcSSc. Cyclophosphamide given orally or intravenously for 1 year provides modest benefit. Although it has shown limited clinical improvement, it is the only evidence-based therapy and is therefore appropriate. High-dose glucocorticoids are frequently used in these patients but are of unclear benefit and may precipitate scleroderma renal crisis; therefore, if used, low doses are typically recommended by experts. Azathioprine may have a role as maintenance therapy.

Agents such as D-penicillamine or methotrexate have not been shown to be beneficial in these patients and should not be used to treat ILD.

Biologic agents, including tumor necrosis factor α inhibitors such as infliximab, have not been shown to have therapeutic benefit in ILD or systemic sclerosis and should not be used in this patient.

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KEY POINT

- Cyclophosphamide has been shown to have some benefit in patients who have interstitial lung disease associated with diffuse cutaneous systemic sclerosis.

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Item 25 Answer: C

Educational Objective: Perform joint aspiration to diagnose acute monoarticular arthritis.

Aspiration of the right knee is the most appropriate next step in management. This patient is likely to have gout based on his risk factors (older man, hypertension, diabetes mellitus, obesity), the description of the symptoms (sudden onset at night with severe pain), and the recent episode of great toe swelling consistent with podagra. The gold standard for diagnosing gout is identification of monosodium needle-shaped urate crystals within leukocytes via synovial fluid analysis. Furthermore, infectious arthritis must be excluded in a patient with monoarticular arthritis. This patient is at increased risk for joint infection given his age and presence of diabetes. Thus, joint aspiration should be performed and synovial fluid sent for Gram stain, cultures, leukocyte count, and crystal analysis. Although uncommon, it is important to note that gout and an infected joint can coexist.

MRI may be useful for a patient with a history of trauma or other reason to suspect a mechanical cause for knee pain. Although MRI may demonstrate inflammation, it does not typically distinguish between infectious and noninfectious causes. Therefore, MRI is not currently indicated in this patient with warmth over the joint as well as fever, which suggests an inflammatory process.

Obtaining a serum urate level may assist in the diagnosis of this patient because an elevated level (>6.8 mg/dL [0.40 mmol/L]) would help support a diagnosis of gout. However, this test is not definitive for the diagnosis. An elevated level does not prove that the patient has gout because asymptomatic hyperuricemia is common in the general population. A relatively low serum urate level also does not exclude gout because serum urate levels can be paradoxically low during acute gout attacks.

Starting colchicine would be an option for the treatment of acute gout in this patient, and resolution of inflammation with colchicine may in fact support a diagnosis of crystal-induced arthritis. However, the diagnosis must first be established and infectious arthritis excluded.

KEY POINT

- Analysis of synovial fluid from joint aspiration is the gold standard to diagnose gout and exclude infection.

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Neogi T. Clinical practice. Gout. N Engl J Med. 2011 Feb 3;364(5):443-52. [PMID: 21288096]

Item 26 Answer: C

Educational Objective: Diagnose psoriatic arthritis.

The most likely diagnosis is psoriatic arthritis. Although estimates of the prevalence of psoriatic arthritis in patients with psoriasis vary, more recent studies using standardized diagnostic criteria indicate that psoriatic arthritis is present in approximately 15% to 20% of those with psoriasis. Patients who have features consistent with psoriatic arthritis should be examined closely for psoriasiform skin lesions on the umbilicus, gluteal cleft, extensor surfaces, posterior auricular region, and scalp. Nails should be examined for pitting or onycholysis. Characteristic features of psoriatic arthritis include enthesitis, dactylitis, tenosynovitis, arthritis of the distal interphalangeal joints, asymmetric oligoarthritis, and spondylitis. The recently developed Classification Criteria for Psoriatic Arthritis (CASPAR) have a sensitivity and specificity of more than 90%, especially for the diagnosis of early psoriatic arthritis. This patient fulfills the CASPAR criteria because she has inflammatory articular disease with psoriasis, psoriatic nail dystrophy, dactylitis, and a negative rheumatoid factor.

This patient does not have symptoms or findings of inflammatory back pain associated with ankylosing spondylitis; her back pain is related to use and improves with rest, which is noninflammatory. HLA-B27 positivity alone is insufficient to diagnose this disease, and peripheral articular disease is not typical for ankylosing spondylitis.

Nearly 50% of patients with inflammatory bowel disease (IBD) develop musculoskeletal symptoms. Peripheral arthritis may be acute and remitting with a pauciarticular distribution commonly involving the knee. Peripheral arthritis can also be chronic or relapsing, with prominent involvement of the metacarpophalangeal joints and less correlation with intestinal inflammation. IBD-associated arthritis is also unlikely because this patient has no symptoms of bowel disease.

Reactive arthritis (formerly known as Reiter syndrome) is a postinfectious arthritis triggered by infections causing urethritis or diarrhea, although patients may be asymptomatic. Arthritis, usually oligoarticular, develops several days to weeks after the infection. Reactive arthritis can cause dactylitis; however, this patient has no history of a preceding infection, making this an unlikely diagnosis.

KEY POINT

- Psoriatic arthritis is associated with psoriasis, enthesitis, dactylitis, tenosynovitis, arthritis of the distal interphalangeal joints, asymmetric oligoarthritis, and spondylitis.

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Coates LC, Conaghan PG, Emery P, et al. Sensitivity and specificity of the classification of psoriatic arthritis criteria in early psoriatic arthritis. Arthritis Rheum. 2012 Oct;64 (10):3150-5. [PMID: 22576997]

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Item 27 Answer: B

Educational Objective: Diagnose eosinophilic granulomatosis with polyangiitis.

This patient most likely has eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome). EGPA is characterized by eosinophilia, migratory pulmonary infiltrates, purpuric skin rash, and mononeuritis multiplex in the setting of antecedent atopy. Although EGPA is considered an ANCA-associated vasculitis (specifically, antimyeloperoxidase/p-ANCA), 40% of patients with EGPA are negative for ANCA. This patient has involvement of the lungs (likely capillaritis with hemoptysis), nerves (mononeuritis multiplex), and skin. In the presence of systemic eosinophilia, elevated serum IgE levels, and a history of asthma, this patient's most likely diagnosis is EGPA. Other systemic multiorgan system diseases are less likely. For example, granulomatosis with polyangiitis (GPA; formerly known as Wegener granulomatosis) and microscopic polyangiitis would be unusual in the absence of ANCA and the presence of eosinophilia (and, in the case of GPA, lack of sinus involvement). Diagnosis of EGPA can be made most definitively by tissue biopsy. Sural nerve biopsy is most likely to yield pathology specific for EGPA, specifically, the presence of necrotizing vasculitis with eosinophilic granulomas. In addition, confirmation that the patient's neurologic findings are due to EGPA is important for characterizing the extent of disease and the level of immunosuppression needed. Such a biopsy would also allow the exclusion of other eosinophilic diseases, such as hypereosinophilic syndrome.

Although cryoglobulinemia commonly affects the nerves and skin (along with the kidneys, which are not involved in this patient), it uncommonly affects the lungs. Furthermore, the high level of eosinophilia is inconsistent with cryoglobulinemia.

KEY POINT

- Eosinophilic granulomatosis with polyangiitis is characterized by eosinophilia, migratory pulmonary infiltrates, purpuric skin rash, and mononeuritis multiplex in the setting of antecedent atopy.

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Mahr A, Moosig F, Neumann T, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): evolutions in classification, etiopathogenesis, assessment and management. Curr Opin Rheumatol. 2014 Jan;26(1):16-23. [PMID: 24257370]

Item 28 Answer: D

Educational Objective: Treat polymyositis using prednisone.

Treatment with prednisone is indicated. This patient's findings of weakness, elevated muscle enzymes, electromyogram and MRI abnormalities, and no skin involvement suggest polymyositis. A definitive diagnosis can only be made by muscle biopsy, and every effort should be done to obtain it quickly. Nonetheless, treatment should be started as soon as possible to prevent complications of active disease, improve symptoms, and have a better long-term prognosis. Treatment should not be withheld if the biopsy is delayed or cannot be obtained. The initial treatment of polymyositis or dermatomyositis with muscle involvement is systemic glucocorticoids, most commonly prednisone given at 1 mg/kg/d. Some patients with severe disease require treatment with intravenous methylprednisolone, and many physicians use methotrexate or azathioprine at onset for their glucocorticoid-sparing benefits. If refractory or recurrent disease is noted, additional agents such as mycophenolate mofetil, intravenous immune globulin, rituximab, cyclophosphamide, or tumor necrosis factor (TNF)-α inhibitors can also be considered.

The TNF-α inhibitor adalimumab is not recommended as initial therapy prior to a trial of prednisone with or without a glucocorticoid-sparing agent in patients with polymyositis or dermatomyositis. TNF-α inhibitors have been reported to be effective in some patients with refractory disease.

Cyclosporine is an immunosuppressant agent that preferentially targets T cells and demonstrates efficacy in several rheumatologic and autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, inflammatory myositis, psoriasis, pyoderma gangrenosum, and inflammatory bowel disease. Toxicity is relatively common (hypertension, nephrotoxicity, tremor, hirsutism); therefore, cyclosporine is mainly used as a third-line agent in rheumatologic diseases.

Leflunomide is approximately as effective as methotrexate for rheumatoid arthritis; its use in other diseases is less explored. Toxicities include liver and hematopoietic abnormalities, infection, and interstitial lung disease. This agent has an extremely long half-life (months) and undergoes enterohepatic circulation.

KEY POINT

- The initial treatment of polymyositis or dermatomyositis with muscle involvement is glucocorticoids, most commonly prednisone.

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Item 29 Answer: C

Educational Objective: Diagnose diffuse idiopathic skeletal hyperostosis.

The most likely diagnosis is diffuse idiopathic skeletal hyperostosis (DISH), which is defined by the presence of flowing osteophytes involving the anterolateral aspect of the thoracic spine at four or more contiguous vertebrae with preservation of the intervertebral disk space and the absence of apophyseal joint or sacroiliac inflammatory changes such as erosions. DISH may occur with or without osteoarthritis or inflammatory arthritis and represents a separate finding of calcification

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and ossification of spinal ligaments and the regions where tendons and ligaments attach to bone (entheses). DISH is a noninflammatory condition of unknown cause that is common in the elderly population. Patients may be asymptomatic or may describe stiffness and reduced range of motion, particularly at the thoracic spine.

Ankylosing spondylitis is an inflammatory disorder that usually becomes symptomatic in adolescence and early adulthood. It is characterized by progressive morning stiffness and low back pain and typically becomes symptomatic in the lumbar spine rather than the thoracic spine early in the course. Radiographs of DISH and ankylosing spondylitis have similarities; however, ankylosing spondylitis demonstrates vertical bridging syndesmophytes rather than the flowing osteophytes that occur in DISH. Plain radiographs of ankylosing spondylitis also characteristically show changes of the sacroiliac joints that can include erosions, evidence of sclerosis, and widening, narrowing, or partial ankylosis.

Degenerative disk disease is thought to arise from age-related changes in proteoglycan content in the nucleus pulposus of the disk. Disks shrink as they become desiccated and more friable. Age-related changes also occur in the annulus fibrosus, which becomes more fibrotic, less elastic, and can shift its position. Vertebral body endplates adjacent to the disk develop sclerosis, and osteophyte formation occurs at the vertebral margins.

Psoriatic arthritis is an inflammatory disorder that can affect the spine as well as peripheral joints. When axial involvement is prominent, sacroiliitis and spondylitis can both be present; however, axial disease rarely presents in the absence of frank inflammatory arthritis of peripheral joints.

KEY POINT

- Diffuse idiopathic skeletal hyperostosis is a noninflammatory condition defined by the presence of flowing osteophytes involving the anterolateral aspect of the thoracic spine at four or more contiguous vertebrae with preservation of the intervertebral disk space and the absence of apophyseal joint or sacroiliac inflammatory changes such as erosions.

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Mader R, Verlaan JJ, Buskila D. Diffuse idiopathic skeletal hyperostosis: clinical features and pathogenic mechanisms. Nat Rev Rheumatol. 2013 Dec;9(12):741-50. [PMID: 24189840]

Item 30 Answer: C

Educational Objective: Diagnose the acute prodromal arthritis of hepatitis B virus infection.

The most likely diagnosis is hepatitis B virus (HBV)-associated arthritis. The patient has rapid-onset symmetric polyarthritis, rash, and elevated aminotransferase levels, which are consistent with the prodromal phase of HBV infection. The differential diagnosis of this symmetric pattern encompasses numerous arthritides; however, the presence of elevated aminotransferase levels, a history of possible exposure risk (works as a home health aide), and the presence of a rash point toward the acute prodromal arthritis of HBV infection, which often presents before frank jaundice. Testing to document acute HBV infection, specifically assessment of hepatitis B core IgM and hepatitis B surface antigen, is indicated in this patient.

Hemochromatosis is characterized by excessive body stores of iron and can cause joint symptoms and liver dysfunction; unlike HBV-associated arthritis, it tends to occur gradually rather than abruptly, and the arthritis tends to resemble osteoarthritis without frank synovitis. Hemochromatosis is also uncommon in women, who are protected from iron accumulation due to menstruation.

Primary biliary cirrhosis and autoimmune hepatitis can cause acute liver enzyme elevation but do not cause acute arthritis or rash.

KEY POINT

- The prodromal stage of hepatitis B virus infection is characterized by rapid-onset symmetric polyarthritis, which is often present before frank jaundice.

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Vassilopoulos D, Calabrese LH. Viral hepatitis: review of arthritis complications and therapy for arthritis in the presence of active HBV/HCV. Curr Rheumatol Rep. 2013 Apr;15(4):319. [PMID: 23436024]

Item 31 Answer: C

Educational Objective: Diagnose vasculitis as a cause of scleritis.

The most likely diagnosis associated with this patient's scleritis is granulomatosis with polyangiitis (formerly known as Wegener granulomatosis). Scleritis is inflammation of the fibrous layer of the eye underlying the conjunctiva and episclera. Scleritis can be caused by autoimmune diseases such as rheumatoid arthritis, relapsing polychondritis, inflammatory bowel disease, or vasculitis. This patient has evidence of systemic inflammation on laboratory testing, hypertension, and an abnormal urinalysis that could represent glomerulonephritis but no clinical evidence of rheumatoid arthritis, chondritis, or inflammatory bowel disease. Vasculitis, especially ANCA-associated vasculitis, should always be considered in the differential diagnosis of scleritis because delay in diagnosis can result in permanent loss of vision. In this case, the sinus symptoms, abnormal urinalysis suggestive of glomerulonephritis, and scleritis are suggestive of granulomatosis with polyangiitis.

Ankylosing spondylitis is characterized by inflammatory back pain that usually presents during the second to third decade of life. The type of ocular inflammation most commonly associated with this entity is anterior uveitis, not scleritis. Uveitis (inflammation of the uvea) commonly presents as a red eye with pain, photophobia, and blurred vision. Anterior uveitis is characterized by circumferential redness (ciliary flush) at the corneal limbus (junction of the cornea

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and sclera). Furthermore, the duration of this patient's back pain (which began after age 45 years) and evidence of osteoarthritis in her fingers suggest degenerative, rather than inflammatory, disease of the spine.

Behçet syndrome is characterized by recurrent oral and/or genital ulcers, eye and skin involvement, and pathergy. This patient has no clinical symptoms to suggest this diagnosis, and it is more commonly associated with uveitis rather than scleritis.

Sarcoidosis is a multisystem disease characterized by granulomas that form in tissues and most commonly affects the lungs. Sarcoidosis is more likely to cause uveitis than scleritis, and this patient has no other clinical symptoms such as respiratory complaints or an abnormal chest radiograph to suggest this diagnosis.

KEY POINT

- Scleritis can be caused by autoimmune diseases such as rheumatoid arthritis, relapsing polychondritis, inflammatory bowel disease, or vasculitis.

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Sims J. Scleritis: presentations, disease associations and management. Postgrad Med J. 2012 Dec;88(1046):713-18. [PMID: 22977282]

Item 32 Answer: D

Educational Objective: Treat a suspected infected joint in the setting of gout.

Antibiotics are appropriate for this patient who has an acute inflammatory monoarthritis, possibly infectious arthritis. Acute crystalline attack can also cause fever and an inflammatory monoarthritis, but a negative Gram stain and/or the presence of crystals do not rule out infection. If infection is suspected, even if not yet confirmed on cultures, empiric therapy with antibiotics should be started without delay. The crystals seen in this patient's synovial fluid are extracellular, which is consistent with a diagnosis or history of gout but not diagnostic of an acute gouty attack; only intracellular crystals are diagnostic of an acute crystalline attack. In the absence of positive findings on Gram stain, initial empiric therapy usually includes coverage for gram-positive organisms (including methicillin-resistant *Staphylococcus aureus* [MRSA], which is increasing in prevalence in many communities) as well as coverage for gram-negative organisms if immunocompromised, at risk for gonococcal infection, or with trauma to the joint. Therapy can be adjusted once results from stains and cultures are available.

Probenecid is sometimes added to allopurinol to control gout when allopurinol alone is insufficient. If the patient were to experience persistent gout, increasing allopurinol to lower the serum urate below 6.0 mg/dL (0.35 mmol/L) would be more appropriate than combination therapy with two agents.

Allopurinol is considered a first-line agent for serum urate reduction in patients with gout. Increasing this patient's allopurinol will not be helpful in treating an acute gouty attack, and it will not treat an infected joint. It may be indicated long term if the patient has persistently elevated serum urate with recurrent attacks of gout.

An intra-articular glucocorticoid injection can be used to treat an acute crystalline attack; however, if an infected joint were suspected, it would not be appropriate because it may worsen infection. It is therefore inappropriate at this time because the cause of this patient's acute inflammatory monoarthritis has not been determined.

Similarly, prednisone should not be started because it may cause worsening of infection. Prednisone is sometimes used short term to treat acute attacks of gout, but if a single large joint is involved, a local injection would avoid the systemic side effects of prednisone therapy.

KEY POINT

- Empiric therapy with antibiotics should be started immediately in the setting of an acute inflammatory monoarthritis if infection is suspected, even if not yet confirmed on cultures.

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Item 33 Answer: E

Educational Objective: Monitor ankylosing spondylitis disease activity with physical examination.

No new imaging is required for this patient with ankylosing spondylitis. She is currently feeling well, continues to respond well to treatment, and has normal inflammatory markers, making new imaging unnecessary. As with any test, imaging to follow disease activity should be performed only if clearly indicated by the clinical situation (for example, if the result is likely to change management). According to the 2010 Assessment of SpondyloArthritis international Society/European League Against Rheumatism (ASAS/EULAR) guidelines, serial imaging of patients with ankylosing spondylitis can be part of a comprehensive monitoring plan that also includes patient history (such as questionnaires like the Bath Ankylosing Spondylitis Functional Index [BASFI] or Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]), clinical parameters (such as physical examination findings like the Schober test), and laboratory tests (such as erythrocyte sedimentation rate and C-reactive protein). The ASAS/EULAR recommendations state that spinal radiography should not be repeated more frequently than every 2 years unless absolutely necessary in specific cases. The Schober test measures range of motion of the lumbar spine and is an inexpensive and noninvasive physical examination tool for assessing spine involvement and progression; greater than 4 cm is normal.

Bone scan, CT, MRI, and plain radiography may demonstrate evidence of inflammation and/or progression of disease, but without a clear indication may unnecessarily

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expose the patient to radiation and to expense. This patient is feeling well, has intact activities of daily living, and had radiographs less than 2 years ago; therefore, no additional imaging is necessary at this time.

KEY POINT

- Patients with ankylosing spondylitis who are responding well to treatment should be monitored clinically and do not require periodic imaging studies less than every 2 years unless absolutely necessary.

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Item 34 Answer: B

Educational Objective: Diagnose Lyme arthritis.

Serologic testing for Lyme disease is appropriate for this patient with arthritis characterized by prominent swelling with stiffness without significant joint pain. He has a risk factor for Lyme arthritis, given his frequent hiking in an endemic area. Patients may not recall a tick bite; therefore, Lyme disease should be suspected even without this history. The knee is most commonly affected, although other large joints can also be involved, usually in a monoarticular or oligoarticular pattern. Serologic testing for *Borrelia burgdorferi* is the diagnostic test of choice for this disease and is typically done with an enzyme-linked immunosorbent assay (ELISA) screening test, followed by confirmation by Western blot.

Blood cultures should always be obtained when there is a suspicion for bacterial infectious arthritis. This patient does not have risk factors for infectious arthritis, with Lyme being the most compelling diagnosis. Arthrocentesis is recommended for routine synovial fluid analysis and symptomatic relief, but blood cultures will not provide the correct diagnosis.

An MRI of the knee is unlikely to have diagnostic benefit in new-onset Lyme arthritis (and even in recurrent cases, it tends to be a nonerosive arthritis). MRI can be helpful in cases in which mechanical damage needs to be excluded or if there is concern for osteomyelitis or other bone pathology.

Synovial fluid cultures tend to be negative in Lyme arthritis. Synovial fluid will show inflammatory fluid with a neutrophil predominance. *B. burgdorferi* can be detected by polymerase chain reaction in synovial fluid.

KEY POINT

- In patients with risk factors for Lyme arthritis (even without a history of a tick bite), serologic tests showing an immunologic response to *Borrelia burgdorferi* are indicated to establish the diagnosis.

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Item 35 Answer: D

Educational Objective: Treat a patient with drug-induced lupus erythematosus caused by minocycline.

Discontinuation of minocycline is indicated for this patient. Minocycline is one of the known causes of drug-induced lupus erythematosus (DILE). Criteria for DILE include a positive antinuclear antibody (ANA) test, exposure to a drug associated with DILE, and at least one clinical feature of lupus in a patient without a known history of lupus. Common symptoms include malaise, fever, arthritis, and rash. Diagnosis is typically confirmed when symptoms resolve several weeks to months after discontinuation of the offending agent. The agents classically associated with DILE, such as procainamide and methyldopa, are not commonly used at present. However, the spectrum of DILE includes other medications that are more commonly used, including hydralazine, diltiazem, isoniazid, minocycline, and certain tumor necrosis factor α inhibitors (such as infliximab and etanercept). Other agents that possibly cause DILE include specific anticonvulsants, antithyroid agents, and certain antibiotics.

The diagnostic laboratory evaluation for DILE is similar to that for patients with suspected idiopathic systemic lupus erythematosus. Antinuclear antibodies are typically positive, whereas anti-double-stranded DNA antibodies are usually negative in DILE, as are most other lupus-associated extractable nuclear autoantibodies. Antihistone antibodies have traditionally been associated with DILE caused by older medications, but their presence may be more variable with DILE induced by newer agents. In addition to causing DILE, certain medications, such as minocycline and hydralazine, may be associated with a p-ANCA syndrome that may also cause a small- to medium-vessel vasculitis with organ involvement. Treatment of DILE, regardless of offending agent, requires discontinuation of the drug. The patient can also be treated symptomatically until manifestations resolve. An NSAID such as naproxen may be helpful, as can low-dose prednisone. Rarely, more substantial therapy may be needed if there is internal organ involvement.

Neither azathioprine nor high-dose prednisone is indicated in this patient because she does not have evidence of internal organ involvement.

Famotidine has not been associated with DILE.

KEY POINT

- The diagnosis of drug-induced lupus erythematosus is typically confirmed when symptoms resolve several weeks to months after discontinuation of the offending agent.

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Item 36 Answer: B

Educational Objective: Diagnose inclusion body myositis.

The most likely diagnosis is inclusion body myositis (IBM), an insidious and slowly progressive inflammatory myopathy that occurs more commonly in men and in those over the age of 50 years. Muscle weakness may be diffuse and involve both the distal and proximal muscles. Although typically symmetric, IBM muscle involvement may be asymmetric in up to 15% of patients. Skin is generally spared. IBM is rarely associated with extramuscular manifestations such as rash, fever, or pulmonary involvement. Patients with IBM typically have only mildly elevated (typically <1000 U/L), or even normal, levels of muscle enzymes. The characteristic triad of electromyographic findings for myopathy includes short-duration, small, low-amplitude polyphasic potentials; fibrillation potentials at rest; and bizarre, high-frequency, repetitive discharges. This older male patient has developed slowly progressive weakness affecting both the proximal and distal muscles without any significant pain or stiffness. This presentation suggests a myopathy with weakness based on his history and physical examination, mild elevation of muscle enzymes, and abnormal electromyogram (EMG) results, all of which are most consistent with IBM.

Amyotrophic lateral sclerosis is characterized by progressive dysfunction of both upper motoneuron and lower motoneuron pathways in one or more areas of the body. Common upper motoneuron features are spasticity, hyperreflexia, and pathologic reflexes, including extensor plantar responses. Typical lower motoneuron features are muscle weakness, atrophy, fasciculations, and cramps. These findings are not present in the patient.

Myasthenia gravis is characterized by fluctuating, fatigable muscle weakness that worsens with activity and improves with rest. Neurologic examination may reveal bilateral asymmetric ptosis worsened by prolonged upward gaze, an expressionless or sagging appearance of facial muscles, a "snarling" smile, nasal speech worsened by prolonged speaking, and limb weakness that increases with exercise. None of these findings are present in this patient.

Statin-induced myopathy most commonly presents with muscle pain, tenderness, and cramping typically within the first 6 months of therapy, and EMG results are normal. This patient has no muscle pain, has an abnormal EMG, and has been taking a stable dose of a stain for years, making statin-induced myopathy unlikely.

KEY POINT

- Inclusion body myositis has an insidious onset, with muscle weakness that may be diffuse and involve both the distal and proximal muscles.

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Item 37 Answer: C

Educational Objective: Diagnose knee osteoarthritis with standing plain radiography.

Standing plain radiography is appropriate for this patient who most likely has osteoarthritis. Osteoarthritis is often clinically identifiable by the presence of bony hypertrophy in a characteristic pattern of joint involvement and the absence of overt inflammatory synovitis. The history generally consists of long-standing and gradually worsening symptoms in middle-aged or older patients. Confirmatory plain radiographs are appropriate to solidify the diagnosis and rule out less common findings such as osteonecrosis, fractures, or malignancies. They are also noninvasive, widely available, and the least expensive radiographic modality. Standing views of the knees can demonstrate a more accurate picture of the joint-space narrowing that is present during functioning, including standing and walking, than radiographs that are obtained supine.

Bone scintigraphy can visualize areas of bone turnover change due to osteophyte formation, subchondral sclerosis, subchondral cyst formation, and bone marrow lesions. However, its limited anatomic resolution and the use of ionizing radiation make it less useful for the diagnosis of osteoarthritis.

MRI is capable of demonstrating numerous findings in soft tissue and cartilage that provide information about the joint as a whole organ. As such, MRI is a critical tool in osteoarthritis research, but its high cost argues against its routine use, particularly because there are no end points apart from joint-space narrowing (easily assessed on plain radiographs as well) visualized on MRI that confer prognostic information.

Although ultrasonography is noninvasive and is appealing because it provides real-time information, its primary use in the management of osteoarthritis is for needle placement in difficult arthrocenteses. Limitations of ultrasonography include that it is an operator-dependent technique and that the physical properties of sound limit its ability to assess deep articular structures and the subchondral bone.

KEY POINT

- In patients with suspected osteoarthritis, confirmatory plain radiographs with standing views are appropriate to solidify the diagnosis and rule out less common findings such as avascular necrosis, fractures, and malignancies.

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Item 38 Answer: B

Educational Objective: Treat dry eyes in a patient with Sjögren syndrome.

Cyclosporine drops are appropriate for this patient. She has primary Sjögren syndrome with dry eyes (keratoconjunctivitis sicca), which has not responded to topical lubrication or punctal plugs. Sjögren syndrome is an immune-mediated disease of unknown cause manifesting primarily as inflammation of exocrine glands, including the major and minor salivary glands, lacrimal glands, and, less commonly, other exocrine glands such as the pancreas. The most prominent clinical feature is dryness (sicca), particularly of the eyes and mouth. Dry eyes can lead to corneal damage and visual impairment. Sicca symptoms are primarily treated with hydration and lubrication, although other local measures and medications may be helpful. Topical cyclosporine has been demonstrated in trials to improve the symptoms of dry eyes in patients with primary Sjögren syndrome. An alternative therapy is punctal occlusion (placement of plugs in the tear drainage duct openings of the lower eyelids to increase eye moisture). There is controversy as to the timing and type of plug to use when performing this procedure.

Certolizumab pegol is a tumor necrosis factor (TNF)-α inhibitor used to treat diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. This agent is not appropriate for this patient because trials of other TNF-α inhibitors (etanercept and infliximab) did not demonstrate benefit for sicca symptoms.

Hydroxychloroquine is used to treat diseases such as systemic lupus erythematosus and rheumatoid arthritis. This agent has not been demonstrated to improve sicca symptoms, although it could be useful for treating arthritic and other systemic symptoms associated with Sjögren syndrome.

Olopatadine drops reduce histamine release from mast cells and are used to treat allergic conjunctivitis; they would therefore not be helpful for Sjögren-related sicca symptoms.

Prednisone is a potent anti-inflammatory agent that is very effective in many rheumatologic diseases. It has not been demonstrated to improve sicca symptoms, although it could be useful for treating systemic manifestations of Sjögren syndrome.

KEY POINT

- Topical cyclosporine improves the symptoms of dry eyes in patients with primary Sjögren syndrome.

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Item 39 Answer: C

Educational Objective: Monitor a patient with Marfan syndrome using echocardiography.

Echocardiography to evaluate for aortic root dilatation is the most appropriate routine monitoring test for this patient with Marfan syndrome. This autosomal dominant condition is characterized by a mutation in the gene *FBN1* responsible for producing fibrillin 1, a structural protein in tissues that contain elastic fibers, such as the arterial wall. Clinical features include tall stature, arachnodactyly, anterior thoracic deformity, spinal curvature, and skin hyperextensibility. The most common cause of morbidity and mortality is aortic root dilatation with possible dissection, rupture, or aortic valve insufficiency. Current guidelines recommend that echocardiography should be performed at the time of diagnosis to determine aortic root and ascending aortic diameters and 6 months later to determine their rate of enlargement. Annual imaging is recommended if stability of the aortic diameter is documented. If the maximal aortic diameter is 4.5 cm or greater, more frequent imaging should be considered.

Patients with Marfan syndrome may develop abdominal aortic aneurysm, but thoracic involvement or thoracic and abdominal aneurysms are much more common. There currently are no recommendations from any organization to routinely screen these patients with abdominal ultrasonography.

Apical lung bullae can form and lead to pneumothorax in patients with Marfan syndrome; however, there are no data to suggest that monitoring with annual chest radiography has any impact on morbidity or mortality.

Likewise, routine monitoring for progressive skeletal abnormalities, including annual spine radiography to monitor this patient's scoliosis, is not indicated because it has no impact on outcome and should be evaluated only when symptomatic. However, counseling regarding joint protection to prevent osteoarthritis is useful.

KEY POINT

- In patients with Marfan syndrome, echocardiography should be performed at the time of diagnosis to determine aortic root and ascending aortic diameters and 6 months later to determine their rate of enlargement.

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Item 40 Answer: A

Educational Objective: Treat a patient who has hypersensitivity vasculitis.

Discontinuation of trimethoprim-sulfamethoxazole is indicated for this patient who developed palpable purpura within days of starting trimethoprim-sulfamethoxazole for a urinary tract infection. The most likely diagnosis is hypersensitivity vasculitis, which is caused by a hypersensitivity reaction to antigens such as medication or infection. Hypersensitivity vasculitis typically resolves when the offending agent is removed. Similar to other forms of small-vessel vasculitis, hypersensitivity vasculitis results from antibodies directed toward the antigens that result in immune

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complex formation. Complement is activated, and neutrophils are attracted to accumulate in capillaries, arterioles, and post-capillary venules. Although a similar reaction associated with the infection itself may occur, this is less likely given the time course of onset and the high degree of association of trimethoprim-sulfamethoxazole with this reaction. Because her reaction is mild and limited to the skin, the most important aspect of treatment is to remove the likely offending agent, after which the condition will resolve.

Prednisone has shown efficacy in hypersensitivity vasculitis and can be used if the vasculitis is severe, is causing discomfort of the skin or other organ damage, or if it is imperative that the agent be continued despite the reactions. Because this is not the case, discontinuing the offending agent remains the highest priority.

Antihistone antibodies occur frequently in patients with either systemic or drug-induced lupus erythematosus. This patient's disease is more consistent with hypersensitivity vasculitis without specific features of drug-induced lupus (for example, malar rash); however, even if drug-induced lupus were the likely diagnosis, discontinuing the offending agent would still be the highest priority.

Palpable purpura is a clinical diagnosis for which a skin biopsy is not generally needed. A skin biopsy could be useful in cases where the mechanism of the rash needs to be understood to facilitate diagnosis or treatment, or when the rash fails to resolve despite management. In this case, the cause of the rash is known, and management should consist of removal of the offending agent before any further work-up is considered.

KEY POINT

- Hypersensitivity vasculitis is caused by a hypersensitivity reaction to antigens such as medication or infection and typically resolves when the offending agent is removed.

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Item 41 Answer: B

Educational Objective: Treat mild systemic lupus erythematosus.

Hydroxychloroquine is an appropriate agent to address milder systemic manifestations of systemic lupus erythematosus (SLE) such as arthritis and pericarditis, and it can act as a glucocorticoid-sparing agent. All patients with SLE who can tolerate it should be taking hydroxychloroquine. Antimalarial therapy such as hydroxychloroquine in SLE has documented benefit for reducing disease activity, improving survival, and reducing the risk of SLE-related thrombosis and myocardial infarction.

Azathioprine is generally reserved for more severe manifestations of SLE not responsive to low-dose prednisone and hydroxychloroquine but can be associated with serious toxicity. Azathioprine has generally been supplanted by the use of mycophenolate mofetil in SLE.

Mycophenolate mofetil may be appropriate for this patient if she had more serious disease activity such as nephritis or if her arthritis or pericarditis recurred while taking hydroxychloroquine.

NSAIDs, often with colchicine, are first-line therapy for most patients with pericarditis, although glucocorticoids may be indicated in patients with pericarditis associated with a systemic inflammatory disease such as in this patient. However, there is no indication to start an NSAID now given resolution of her symptoms, and doing so would increase her risk of gastrointestinal complications if used along with her daily glucocorticoid.

KEY POINT

- Antimalarial therapy such as hydroxychloroquine in systemic lupus erythematosus (SLE) has documented benefit for reducing disease activity, improving survival, and reducing the risk of SLE-related thrombosis and myocardial infarction.

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Item 42 Answer: C

Educational Objective: Treat gout with urate-lowering therapy.

Initiation of allopurinol is appropriate for this patient with gout who has had two attacks of podagra within the past year. The American College of Rheumatology (ACR) guidelines currently recommend that urate-lowering therapy should be initiated in patients with gout who have had two or more attacks within a 1-year period, one attack in the setting of chronic kidney disease of stage 2 or worse, one attack with the presence of tophi visible on examination or imaging, or one attack with a history of urolithiasis. Allopurinol, a xanthine oxidase inhibitor, is an appropriate first-line agent for urate reduction. Flare prophylaxis should be maintained when urate-lowering therapy is undertaken.

Low-dose aspirin can increase serum urate due to effects on renal uric acid transport; however, the ACR does not currently recommend aspirin discontinuation in patients for whom it is indicated, such as this patient with coronary artery disease.

This patient needs to begin urate-lowering therapy, and his flare prophylaxis (colchicine) should be maintained during this period given the paradoxical increased risk of flare during acute serum urate reduction. In the absence of active disease, the ACR currently recommends that prophylaxis should be continued for the greater of the following: 6 months; 3 months after achieving the target serum urate level for a patient without tophi; or 6 months after achieving the target serum urate level where there has been resolution of tophi.

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Probenecid is a uricosuric agent (promotes kidney uric acid excretion) and is a viable alternative first-line urate-lowering agent in patients who cannot tolerate or have a contraindication to xanthine oxidase inhibitor therapy. However, allopurinol is generally more appropriate in patients such as in this case who have no contraindication to urate-lowering therapy. Moreover, the patient's history of urolithiasis makes probenecid relatively contraindicated because this medication increases the risk of kidney stones.

KEY POINT

- Urate-lowering therapy should be initiated in patients with gout who have had two or more attacks within a 1-year period, one attack in the setting of chronic kidney disease of stage 2 or worse, one attack with the presence of tophi visible on examination or imaging, or one attack with a history of urolithiasis.

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Item 43 Answer: E

Educational Objective: Clinically diagnose osteoarthritis of the hands.

No further testing is necessary for this patient who clinically appears to have hand osteoarthritis. Osteoarthritis is a clinical diagnosis, and the cardinal symptom is pain with activity that is relieved with rest. Affected patients also typically experience morning stiffness that lasts for less than 30 minutes daily. Bony hypertrophy is commonly detected in the fingers, and Heberden and Bouchard nodes may be easily palpated. Osteoarthritis also may cause squaring or boxing of the carpometacarpal joint at the base of the thumb.

This patient has no clinical signs or symptoms suggestive of a systemic inflammatory disease and therefore does not require diagnostic testing with antinuclear antibodies (ANA) or anti-double-stranded DNA antibodies. A positive ANA test result has low predictive value when the pretest probability of systemic lupus erythematosus or a related disease is low. Therefore, this test should not be used to screen indiscriminately for the presence of rheumatologic disease. The American College of Rheumatology recommends not testing ANA subserologies such as anti-double-stranded DNA without the combination of a positive ANA and elevated clinical suspicion of autoimmune disease, which is not present in this patient.

Radiography is not needed to confirm the diagnosis of osteoarthritis in patients with a history and physical examination compatible with this condition. Clinical examination is more sensitive and specific for the diagnosis of hand osteoarthritis compared with radiography.

The key features of rheumatoid arthritis (RA) are swelling and tenderness in and around the joints. Prominent morning stiffness that usually lasts more than 1 hour characterizes early RA. Rheumatoid factor positivity is characteristic of RA, although rheumatoid factor has a low specificity for diagnosis of RA. Rheumatoid factor may be present in healthy persons, especially at older ages. Because this patient has no clinical evidence of RA, testing for rheumatoid factor is unnecessary.

KEY POINT

- Additional testing such as autoantibody measurements or radiography is unnecessary in patients with clinically diagnosed hand osteoarthritis.

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Item 44 Answer: D

Educational Objective: Treat polymyalgia rheumatica with low-dose prednisone.

Treatment with prednisone, 15 mg/d, is appropriate. This 74-year-old man presents with shoulder and hip girdle pain and limitation accompanied by signs of systemic inflammation, including low-grade fever, weight loss, malaise, and a markedly elevated erythrocyte sedimentation rate (ESR). This constellation of findings is classic for polymyalgia rheumatica (PMR), especially in this age group. Treatment of PMR, typically prednisone initiated at a dose of 10 to 20 mg/d, is warranted and should result in rapid resolution of symptoms. Prednisone can be tapered over a 6-month period in some patients, but others experience flares with tapering and require more prolonged therapy, for as long as 1 to 3 years. Methotrexate can be tried as a glucocorticoid-sparing agent, but studies suggest limited efficacy.

Low-dose aspirin (81 mg/d) may be useful to reduce ocular complications in patients with giant cell arteritis (GCA), which can co-occur with PMR; however, this patient has no signs or symptoms consistent with GCA such as jaw claudication, temporal headache, or visual loss.

Aspirin, 650 mg three times daily, functions in a manner similar to other traditional NSAIDs, with analgesic, anti-inflammatory, and antipyretic effects. However, like other NSAIDs, it is not a treatment for PMR and is not effective for this condition.

Duloxetine is a dual serotonin-norepinephrine reuptake inhibitor that is used as an antidepressant, to modulate pain due to fibromyalgia and other chronic central pain syndromes, and for chronic musculoskeletal pain. Although the patient has pain and a depressed affect–a common constellation in fibromyalgia–his pain is in a classic distribution for PMR and his depressed affect is common in patients with PMR pain. Since low-dose prednisone will likely be curative, duloxetine therapy should not be needed.

High-dose prednisone is indicated for GCA and severe or life-threatening forms of autoimmunity but carries a high rate of toxicity. This patient has no signs or symptoms of GCA or any other disease except PMR; therefore, high-dose prednisone is not warranted.

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KEY POINT

- Treatment of polymyalgia rheumatica typically consists of low-dose prednisone, initially at 10 to 20 mg/d, which should result in rapid resolution of symptoms.

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Item 45 Answer: C

Educational Objective: Diagnose chlamydia infection associated with reactive arthritis.

The most appropriate diagnostic test to perform next is a DNA amplification urine test for *Chlamydia trachomatis*. This patient has a presentation consistent with reactive arthritis (oligoarticular lower extremity dactylitis, keratoderma blennorrhagicum). Up to 30% of patients with reactive arthritis develop keratoderma blenorrhagicum, a hyperkeratotic rash found on the soles and palms that may be indistinguishable from pustular psoriasis. Chlamydia infection is a common cause of reactive arthritis and is often asymptomatic. Patients with reactive arthritis, even if asymptomatic, should be tested for chlamydia because they may have persistent infection or carriage of this organism. If chlamydia is identified, these patients, as well as their partners, should receive treatment to prevent recurrence or transmission of infection. More studies are needed to determine whether antibiotics are helpful in treating arthritic symptoms. Antibiotics are not indicated for non-chlamydia-related reactive arthritis unless there is documentation of persistent infection because they have not been shown to alter the course of arthritis.

Anti-cyclic citrullinated peptide antibodies are associated with rheumatoid arthritis, which is characterized by a symmetric small joint polyarthritis typically without dactylitis. This patient does not have this typical presentation; therefore, testing for these antibodies is not indicated.

Antinuclear antibodies are associated with systemic lupus erythematosus (SLE); with the exception of arthritis, this patient has no clinical evidence of SLE, including alopecia, aphthous ulcers, pericardial and pleural serositis, kidney disease, rash, and cytopenias, and does not need to be tested for these antibodies.

Although many patients with reactive arthritis are positive for HLA-B27, it will not add any further value to the diagnosis or management. This patient has several typical features to establish a diagnosis of reactive arthritis, and management with anti-inflammatory medication for arthritis will be effective in the presence or absence of HLA-B27.

KEY POINT

- Patients with reactive arthritis, even if asymptomatic, should be tested for chlamydia infection using a DNA amplification urine test.

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Item 46 Answer: A

Educational Objective: Treat inadequately controlled rheumatoid arthritis.

Addition of a tumor necrosis factor (TNF)-α inhibitor such as etanercept is indicated for this patient with inadequately controlled rheumatoid arthritis (RA). He has been appropriately started on the recommended initial agent, methotrexate, with the dose appropriately titrated up because of continued disease activity. Symptomatic relief has been sought with the use of prednisone and naproxen, but he continues to have active synovitis. Because he has been given an appropriate dose of methotrexate for an adequate period of time, the most appropriate next step is to add a TNF-α inhibitor such as etanercept. TNF-α inhibitors remain the most widely used biologics for RA and are highly effective in the treatment of RA, leading to a 20% improvement in signs and symptoms of disease within weeks for over half of patients.

Rituximab is indicated for use in patients with moderate to severe RA who are also taking methotrexate but have not responded to TNF-α inhibitors. Having never been treated with a TNF-α inhibitor, it is most appropriate to add a TNF-α inhibitor to this patient's regimen rather than rituximab. Other biologics are available, and a number have different mechanisms of action and can be used in combination with methotrexate.

The patient has been on methotrexate since diagnosis and is taking a dose that would be expected to improve his symptoms; however, he continues to have significant disease activity. It is unlikely that continuing to increase the dose will adequately control his disease; this will also increase the risk of toxicity.

Increasing prednisone may offer short-term relief of flares in patients with RA. However, this patient has been on chronic glucocorticoids and high-dose methotrexate, yet continues to have a considerable amount of synovitis. Given the chronic nature of RA and need for long-term treatment, exposing patients to the numerous side effects associated with higher doses of glucocorticoids is not optimal. Furthermore, in this patient with known seropositive erosive disease, therapy with disease-modifying agents is required, and prednisone does not halt bony destruction.

KEY POINT

- In patients with inadequately controlled rheumatoid arthritis who are taking methotrexate, the addition of a tumor necrosis factor α inhibitor is appropriate to improve signs and symptoms of disease.

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Item 47 Answer: E

Educational Objective: Diagnose cryoglobulinemic vasculitis.

Measurement of serum cryoglobulin levels is most likely to establish the diagnosis of cryoglobulinemic vasculitis. This patient presents with palpable purpura, glomerulonephritis (elevated serum creatinine, active urine sediment with cellular casts), mononeuritis, and skin infarctions of the fingers and ears. Although several vasculitic diseases may present with this picture, the presence of ear infarctions is most consistent with a diagnosis of cryoglobulinemia. Moreover, low C4 with a normal (or relatively unaffected) C3, in the presence of rheumatoid factor and a monoclonal paraprotein (the rheumatoid factor itself), is the classic pattern for cryoglobulinemic vasculitis. Thus, the test most likely to establish the diagnosis is a serum cryoglobulin level. Because more than 90% of patients with essential mixed cryoglobulinemia are infected with hepatitis C virus, this patient should be screened and treated for this infection.

Anti–cyclic citrullinated peptide antibodies are found in patients with rheumatoid arthritis (RA). Because this patient lacks arthritis, this diagnosis can be excluded, with the rheumatoid factor (also associated with RA) explained by the patient's cryoglobulinemia.

Anti-glomerular basement membrane antibodies can produce glomerulonephritis but would be less likely to cause the skin findings that are seen in this patient and would be inconsistent with the other serologies presented.

Antinuclear antibodies are present in nearly all patients with systemic lupus erythematosus, a disease of protean manifestations that could indeed present in this manner. However, the presence of a normal C3 with a low C4 is atypical in lupus.

p-ANCA is found in several forms of vasculitis, all of which may involve the kidneys and the skin. However, external auricular involvement is not classic, and the C4 is not reduced.

KEY POINT

- Patients presenting with a multisystem vasculitic disease should be considered for cryoglobulinemia, particularly if the C4 is low, the C3 is relatively preserved, and rheumatoid factor is present.

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Item 48 Answer: C

Educational Objective: Diagnose basic calcium phosphate deposition.

This patient has Milwaukee shoulder syndrome, caused by basic calcium phosphate deposition. Milwaukee shoulder syndrome is characterized by symptoms of pain, stiffness, and swelling that tend to occur gradually over time, often with a preceding trauma or history of overuse on the affected side; this entity is classically described in women over the age of 70 years. This patient has typical features of the syndrome, including a large effusion on examination and synovial fluid that is blood tinged with a low leukocyte count. The crystals are often not visible by routine light microscopy due to their small size, and they are not birefringent (hence, not appreciated with a polarizing microscope); however, they may be revealed with alizarin red staining (with crystals visualized as red, globular clumps). This patient's shoulder radiograph reveals narrowing of the glenohumeral joint, calcification of the periarticular cartilage, and erosive changes of the humeral head, all typical findings in this syndrome. Upward subluxation of the humeral head due to rotator cuff destruction and bony cysts are also common.

Acute calcium pyrophosphate crystal arthritis (also known as pseudogout) can lead to significant joint swelling; however, the absence of inflammatory synovial fluid makes this diagnosis unlikely.

This patient has a history of gout; however, her current symptoms are atypical for a gout attack, particularly the gradual onset of these symptoms. The synovial fluid is also very uncharacteristic for gout, which typically causes an inflammatory effusion. The absence of crystals in the synovial fluid further speaks against gout, although monosodium urate crystals are sometimes missed on synovial fluid analysis.

Monoarticular joint swelling must always raise suspicion for an infected joint; however, in this case, the slow onset of symptoms, lack of fever, and normal serum leukocyte count go against this diagnosis. Synovial fluid with low leukocyte count and negative Gram stain also point away from a diagnosis of an infected joint.

KEY POINT

- Milwaukee shoulder syndrome, caused by basic calcium phosphate deposition, is characterized by pain, stiffness, and swelling that tend to occur gradually over time, often with a preceding trauma or history of overuse on the affected side, with a predilection for women older than the age of 70 years.

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Item 49 Answer: A

Educational Objective: Diagnose disseminated gonococcal infection.

Cervical culture is the most appropriate diagnostic test to perform in this patient who most likely has disseminated gonococcal infection (DGI). DGI occurs in up to 3% of patients with *Neisseria gonorrhoeae* and can cause two distinct clinical presentations. In the setting of bacteremia from DGI, patients

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present with vesiculopustular or hemorrhagic macular skin lesions, fever, polyarthralgia, and tenosynovitis. Arthritis typically is nonpurulent, and synovial fluid cultures tend to be negative. Blood cultures or cultures of the genitourinary tract or pharynx are often positive. Therefore, a cervical culture is appropriate for this patient; cultures of the throat, skin, and rectum should also be ordered to maximize the chance of organism identification.

The second presentation of DGI is purulent arthritis without the rash or other features of gonococcal bacteremia. Synovial fluid cultures are often positive for *N. gonorrhoeae* in these patients. This patient does not exhibit these symptoms; therefore, synovial fluid analysis is unnecessary.

Hepatitis B virus infection can also present with arthralgia, fever, and rash; however, this patient's rash is not typical for hepatitis B, and her liver chemistry studies are normal. Hepatitis B serologies therefore will not be diagnostic.

A positive rapid streptococcal antigen test is helpful to diagnose acute rheumatic fever; however, this patient lacks the sore throat, characteristic rash, and other findings such as cardiac or neurologic involvement that are associated with acute rheumatic fever.

KEY POINT

- Blood cultures or cultures of the genitourinary tract or pharynx are useful diagnostic tests in the setting of bacteremia from disseminated gonococcal infection.

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Item 50 Answer: B

Educational Objective: Manage rheumatoid arthritis medications in a patient of childbearing age.

Discontinuation of methotrexate is indicated for this patient with rheumatoid arthritis (RA) who is interested in becoming pregnant. This nonbiologic disease-modifying antirheumatic drug is both highly teratogenic and abortifacient and must be discontinued 3 months prior to attempting to conceive. Although this patient is taking folic acid to help reduce her incidence of methotrexate side effects, taking folic acid supplements during pregnancy can reduce the risk of certain neural tube birth defects. Therefore, she should not discontinue folic acid even if she discontinues methotrexate.

Considerable epidemiologic evidence in patients with systemic lupus erythematosus as well as RA supports the use of hydroxychloroquine during pregnancy. The risks to mothers and their fetuses appear low, particularly when balanced against the consequences of discontinuing treatment in anticipation of pregnancy. Greater disease activity during pregnancy is associated with small gestational age and preterm delivery. In addition, patients in whom all medications are stopped, including hydroxychloroquine, run the risk of flare, which can impair their physical functioning and make coping with pregnancy more difficult. No increases in adverse maternal or fetal outcomes have been observed in a number of studies in which hydroxychloroquine has been continued throughout pregnancy.

Low-dose glucocorticoids are frequently used but should be avoided if possible before 14 weeks of gestation because of the risk of cleft palate. Glucocorticoid use can contribute to gestational diabetes and hypertension. However, they can be useful in the management of RA in pregnancy if the benefit of treatment is thought to exceed risk.

KEY POINT

- Women taking methotrexate must discontinue this medication 3 months prior to attempting to conceive.

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Item 51 Answer: B

Educational Objective: Diagnose IgG4-related disease.

The most likely diagnosis is IgG4-related disease, a recently described condition characterized by lymphoplasmacytic infiltration and enlargement of various structures, including the pancreas, lymph nodes, salivary glands, periaortic region leading to retroperitoneal fibrosis, kidneys, and skin. Most patients are men (60%-80%) over the age of 50 years. Typical presentation is the subacute development of a mass in the affected organ (for example, an orbital pseudotumor) or diffuse organ enlargement. Up to 90% of patients have multiple organ involvement. Lymphadenopathy is common, as is lacrimal and salivary gland involvement. Most patients lack constitutional symptoms at the time of diagnosis and generally feel well. Staining for IgG4-producing plasma cells reveals large numbers in the tissue.

Hodgkin lymphoma usually presents with palpable lymphadenopathy or a mediastinal mass that requires tissue biopsy for diagnosis. Biopsy is likely to show mainly clonal malignant Hodgkin/Reed-Sternberg cells in a background of granulocytes, plasma cells, and lymphocytes. Reed-Sternberg cells appear as large cells with large, pale nuclei containing large purple nucleoli, and their appearance is indicative of Hodgkin disease. The patient's biopsy findings are not consistent with Hodgkin lymphoma.

Sarcoidosis is a multisystem disease characterized by noncaseating granulomas that form in tissues and most commonly affects the lungs. The absence of granulomas on biopsy is helpful to distinguish IgG4-related disease from sarcoidosis.

Sjögren syndrome can present with enlargement of the salivary glands. However, it is associated with focal, centrilobular collections of lymphocytes on biopsy without the histology characteristic for IgG4-related disease present in this patient. Patients with Sjögren syndrome also usually have positive anti-Ro/SSA and anti-La/SSB antibodies, which are not present in this patient.

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KEY POINT

- IgG4-related disease is characterized by the lymphoplasmacytic infiltration and enlargement of various structures, including the pancreas, lymph nodes, salivary glands, periaortic region leading to retroperitoneal fibrosis, kidneys, and skin.

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Item 52 Answer: A

Educational Objective: Diagnose erosive osteoarthritis.

The most likely diagnosis is erosive osteoarthritis (OA). Distinguishing erosive OA from rheumatoid arthritis (RA) can be difficult because both diseases disproportionately affect women, are polyarticular, and preferentially affect the hand joints. Signs of inflammation (warmth, erythema, swelling, tenderness, reduced function) are present in both entities, although generally involving more joints for longer periods of time in RA. In contrast to RA, erosive OA is common in the distal interphalangeal and carpometacarpal joints, does not typically affect the wrists or elbows, and is not associated with rheumatoid factor, anti-cyclic citrullinated peptide antibodies, or an elevated erythrocyte sedimentation rate or C-reactive protein level. Both types of arthritis can lead to erosions seen on plain radiographs. In erosive OA, these erosions are centrally located in the joint and are accompanied by proliferative changes. In RA, erosions are located at the joint margins, and periarticular osteopenia is likely to be present.

Reactive arthritis is a noninfectious inflammatory arthritis that can occur after a gastrointestinal or genitourinary infection. It is not commonly associated with erosive changes on radiographs.

Tophaceous gout can occur in either gender and is more frequent in women after menopause. It can occasionally have a polyarticular presentation in the hands, but extensive disease is typically accompanied by the obvious presence of multiple tophi in the skin. When inflammation is evident, an acute gout flare is occurring in the presence of tophaceous gout. Tophi can occur in many locations and can create the appearance of erosions with overhanging edges in affected bones, which are sometimes found adjacent to joints. Highly destructive changes can occur that can lead to loss of joint space with long-standing tophaceous gout.

KEY POINT

- In contrast to rheumatoid arthritis, erosive osteoarthritis is common in the distal interphalangeal and carpometacarpal joints, is associated with erosions that are centrally located in the joint and accompanied by proliferative changes, does not typically affect the wrists or elbows, and is not associated with inflammatory markers.

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Item 53 Answer: B

Educational Objective: Diagnose limited cutaneous systemic sclerosis.

The most likely diagnosis is limited cutaneous systemic sclerosis (LcSSc), a form of systemic sclerosis that is characterized by distal (face, neck, and hands) but not proximal skin thickening and is typically not accompanied by internal organ fibrosis. Patients with LcSSc may display features of the CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome and are more likely to develop Raynaud phenomenon early in the disease course. Pulmonary arterial hypertension is more common in patients with LcSSc compared with diffuse cutaneous systemic sclerosis. This patient presents with skin thickening involving the distal extremities and face as well as Raynaud phenomenon; he also has nodules on the extremities, which are suggestive of calcinosis cutis. A number of patients may present with only one or two clinical features, and negative serologies (including antinuclear antibodies) are seen in up to 10% to 25% of patients with LcSSc. He does not have CREST syndrome, which is a variant of LcSSc characterized by the presence of telangiectasias and esophageal dysmotility as well as positive antinuclear and anticentromere antibodies.

Eosinophilia myalgia syndrome is characterized by fasciitis and dermal induration linked to consuming contaminated L-tryptophan, a nutritional supplement. Patients also develop neuropathy and myopathy but not Raynaud phenomenon or scleroderma-specific autoantibodies. New cases are rare since the identification of the toxin several years ago. This patient consumes no nutritional supplements and has Raynaud phenomenon, making eosinophilia myalgia syndrome unlikely.

Morphea is characterized by a localized area of skin thickening, usually on the torso; systemic manifestations or Raynaud phenomenon is extremely rare in patients with this condition.

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease of unknown cause affecting middle-aged women. Fatigue, dry eyes, dry mouth, and pruritus are the most common symptoms. Jaundice, cutaneous hyperpigmentation, hepatosplenomegaly, and xanthelasmas are rarely observed at diagnosis. Raynaud phenomenon and skin thickening are not consistent with PBC.

KEY POINT

- Limited cutaneous systemic sclerosis is characterized by distal skin thickening (face, neck, and hands) and is typically not accompanied by internal organ fibrosis; patients may display features of the CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome.

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Item 54 Answer: B

Educational Objective: Treat rheumatoid arthritis with methotrexate.

Treatment with methotrexate is indicated for this patient with rheumatoid arthritis (RA). She has a polyarticular inflammatory arthritis involving the small joints of the hands as well as a wrist and an ankle, with radiographically demonstrated marginal erosions and periarticular osteopenia and positive anti–cyclic citrullinated peptide antibodies and rheumatoid factor, all of which support a diagnosis of RA. Methotrexate with or without the addition of another disease-modifying antirheumatic drug (DMARD) should be instituted immediately in patients with erosive disease documented at disease onset. Methotrexate is the gold standard therapy because it is usually better tolerated than other DMARDs and has good efficacy, long-term compliance rates, and relatively low cost.

Hydroxychloroquine is indicated to treat early, mild, and nonerosive disease. Hydroxychloroquine therapy alone has not been shown to retard radiographic progression of RA and therefore should be used only in patients whose disease has remained nonerosive for several years. This patient has erosive disease, and hydroxychloroquine as a single agent is not appropriate.

Rituximab, the anti-CD20 B-cell depleting monoclonal antibody, is FDA approved for the treatment of moderately to severely active RA in combination with methotrexate in patients who have had an inadequate response to tumor necrosis factor α inhibitor therapy. Rituximab may also be considered for patients with high disease activity and poor prognostic features despite sequential nonbiologic DMARDs or methotrexate in combination with other DMARDs. It is not appropriate initial treatment for RA in a patient who has not been given a trial of methotrexate.

Tofacitinib is also indicated for use in the management of RA but only in patients who have already not responded to methotrexate alone. This relatively recent addition to the treatment armamentarium for RA is the first oral agent to be introduced in decades but is indicated for use in patients who are intolerant to or have had an inadequate response to methotrexate.

KEY POINT

- Methotrexate is the initial treatment of choice for patients with new-onset, rapidly progressive, or erosive rheumatoid arthritis.

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Item 55 Answer: A

Educational Objective: Diagnose mixed connective tissue disease.

The most likely diagnosis is mixed connective tissue disease (MCTD), an overlap syndrome that includes features of systemic lupus erythematosus (SLE), systemic sclerosis, and/or polymyositis in the setting of positive anti-U1-ribonucleoprotein (RNP) antibodies. Patients with MCTD must have positive anti-U1-RNP antibodies and at least three of the following five features: Raynaud phenomenon, edema of the hands, sclerodactyly, synovitis, and myositis. Patients with MCTD usually have positive antinuclear antibodies (ANA), negative anti–double-stranded DNA antibodies, normal complement levels, and a low incidence of kidney disease. These criteria have a sensitivity of 63% and specificity of 86% in the diagnosis of MCTD. These patients are more likely to have myositis and pulmonary hypertension, an important cause of mortality, than patients with SLE.

Polymyositis is a form of inflammatory myopathy characterized by symmetric proximal muscle weakness with little or no pain, and muscle enzymes such as creatine kinase are usually elevated 10- to 50-fold the upper limit of normal. However, polymyositis is not associated with anti-U1-RNP antibodies and does not result in puffy hands or sicca symptoms.

Although the patient has a positive ANA, the diagnosis of SLE is less likely in the context of the negative anti-Smith and anti–double-stranded DNA antibodies as well as the normal complement levels, serum creatinine, and urinalysis.

The absence of sclerodactyly, sclerodermatous skin changes, and esophageal involvement makes systemic sclerosis an unlikely diagnosis.

Undifferentiated connective tissue disease (UCTD) is not an overlap syndrome but instead refers to nonspecific clinical features (such as Raynaud phenomenon and arthralgia), no disease-specific findings, and nonspecific positive autoantibodies (such as ANA). UCTD may exist for some time prior to a clear emergence of symptoms characteristic enough to define a single rheumatologic disease.

KEY POINT

- Mixed connective tissue disease is an overlap syndrome that includes features of systemic lupus erythematosus, systemic sclerosis, and/or polymyositis in the setting of positive anti-U1-ribonucleoprotein antibodies.

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Hajas A, Szodoray P, Nakken B, et al. Clinical course, prognosis, and causes of death in mixed connective tissue disease. J Rheumatol. 2013 Jul;40(7):1134-42. [PMID: 23637328]

Item 56 Answer: A

Educational Objective: Diagnose diffuse alveolar hemorrhage in a patient with systemic lupus erythematosus.

Bronchoscopy with bronchoalveolar lavage (BAL) and biopsy is the most appropriate diagnostic test to perform next in this

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H CONT. patient with suspected diffuse alveolar hemorrhage (DAH), a rare but severe manifestation of systemic lupus erythematosus (SLE). The triad of hypoxemia, new infiltrates found on chest radiograph, and decreasing hematocrit is highly predictive of underlying DAH; only about 50% of patients have hemoptysis. DAH occurs in the setting of active SLE, and up to 90% of patients have evidence of nephritis. Chest radiograph demonstrates bilateral infiltrates often sparing the lung apices. Diagnosis is by BAL during bronchoscopy to demonstrate bleeding and rule out infection. Lung biopsy is the definitive diagnostic test, which typically shows a capillaritis with immune complex deposition. Mechanical ventilation and aggressive immunosuppression are generally required, but mortality rates still are as high as 70%.

Although DAH can be suggested by the presence of ground-glass opacities on chest CT, the diagnosis is established only with bronchoalveolar lavage and biopsy.

MRI of the chest can be used to determine if the infiltrates are blood and could be used in rare cases in which bronchoalveolar lavage and biopsy are unable to be done.

Because DAH is typically a pulmonary capillaritis, angiography will not image vessels of this size and will not be useful in establishing the diagnosis.

KEY POINT

- The triad of hypoxemia, new pulmonary infiltrates on chest radiograph, and decreasing hematocrit is highly predictive of underlying diffuse alveolar hemorrhage associated with systemic lupus erythematosus.

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Item 57 Answer: D

Educational Objective: Treat a patient who has Löfgren syndrome.

An NSAID such as naproxen is appropriate for this patient who has Löfgren syndrome, a self-limiting form of sarcoidosis characterized by a triad of acute arthritis in combination with bilateral hilar lymphadenopathy and erythema nodosum. The "arthritis" associated with Löfgren syndrome is actually a nondestructive periarthritis of the soft tissue, entheses, and tenosynovium around the joints. Symmetric involvement of the ankles is classic, but knees, wrists, and elbows can also be involved. Ninety percent of patients remit within 12 months. When the triad of features occurs, it has a 95% specificity for diagnosis, and further diagnostic tests (such as radiography or serologic testing) are unnecessary. This patient presents with the classic triad of hilar lymphadenopathy, erythema nodosum, and acute arthritis involving the ankles and therefore has Löfgren syndrome. Erythema nodosum may occur in association with a wide array of causes, including infections, medications, and systemic disease, or it may be idiopathic. Sarcoidosis and inflammatory bowel disease are the most frequently associated systemic diseases. The lesions of erythema nodosum are tender, subcutaneous nodules presenting as barely appreciable convexities on the skin surface, with a reddish hue in the acute phase. As the lesions resolve, a dull brown circular patch is often left behind. Erythema nodosum is frequently bilateral and symmetric, and it usually occurs on the distal lower extremities. Löfgren is more common among Europeans. Initial treatment is generally with NSAIDs (such as naproxen), colchicine, or low-dose prednisone.

Methotrexate, high-dose prednisone, or a tumor necrosis factor α inhibitor such as adalimumab are reserved for patients with chronic, organ-damaging forms of sarcoidosis.

KEY POINT

- Löfgren syndrome is a self-limiting form of sarcoidosis characterized by acute arthritis, bilateral hilar lymphadenopathy, and erythema nodosum.

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Item 58 Answer: C

Educational Objective: Diagnose reactive arthritis.

The most likely diagnosis is reactive arthritis (formerly known as Reiter syndrome), a noninfectious inflammatory arthritis that can occur approximately 3 to 6 weeks after a gastrointestinal or genitourinary infection. It is common for infection to have resolved and stool culture to become negative by the time arthritis begins. Asymmetric monoarthritis or oligoarthritis in the lower extremities is the most common presentation, but up to 20% of patients have polyarthritis. Enthesopathy (inflammation at the site where ligaments, tendons, joint capsule or fascia attaches to bone), dactylitis, and sacroiliitis may occur. Erosive disease is uncommon. Ophthalmologic inflammation is a feature of this disease in up to 30% of patients and can manifest as uveitis or conjunctivitis. This patient's manifestations, including a diarrheal illness that preceded the onset of arthritis by 2 to 3 weeks, inflammatory oligoarticular involvement of lower extremities, inflammation of the insertion of the Achilles tendon, and anterior uveitis, are typical of reactive arthritis.

In bacterial infections, synovial fluid analysis typically reveals a neutrophilic leukocytosis (typically >50,000/μL [50 × 10^9/L]), but synovial fluid leukocyte counts ≤50,000/μL (50 × 10^9/L) do not definitively rule out infection. In this patient, infectious arthritis is less likely because this patient has no fever or leukocytosis on complete blood count.

Although psoriatic arthritis can present as an oligoarthritis, it is also less likely because the patient has no evidence of psoriasis on physical examination.

Rheumatoid arthritis is unlikely because it usually is a symmetric small joint polyarthritis rather than large joint oligoarthritis, and enthesopathy is not common.

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KEY POINT

- Reactive arthritis can occur after a gastrointestinal or genitourinary infection and is characterized by an asymmetric monoarthritis or oligoarthritis in the lower extremities as well as enthesopathy, dactylitis, and sacroiliitis.

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Item 59 Answer: C

Educational Objective: Treat tophaceous gout.

Continuation of colchicine for flare prophylaxis and allopurinol for urate lowering is indicated for this patient with tophaceous gout. He is having a good response to colchicine and allopurinol, with a serum urate level currently at the target goal of less than 6.0 mg/dL (0.35 mmol/L), resolution of flares, and reduction in size of tophi (reservoirs of monosodium urate). The American College of Rheumatology currently recommends continuation of flare prophylaxis if there is any evidence of active disease, including flares or tophi as seen in this patient. Hence, both agents should be continued at this time. The guidelines further suggest that in the absence of active disease and once target serum urate is reached, colchicine should be continued for the longer of the following: 6 months; 3 months after reaching target serum urate in a patient without baseline tophi; or 6 months after reaching target serum urate in a patient with baseline tophi that have resolved.

Changing this patient's urate-lowering regimen by adding probenecid or changing allopurinol to febuxostat is unnecessary in this patient who has reached the target serum urate level by taking allopurinol. His gout symptoms have improved, and the tophi have begun to shrink in size. If he was not at goal or was having ongoing flares or resistance of tophi to dissolve on his current regimen, options would be to further increase allopurinol, switch to febuxostat (a newer, more expensive xanthine oxidase inhibitor), or add probenecid.

Colchicine should be maintained at daily dosing because the patient still needs ongoing protection against flares, given the presence of tophi.

KEY POINT

- In patients with gout, continuation of flare prophylaxis and urate-lowering therapy is currently indicated if there is any evidence of active disease, including flares or tophi.

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Item 60 Answer: A

Educational Objective: Treat ankylosing spondylitis with a tumor necrosis factor α inhibitor.

Treatment with adalimumab is appropriate for this patient with ankylosing spondylitis, a form of spondyloarthritis that predominantly affects the axial skeleton. Inflammatory back pain is a hallmark feature, manifesting as pain and stiffness in the spine that is worse after immobility and better with use. Symptoms are prominent in the morning and can be symptomatic during the night. Buttock pain is common and correlates with sacroiliitis. Fusion of the spine may occur over time, leading to rigidity and kyphosis. Exercise to preserve range of motion and strengthen the spine extensor muscles to prevent kyphosis is essential. Physical therapy may be indicated to assist patients in developing a home exercise routine. NSAIDs are considered first-line therapy for symptomatic patients. If the patient does not adequately respond to a minimum of two different trials of NSAIDs used at least 4 weeks total, the Assessment of SpondyloArthritis international Society/European League Against Rheumatism (ASAS/EULAR) guidelines recommend treatment with a tumor necrosis factor (TNF)-α inhibitor. This patient has not adequately responded to either naproxen or indomethacin; therefore, a TNF-α inhibitor such as adalimumab is appropriate. The currently available TNF-α inhibitors appear to be equally effective when compared with placebo. Response is rapid, often within the first 6 weeks of therapy. Patients who do not respond to one agent may respond to an alternative. Because long-term safety is unknown, TNF-α inhibitors remain second-line therapy to NSAIDs.

Nonbiologic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine have not been demonstrated to be efficacious for axial disease but may be considered for peripheral arthritis.

Rituximab is a biologic DMARD used to treat moderate to severe rheumatoid arthritis in combination with methotrexate in patients who have had an inadequate response to TNF-α inhibitor therapy and is also used in ANCA-associated vasculitis. There is no evidence showing benefit of this agent in ankylosing spondylitis.

KEY POINT

- In patients with ankylosing spondylitis, treatment with a tumor necrosis factor α inhibitor is currently recommended if first-line therapy with NSAIDs is inadequate.

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Item 61 Answer: B

Educational Objective: Diagnose acute osteonecrosis in a patient with systemic lupus erythematosus.

MRI of the left hip is the most appropriate diagnostic test to perform next in this patient with systemic lupus

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erythematosus (SLE) who has symptoms associated with osteonecrosis. Patients with SLE who have pain or limitation of motion of the large joints, especially the hips, should be evaluated for osteonecrosis. MRI is the best method for detecting early bone edema caused by osteonecrosis when plain radiographs are normal. MRI can also be prognostic: If more than 20% of the femoral volume demonstrates necrosis and edema on MRI, progressive disease (subchondral fracture and femoral head collapse) is the rule, whereas smaller infarcts rarely progress. Up to 37% of patients with SLE may have osteonecrosis by serial MRI monitoring, although less than 10% become symptomatic. Cushingoid features indicate a risk for osteonecrosis because enlargement of fat cells in the face is a marker for enlargement of fat cells in the ends of long bones. Increased adipose volume causes compression of small sinusoidal vessels that leads to interosseous hypertension and impairment of arterial inflow. Use of daily oral prednisone more than 20 mg/d for 4 to 6 weeks is also a risk factor, whereas use of intravenous glucocorticoids may not have the same risk. This patient has hip pain, cushingoid features, and recent use of high-dose prednisone, all indicators that she should be evaluated for osteonecrosis despite the normal hip radiograph.

MRI remains the gold standard to diagnose osteonecrosis. CT is less sensitive than MRI and exposes the patient to unnecessary radiation.

Plain radiography may not detect changes of osteonecrosis for several months following the onset of symptoms. Early radiographic findings include bone density changes, sclerosis, and, eventually, cyst formation. Subchondral radiolucency producing the "crescent sign" indicates subchondral collapse. End-stage disease is characterized by collapse of the femoral head, joint-space narrowing, and degenerative changes.

Ultrasonography can be used to evaluate for trochanteric bursitis as the cause of lateral hip pain but would not be useful to check for osteonecrosis. Trochanteric bursitis can be confirmed in patients in whom hip adduction intensifies the pain or in those in whom the examination reveals pain and tenderness over the bursa. Pain at night is present when the patient sleeps on the affected side.

KEY POINT

- Patients with systemic lupus erythematosus who have pain or limitation of motion of the large joints, especially the hips, should be evaluated for osteonecrosis using MRI when plain radiographs are normal.

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Item 62 Answer: E

Educational Objective: Diagnose ovarian cancer in a patient with dermatomyositis.

Transvaginal pelvic ultrasonography is indicated for this patient with dermatomyositis, which may be associated with an underlying malignancy, especially in the first 2 years after diagnosis. Malignancy risk may also be higher in the presence of vasculitis (as seen in this patient) or cutaneous necrosis as well as in patients who are of older age at onset. Patients with dermatomyositis have an increased standardized incidence ratio of solid malignancies such as adenocarcinomas of the lung, cervix, ovaries, pancreas, colorectal, stomach, and bladder as well as non-Hodgkin lymphoma. Risk of ovarian cancer may be especially increased. In a population-based study, the standardized incidence ratio was 10.5 for ovarian cancer, highest among all cancers diagnosed. Therefore, obtaining a transvaginal pelvic ultrasonography to look for ovarian pathology, especially ovarian cancer, is recommended for this patient who has worsening dermatomyositis and new-onset ascites on examination.

Chest CT is helpful in diagnosing interstitial lung disease in patients with myositis and in evaluating malignancy; however, this patient has no evidence of respiratory symptoms but does have new-onset ascites, making ovarian cancer a more likely diagnosis.

Although this patient has elevated aspartate aminotransferase, it is likely of muscle origin and abnormal due to active myositis. Liver biopsy is not needed prior to obtaining other noninvasive studies for her abnormal liver chemistry tests and evaluation for ovarian cancer.

The diagnosis of advanced ovarian cancer is usually made by CT- or ultrasound-guided biopsy of a suspicious mass or cytologic examination of ascitic fluid. PET scan is likely to show abnormalities in her abdomen but will not lead to the correct diagnosis and is not cost-effective.

Thigh muscle MRI with specialized (STIR protocol) images may show evidence of actively involved muscle with myositis and support the diagnosis of dermatomyositis. However, this study is not needed in this patient who already has been diagnosed with dermatomyositis and has evidence of the classic rash, weakness, and elevated muscle enzymes.

KEY POINT

- The risk of ovarian cancer may be especially increased in women with dermatomyositis.

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Item 63 Answer: D

Educational Objective: Diagnose polyarteritis nodosa.

The most likely diagnosis is polyarteritis nodosa (PAN), the most common medium-sized vasculitis that affects the mesenteric and renal arteries. Patients usually present with nonspecific inflammatory symptoms as well as abdominal symptoms (chronic or intermittent ischemic pain), neurologic involvement (mononeuritis multiplex), and skin findings (livedo reticularis, purpura, and painful subcutaneous nodules). Kidney disease is based on decreased renal artery

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blood flow rather than glomerulonephritis. The presence of hepatitis B virus (HBV) infection is a strong risk factor for the development of PAN, although in areas where HBV vaccination is common, the incidence of HBV-associated PAN has diminished greatly. This patient with HBV infection (positive hepatitis B surface antigen) presents with involvement of the abdomen, kidneys, nerves, joints, and skin, accompanied by hypertension but sparing the upper and lower respiratory tracts. He also has mononeuropathy, arthralgia, fever, and livedo reticularis (shown in the figure) but lacks the active urine sediment characteristic of glomerulonephritis. Together these findings suggest a systemic vasculitis of which PAN is the most likely. Testicular involvement is also common, as in this case. Diagnosis of PAN is best established by demonstrating necrotizing arteritis in biopsy specimens, or characteristic medium-sized artery aneurysms and stenoses on imaging studies of the mesenteric or renal arteries using either angiography or CT angiography.

Goodpasture syndrome affects the kidneys and often the lungs. The lack of active urine sediment and the presence of medium arterial involvement are inconsistent with Goodpasture syndrome, as are the abdominal symptoms.

Granulomatosis with polyangiitis (GPA; formerly known as Wegener granulomatosis) can involve the kidneys, and neuropathy and purpura can occur; however, this disease is associated with glomerulonephritis, which is absent in this patient. Furthermore, medium-sized artery involvement does not occur in GPA, and the absence of ANCA makes GPA much less likely.

Henoch-Schönlein purpura (HSP) can affect the kidneys, nerves, and skin as well as cause abdominal pain. However, HSP is an immune complex disease affecting small vessels; active urine sediment is common, complements (particularly C4) are typically low, and IgA levels may be elevated, none of which is the case in this patient.

KEY POINT

- Patients with polyarteritis nodosa typically present with fever, arthralgia, myalgia, skin findings, abdominal pain, weight loss, and peripheral nerve manifestations, most commonly mononeuropathy or mononeuritis multiplex.

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Item 64 Answer: C

Educational Objective: Recognize the risk of early-onset knee osteoarthritis following meniscectomy.

The most likely cause of this patient's left knee osteoarthritis is meniscectomy. The history of prior injury followed by meniscectomy puts this patient at substantial risk for the development of osteoarthritis at an earlier age than would otherwise be predicted. A recent prospective study with a 40-year follow-up concluded that meniscectomy leads to osteoarthritis of the knee with a resultant 132-fold increase in the rate of total knee replacement in comparison to their matched controls. The risk of osteoarthritis of the knee following meniscus injury and removal is also well documented for adolescent athletes and, as recognition of this link has become more widespread, the incidence of meniscus repair rather than meniscectomy has risen.

Other factors for osteoarthritis are advancing age, obesity, female gender, and genetic factors. For example, obesity is the most important modifiable risk factor for osteoarthritis of the knee, but this patient is not obese. The incidence of knee osteoarthritis is also increased by occupations with repetitive bending, which this patient does not experience. The prevalence of osteoarthritis of the hip and knee is nearly two times higher in women than in men. Osteoarthritis of the hand has strong female and genetic predilections; it is also associated with obesity. His mother's hand osteoarthritis is probably not relevant for this patient who developed knee osteoarthritis at an early age following meniscectomy.

KEY POINT

- There is an increased risk of early-onset knee osteoarthritis in patients with a history of prior injury followed by meniscectomy.

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Item 65 Answer: B

Educational Objective: Manage a prosthetic joint infection.

Obtaining blood and synovial fluid cultures is the most appropriate next step in management for this patient with suspected prosthetic joint infection. Infections may occur early (within 3 months of surgery), have delayed onset (3-12 months), or have late onset (>12 months after surgery). Early-onset infections typically present with joint swelling, erythema, wound drainage, and/or fever. Delayed-onset infections present more insidiously with prolonged joint pain, often without fever. Late-onset infections present as acute pain and swelling, often in the setting of a nidus for hematogenous seeding such as a vascular catheter or other site of infection remote from the affected joint. This patient has acute onset of pain and swelling of the right knee, along with fevers, an elevated leukocyte count with a left shift, and elevated inflammatory markers, occurring 2 months after knee replacement. Urgent surgical consultation is warranted, and blood and synovial fluid cultures should be obtained before administration of antibiotics, whenever possible, to allow for more accurate culture data. Blood cultures are essential (even when fever is absent); although the infection likely arose locally at the surgical site in this patient, most cases of infectious arthritis arise from hematogenous spread. Blood cultures are also important

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because, even in cases in which the infection arises directly at the joint, the organism may occasionally be identified in the blood cultures. Before initiating antibiotics, synovial fluid cultures should be obtained via arthrocentesis or in the operating room if surgical intervention is imminent and the patient is stable enough to withhold antibiotics until surgery.

This patient will need antibiotics shortly, but she is stable enough to await surgical evaluation and collection of blood and synovial fluid cultures.

More advanced imaging such as a CT, bone scan, or MRI is generally not indicated in the preliminary evaluation and treatment of a suspected prosthetic joint infection because these studies delay the more urgent management of the patient and do not change the initial management.

KEY POINT

- In patients with suspected prosthetic joint infection, blood and synovial fluid cultures should be obtained before initiation of antibiotics to allow for more accurate culture data.

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Item 66 Answer: B

Educational Objective: Manage gout with dietary modifications.

The addition of low-fat dairy products is appropriate for this patient with gout. Low-fat dairy products have been shown to decrease the risk of gout flares both through uricosuric and anti-inflammatory properties. He should also be advised to reduce intake of high-fructose beverages such as soft drinks because they are associated with gout flares due to metabolic pathways utilized in the metabolism of fructose, which lead to increased uric acid generation. Obesity is also a risk factor for gout and should be addressed as needed.

Some leafy green vegetables are high in purines, the nucleic acid component that is metabolized to uric acid. Thus, a recommendation to increase leafy greens as a dietary approach to gout treatment would be incorrect. However, intake of leafy green vegetables has not been shown to increase the risk of flares in population-based studies.

Alcohol is a well-established trigger for gout, probably due to several mechanisms, including uric acid production and kidney urate handling. Although wine has been found less likely to trigger gout flares than beer, alcohol consumption of any sort will increase the risk of flares overall.

Shellfish have long been established as a food that is likely to trigger a gout flare due to the high purine load and should therefore be restricted in this patient's diet.

KEY POINT

- In patients with gout, lifestyle and dietary modifications, including weight loss if appropriate, reduction of high-fructose and high-purine foods, alcohol restriction, and increased low-fat dairy intake, may help decrease the risk of gout flares.

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Item 67 Answer: D

Educational Objective: Treat a patient who has fibromyalgia.

An aerobic exercise program is appropriate for this patient with fibromyalgia, which is characterized by chronic widespread pain, tenderness of skin and muscles to pressure, fatigue, sleep disturbance, and exercise intolerance. Nonpharmacologic therapy is the cornerstone of treatment and should be initiated in all affected patients. Regular aerobic exercise has been shown to be effective in this setting. Exercise regimens should be individualized and titrated up to 30 minutes most days of the week. Physical therapy may also be helpful initially to develop a stretching and progressive aerobic program. Cognitive behavioral therapy has been shown to be beneficial but is not always covered by insurance plans.

NSAIDs such as ibuprofen have not been shown to be particularly useful in fibromyalgia, and most patients have tried them before seeking medical care for their symptoms. Although possibly helpful when taken on an as-needed basis for other musculoskeletal pain, NSAIDs as a primary therapy for fibromyalgia would not be appropriate.

This patient also has hypothyroidism but has a normal thyroid-stimulating hormone level, indicating that she is being treated properly and does not need an increase of her levothyroxine dose.

Fibromyalgia may co-occur in patients with inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome, but this patient does not have any clinical signs or laboratory features that would suggest an inflammatory disease. Thus, an antinuclear antibody (ANA) panel would not be helpful, and a clinically insignificant low-level positive ANA may actually lead to further unnecessary testing and specialist referral.

KEY POINT

- Nonpharmacologic therapy, including regular aerobic exercise, is the cornerstone of fibromyalgia treatment and should be initiated in all affected patients.

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Item 68 Answer: C

Educational Objective: Manage NSAID gastrointestinal risk in an older patient by using topical NSAID therapy.

Discontinuation of oral naproxen and initiation of a topical NSAID is the most appropriate therapy for this 75-year-old patient with knee osteoarthritis. The major risks of NSAIDs include gastrointestinal toxicity, cardiovascular disease, hypertension, and kidney disease. Among these, NSAID gastrointestinal risk is higher among older patients and needs to be managed. The American College of Rheumatology currently recommends topical NSAIDs rather than oral NSAIDs for patients aged 75 years or older. A 2012 Cochrane review of topical NSAIDs for chronic musculoskeletal pain included 34 studies with 7688 participants. Topical NSAIDs were superior to placebo for pain relief, with the most data available for topical diclofenac. Topical and oral NSAIDs did not differ with regard to pain relief. Topical NSAIDs led to more skin reactions than placebo or oral NSAIDs and fewer gastrointestinal events than oral NSAIDs.

Discontinuing naproxen and adding celecoxib would reduce the risk of gastrointestinal toxicity to an extent similar to that of adding a proton pump inhibitor (PPI) to naproxen but would be unwarranted in the setting of a good response to topical naproxen. In patients with particularly high risk who require therapy with oral NSAIDs, simultaneously switching to celecoxib and adding a PPI could be considered.

Joint replacement should be considered in patients who have knee osteoarthritis with function and/or pain that cannot be managed using nonsurgical interventions. Because this patient has neither pain nor limitation on his current therapy, consideration of joint replacement would be premature.

KEY POINT

- Older patients with osteoarthritis who require NSAID therapy to control pain should be considered for topical NSAID therapy to manage gastrointestinal toxicity.

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Item 69 Answer: B

Educational Objective: Diagnose seronegative rheumatoid arthritis.

The most likely diagnosis is rheumatoid arthritis (RA), which is characterized by a symmetric inflammatory polyarthritis of the small joints. Autoantibodies such as rheumatoid factor or anti-cyclic citrullinated peptide (CCP) antibodies may be present, although autoantibodies are neither necessary nor sufficient for diagnosis. Anti-CCP antibodies occur less frequently than rheumatoid factor, but their presence has more diagnostic specificity for RA. Some patients with RA also lack rheumatoid factor. Seronegative RA has an identical clinical appearance as seropositive RA but is more likely to occur in men. Despite a negative rheumatoid factor and anti-CCP antibodies, this patient's clinical presentation of polyarticular inflammatory arthritis involving multiple and bilateral interphalangeal joints of the fingers, metacarpophalangeal joints, a wrist, and an ankle as well as prolonged morning stiffness and radiographic findings of marginal erosion and periarticular osteopenia, is characteristic of RA. Over time, some patients who are initially seronegative develop a positive rheumatoid factor.

This patient does not have monoarticular or oligoarticular disease or radiographs showing bony sclerosis or osteophyte formation, all of which are typical of osteoarthritis. This patient's symmetric polyarticular inflammatory arthritis associated with prolonged morning stiffness is not consistent with osteoarthritis, in which joint swelling is not found and morning stiffness lasts less than 30 minutes.

Although sarcoidosis can occasionally cause joint involvement, it is unlikely to present with joint symptoms alone. Chronic sarcoid arthropathy most commonly involves the ankles, knees, hands, wrists, and metacarpophalangeal and proximal interphalangeal joints and is usually accompanied by parenchymal pulmonary disease. It is unlikely to be the cause of inflammatory polyarthritis in a previously healthy middle-aged man.

Although systemic lupus erythematosus (SLE) can cause seronegative polyarticular inflammatory arthritis, the initial presentation in a middle-aged man as an explanation for polyarticular inflammatory arthritis would be exceedingly unlikely, and erosions are not seen as a result of arthritis in SLE. The patient has no signs or symptoms otherwise suggestive of SLE such as brain, kidney, lung, heart, or skin manifestations.

KEY POINT

- Seronegative rheumatoid arthritis has an identical clinical appearance as seropositive rheumatoid arthritis but is more likely to occur in men.

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Item 70 Answer: B

Educational Objective: Diagnose adult-onset Still disease.

The most likely diagnosis is adult-onset Still disease (AOSD), a multisystem inflammatory disease characterized by high spiking fevers, arthritis, rash, high neutrophil counts, and markedly elevated serum ferritin. The rash is a nonpruritic salmon-colored macular/maculopapular rash on the trunk or extremities. Serum ferritin is elevated in many patients, often to extremely high levels, and is a marker of macrophage

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activation. Erythrocyte sedimentation rate and C-reactive protein can also be impressively elevated. Diagnosis is clinical, based on exclusion of infection, malignancy, or other rheumatologic diseases. Clinical criteria have been developed to assist in the diagnosis of AOSD. The most sensitive of these are the Yamaguchi classification criteria. Diagnosis requires fulfilling at least five criteria, two of which must be major. This patient fulfills three major criteria (fever, rash, joint involvement) and three minor criteria (splenomegaly, lymphadenopathy, elevated liver chemistries). Very few other diseases elevate ferritin to this level, although this is not currently one of the criteria.

Acute myeloid leukemia (AML) is a malignancy of myeloid progenitor cells. Clinical manifestations of bone marrow failure develop over days to months and include fatigue, dyspnea, and easy bleeding. Fever is commonly caused by infection. The leukocyte count can be low, normal, or high, but circulating myeloblasts are present in most cases. This patient has a significant leukocytosis but no circulating blasts, thus excluding the diagnosis of AML.

Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) is also a multisystem disorder characterized by upper respiratory, lower respiratory, and kidney involvement. More than 70% of patients have upper airway manifestations such as sinusitis or nasal, inner ear, or laryngotracheal inflammation. This patient has none of these manifestations.

Systemic lupus erythematosus (SLE) is also a multisystem disease with early nonspecific constitutional symptoms, including fever, fatigue, and weight loss. Common presentations include a photosensitive rash and symmetric polyarthritis. Cytopenia is common, whereas leukocytosis and extremely elevated serum ferritin levels are not characteristic of SLE.

KEY POINT

- Adult-onset Still disease is characterized by high spiking fevers, arthritis, rash, high neutrophil counts, and markedly elevated serum ferritin.

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Item 71 Answer: A

Educational Objective: Diagnose Behçet syndrome.

The most likely diagnosis is Behçet syndrome, a form of vasculitis that can affect small to large arterial vessels and is one of the few forms of vasculitis that also can affect veins. Behçet syndrome has an increased prevalence in a belt from East Asia to Turkey and therefore conveys an ethnic/genetic risk in those with a Mediterranean/Asian background. Behçet syndrome is characterized by recurrent painful oral ulcers plus at least two of the following: recurrent painful genital ulcers, eye involvement, skin involvement (typically acneiform lesions), and pathergy (development of a pustule following a needle stick). Oral ulcers typically resolve spontaneously after 1 to 3 weeks. Eye involvement can be severe, especially when there is a posterior uveitis/retinal vasculitis, and can lead to blindness. Hypopyon (suppurative fluid seen in the anterior chamber) is also a distinctive feature. The combination of recurrent painful oral ulcerations, genital ulcerations, and uveitis make Behçet syndrome the most likely diagnosis in this patient. Other clinical findings include gastrointestinal ulceration that may make it challenging to differentiate Behçet syndrome from Crohn disease with extraintestinal manifestations. Arthritis affecting medium and large joints is common, and the vasculitic process may cause neurologic, cardiopulmonary, kidney, and vascular complications.

Clinical manifestations of cytomegalovirus infection (CMV) include a mononucleosis-like illness with findings ranging from fever and lymphadenopathy to colitis, hepatitis, and even retinitis. Oral ulcers, genital ulcers, and hypopyon are not features of acute CMV infection.

Herpes simplex virus type 1 (HSV-1) infection has been classically associated with causing recurrent painful oral ulcerations. Although HSV-1 is being increasingly recognized as a cause of genital ulceration, it is much less common than with HSV type 2 infection. Systemic symptoms, such as fever, may be associated with primary herpes virus infection but are less common with recurrent episodes of viral activation. Additionally, HSV-1 may also be associated with ocular disease, although keratitis is the most common manifestation seen with HSV-1 infection and not hypopyon, as seen in this patient.

Reactive arthritis (formerly known as Reiter syndrome) is a postinfectious, noninfectious arthritis that occurs in both men and women. Arthritis, usually oligoarticular, develops several days to weeks after a genitourinary or gastrointestinal infection and can be associated with oral and genital lesions as well as uveitis. Unlike Behçet, the oral ulcers are painless, the genital lesions are hyperkeratotic rather than ulcerative, and hypopyon is not typical.

KEY POINT

- Behçet syndrome is characterized by recurrent painful oral ulcers plus at least two of the following: recurrent painful genital ulcers, eye involvement, skin involvement, and pathergy.

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Item 72 Answer: A

Educational Objective: Select acetaminophen as a first-line pharmacologic agent in the treatment of knee osteoarthritis.

Treatment with acetaminophen is appropriate for this patient with knee osteoarthritis (OA). The presence of progressive knee pain in this older individual that is worse with walking

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and is accompanied by unicompartmental joint-space narrowing and osteophytosis in the absence of extensive inflammation is pathognomonic for OA. Although OA includes a component of low-level inflammation, the goal of treatment is relief of pain and restoration of function. Most treatment guidelines suggest the initial use of acetaminophen for pain control in patients with knee OA. Acetaminophen is usually at least moderately effective in OA management; at doses of up to 3 to 4 g/d, it is considered safe and well tolerated. Additionally, it causes little or no gastrointestinal intolerance in most patients, does not affect blood pressure, and has significantly less nephrotoxicity than NSAIDs.

Both selective cyclooxygenase (COX)-2 inhibitors and traditional nonselective NSAIDs (such as ibuprofen) are of proven benefit in patients with OA and may be incrementally more effective than acetaminophen; selective COX-2 inhibitors have improved gastrointestinal tolerance and might be a better choice than a traditional NSAID in this patient given his gastric symptoms. However, both selective COX-2 inhibitors and traditional NSAIDs promote hypertension and can cause or exacerbate kidney disease; this patient's chronic kidney disease therefore makes them even less desirable as first-line therapy compared with acetaminophen. Other options for pharmacotherapy include local and topical therapy, intra-articular management, tramadol, and, if absolutely necessary, opiates.

Colchicine is an anti-inflammatory agent commonly used in gout and is not recommended for OA therapy.

KEY POINT

- In patients with osteoarthritis, initial treatment with acetaminophen for pain control is generally recommended.

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Item 73 Answer: D

Educational Objective: Evaluate a patient with primary Raynaud phenomenon.

Clinical observation is the most appropriate next step in management. This patient's presentation is suggestive of primary Raynaud phenomenon, a common occurrence in young women that may be seen in up to 30% of women who are white. Raynaud phenomenon may also be the initial symptom of an underlying fibrosing connective tissue disease (CTD) such as mixed connective tissue disease or systemic sclerosis; the predictors/features include severe and prolonged episodes of vasospasm, asymmetric involvement of the digits, and abnormal nailfold capillary examination and/or digital pitting. This patient has none of these features, has a negative family history for CTD, and has undergone nailfold capillary examination, which is normal. She is at a low risk for progressing to a CTD, should be reassured, and can be followed periodically. In these patients, most episodes of Raynaud phenomenon are self-limiting and do not require treatment. Persistently symptomatic patients can be treated with a peripherally acting calcium channel blocker such as nifedipine or amlodipine. Sildenafil and endothelin-1 blockers can be used in refractory cases.

This patient's likelihood of developing a CTD is low, and measuring antinuclear and anti-U1-ribonucleoprotein antibodies would be of extremely low yield and would not be cost-effective.

Similarly, obtaining an antiphospholipid antibody panel and cryoglobulins in a patient who has no history or evidence of thrombosis, pregnancy loss, or vasculitis is unnecessary and not cost-effective.

Digital arteriography is an invasive test and is usually normal in patients with Raynaud phenomenon. Obtaining this study would be appropriate if thromboangiitis obliterans ("Buerger disease") were suspected, which is a nonatherosclerotic vascular inflammatory disease affecting the medium and small vessels of the extremities and digits that has a strong association with smoking and male gender.

KEY POINT

- Raynaud phenomenon may be the initial symptom of an underlying connective tissue disease; the predictors/features include severe and prolonged vasospastic episodes, asymmetric involvement of the digits, and abnormal nailfold capillary examination and/or digital pitting.

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Item 74 Answer: D

Educational Objective: Evaluate a patient for primary angiitis of the central nervous system.

The most appropriate next step in management is to obtain an intracerebral angiography and brain biopsy. This patient, presenting with recurrent headaches and rapidly progressive encephalopathy but no clear evidence of stroke or infection, requires consideration for primary angiitis of the central nervous system (PACNS). PACNS is a rare and challenging, but treatable, diagnosis because it is isolated to the CNS with no evidence of systemic involvement. His change in mental status could alternatively represent Alzheimer disease, or dementia on a vascular basis given his history of hypertension and smoking; however, the time course would be unusual, headaches are somewhat atypical for dementia, and the presence of an abnormal cerebrospinal fluid suggests an inflammatory process. Other diagnoses to consider include reversible vasoconstriction syndrome, infection, and intravascular malignancy. MR angiography (MRA) is insufficiently sensitive for a

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negative result, as in this patient's case, to suggest an absence of vasculitis, and insufficiently specific for a positive finding to abrogate further work-up. Because treatment of PACNS is aggressive and not without hazard, it is important to definitively establish a diagnosis whenever possible. Angiography is generally used to define the extent of vasculitic disease. Although it is more sensitive than MRA, it is still insufficiently sensitive and specific to establish a PACNS diagnosis alone. Brain biopsy is the gold standard, although it also has sensitivity limitations. The combination of intracerebral angiography and brain biopsy is therefore the preferred approach.

If PACNS were confirmed, treatment would generally require initiation of cyclophosphamide and high-dose glucocorticoids; however, such treatment should only be initiated after the brain biopsy or empirically if a brain biopsy cannot be carried out.

Azathioprine is a somewhat safer immunosuppressant than cyclophosphamide but has not been shown to be a treatment of first choice in PACNS; however, azathioprine may be utilized to reduce relapse rates among patients already treated and in remission.

Functional MRI (fMRI) could provide information about this patient's overall brain functioning; however, to date there are no specific signatures on fMRI that would permit specific diagnosis of PACNS.

KEY POINT

- Intracerebral angiography with brain biopsy can provide a definitive diagnosis in patients with suspected primary angiitis of the central nervous system.

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Item 75 Answer: B

Educational Objective: Manage liver toxicity in a patient taking leflunomide.

Discontinuation of the nonbiologic disease-modifying antirheumatic drug leflunomide is appropriate for this patient with rheumatoid arthritis who has developed abdominal pain and tenderness with acute hepatitis. The most likely diagnosis is leflunomide-induced hepatitis. Leflunomide-induced elevation of liver chemistries can occur in up to 20% of patients taking the medication, and a threefold elevation of serum aminotransferase levels has been noted in up to 13% of patients treated with leflunomide. She is at a slight increased risk for it due to concomitant NSAID use. Mild elevations less than three times the upper limit of normal are usually reversible with dose reduction or drug discontinuation. Hence, temporary or permanent discontinuation of leflunomide is indicated in this patient. In patients with more severe elevations (> three times), additional therapy with cholestyramine to quickly decrease the drug levels would also be indicated because leflunomide undergoes significant enterohepatic circulation. The current American College of Rheumatology treatment guidelines recommend periodic monitoring of liver chemistry tests (every 8-12 weeks) in patients being treated with leflunomide.

Etanercept is a receptor fusion protein, which blocks tumor factor necrosis α. Etanercept-induced liver disease is extremely rare and should not be considered the likely diagnosis.

The usual presentation of biliary colic is episodic, with severe abdominal pain typically in the epigastrium and/or right upper quadrant. The pain rapidly intensifies over a 15-minute interval to a steady plateau that lasts as long as 3 hours and resolves slowly. The pain is often associated with nausea or vomiting, and there is no jaundice. This patient's symptoms are not suggestive of biliary colic; therefore, cholecystectomy is not indicated.

Liver biopsy may be needed to evaluate the cause of liver disease, but it is an invasive process and is only recommended if repeat testing and discontinuation of a known offending agent do not lead to resolution, if the cause of liver disease is uncertain, or if there is evidence of chronic liver disease.

KEY POINT

- Leflunomide can induce elevation of liver chemistries, which is usually reversible with dose reduction or drug discontinuation.

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Item 76 Answer: A

Educational Objective: Identify azathioprine as a contraindication to the use of febuxostat.

Azathioprine is a contraindication to the use of febuxostat in this patient with gout. Febuxostat is a purine analogue that blocks urate synthesis by inhibiting xanthine oxidase, the final enzyme in the pathway of urate synthesis from purine precursors. It can be utilized when a patient has intolerance to or failure of allopurinol. Azathioprine, a purine analogue used in the treatment of inflammatory bowel disease, undergoes metabolism via xanthine oxidase. Thus, concomitant use of febuxostat (a xanthine oxidase inhibitor) can lead to dangerously high levels of azathioprine. Of note, use of allopurinol (also a xanthine oxidase inhibitor) concomitantly with azathioprine also poses a risk and is relatively contraindicated; however, some practitioners have used allopurinol in this setting with dose reduction and careful monitoring.

Use of diltiazem is a relative contraindication to colchicine, not febuxostat. Diltiazem is a moderate CYP34A inhibitor, and coadministration of this agent with colchicine can cause elevated colchicine levels.

Moderate chronic kidney disease (estimated glomerular filtration rate, 30-59 mL/min/1.73 m^2) is not a contraindication

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to the use of febuxostat; no dose adjustment to this medication is needed in the setting of mild to moderate kidney impairment.

Nonalcoholic fatty liver disease is not a contraindication to febuxostat use, although monitoring of hepatic function with administration of the drug is indicated.

KEY POINT

- The xanthine oxidase inhibitor febuxostat is contraindicated in patients taking azathioprine, which undergoes metabolism via xanthine oxidase; concomitant use of these agents can lead to dangerously high levels of azathioprine.

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Item 77 Answer: C

Educational Objective: Diagnose Takayasu arteritis.

The most appropriate diagnostic test to perform next is aortic arteriography in this patient who most likely has Takayasu arteritis. She presents with arterial compromise in the setting of a systemic febrile illness. Asymmetric blood pressure in the arms suggests arm involvement, and a midabdominal bruit, leg symptoms, and hypertension suggest aortic and renal artery obstruction. The differential diagnosis includes other forms of vasculitis and/or thrombosis. Given her age, sex, and high erythrocyte sedimentation rate, a diagnosis of Takayasu arteritis is likely. Because there are no specific laboratory tests used to diagnose or define Takayasu arteritis, arteriography of the aorta and its branches is used to confirm the diagnosis and define the extent of the problem. Alternative imaging modalities such as CT angiography or MR angiography might also be used for the same purpose.

An antimyeloperoxidase antibody assay would be useful if microscopic polyangiitis (MPA) were a diagnostic consideration; however, the kidney disease seen in this patient is due to renal artery obstruction and occurs in the absence of active urine sediment such as would be expected in MPA glomerulonephritis. Moreover, peripheral artery involvement would not be expected in MPA, a small-vessel disease.

The presence of antiphospholipid antibodies would be consistent with the antiphospholipid antibody syndrome and with the presence of thrombotic disease potentially occluding the arm, aorta, and renal arteries. However, her normal prothrombin and partial thromboplastin times indicate the absence of a lupus anticoagulant (one criterion for antiphospholipid antibody syndrome), and the lack of elevation in fibrin degradation products (D-dimer) argues against a thrombotic disease.

Although Takayasu arteritis and giant cell arteritis (GCA) share remarkably similar pathology, GCA occurs in older patients and is characterized by temporal arteritis, whereas Takayasu arteritis is a disease of the young that rarely, if ever, involves temporal arteries. Thus, a temporal artery biopsy is not indicated.

KEY POINT

- Arteriography of the aorta and its branches can be used to confirm the diagnosis of Takayasu arteritis.

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Item 78 Answer: B

Educational Objective: Manage pregnancy planning in a patient with systemic lupus erythematosus who is taking mycophenolate mofetil.

Discontinuation of mycophenolate mofetil is indicated for this patient with systemic lupus erythematosus (SLE) who plans to become pregnant. Pregnancy outcomes in patients with SLE are better if their disease has been well controlled for 6 months prior to becoming pregnant. SLE can worsen during pregnancy in up to one third of patients, and hydroxychloroquine can reduce this risk. In addition, most rheumatologists continue stable low-dose prednisone during the pregnancy. Many medications used in SLE are contraindicated in pregnancy; permitted medications include prednisone, hydroxychloroquine, and azathioprine. Mycophenolate mofetil was developed to prevent transplant rejection but in recent years has been used as a treatment for SLE. Mycophenolate works by inhibiting the purine pathway in nucleotide synthesis and may be at least as effective as cyclophosphamide for SLE (including lupus nephritis) but with fewer and milder side effects. This agent is teratogenic and must be stopped for 3 months prior to becoming pregnant. Mycophenolate mofetil use may also be associated with difficulty in conception in some cases. This patient with SLE plans to become pregnant and has stable disease, and her laboratory parameters show no significant activity. Stopping mycophenolate is the only necessary intervention, and both hydroxychloroquine and prednisone should be continued unchanged.

Stopping all three medications would put this patient at unnecessary increased risk of a flare-up during pregnancy.

KEY POINT

- Mycophenolate mofetil is teratogenic and must be stopped for 3 months prior to becoming pregnant.

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Item 79 Answer: B

Educational Objective: Diagnose *Mycobacterium tuberculosis* infection.

The most likely diagnosis is *Mycobacterium tuberculosis* infection of the hip. Joint infections with *M. tuberculosis*

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present as an indolent process, often in the hip, knee, or spine (Pott disease). Constitutional symptoms are frequently absent, and imaging may reveal nonspecific erosions that may be interpreted as osteoarthritis. Moderate elevation of the erythrocyte sedimentation rate is common. The diagnosis is made by joint aspiration with fluid sent for mycobacterial cultures. This patient is at increased risk due to origination from and travel to an endemic area (India) and the recent initiation of the tumor necrosis factor (TNF)-α inhibitor etanercept for treatment of rheumatoid arthritis. TNF-α inhibitors increase the risk of tuberculosis reactivation. Patients should be screened for latent infection prior to start of therapy and monitored for signs of infection during therapy. In this case, the patient had appropriate treatment for latent tuberculosis infection in the past but may have had an incomplete response or contracted another latent infection.

Gout rarely occurs in premenopausal women and typically presents in peripheral joints, with the great toe (podagra) the classic site of the first attack.

This patient is not sexually active and thus is not at risk for *Neisseria gonorrhoeae* infection. Furthermore, gonococcal arthritis typically spares the axial skeleton.

Rheumatoid arthritis (RA) is always a consideration in a patient with RA and joint pain. However, it is unusual for a single joint to be involved in an RA flare, and her arthritis appears well controlled overall. Isolated inflammation of a single joint out of proportion to other joints is a clue to infection.

KEY POINT

- Patients should be screened for latent tuberculosis prior to start of tumor necrosis factor α inhibitor therapy and monitored for signs of infection during therapy.

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Item 80 Answer: B

Educational Objective: Evaluate a patient with systemic lupus erythematosus who has developed mononeuritis multiplex.

Electromyography (EMG) and nerve conduction studies (NCS) are appropriate for this patient with systemic lupus erythematosus (SLE) who most likely has mononeuritis multiplex. Mononeuritis multiplex is characterized by abnormal findings in the territory of two or more nerves in separate parts of the body. She has a foot drop with normal reflexes that suggests an injury to the peroneal nerve and wrist drop that suggests injury to the radial nerve. EMG/NCS would most likely document a peripheral neuropathy. Mononeuritis multiplex is highly specific for vasculitic disorders that affect the vasa vasorum or nerve vascular supply but can also occur in systemic inflammatory disorders such as SLE. The peroneal nerve is the most commonly affected nerve. Approximately 14% of patients with SLE have a peripheral neuropathy with the majority (60%) due to SLE. Risk factors for the development of SLE-associated peripheral neuropathy include moderate to severe disease and the presence of other neuropsychiatric SLE manifestations. Approximately two thirds of patients improve with more aggressive immunosuppression. EMG/NCS can identify a nerve (usually the sural nerve) that might be amenable to biopsy to document the vasculitis prior to aggressive immunosuppression.

Hydroxychloroquine can cause a neuromyopathy manifested by proximal muscle weakness and areflexia. Biopsy demonstrates vacuoles in the muscle cells. However, hydroxychloroquine has not been associated with mononeuritis multiplex.

SLE may rarely cause transverse myelitis, which is characterized by a rapidly progressing paraparesis associated with a sensory level. Autonomic symptoms, including increased urinary urgency, bladder and bowel incontinence, and sexual dysfunction, may be present. The patient has no symptoms suggesting transverse myelitis, and a spine MRI is not indicated.

A small-fiber neuropathy causes a burning pain in the extremities and has been associated with autoimmune diseases such as SLE but does not cause motor symptoms. Diagnosis is made by skin biopsy, which demonstrates a reduced density of small sensory nerve fibers in the skin.

KEY POINT

- Mononeuritis multiplex is characterized by abnormal findings in the territory of two or more nerves in separate parts of the body and is highly specific for vasculitis but can occur in systemic inflammatory disorders such as systemic lupus erythematosus.

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Florica B, Aghdassi E, Su J, et al. Peripheral neuropathy in patients with systemic lupus erythematosus. Semin Arthritis Rheum. 2011 Oct;41(2):203-11. [PMID: 21641018]

Item 81 Answer: B

Educational Objective: Diagnose HIV infection as the cause of a severe flare of psoriatic arthritis.

HIV antibody testing is indicated for this patient with a severe flare of psoriatic arthritis. HIV infection can trigger the onset of or exacerbate preexisting psoriatic arthritis and psoriasis. Skin and joint symptoms tend to be severe. Explosive onset or severe flare-up of psoriatic arthritis should therefore raise suspicion for concomitant HIV infection. This patient had previously well-controlled psoriatic arthritis until a recent severe flare, as manifested by severe pain and swelling of multiple joints and psoriasis, and should therefore be tested for HIV infection.

Although viral infections other than HIV can trigger flares of psoriasis, infectious mononucleosis is characterized by sore throat, lymphadenopathy, and splenomegaly, none of

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which (except adenopathy) is seen in this patient. Therefore, heterophile antibody testing is not indicated.

HLA-B27 is associated with psoriatic arthritis but not with psoriasis; furthermore, it neither confirms the diagnosis nor explains the flare-up of psoriasis.

The initial clinical manifestation of early localized Lyme disease is erythema migrans, an erythematous skin lesion that is noted in 70% to 80% of patients with confirmed infection. Early disseminated Lyme disease develops several weeks after the initial infection. Patients frequently present with a febrile illness associated with myalgia, headache, fatigue, and lymphadenopathy. Although Lyme disease may trigger a flare of psoriasis, as most acute infections can, it cannot account for the patient's thrush.

Streptococcal pharyngitis is a common trigger of guttate psoriasis, especially in children. Guttate psoriasis can also be the first sign of a flare in previously stable chronic plaque psoriasis. Guttate psoriasis consists of many small raindrop-like papules and plaques on the trunk. This patient's psoriatic pattern does not suggest guttate psoriasis, and testing for streptococcal infection is not indicated.

KEY POINT

- The development of explosive onset or severe flare of psoriatic arthritis should raise suspicion for concomitant HIV infection.

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Item 82 Answer: B

Educational Objective: Treat a patient who has parvovirus B19 infection.

This patient has parvovirus B19 infection, and an NSAID such as ibuprofen is the appropriate initial treatment. This infection most commonly occurs in children and is characterized by acute polyarthritis with symmetric swelling and stiffness, the classic "slapped cheek" rash, and flu-like symptoms. Adults tend to contract the virus from children, but the rash may be absent or atypical in adults. Therefore, diagnosis should be suspected in adults with other characteristic findings as well as exposure to sick children. This patient shows evidence of a symmetric, small joint arthritis of the hands, a pattern consistent with rheumatoid arthritis as well as several forms of viral arthritis, most characteristically the arthritis that accompanies parvovirus B19 infection. This patient is at risk for parvovirus B19 infection given her occupation as an elementary school teacher, and the presence of IgM antibodies for parvovirus is definitive and establishes the diagnosis. Parvovirus B19 infection and its associated arthritis are generally self-limited; therefore, management is symptomatic, and an NSAID such as ibuprofen should alleviate symptoms until the episode resolves.

Azithromycin therapy may be appropriate for treatment of *Chlamydia* infection associated with reactive arthritis, a form of spondyloarthritis associated with a specific group of urogenital and gastrointestinal pathogens. However, antibiotic therapy is not indicated for parvovirus B19 infection.

Interferon alfa is of value for treating some viruses, particularly hepatitis. However, this agent is not needed to treat parvovirus B19 infection, which is self-limited.

Glucocorticoid therapy is not indicated in uncomplicated parvovirus B19 infection due to the self-limited nature of the infection and associated arthritis.

KEY POINT

- Parvovirus B19 infection and its associated arthritis are generally self-limited; therefore, management is symptomatic, and an NSAID such as ibuprofen should alleviate symptoms until the episode resolves.

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Item 83 Answer: C

Educational Objective: Diagnose granulomatosis with polyangiitis.

The presence of antiproteinase 3 (PR3) antibodies will be diagnostic in this patient who most likely has granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), a systemic necrotizing vasculitis that predominantly affects the upper and lower respiratory tract and kidneys. More than 70% of patients have upper airway manifestations such as sinusitis or nasal, inner ear, or laryngotracheal inflammation. Purpura and ulcers are common skin manifestations. Mononeuritis multiplex may also occur. Pulmonary manifestations can present as cough, hemoptysis, and pleurisy. Characteristic radiographic findings include multifocal infiltrates or nodules, some of which may cavitate; diffuse opacities are seen in patients with pulmonary hemorrhage. Pauci-immune glomerulonephritis occurs in up to 80% of patients. Diagnosis is best established by lung or kidney biopsy. However, the presence of anti-PR3 antibodies is sufficient to establish a diagnosis in patients with classic upper airway manifestations, pulmonary infiltrates nodules, and urinary abnormalities consistent with glomerulonephritis.

Anti-double-stranded DNA antibodies are specific but relatively insensitive for systemic lupus erythematosus (SLE). SLE is an unlikely diagnosis in this patient because the involvement of the upper airways, particularly with erosion of the sinuses, is uncommon in SLE, the disease is much less common in men than women, and complement levels are typically reduced during active disease.

Antimyeloperoxidase antibodies reflect the presence of ANCA in a perinuclear rather than cytosolic pattern and are associated with microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome), and rapidly progressive glomerulonephritis. However, the presence of upper airway disease essentially rules out these conditions in this patient.

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Serum cryoglobulins can be elevated in cryoglobulinemia, which can characteristically affect the kidneys, skin, and nerves and can less commonly affect the lungs. However, upper airway involvement is uncommon, and the normal complement levels, especially a normal C4, also argue against cryoglobulinemia as a diagnosis.

KEY POINT

- The presence of antiproteinase 3 antibodies is sufficient to establish a diagnosis of granulomatosis with polyangiitis in patients with classic upper airway manifestations, pulmonary infiltrates/nodules, and urinary abnormalities consistent with glomerulonephritis.

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Lutalo PMK, D'Cruz DP. Diagnosis and classification of granulomatosis with polyangiitis (aka Wegener's granulomatosis). J Autoimmun. 2014 Feb-Mar;48-49:94-8. [PMID: 24485158]

Item 84 Answer: C

Educational Objective: Evaluate a patient with suspected lupus nephritis using a kidney biopsy.

A kidney biopsy is appropriate for this patient with systemic lupus erythematosus (SLE). Kidney disease occurs in some form in up to 70% of patients with SLE, especially in those who express anti–double-stranded DNA antibodies, which typically rise and fall with disease activity. Diagnosis of lupus nephritis is suggested by proteinuria (>500 mg/24 h) or cellular casts (erythrocytes or leukocytes) in the urine sediment of patients fulfilling the formal criteria for the diagnosis of SLE. Most patients with active lupus nephritis have low serum complement levels. According to the 2012 American College of Rheumatology guidelines for evaluating and treating lupus nephritis, this patient meets the criteria for kidney biopsy. Unless contraindicated, biopsy should be done before initiating therapy. This patient will most likely have a proliferative form of lupus nephritis (class III/IV) and will require aggressive immunosuppressive therapy.

The usual therapeutic agents for proliferative forms of lupus nephritis are either cyclophosphamide or mycophenolate mofetil. There are no data to suggest that methotrexate is useful in this setting. Methotrexate is renally excreted, and toxicity increases in the setting of kidney disease.

Without adequate management, class III, class IV, or class V combined with class III or class IV generally are progressive, with a probability of end-stage kidney disease as high as 50% to 70% after 5 to 10 years of diagnosis. Therefore, there is no reason to wait another month to repeat laboratory testing in this patient given the present abnormalities.

Because the vascular lesion in lupus nephritis is at the level of the arteriole, a renal artery Doppler examination will not be useful for treatment decisions.

KEY POINT

- The diagnosis of lupus nephritis, suggested by proteinuria (>500 mg/24 h) or cellular casts (erythrocytes or leukocytes) in the urine sediment, must be confirmed and classified with a kidney biopsy.

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Item 85 Answer: C

Educational Objective: Treat hypertension in a patient with hyperuricemia who is at increased risk for acute gout.

The angiotensin receptor blocker (ARB) losartan is the most appropriate antihypertensive drug for this patient with hyperuricemia who is at increased risk for acute gout. Hypertension is a common comorbidity of gout and is found in approximately 74% of patients with gout. Antihypertensive drugs have variable effects on serum urate levels and risk of acute gout. A population-based, nested-case control study compared nearly 25,000 patients with a new diagnosis of gout with 50,000 control patients. The risk of gout was assessed according to antihypertensive drug class. Losartan, but not other ARBs, and calcium channel blockers were associated with a reduced risk of gout (relative risk for losartan: 0.81 [95% CI, 0.7-0.84]; relative risk for calcium channel blockers: 0.87 [95% CI, 0.82-0.93]). Both losartan and calcium channel blockers lower serum urate. Losartan, like probenecid, interferes with the urate-reabsorbing transporter, thereby promoting kidney urate excretion. The mechanism by which calcium channel blockers lower urate levels is unclear but may be mediated through increased glomerular filtration rate and increased urate clearance. Based upon these data, losartan and calcium channel blockers are the preferred antihypertensive agents if reducing the risk of gout is clinically relevant.

In this same study, ACE inhibitors, non-losartan ARBs, β-blockers, and diuretics were all associated with an increased risk of gout. The absolute risk of gout was greatest with diuretics, with an estimated risk of six events per 1000 person-years.

KEY POINT

- The angiotensin receptor blocker losartan and calcium channel blockers lower serum urate and may be useful to treat patients in whom hypertension and gout are both clinical concerns.

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Item 86 Answer: D

Educational Objective: Treat tophaceous gout with pegloticase in a patient who has not responded to oral urate-lowering therapy.

Switching febuxostat to pegloticase is appropriate for this patient. He has severe tophaceous gout and persistent hyperuricemia and has not responded to oral urate-lowering therapy, including the xanthine oxidase inhibitors allopurinol and febuxostat. He therefore warrants a trial of the synthetic uricase replacement pegloticase, an intravenous medication FDA approved for treatment-failure gout. Patients with bothersome persistent tophi or recurrent gout flares despite oral urate-lowering therapy (or with contraindications to available oral therapy) should be considered for pegloticase treatment, in consultation with a rheumatologist.

Xanthine oxidase inhibitors such as febuxostat should be discontinued when initiating pegloticase. Immunogenicity to pegloticase can result in infusion reactions; loss of response to the drug suggests the presence of neutralizing antibodies to the drug and indicates increased risk of infusion reactions. Therefore, drugs that might otherwise lower the serum urate level should be discontinued because they may mask a rising serum urate level that would signal the presence of pegloticase antibodies and its attendant loss of effectiveness and increased risk of a serious infusion reaction. Pegloticase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.

This patient's current gout flare is nearly resolved and therefore does not require prednisone. Moreover, prednisone is not effective in reducing serum urate levels, and it is not an appropriate drug to prevent recurrent attacks of acute gout due to its many long-term side effects.

Colchicine is generally working well in reducing gout flares in this patient. If this were ineffective or not tolerated, another agent would need to be considered for prophylaxis (or treatment of acute flares). Anakinra is an interleukin-1β inhibitor that may be considered for off-label use for gout prophylaxis and flare treatment in patients in whom other more conventional agents are ineffective or contraindicated, which is not the case for this patient.

KEY POINT

- Pegloticase may be considered for patients with resistant gout who have not responded to oral urate-lowering therapy.

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Item 87 Answer: A

Educational Objective: Confirm a flare of systemic lupus erythematosus with an anti-double-stranded DNA antibody measurement.

Measurement of anti-double-stranded DNA antibodies is appropriate for this patient who is having a flare of systemic lupus erythematosus (SLE). She has symptoms of fatigue, joint pain, rash, leukopenia, and lymphopenia. Urinalysis shows proteinuria and hematuria, indicating that she may have glomerulonephritis as well. Levels of anti-double-stranded DNA antibodies correlate with SLE disease activity; in particular, they correlate with active kidney disease or glomerulonephritis and might prompt further evaluation such as kidney biopsy. Thus, measuring anti-double-stranded DNA antibody titers may be useful in assessing this patient's recent symptoms. Following anti-double-stranded DNA antibody titers over time can be useful because it is a marker for risk of developing lupus nephritis.

Antinuclear antibody (ANA) testing is a useful screening tool for SLE because more than 95% of patients with SLE are positive for ANA; however, ANA does not correlate with disease activity.

Anti-Ro/SSA and anti-La/SSB antibodies can be present in patients with Sjögren syndrome as well as SLE. These antibodies correlate with SLE rashes and photosensitivity and are a risk factor for the development of neonatal lupus erythematosus; however, they do not correlate with disease activity.

Anti-Smith antibodies are highly specific for the diagnosis of SLE; however, these antibodies also do not correlate with disease activity.

Anti-U1-ribonucleoprotein antibodies are found in patients with SLE and with mixed connective tissue disease but do not correlate with disease activity.

KEY POINT

- Anti-double-stranded DNA antibodies correlate with systemic lupus erythematosus disease activity, particularly active kidney disease or glomerulonephritis.

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Item 88 Answer: A

Educational Objective: Treat a patient who has scleroderma renal crisis.

The ACE inhibitor captopril is the most appropriate treatment for this patient who most likely has scleroderma renal crisis (SRC) in the setting of diffuse cutaneous systemic sclerosis (DcSSc). SRC occurs in 10% to 15% of patients with systemic sclerosis and is more frequent in DcSSc compared with limited cutaneous systemic sclerosis. Vascular involvement of afferent arterioles leads to glomerular ischemia and hyperreninemia. The typical presentation is acute onset of oliguric kidney disease and severe hypertension, mild proteinuria, urinalysis with few cells or casts, microangiopathic hemolytic anemia, and thrombocytopenia.

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Some patients develop pulmonary edema and hypertensive encephalopathy. Normal blood pressure may be present in up to 10%. This patient presents acutely with a rapid rise in serum creatinine consistent with acute kidney injury, with a bland urinalysis and non-nephrotic-range proteinuria as well as neurologic symptoms suggestive of encephalopathy. Although her blood pressure is almost normal, these findings are highly suggestive of SRC. Treatment with an ACE inhibitor is essential to restore kidney function and manage hypertension associated with SRC. Captopril is the preferred ACE inhibitor because it has been the most extensively studied agent in this clinical setting, and its short half-life allows rapid titration.

Cyclophosphamide is a potent immunosuppressant used to treat severe or life-threatening manifestations of certain diseases such as systemic lupus erythematosus or systemic vasculitis. It is ineffective in treating SRC, which is vascular and noninflammatory.

This patient does not have inflammatory end-organ involvement; therefore, methylprednisolone is not needed. Glucocorticoids are not useful in SRC, and intravenous glucocorticoids may cause worsening symptoms.

Sildenafil can be used to treat pulmonary hypertension or finger ulcerations but is not appropriate for SRC, which is primarily mediated through the renin-angiotensin axis.

KEY POINT

- In patients with scleroderma renal crisis, treatment with an ACE inhibitor is essential to restore kidney function and manage hypertension.

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Item 89 Answer: B

Educational Objective: Treat a patient who has inadequately controlled knee osteoarthritis.

An NSAID such as diclofenac is indicated for this patient with knee osteoarthritis. In addition to the implementation of nonpharmacologic measures such as an exercise regimen and/or assistive devices, the initial pharmacologic management of osteoarthritis recommended in guidelines issued by various societies is acetaminophen in doses ≤3 g/d. If this offers inadequate relief, NSAIDs can be used. NSAIDs are more efficacious than acetaminophen in the relief of osteoarthritis pain. Treatment guidelines suggest using the lowest possible effective dose for the shortest time period because side effects are common and occasionally severe. However, many patients require years of NSAID use given the prolonged timeframe over which the disease is symptomatic and the small number of alternative pharmacologic treatments. NSAIDs are associated with important toxicities, particularly with prolonged exposure. The risk of peptic ulcer disease and gastrointestinal bleeding can be reduced with concomitant use of proton pump inhibitors. Cardiovascular risks can be mitigated by appropriate patient selection for chronic NSAID use.

Topical capsaicin can be used at any time to treat osteoarthritis as well; however, in the absence of an effect from acetaminophen, an NSAID is likely to give this patient more substantial relief of symptoms.

Duloxetine is a serotonin-norepinephrine reuptake inhibitor approved to treat osteoarthritis pain but is slower acting than NSAIDs and requires ongoing, rather than intermittent and as-needed, administration.

Hyaluronic acid injections have shown only a minimal degree of benefit in the treatment of knee osteoarthritis; they also require an invasive procedure for administration and are expensive. Therefore, they would not be preferred to treatment with an NSAID.

Narcotics such as hydrocodone should be reserved for patients who have not responded to nonpharmacologic measures in addition to NSAIDs. An alternative to hydrocodone is tramadol, a centrally acting synthetic opioid analgesic that binds to μ-opioid receptors and inhibits reuptake of norepinephrine and serotonin. It can be used for analgesia when NSAIDs are not tolerated or are contraindicated. Side effects include headaches and dizziness. Tolerance can occur with long-term use; withdrawal symptoms can occur with discontinuation.

KEY POINT

- An NSAID should be initiated in patients with osteoarthritis if first-line therapy with acetaminophen does not provide adequate relief.

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Item 90 Answer: B

Educational Objective: Diagnose bladder cancer in a patient who has received cyclophosphamide.

Cystoscopy is the most appropriate diagnostic test to perform next in this patient. He has painless hematuria with a history of granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), which was treated with the nonbiologic disease-modifying antirheumatic alkylating agent cyclophosphamide. Both the underlying rheumatologic condition and the medication used for its treatment are associated with increased risk of malignancy, especially bladder cancer. Bladder cancer usually presents with painless frank (usually not microscopic) hematuria, and cystoscopy with biopsy is most likely to lead to the correct diagnosis. In contrast, kidney involvement due to the disease is associated with glomerulonephritis, and urinalysis shows erythrocyte casts or dysmorphic erythrocytes, which is not the case here. The risk of bladder cancer is higher if the patient has received oral

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cyclophosphamide because there is prolonged daily exposure to the metabolites associated with causing mucosal irritation and metaplasia. The incidence of cystitis and bladder cancer is lower with intermittent intravenous cyclophosphamide, especially when given with mesna, an adjuvant therapy given with cyclophosphamide to detoxify urotoxic metabolites. Importantly, bladder cancers associated with cyclophosphamide exposure may be more aggressive and should be urgently evaluated even when suspicion is low.

CT and ultrasonography may show large lesions affecting the kidneys and gastrointestinal tract but do not detect small and superficial lesions, which can only be detected on cystoscopy.

The patient had no new drug exposure, and urinalysis does not show significant findings of nephritis; therefore, there is no reason to suspect a drug reaction or interstitial nephritis and obtain urine eosinophils.

Urine protein-creatinine ratio to look for glomerular disease is not helpful in evaluating a patient with hematuria when suspicion for the underlying vasculitis is low, as seen in this patient with a negative p-ANCA.

KEY POINT

- The use of cyclophosphamide is associated with increased risk of malignancy, especially bladder cancer, and patients should be evaluated accordingly.

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Item 91 Answer: A

Educational Objective: Diagnose cardiomyopathy in a patient with systemic sclerosis.

The most likely diagnosis is cardiomyopathy in this patient with systemic sclerosis. Cardiomyopathy due to systemic sclerosis–induced coronary vasospasm and microvascular disease leading to patchy myocardial fibrosis is the most common symptomatic manifestation of heart involvement in systemic sclerosis. Although accelerated macroscopic coronary atherosclerosis has been associated with other autoimmune inflammatory diseases, coronary vascular involvement in systemic sclerosis is most often microvascular, with ischemia due to structural changes and recurrent spasm of small vessels. This results in contraction band necrosis, a pathologic finding due to episodes of myocardial ischemia followed by reperfusion. This process may ultimately lead to patchy fibrosis resulting in cardiomyopathy and heart failure. Patients who have systemic sclerosis with symptomatic cardiac involvement have a poor prognosis and mortality rate of 75% at 5 years. This patient presents with evidence of fluid overload due to heart failure as seen on her physical examination and confirmed by an abnormal chest radiograph and an echocardiogram suggesting diffuse myocardial dysfunction, consistent with this cause. Infiltrative myocardial fibrosis and conduction abnormalities may also contribute to the cardiac dysfunction but are less common causes of systemic sclerosis heart disease.

Constrictive pericarditis is a chronic disorder resulting from inflammation and fibrosis of the pericardium with loss of elasticity and resulting noncompliance of the pericardium. Although it may be associated with connective tissue disease, this patient does not have specific clinical findings typically associated with constrictive pericarditis such as a pericardial knock or pulsus paradoxus; furthermore, her echocardiogram shows evidence of diffuse myocardial dysfunction and no evidence of impaired cardiac filling with normal ventricular function as would be expected with constrictive pericarditis.

Pulmonary arterial hypertension is a common complication of systemic sclerosis and may lead to cor pulmonale and primarily right-sided heart failure. This patient's clinical presentation is more consistent with generalized myocardial dysfunction due to cardiomyopathy.

The kidneys are frequently involved in systemic sclerosis, with scleroderma renal crisis (SRC) occurring in 10% to 15% of patients. SRC causes acute-onset oliguric kidney disease, severe hypertension, and often microangiopathic hemolysis and thrombocytopenia. Except for evidence of impaired kidney function likely due to heart failure, this patient's clinical presentation is not consistent with SRC.

KEY POINT

- Microvascular cardiomyopathy is the most common symptomatic manifestation of heart involvement in systemic sclerosis and presents with heart failure.

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Item 92 Answer: D

Educational Objective: Diagnose bacterial overgrowth syndrome due to systemic sclerosis–associated intestinal disease.

A glucose hydrogen breath test is indicated. This patient has an 8-year history of diffuse cutaneous systemic sclerosis (DcSSc) and now presents with weight loss, abdominal cramping, and loose stools. She is at high risk for developing malabsorption from bacterial overgrowth (also known as blind loop syndrome) due to altered peristalsis caused by fibrosis associated with her underlying disease. She has unexplained weight loss as well as loose stools without any increase in symptoms of dysphagia, nausea, or vomiting. The most appropriate study for her evaluation at this time is the glucose hydrogen breath test. The gold standard for the detection of bacterial overgrowth is small bowel aspiration, but this study is not frequently performed because it is invasive. By comparison, the glucose hydrogen breath test is noninvasive and has a high sensitivity and specificity. Barium study may also be done to

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confirm these findings, but obtaining a CT scan at this point is unnecessary and costly. MRI may also be useful in the future for assessment of disease and exclusion of other pathologies.

She does not have bloody bowel movements or colitis, and performing a colonoscopy is unlikely to lead to the correct diagnosis because the primary pathology is in the small bowel and not the colon.

Endoscopic retrograde cholangiopancreatography is the diagnostic test of choice for suspected pancreatic or extrahepatic biliary tract pathology. She has no evidence of biliary tract blockage or pancreatic disease.

KEY POINT

- In patients with systemic sclerosis, malabsorption due to bacterial overgrowth is evaluated by obtaining a glucose hydrogen breath test.

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Forbes A, Marie I. Gastrointestinal complications: the most frequent internal complications of systemic sclerosis. Rheumatology. 2008 Jun;48(Suppl 3):iii36-39. [PMID: 19487222]

Item 93 Answer: B

Educational Objective: Diagnose osteoarthritis with calcium pyrophosphate deposition.

This patient most likely has pyrophosphate arthropathy, specifically osteoarthritis with calcium pyrophosphate deposition (CPPD). She has symptoms consistent with degenerative arthritis (pain worse with activity, brief morning stiffness) and signs of osteoarthritis of her hands. Her radiograph shows calcification (also known as chondrocalcinosis) of the triangular fibrocartilage, seen as calcific densities in the region of the distal ulna and ulnar styloid, consistent with CPPD; there is also some narrowing of the carpal metacarpal joints consistent with osteoarthritis. In osteoarthritis with CPPD, patients often have osteoarthritis in joints not typically involved with traditional osteoarthritis, including non-weight-bearing joints such as the shoulders and wrists.

This patient has risk factors for gout (postmenopausal woman, hypertension and taking a diuretic, diabetes mellitus, overweight). However, she lacks a history of episodic joint inflammation that typically precedes chronic gouty arthropathy.

The distribution of involved joints, including the distal interphalangeal (DIP) joints, is consistent with psoriatic arthritis; however, there is no evidence or symptoms of inflammatory arthritis. This patient also has no skin or nail findings to support the diagnosis of psoriasis. Although some patients develop skin involvement after the onset of arthritis, psoriatic arthritis cannot account for the finding of chondrocalcinosis seen in this patient.

The absence of synovial thickening and limited morning stiffness are not consistent with inflammatory arthritis such as rheumatoid arthritis. Rheumatoid factor is also negative, and inflammatory markers are within normal limits. Finally, examination and radiographic findings indicate involvement of the DIP joints, which tend to be spared in rheumatoid arthritis.

KEY POINT

- Osteoarthritis with calcium pyrophosphate deposition is a form of pyrophosphate arthropathy in which patients often have osteoarthritis in joints not typically involved with traditional osteoarthritis, including non-weight-bearing joints such as the shoulders and wrists.

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Item 94 Answer: D

Educational Objective: Identify the cause of an elevated erythrocyte sedimentation rate.

Continuing this patient's current treatment is appropriate at this time. This patient has polymyalgia rheumatica (PMR); she feels well, and her laboratory studies have improved over time. Although her erythrocyte sedimentation rate (ESR) remains elevated, it likely does not represent ongoing disease activity. The most likely cause of this patient's persistently elevated ESR is her age; it may also be elevated because of uncontrolled diabetes mellitus (possibly exacerbated by prednisone). The degree of elevation is related to the serum globulin concentration, the albumin-globulin ratio, the serum fibrinogen concentration, and the percent of hemoglobin A_{1c} but not the fasting serum glucose concentrations. ESR is dictated by characteristics of the erythrocytes themselves and by the presence of specific plasma proteins that alter the normal repulsive forces between erythrocytes and influence their ability to aggregate, form rouleaux, and sediment more quickly. These plasma proteins include acute phase reactants (such as fibrinogen) produced by the liver in response to proinflammatory cytokines occurring in rheumatologic disease, infection, and malignancy that neutralize these negative surface charges and increase ESR. Noninflammatory conditions causing elevated fibrinogen, including kidney disease, diabetes, pregnancy, and obesity, can also result in an elevated ESR. Normal aging can also cause an elevated ESR; for this female patient, an equation to find the estimate of the maximal expected ESR is (age in years + 10)/2, resulting in 42 mm/h.

It is important to recognize underlying factors that influence laboratory studies such as ESR; misinterpreting an elevated ESR as indicative of persistent inflammation or other disease can lead to inappropriate treatment such as prolongation or increase of glucocorticoid therapy. Thus, increasing prednisone or adding methotrexate is not indicated at this time.

This patient reports no headache, jaw claudication, or visual changes, all of which are clinical signs of giant cell arteritis; therefore, temporal artery biopsy is not indicated.

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KEY POINT

- Noninflammatory conditions (kidney disease, diabetes mellitus, pregnancy, obesity) as well as normal aging can cause an elevated erythrocyte sedimentation rate.

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Item 95 Answer: D

Educational Objective: Identify rheumatoid arthritis as the cause of pericarditis.

Rheumatoid arthritis (RA) is the most likely cause of this patient's pericarditis. RA is an independent risk factor for both coronary artery disease and heart failure; patients with severe extra-articular disease are at particularly increased risk of cardiovascular death. Pericarditis is the most common cardiac manifestation of RA and is often asymptomatic. Approximately one third of patients with RA can be found to have an asymptomatic pericardial effusion, and 10% of patients with RA will have symptomatic pericarditis at some point during the course of their disease. Most of those with symptomatic disease have a positive rheumatoid factor and active synovitis; however, when symptomatic, the manifestations are likely to be similar to those of any other cause of pericarditis. Diagnosis is most often made by confirming two of three classic findings: chest pain, often with a pleuritic component; friction rub; and diffuse ST-segment elevation on electrocardiogram.

Ankylosing spondylitis is a form of spondyloarthritis that manifests primarily by axial inflammation and bony ankylosis (fusion across joints). Inflammatory arthritis involvement of the hands tends to present as "sausage digits" rather than the symmetric polyarthritis seen in RA. Although conduction defects and aortitis with dilatation of the aortic valve ring and aortic regurgitation occur, pericarditis is not seen in patients with ankylosing spondylitis.

Polymyalgia rheumatica occurs in patients over the age of 50 years and causes diffuse achiness at the neck, shoulder girdle, and pelvic girdle. It is rarely associated with synovitis and is not associated with pericarditis.

Psoriatic arthritis is associated with an increased risk of coronary artery disease, as is RA. It can also cause a symmetric polyarticular inflammatory arthritis involving the small joints of the hands. However, psoriatic arthritis is not a common cause of pericarditis.

KEY POINT

- Pericarditis is the most common cardiac manifestation of rheumatoid arthritis and is often asymptomatic.

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Item 96 Answer: C

Educational Objective: Evaluate synovial fluid for infection and crystal-related disease.

Gram stain, culture, and crystal analysis are the most helpful and appropriate diagnostic tests to perform next on this patient's synovial fluid. Synovial fluid aspiration is essential when evaluating for infection and crystal-related disease and is useful in distinguishing between inflammatory and noninflammatory disease. On physical examination, this febrile patient has evidence of a monoarthritis with inflammation in her knee, which is confirmed by the cloudy appearance of the synovial fluid at the bedside and her elevated synovial fluid leukocyte count (15,000/μL [15×10^9/L]). Synovial fluid leukocyte counts greater than 2000/μL (2.0×10^9/L) are consistent with inflammatory fluid; the higher the count is, the more inflammatory the fluid and the greater the suspicion for crystal-related or infectious disease. An acute hospitalization or illness can precipitate an attack of crystal-related arthritis (either gout or pseudogout) and/or infection, and these entities can be evaluated for by synovial fluid analysis. It is important to note that the presence of crystals does not rule out concomitant infection. The most useful tests to obtain when analyzing synovial fluid are leukocyte count, stains, cultures, and crystal analysis. Sometimes the amount of synovial fluid available for analysis may be small; therefore, it is important to order only the most useful tests.

Antinuclear antibodies, glucose levels, and protein levels do not add any useful information and do not distinguish between infectious and noninfectious synovial fluid.

KEY POINT

- The most useful tests to obtain from synovial fluid are leukocyte count, Gram stains, cultures, and crystal analysis to evaluate for infection and crystal-related disease and to distinguish between inflammatory and noninflammatory disease.

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